THE MONITORING ROLE OF RIGHT LATERAL PREFRONTAL CORTEX:

EVIDENCE FROM VARIABLE FOREPERIOD AND SOURCE MEMORY TASKS

CANDIDATE
Antonino Vallesi

SUPERVISOR
Professor Tim Shallice

Thesis submitted for the degree of
Philosophiæ Doctor in Cognitive Neuroscience at
International School for Advanced Studies,
Trieste, Italy

Academic Year: 2006/2007

“Io stimo più il trovar un vero benché di
cosa leggiera ché il disputar lungamente
delle massime questioni senza conseguir
verità nissuna”

“I appreciate more to find a truth, even
if it concerns a little fact, than to talk at
length about chief issues, without
achieving any truth”

– Galileo Galilei

Summary

Abstract

The main purpose of this research project was to investigate the monitoring function of the right dorsolateral prefrontal cortex using different tasks in two domains. To that purpose, the architecture of the cognitive processes required to perform each task was extracted by means of different approaches of functional dissociation.

A variable foreperiod (FP) task was initially adopted. In such a task, simple/choice RTs are required while FPs of different duration vary on a trial-by-trial basis equiprobably in a rectangular distribution but randomly. As a result, the conditional probability is higher later in the FP range and RT is faster as the FP increases. This is the variable FP effect, which a recent neuropsychological study shows to be impaired in right lateral prefrontal patients. Another phenomenon usually obtained with such a paradigm is that of the sequential effects: RT becomes slower as the FP on the preceding trial gets longer. Contrasting views in the literature propose either multi-process strategic accounts, or a single-process conditioning account. In the project, these alternative theories were tested using behavioural studies on adults and children. The findings of these studies were not fully compatible with the previous views. A composite dual-process account, which shares some aspects with the previous accounts, was put forward and discussed. On this account, sequential effects are due to automatic processes acting on the arousal level, whereas the FP effect is due to a strategic process monitoring the conditional probability of stimulus occurrence.

Results of two TMS experiments confirm that the right dorsolateral prefrontal cortex is responsible for the FP effect, but not for the sequential effects. A neuropsychological study on tumor patients further corroborates this finding and suggests that left premotor areas are more likely to be the locus of the sequential effects.

In order to test whether the explicit temporal judgment has an influence on the nature of the FP phenomena, a series of behavioural experiments was conducted using a modified version of the variable FP paradigm. In the basic task, explicit judgments about the FP length were required. No modulation of the FP phenomena was obtained. However, a new stimulus-response compatibility effect was found: RT was faster when short and long FPs had to be responded to with left and right response-keys, respectively, than with the opposite stimulus-response mapping. This effect suggests that elapsing time is represented, in some circumstances, by means of spatial coordinates. Control experiments enable us to reject accounts based on hand/hemispheric asymmetries, but not accounts based on more categorical factors such as the linguistic markedness of the words used to label the stimuli and the responses.

The last part of the project aimed at extending results about a monitoring role (intended in a broad sense) of the right prefrontal cortex to a domain different from non-specific preparation. Two experiments in the source memory domain were run recording ERPs in the retrieval phase. The results show that prefrontal ERPs are not modulated by retrieval success, but by retrieval confidence, with low-confidence responses being associated with more positive waves than high-confidence ones, bilaterally, in the anterior prefrontal sites. Moreover, prefrontal waves were asymmetrically more positive in the right than in the left scalp regions, independently of confidence and accuracy. On the basis of these results, we could reject accounts linked to retrieval success. The results are instead interpreted in terms of different prefrontally-located monitoring processes in source memory retrieval.

Overall, the project represents an instantiation of the fractionation approach recently adopted to study the supervisory functions of the prefrontal cortex. This approach was used here in order to understand the differential role of a particular prefrontal area (i.e., the right dorsolateral prefrontal cortex) in a rather specific function (i.e., monitoring). This goal was developed in synchrony with the attainment of a better functional description of the tasks employed.

Acknowledgments

I would like to thank my supervisor, Tim Shallice. I could not have imagined having a better advisor for my PhD. I owe to him a great debt of gratitude for his inspiration and stimulating discussions on each single brick of this project.

I especially thank Vincent Walsh, for offering me the chance to learn the TMS technique, in its most recent applications. Thanks to this opportunity, I could perform the TMS studies reported on chapter 3.

I sincerely express gratitude to Raffaella Rumiati, for her trust in me and for all the precious help she provided on a lot of matters.

I must not forget to mention Carlo Arrigo Umiltà, who contributed a great deal to my maturation as a researcher.

Data on tumor patients of the experiment 9 (chapter 3) were collected by Alessandro Mussoni. To him I would like to express my acknowledgments for this hard work.

I would also like to thank Alessio Toraldo, Alessio Isaja, Corrado Corradi Dell'Acqua, Enea Francesco Pavone, Carlo Reverberi, Giorgio Fuggetta, Gorana Pobric, Neil Muggleton, and Mohinish Shukla, for the fruitful discussions ad help on a number of technical, methodological and statistical issues.

My thanks also to Gioia Negri and CCD, for their help in building up the linguistic material of experiments reported in chapter 5.

Thanks to Emilio Kropff Causa, for his help on mathematical issues and for his genuine friendship.

It was a great pleasure for me to work close to all the fantastic people in my lab at SISSA Stock-town and, before, in Via dell'Orologio. I thank all my colleagues and friends who contributed to my maturation as a researcher with the challenging scientific and methodological issues which we have faced together. But, above all, I warmly thank them

for the fantastic homely atmosphere which we have successfully created jointly at SISSA and outside it.

Thanks Tina Spinton and Livia Volpinis…for hundreds of reasons.

Last, but not least, I want to thank my great family, for their strong support during all my years of study, and for having endured, with adorable and discreet patience, my physical distance from them for most of the time.

Some of the experiments reported in the thesis have also been submitted elsewhere. Specifically, experiments 3a, 3b and 4 are currently under review for the *Journal of Experimental Psychology: HPP* [Authors: Vallesi, A. & Shallice, T.]; experiments 7 and 8 have been presented in an article recently published in *Cerebral Cortex* [Vallesi, A., Shallice, T., & Walsh, V. (2007), *Cerebral Cortex, 17(2),* 466-74]; Experiment 9 is under review for the journal *Neuropsychologia* [Authors: Vallesi, A., Mussoni, A., Mondani, M., Budai, R., Skrap, M., & Shallice, T.]; experiments 10-14 are part of a manuscript under review for *Cognition* [Authors: Vallesi, A. & Shallice, T.]; experiments 15 and 16 appeared last year on *Brain Research* (Vallesi, A. & Shallice, T. (2006), *Brain Research, 1124(1),* 111-25).

Chapter 1

1.1. The frontal lobes: Anatomo-functional considerations

The frontal lobes are the most anterior part of human brain. They are separated from the parietal lobes by the central sulcus, and from the temporal lobes by the Sylvian fissure. A broad distinction within the frontal lobes is between the rostral part, the so-called prefrontal cortex (PFC), and the more posterior part, namely the motor, premotor and supplementary motor areas. A simple anatomical classification of PFC comprises three frontal surfaces of the pyramid formed by the PFC (Fuster, 1999): the curved lateral wall, which corresponds to the so-called lateral PFC (Brodmann areas (BA) 8, 9, 10, 11, 44, 45, 46, and 47), the flat floor orbital surface, that is the orbitofrontal cortex (BA 10, 11, 13, and 47), and the flat medial wall, the medial PFC (BA 8, 9, 10, 11, 12, 25, and 32).

The special status of the PFC with respect to other brain areas appears on many aspects. Phylogenetically, it has undergone a substantial expansion across mammals, being mainly present in the neocortex of primates, and culminating in great apes and humans (e.g., Semendeferi & Damasio, 2000), where it reaches more than one third of the whole cerebral cortex. Ontogenetically, it is the last part of the brain to develop in humans, reaching full maturation during early adulthood (Fuster, 1997; Krasnegor, Lyon, & Goldman-Rakic, 1997; Thatcher, 1997). This unique evolutionary destiny suggests the great importance of this area for mental functions which are typically considered as human (Amati & Shallice, in press). However, the frontal lobes, especially in the right hemisphere, were considered in the past as the ‘silent’ portion of the brain, since dysfunctions in this area were not straightforward to be identified clinically. Electrical stimulation of the PFC, for instance, did not result in clearly detectable motor or perceptual symptoms (Fritsch & Hitzig, 1870).

A first Kuhnian paradigm shift in the study of frontal cortex is historically represented by the well-known case report of Phineas Cage (Harlow, 1848). In 1847, this Irish workman was involved in a rock blasting accident during which an iron bar passed through the frontal region of his brain. Amazingly enough, he survived the incident, but not without consequences. Indeed, marked changes occurred in his personality after the bar run through his brain. Where before the accident Cage had a well-balanced mind and was considered a very efficient and capable foreman, he had now become irreverent, aggressive, and unable to select and execute any of the plans he developed for future action (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Harlow, 1869).

After that, the number of reports on the clinical consequences of prefrontal lesions has increased (e.g., Bianchi, 1895; Ferrier & Yeo, 1884; Feuchtwanger, 1923; Welt, 1888), and the idea that PFC is at the top of any hierarchical classification of mental functions began to spread in the neuroscientific community (e.g., Donath, 1923; Franz, 1907). However, little was known about the PFC, and this region, although acknowledged to be important for human behaviour, was considered less accessible to investigation than many other areas of the cortex, such as the primary visual cortex, which were easier to study both behaviourally and anatomically.

A second important discovery in the study of PFC can be identified in the early work by Jacobsen (1936), who found that monkeys with large bilateral frontal lobe lesions show a specific deficit in performing a delayed response task. A typical trial from this task consists of first showing a target stimulus, then presenting a delay during which the target is hidden, and finally prompting the subject to respond according to relevant information about the target. The importance of Jacobsen's work was the demonstration that the PFC is critical to a specific cognitive function, or set of functions, which he called 'immediate memory', and corresponds to what is nowadays known as 'working memory', that is the capacity to retain information in memory for on-line cognitive processing (e.g., Stuss & Knight, 2002; Warren & Akert, 1964; see Paragraph 1.1.2.1.). With the development of single-cell recording techniques, it was additionally shown that many neurons in the dorsolateral prefrontal cortex (DLPFC) remain active during the delay (e.g., Fuster & Alexander, 1971; Fuster, 1997; Goldman-Rakic, 1987).

Another important finding was that the PFC had a modular structure, as several areas are differentiated on the basis of cyto-architectonic criteria (Brodmann, 1905; 1909; Preuss & Goldman-Rakic, 1991; Petrides & Pandya, 1994), and of distinct connections with other cortical and subcortical regions (e.g., Jones, 1985; Schmahmann & Pandya, 1997). These findings led to the testable working hypothesis that different parts of the PFC might also have different functions. These functions, in turn, can therefore be studied in a similar fashion as the functions carried out by other portions of the brain (e.g., Goldman-Rakic, 1987).

1.1.1. Supervisory Attentional System

One of the models which have been used to explain the functions of the PFC is the Supervisory Attentional System (SAS) model (Norman & Shallice, 1980). The theoretical background from which this model derives is represented by the distinction between automatic and controlled processes, which some authors put forward in the domain of attention research (Posner & Snyder, 1975; Shiffrin & Schneider, 1977a, 1977b).

The terms ‘automatic’ and ‘controlled’ were initially defined as mutually exclusive. For automatic processes, authors intended processes which are initiated by appropriate inputs and then proceed automatically, without requiring effort or suffering from dual-task interference (i.e., parallel processing). Conversely, for controlled processes, they intended those processes which begin with an act of the will, are effortful and consequently suffer from dual-task interference (i.e., serial processing), and can be stopped while they are still going on (Shiffrin & Schneider, 1977a). Since then, the dichotomy between automatic and controlled processes has been also extended to domains different from attention, like for instance memory (e.g., Hasher & Zacks, 1979). Subsequently, they have been broadened in order to explain how the whole human information processing system works (e.g., Jonides, Naveh-Benjamin, & Palmer, 1985). Although the tough distinction between automatic and controlled processes has been smoothed by many subsequent empirical works (e.g., Naveh-Benjamin, 1987; Jonides et al., 1985, Kahneman & Treisman, 1984; Pritchard & Warm, 1983), it has given rise to fruitful theoretical modelling and empirical research.

The SAS model developed by Norman and Shallice (1980; 1986; Shallice, 1988; Burgess & Shallice, 1994) represents an influential framework inspired by the difference between controlled and automatic processes (see Baddeley, 1986; 1990, for a related model). The main assumption of this model is that there exist two systems underlying cognitive processing: a low-level system, the contention scheduling, which produces automatic processes, and a high-level system, the SAS, which is critical for controlled processes.

The contention scheduling is a mechanism by which over-learned and highly familiar responses, the so-called schemata, compete against each other for the control of perceptual and motor systems. The winner schema depends on the level of activation of each schema relative to all possible competitors. The level of activation, in turn, depends on the associative strength of each schema with internal or external triggers, on the one hand, and with particular patterns of behaviour, on the other. On this model, even complex activities, such as playing a musical instrument or driving a car, can be executed appropriately although in a rather automatic fashion (viz., without demanding attention). These 'hardwired' schemata are advantageous because they allow routine behaviours to be executed rapidly and automatically (Miller & Cohen, 2001). However, schemata are rigid reactions elicited by just the proper trigger cue, need extensive time and practice to develop, and do not generalize well to novel situations.

The second component of Norman and Shallice's (1980) model, the SAS, biases the selections of the contention scheduling in novel or non-routine situations. In other words, the role of the SAS is to build up, implement and monitor new schemata (Shallice & Burgess, 1996), on the one side, and to adjust or inhibit activation of prepotent schemata which are unsuitable for a current purpose, on the other side (Burgess & Shallice, 1996c; Norman & Shallice, 1980; 1986). Some examples of the SAS functions will be described in the next paragraph.

1.1.1.1. Supervisory Attentional System and Frontal Lobes

Not only the SAS model, but also a number of models related to it, postulate the existence of an anterior attentional system with a set of high-level functions, mainly located in the PFC, which receives input from and modulates more specific lower-level functions, centred in other brain areas, such as the parietal lobes (e.g., Posner & Petersen, 1990a; Shallice, 1982), the temporal lobes (e.g., Moscovitch, 1992), and the basal ganglia (e.g., Alexander, Delong, & Strick, 1986).

The correspondence between SAS and frontal lobes has been assumed since the first proposal of the SAS model (Norman & Shallice, 1980). The prediction was made that the disruption of the SAS after damage in the PFC should lead to behaviour controlled by contention scheduling. Evidence from different domains supports this prediction. Some examples, mainly taken from the neuropsychological literature, follow.

Patients with PFC dysfunction may show deficits related to the loss of SAS functionality (e.g., Luria, 1966; Norman et al., 1980; Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005; Stuss & Benson, 1986; but see Andrés & Van der Linden, 2001). For instance, if the SAS fails to inhibit schemata triggered by strong external stimuli or internal tendencies, a disinhibition deficit is observed. A dramatic example of such a deficit is 'utilization behaviour' first described by Lhermitte (1983; Shallice, Burgess, Schon, & Baxter, 1989). When prefrontal patients undergo a tactile, visuo-tactile or visual presentation of objects, they are compelled to grasp and use them, even if this behaviour is contextually and socially inappropriate, and they have been told by the experimenter not to do so (Lhermitte, 1983). Historically, it has been shown that patients with frontal lobe lesions fail to switch flexibly between different tasks or rules (Burgess & Shallice, 1996c; Drewe, 1974; Milner, 1964; Stuss, Floden, Alexander, Levine, & Katz, 2001). In the Wisconsin Card Sort Task (WCST), for instance, participants are asked to match test cards to reference cards according to a rule which changes cyclically but without notice. Thus, the WCST measures, among other functions, the ability to change a well-acquired response schema when contingencies vary. Prefrontal patients are able to acquire the initial rule without much difficulty, but are unable to adapt their behaviour when the rule changes. In other words, they show perseverative behaviour, remaining stuck to a rule, once they have discovered it, even if this rule is no longer valid (e.g., Drewe, 1974; Milner, 1963; 1964; Nelson, 1976). Monkeys with PFC lesions are impaired in a task analogue to the WCST (Dias, Robbins, & Roberts, 1996; 1997; see also Rossi, Rotter, Desimone, & Ungerleiden, 1999).

Another example is represented by performance of the random number generation task (Spatt & Goldenberg, 1993). This task requires participants to randomly generate strings of numbers. Among other processes assumed to be involved to perform well this ‘randomization’ task, one is particularly challenging (Baddeley, 1986). This process consists of inhibiting the most familiar strategy of counting upwards or downwards in ones which, in the terminology of the SAS model, is the strongest schema in the contention scheduling mechanism (e.g., Ginsburg & Karpiuk, 1994; (Ginsburg & Karpiuk, 1994; Baddeley, Emslie, Kolodny, & Duncan, 1998; Shallice, 2004). Prefrontal patients (Spatt & Goldenberg, 1993), and healthy participants undergoing TMS over the left DLPFC (Jahanshahi et al., 1998; see also Jahanshahi et al., 1998; Jahanshahi, Dirnberger, Fuller, & Frith, 2000), show an increase in the frequency of counting up or down in ones, and a decrease in the rate of counting in twos. This pattern is also interpreted as a failure of the SAS in inhibiting strong routine schemata within the contention scheduling (i.e., counting in ones) in favour of less common schemata (i.e., counting in twos), necessary to accomplish the task requests.

On the other hand, in situations where planning is required, that is when the SAS have to generate new schemata in the absence of a discrete internal or external trigger that signals the appropriate action, apathy, disengagement, and loss of initiative are observed if the SAS is disrupted by a PFC lesion (Duncan, 1986; Shallice, 1982; Stuss & Benson, 1986). One of the most representative examples of this deficit is abulia, which in its extreme form is called ‘akinetic mutism’, a clinical syndrome characterized by a loss of spontaneous motor and speech activity in patients with bilateral lesions of anterior cingulate and SMA or interruptions of sub-cortical circuits connected with these frontal structures (e.g., Alexander, 2001; Mega & Cohenour, 1997; Nagaratnam, Nagaratnam, Ng & Diu, 2004; Plum & Posner, 1980; Tengvar, Johansson, & Sorensen, 2004). Reflexes and routine actions seem to be well-preserved. Patients, who usually lay in their bed without moving or speaking, may suddenly brush a fly away from their face, pick their nose, continue singing or reciting verses when others have started well-known songs or poetries, and even dance (e.g., Fisher, 1983; Grotjahn, 1936; Von Economo, 1926). A paradoxical phenomenon, known as the telephone effect (Fisher, 1983), is that some patients, who do not speak or follow commands when the experimenter is present in the room, may in fact answer to a number of questions when spoken to on a telephone, supposedly because the telephone ring sound triggers the conversation.

As another example, in a recent neuropsychological study (Daffner et al., 2000), frontal patients were asked to look at line-drawings which were a frequent non-target stimulus (70%), an infrequent target stimulus (15%), or a novel non-target item (15%). They had to respond to the target stimulus by pressing a foot pedal. They controlled the viewing duration of each item by pressing a button. Frontal patients have on average shorter viewing durations on novel stimuli than healthy controls, demonstrating a deficit in the engagement of attention to novel stimuli.

A final example comes from brain imaging field. In a PET study (Jueptner et al, 1997; see also Jenkins et al. 1994), new sequences of finger movements had to be learned and re-executed after learning. These conditions were contrasted to previously over-learned sequences of finger movements, which could then be executed automatically. PFC was activated during new learning and, to a minor extent, when participants had to attend again to the performance of the just learned sequences, but not during the execution of over-learned sequences, demonstrating a strong association between PFC and acquisition of new or ill-learned schemata, which is a typical SAS process.

1.1.1.2. The study of frontal lobes: a difficult enterprise

Although in its initial formulation the SAS model did not go into much detail about the precise processes involved and the prefrontal sub-regions underlying them (Norman &

Shallice, 1980), it was however a very influential framework, inspiring a long tradition of empirical research.

At the time of writing, a scientific database such as PubMed provides more than 14,930 papers when the word ‘prefrontal’ is inserted as a keyword. Despite the impressive amount of empirical studies, however, there is still little agreement on which specific processes are performed and where within the PFC. There are many possible reasons for this relative failure. One of them could be that the nature of the subprocesses implemented within the PFC is too abstract to be captured by the stimulus-response constructs of traditional experimental psychology (Shallice, 2001).

However, it could be argued that the measures adopted to study PFC functions, and not the functions of the PFC per se, are too vague and imprecise. A terminological and conceptual ambiguity might have been partially responsible for the massive use of tests that emphasize complexity and novelty in order to study PFC functions (Stuss & Benson, 1984, 1986; Rabbitt, Lowe, & Shilling, 2001). Indeed, terms like ‘supervisory’, ‘executive’ or ‘control’ functions have been usually left ill-defined and are too general to be tested properly (e.g., Stuss & Alexander, 2000). As Stuss and Alexander (2000) pointed out, frontal-type tasks are usually multi-factorial, in the sense that many processes conceivably underlie the performance of these tasks.

This would explain, for instance, the low correlation among frontal lobe tasks, and the low specificity of these tasks in measuring the ‘frontal’ function. For example, the WCST has been thought as a typical PFC-related task. However, there is no doubt that this is a multi-componential task (Stuss, et al., 2000), with some components probably not relying on PFC. Indeed, impairment on this task could be found after lesions in many brain regions different from the frontal lobes (Andres, 2003; Corcoran & Upton, 1993; Grafman, Jonas, & Salazar, 1990; Upton & Corcoran, 1995). Moreover, some patients with definite frontal lobe damage perform well on the WCST (e.g., Anderson, Damasio, Jones, & Tranel, 1991).

In reaction to this kind of heuristic impasse, two different approaches have been adopted, as we will describe in more detail later. Some researchers have identified the ‘frontal function’ with general intelligence, stressing the high adaptability of PFC to a wide range of cognitive tasks (e.g., Duncan, 2005; see Paragraph 1.1.2.2.). In a quite opposite direction, other groups of researchers have moved to simpler measures and tests to map various elementary processes ascribable to the SAS within the frontal lobes (e.g., Decary &

Richer, 1995; Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999; Stuss, Shallice, Alexander, & Picton, 1995; see Paragraph 1.1.2.3).

1.1.2. Different scientific attacks for the study of Dorsolateral Prefrontal Cortex

The DLPFC has attracted historically relatively more research interest with respect to other prefrontal areas (Shallice, 2004). A number of cognitive processes of the SAS have been linked to this brain region (e.g., Norman & Shallice, 1986; Shallice, 1988). From the beginning of the last century onward, many approaches have been adopted to study the different functions of the PFC in general, and of the DLPFC in particular (Shallice, 2004). The earliest of these theoretical frameworks is the working memory approach (e.g., Goldman-Rakic, 1987). More recently, DLPFC has been studied within the already mentioned frameworks of the general intelligence approach (e.g., Duncan, 2005) and the fractionation approach (e.g., Stuss et al., 2005). We will describe in more detail each of these approaches in the following sub-paragraphs.

1.1.2.1. Working memory

As mentioned earlier in this chapter, a key step in the study of frontal lobe functions was Jacobsen's (1936) discovery that lateral PFC of monkeys is important for the performance on the delay-response task. These results were then extended by single-cell recording studies, which demonstrated that many DLPFC neurons remain active during the delay phase of this paradigm (e.g. Fuster & Alexander, 1971). Similar results were found in human DLPFC (e.g., Cohen, et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997).

The approach became more detailed with the work by Goldman-Rakic (1987), who made the specific hypothesis that discrete regions of PFC each support working memory of different stimulus domains. Specifically, it was supposed that the 'where' and 'when' visual streams (Ungerleider & Mishkin, 1982) had a corresponding functional-anatomical prolongation in the lateral PFC, with a dorsal area within the caudal part of sulcus principalis, important for spatial working memory, and a ventral area in the inferior convexity of ventrolateral PFC, dedicated to working memory for object information (Wilson, Scalaidhe, & Goldman-Rakic, 1993). Evidence in favour of this hypothesis, known as the 'labeled-line model', is however controversial. In agreement with the model, neuropsychological studies show that lesions of the DLPFC impair spatial working memory (Gross, 1963; Lewy & Goldman-Rakic, 1999), whereas lesions of more ventral lateral PFC impair non-spatial working memory (Passingham, 1975; Mishkin & Manning, 1978). Other studies using functional Magnetic Resonance Imaging (fMRI) confirmed that lateral PFC in humans is active during maintenance of information across short delay epochs of delayed recognition tasks (e.g., Courtney et al., 1997; Zarahn, Aguirre, & D'Esposito, 1997; 1999). However, brain imaging data were controversial regarding the labeled-line model, with some of them consistent with it (e.g., Courtney, Ungerleider, Keil, & Haxby, 1996; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998) and some others not (e.g., Postle, Berger, Taich, & D'Esposito, 2000). A meta-analysis (D'Esposito et al., 1998) demonstrated no evidence for a clear dorsal/ventral dissociation of PFC activity by 'where' and 'what' stimulus information.

An additional fractionation model for domain specificity within working memory hypothesized asymmetry along the two hemispheres, with left PFC more involved in non-spatial, analytic (especially verbal) working memory and right PFC more involved in spatial, image-based working memory (Courtney et al., 1998). Also this model received controversial evidence with some studies corroborating (McCarthy et al., 1996; Smith et al., 1995; Smith, Jonides, & Koeppe, 1996) and some others disconfirming it (D'Esposito et al., 1998; Owen et al., 1998; Postle, Stern, Rosen, & Corkin, 2000).

Another complementary approach in the working memory domain is more centred on the processes involved instead of the material used, and holds that multiple working memory-related processes rely upon different prefrontal areas. Initially, it was thought that DLPFC was related to the storage of working memory because its activity was found to increase proportionally to the working memory load (Manoach et al., 1997; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). However, these data may be interpreted as an indication that when information to be maintained in memory exceeds working memory capacity, additional encoding demands are required, and these demands engage DLPFC more (Rypma et al., 1999). More recent evidence shows that even if DLPFC activity increases with the working memory load, this activity is enhanced to a larger extent when working memory content has to be manipulated. In a fMRI study by Rowe and colleagues (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000), for instance, DLPFC was activated only when the information being held in working memory was response-relevant and not when it had to be merely maintained. Moreover, the PFC neurons have been demonstrated also to respond selectively to many non-delay portions of the response delay task, such as to target and probe presentation and response, indicating a broader role of this area in various sub-components of working memory tasks, such as stimulus encoding (D'Esposito & Postle, 2002; Waugh & Norman, 1965), shifting of attention among stored items (McElree & Dosher, 1987), manipulation and selection of working memory content (e.g., Rowe et al., 2000), and decision about the probe and response preparation (Rowe et al., 2000; Jha & McCarthy, 2000).

1.1.2.2. Equipotentiality hypothesis

This lack of clear evidence about specialization of working memory within PFC according to different stimulus domains or processes was somehow preparatory to the emergence of an alternative approach, assuming that various PFC areas have an equipotential and undifferentiated role (e.g., Duncan, Burgess, & Emslie, 1995; Duncan, 2001; 2005; Duncan & Miller, 2002; Duncan & Owen, 2000). At first glance, this approach may be viewed as provocative. However, it also fits with converging evidence from both animal neurophysiology and imaging data on humans.

Thus, in the lateral PFC of monkeys, a considerable amount of neurons will usually respond to whatever information is critical for the performance of any task (e.g., Asaad, Rainer, & Miller, 2000; Fuster, 2002; Wallis, Dias, Robbins, & Roberts, 2001). Moreover, single-cell recording studies in animals have demonstrated that even a specific neuron in the lateral PFC may adapt its activity in order to code different information, depending on the specific task demands (e.g. Everling, Tinsley, Gaffan, & Duncan, 2002; Freedman, Riesenhuber, Poggio, & Miller, 2001; Sakagami & Niki, 1994).

In Duncan and colleagues' view, this high adaptability of the PFC is also suggested by functional imaging research, where comparison across studies adopting tasks with different cognitive demands shows, despite of some anatomical specificity, very little cognitive specificity (i.e., a specific pattern of prefrontal activation is observed for very different cognitive tasks). Indeed, very similar activation patterns have been observed for different task conditions, in line with an interpretation of the role of lateral PFC in terms of general intelligence (see Duncan & Owen, 2000, for a meta-analysis; and Duncan, 2005, for a review; Fassbender et al., 2006). On the strongest version of this approach, the flexibility of neural properties within the prefrontal region, which is considered a "general computational resource" (Duncan & Miller, 2002), makes any attempt of localization of functions within this region unproductive.

Problems for the equipotentiality hypothesis

As reported in the previous paragraph, the neurophysiological evidence in support of the equipotentiality hypothesis is straightforward (e.g., Freedman et al., 2001). However, evidence derived from fMRI results is less convincing, given that fMRI data only show whether a given brain region is merely active when a process occurs, that is only correlational conclusions can be drawn.

Moreover, even authors sustaining the general intelligence approach (e.g., Duncan, 2005) admit that there should be some relative specializations. In the episodic memory domain, for instance, neuropsychological, TMS and brain imaging evidence shows that encoding and retrieval activate PFC asymmetrically: encoding tends to be left lateralized and whereas retrieval tends to be right lateralized, a pattern known as hemispheric encoding/retrieval asymmetry (HERA) (e.g., Rossi et al., 2001; Schacter et al., 1996b; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). As another example, semantic encoding and even retrieval usually produce stronger activity in left PFC than in right (Demb et al., 1995; Fletcher, Shallice, & Dolan, 1998; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001; but see MacLeod, Buckner, Miezin, Petersen, & Raichle, 1998).

An assumption of the equipotentiality hypothesis is that the more complex a function is, the more likely it is that this function is located within the frontal lobes, whose main characteristic is their high adaptability. This has been demonstrated not to be the case at least in some circumstances. In a study by Stuss and colleagues (Stuss et al., 1999), for instance, a patient group with left posterior lesions showed more impairment with increasing complexity of a task on a measure of an attentional phenomenon known as inhibition of return (Posner & Cohen, 1984), whereas left frontal patients showed a general impairment not modulated by task complexity. Even harder to explain from the point of view of the equipotentiality approach, right frontal patients were not impaired at all on the inhibition of return.

1.1.2.3. Fractionation approach

In early studies on the frontal lobes, patients were merely classified as frontal if they had a lesion anywhere in the frontal lobes, and were usually contrasted with patients suffering from generic posterior lesions (e.g., Della Malva, Stuss, D'Alton, & Willmer, 1993). A progress in the study of frontal lobes was represented by the development of methods to carry out fine-grained lesion analyses (e.g., Shammi & Stuss, 1999; Stuss et al., 2005). This methodological improvement favoured research adopting an approach focused on the fractionation of the SAS.

This approach has been developed in order to overcome a conceptual lack of specification on how the SAS works (e.g., Stuss et al., 1995; Shallice & Burgess, 1996), present in the original version of the SAS model (e.g., Norman & Shallice, 1980). On the fractionation approach, the multi-factorial nature of the SAS is stressed, proposing a deconstruction of its high-level functions used to face non-routine situations, each of which is computationally different from the others. Moreover, it is supposed that a functional specialization of each of these functions existed within at least partially separable networks involving PFC areas (Shallice & Burgess, 1996; see also Baddeley, 1996; Faw, 2003; Shallice, 2004; Stuss et al., 2005).

The methodological implications of this approach have changed the way in which functions of the PFC are studied. It is now clear that different processes are required to perform single tasks, each of which may rely on different brain areas (e.g., Stuss et al., 1995). A correct specification of the subprocesses involved in a given task (e.g., Sternberg, 1975; 2001), and the use of simplified tasks that allow comparisons based on specific rather than overall performance measures (e.g., Stuss et al., 2005), are then important tools in order to understand the fractionated nature of the PFC supervisory operations. On the other hand, functional-anatomical differentiation of PFC may, in turn, be informative about which cognitive processes are involved in a given task, as shown, for instance, by the method of neuropsychological dissociations (e.g., Shallice, 1988; see also McCloskey, 2003).

The fractionating approach has received considerable empirical support. For instance, both attention-deficit/hyperactivity disorder (ADHD) and autism show substantial deficits in SAS functions, despite the fact that very different clinical hallmarks characterize the two disorders. Apparently, one might then expect SAS dysfunction to be somewhat unspecific, in line with the equipotentiality approach. However, studies that adopt an information-processing analysis have revealed both quantitative and qualitative distinctions between SAS impairments in these two syndromes. When compared on tasks tapping on different cognitive demands, for instance, the autistic patients are more impaired on response selection/monitoring in a cognitive estimates task, whereas the ADHD group shows greater inhibitory problems on a Go-no-Go task (Happe, Booth, Charlton, & Hughes, 2006; but see Shallice et al., 2002). A broader range of examples of studies adopting the fractionation approach will be summarized in the next subparagraph.

Fractionation of attention within the prefrontal cortex: empirical evidence

Evidence for the fractionation of attentional processes within PFC can be extensively found in the neuropsychological literature (Milner, 1963, 1964; Godefroy et al., 1999; Burgess, Veitch, de Lacy, & Shallice, 2000; Mirsky & Duncan, 2001). An example of the fruitfulness of the fractionation approach for the study of frontal lobes is represented by the works of Stuss and his collaborators (Alexander, Stuss, & Fansabedian, 2003; Alexander, Stuss, Shallice, Picton, & Gillingham, 2005; Picton et al., in press; Stuss et al., 1995; Stuss et al., 1999; Stuss, Binns, Murphy, & Alexander, 2002; Stuss et al., 2005), who have provided over years a considerable amount of evidence in favour of a deconstruction of processes within PFC.

These authors precisely defined which attentional processes may characterize the SAS (e.g., Stuss et al., 1995; Stuss, 2006). Some of the identified processes are: energizing schemata, which can be considered as the allocation of arousal's energy to the neural systems required to perform a given task; monitoring environmental contingencies and behaviour in order to adjust the level of activity in schemata accordingly; task-setting, that is the process of representing the task demands in an early stage of performance in order to accomplish them appropriately; inhibiting task-irrelevant schemata, as required, for instance, when an infrequent but prepotent response should not be executed. These processes do not coincide with precise tasks, but underlie performance of several apparently different tasks (e.g., Stuss et al., 2005).

The model derived from this cognitive analysis was then tested on a broad group of patients with different focal frontal lesions, caused by various aetiologies. Patients underwent various tasks composing a neuropsychological battery, the so-called Rotman-Baycrest Battery to Investigate Attention (ROBBIA). To isolate the distinct processes involved, the tests were designed by progressively modifying the same basic RT paradigm. For instance, three of these tasks were: simple RT, choice RT, and prepare RT task (Stuss et al., 2005). These 3 paradigms provide the opportunity to isolate the most basic processes related to the SAS. Simple RT task required a constant response to a target occurring at random intervals, called foreperiods (FPs), between 3 and 7 sec (i.e., variable FP paradigm). Choice RT task, which adopted the same variable FP paradigm, required the same response to the target, which now appeared randomly intermixed with other stimuli requiring a different response. The variable FP paradigm used in these two tests is known to produce the so-called FP effect: RTs decrease with the FP length. This effect is held to be a measure of the efficiency of a monitoring process, held to check the increasing conditional probability of stimulus occurrence as the FP elapses (e.g., Näätänen, 1970; see Paragraph 1.2.1.1.).

A third test, the prepare RT task, was the same as the choice RT task with the insertion of a warning signal occurring either 1 or 3 sec prior to the stimulus (i.e., short and long FPs), this time administered in fixed blocks. On this paradigm, known as the fixed FP paradigm, participants are held to use the warning signal to estimate the time at which the target should occur in order to optimize response preparation (Niemi and Näätänen, 1981). As time estimation is only optimal for relatively short FPs (see the scalar theory of time perception, Gibbon et al., 1984), when a fixed FP paradigm is used, RTs are typically faster with relatively short FPs than with long ones (Mattes & Ulrich, 1997; Teichner, 1954; Woodrow, 1914), which is the opposite of what is found with the variable FP task.

In another study (Alexander et al., 2005), a continuous rapid performance task was administered. On this task 5 LEDs, with a button response under each, were randomly illuminated, with the requirement to respond by pressing the button spatially corresponding to the illuminated LED. This task examined the ability of the patients to concentrate and set up appropriate schemata.

Another task used was the feature integration task (Stuss et al., 2002), which was similar to the simple and choice RT tasks, with the exception that there was an additional level of difficulty derived from the complexity of feature integration required to perform the task. In this more complex task, indeed, patients had to identify and respond to a target according to 3 distinct features (color, shape, and orientation of lines within the shape). Progressive complexity was reached in this task by using non-targets with none, 1, or 2 features similar to the target.

The results of the performance of the various prefrontal patient groups on the ROBBIA battery were straightforward. The most replicable finding was that patients with lesions of the superior medial frontal regions had the greatest slowing in RT in all the tests administered. Moreover, this group did not show the advantage of a warning signal with a fixed FP paradigm. Instead medial frontal patients showed a significant decline in preparatory activation from 1 to 3 sec after a warning stimulus (Stuss et al., 2005). These results were interpreted as an indication of a deficit in the energization process hypothesized in the ROBBIA model (e.g., Stuss et al., 2005). More precisely, this deficit is interpreted as decreased energizing (SAS-like process) of the neural systems in parietal cortex, supplementary motor areas, or motor cortex, that are needed to select and/or initiate (contention scheduling processes) the responses (schemata) when relevant input is provided. A clearer example of defective energization process is represented by akinetic mutism, which has been described earlier (see Paragraph 1.1.1.1).

Another attentional process related to a specific region within the frontal lobes was revealed through both the continuous rapid performance task and the feature integration task. On the first task, only patients with lesions in left lateral frontal regions made significantly more errors, and the increase was only observed in the first 20% of the trials. This pattern was interpreted as a deficit in setting up specific stimulus-response contingencies (Alexander et al., 2005). On the feature integration task, the same group of patients showed an impaired bias or criterion setting, with an increased rate of false alarms, again interpreted as a task-setting deficit (Stuss et al., 2002). In support of this interpretation, a PET study found that activation of left DLPFC was associated with the production and execution of strategies in the organization of a to-be-remembered list of items (Fletcher et al., 1998; see also Frith, 2000).

Finally and more relevant for the present purposes, a monitoring process was impaired in patients with damage in the right PFC. These patients had a significant decline in sensitivity in the feature integration task (Stuss et al., 2002), where they generally had low accuracy (increased frequency of misses and false alarms). This pattern was interpreted as a deficit in monitoring the difference between targets and non-targets in order to reduce errors. A similar deficit was also demonstrated using the variable FP paradigm. As already mentioned earlier in this paragraph, this paradigm usually produces the FP effect, defined as decreasing RT with increasing FPs (Niemi & Näätänen, 1981; see also Paragraph 1.2.). This effect was selectively absent in right lateral frontal patients. According to the proposed interpretation (Stuss et al., 1995), this deficit would be due to decreased monitoring. More specifically, right PFC patients failed to check whether a stimulus has occurred over a few seconds, not increasing their readiness to respond as time elapsed, if it had not yet occurred.

This account fits a range of neuropsychological and functional imaging paradigms which assign a monitoring role to the right dorsolateral prefrontal cortex (rDLPFC; e.g., Coull, Frith, Buchel, & Nobre, 2000; see Fletcher & Henson, 2001; Shallice, 2002; 2004 for reviews; Posner & Peterson, 1990, for a somewhat related position). An involvement of the right DLPFC has been documented, for instance, in the episodic memory domain, especially during retrieval, in situations where checking/monitoring was required. These situations, according to Shallice (2006), occur under conditions of uncertainty, such as when valid alternatives need to be excluded (e.g., Henson, Shallice, Josephs, & Dolan, 2002) or when a solution has already been sketched and its consequences need to be evaluated, implying that they occur late in time (e.g., Wilding & Rugg, 1996). These situations cannot merely coincide to conditions requiring unspecific cognitive effort. Moreover, a disruption of the checking process would lead to more capture errors and false positive errors, suggesting a problem in criterion setting (e.g., Rossi et al., 2001).

As shown by this short review, the fractionation approach is therefore a valuable framework, because it is guiding research by suggesting testable hypotheses, which have been shown to be empirically plausible, and by increasing our knowledge about frontal lobes. A common taxonomy derived by a detailed analysis of all the specific components of executive functions is far from being reached yet (e.g., Smith & Jonides, 1999). Moreover, fractionating functions relying on PFC may complicate matters multiplying the number of processes labelled as ‘executive’ or ‘prefrontal’.

However, in contrast to the traditional unitary executive function view, the process of SAS fractionation overcomes the anti-heuristic problem known as the ‘homunculus’ problem (Dennett, 1998), that is the assumption of the existence of a suitably intelligent but not clearly defined agent (Monsell & Driver, 2000). Instead, trying to deconstruct the SAS into small components makes this set of high-level functions more understandable and scientifically attackable (e.g., Hommel, Daum, Kluwe, 2004; Hommel, Ridderinkhof, & Theeuwes, 2002).

1.2. The FP phenomena

As anticipated in the introduction, the main paradigm on which the current project focuses, in order to study the monitoring role of DLPFC, is the variable FP paradigm. It is thus propaedeutic to the comprehension of the whole dissertation to illustrate in more detail this paradigm, the behavioural effects usually found analyzing the performance on this task, and the cognitive processes supposed to underlie these effects.

Preparation is an important ability required in virtually all cognitive tasks. In cognitive terms, preparation is the ability to prepare an optimized response to forthcoming stimuli. It can take advantage of human capacity of anticipating future events, reducing uncertainty about them, and thus optimizing processes necessary for responding to them (Brunia & Van Boxtel, 2000). In particular, unspecific preparation over time usually implies the reduction of uncertainty about ‘when’ a response (regardless of ‘what’ specific response) should be executed. This capacity is used in everyday life. In soccer, for instance, a goalkeeper does not know in advance when an opponent will kick the ball towards the goal; as time elapses, however, the probability that the other player will decide to kick the ball increases and the goalkeeper has to increase his readiness consequently. In a more common situation, when a driver waits in her car for the traffic light to turn green, especially if she is in a hurry, her right foot is more and more prepared to push the accelerator as time goes on with the traffic light still displaying red. In spite of its ubiquity, preparation is a poorly understood aspect of human cognition (Sanders, 1998). Specifically, the way in which preparation evolves over time and the factors modulating it are yet unresolved issues.

Experimentally, temporal preparation has been extensively investigated in studies using the variable FP paradigm. In this paradigm, the FP is the unfilled time-interval between a neutral warning stimulus and the stimulus requiring a response, the so-called Imperative Stimulus (IS). The warning stimulus is a signal (typically visual or auditory) informing the participant about the forthcoming IS; it might also be omitted as its function can be represented by the participant’s last response (e.g., Stuss et al., 2005). In a typical variable FP paradigm, a range of different FPs randomly occurs over trials, so that it is impossible for the participants to know in advance when the IS will occur on the next trial. Participants are usually instructed to respond as fast as possible to the IS by obeying the task rule (e.g., simple and choice RT tasks).

When the range of FPs used is randomly drawn from a rectangular distribution, so that every FP in a given range has the same a priori probability of occurring on a trial, RTs vary as a negatively accelerating function of the current FP: they are slower for shorter FPs and faster for middle and longer FPs. This is the variable FP effect (Drazin, 1961; Karlin, 1959; Klemmer, 1956; Woodrow, 1914; see Niemi & Näätänen, 1981, for a review).

A second phenomenon occurring in this paradigm concerns asymmetric sequential effects: slower RTs are found for a given FP when it is preceded by a longer FP than when it is preceded by an equally long or shorter one (Drazin, 1961; Karlin, 1959). This is particularly the case for the shortest FPs in a block of trials.

Thus, even if the unspecific preparation required to perform the variable FP task is apparently simple, it probably includes several more elementary processes, which produce separable but interacting behavioural effects. However, a strong point of this paradigm is that the effects produced are highly replicable and robust within a wide variety of experimental conditions. According to the literature (e.g., Niemi & Näätänen, 1981) and to the experience accumulated within our lab, these two effects are highly replicable across subjects and are found across a number of experimental conditions. Indeed, they have been replicated, without substantial qualitative differences, for different FP averages and ranges, at least within certain lower and upper limits (e.g., Alegria, 1975; Bevan, Hardesty, Avant, 1965; Karlin, 1959; Niemi & Näätänen, 1981), using both simple RT and choice RT tasks (Bertelson & Boons, 1960; Frith & Done, 1986; Sanders, 1980), with and without warning stimuli (e.g., Drazin. 1961; Stuss et al., 2005).

In spite of the high replicability of the FP phenomena, there is to date no agreement on which cognitive mechanisms are responsible for these behavioural effects. Indeed, as we will show in the next paragraphs, several contrasting theories have been developed in order to explain the FP and the sequential effects.

1.2.1.1. The strategic accounts

Traditionally, the FP effect has mainly been attributed to strategic processes (Niemi & Näätänen, 1981). In a typical variable FP paradigm, each FP in the range occurs equally often across trials, so that the a priori probability of stimulus occurrence is equal across the various FPs. This, in principle, makes it impossible to predict the exact moment at which the imperative stimulus will occur on each trial. However, the elapsing time itself provides information about the next occurrence of the stimulus (Elithorn & Lawrence, 1955). Indeed, as time flows during the FP without the imperative stimulus occurring, the conditional probability of the imperative stimulus being presented in the next time-interval increases. This increase in the conditional probability of stimulus occurrence during relatively longer FPs is held to compensate for the disadvantageous effects of the concurrently lengthening of the FP observed in the fixed design (e.g., Woodrow, 1914). The cognitive system presumably learns this changing conditional probability during the experimental session and exploits it to endogenously increase response preparation (e.g., Elithorn & Lawrence, 1955; Näätänen, 1970; Nickerson, 1967; Sanders, 1966; Thomas, 1967). In the context of temporal cueing studies, Coull and Nobre (1998; see also Nobre, 2001) provide a clear definition of an analogous endogenous process, which the authors term ‘attentional orienting in time’. This process is described as the ability to exploit any information about time intervals to orient attention to a point in time at which a relevant event is expected, in order to achieve optimal performance as, for instance, in producing a speeded response to that event. In the case of the variable FP task, this top-down process exploits the information derived from the increasing conditional probability of the IS occurring as time elapses, in order to enhance preparation.

However, despite its simplicity, this account has a major limitation, in that it fails to recognize that the shape of the FP effect derives, at least in part, from the sequential FP effect (Baumeister & Joubert, 1969; Karlin, 1959; Woodrow, 1914): RTs on the current trial (FP_n) are slower when preceded by a longer FP on the previous trial (FP_{n-1}) than when preceded by an equally long or shorter one. Such effects are usually asymmetric, being mainly present with the shortest FP_n in a block of trials.

To explain the sequential effects, traditional theories have to make further assumptions. One of these assumptions is that the participant expects a repetition of the previous FP_{n-1}, so that peak preparedness is reached at the same FP as that which occurred on the previous trial (e.g., Drazin, 1961; Karlin, 1959). If FP_n is shorter than FP_{n-1}, then peak preparedness will not have been reached when the IS occurs and a relatively slow RT will result. When instead the expectancy is disconfirmed because FP_n is longer than FP_{n-1}, it is assumed that participants can voluntarily extend the period of optimal preparation or cyclically reprepare, so accounting for the asymmetry in the sequential effects (e.g., Alegria, 1975; Karlin, 1959; Thomas, 1967).

A difference between the conditional probability monitoring and the repreparation/maintenance hypothesis is that the former is a stand-alone process (which however does not account for sequential effects), whereas the latter can hold only if the FP repetition expectancy account also holds. At first glance, the traditional accounts of the FP effect seem in fact redundant, as the contribution of the repreparation/maintenance process to the FP_n-RT function is qualitatively similar to that derived from the process of monitoring the conditional probability. However, although the two processes have the same consequences on RTs if one considers the effect of FP_n only, the repreparation/maintenance account has the additional advantage of explaining the asymmetry of the sequential effects. A shortcoming of such traditional accounts of the sequential effects is that they propose two entirely different strategically mediated processes to explain different aspects of the same results.

1.2.1.2. The conditioning view

Los and den Heuvel (2001) argue that the strategic positions have both conceptual and empirical problems. Conceptually, if preparation is fully strategic in nature, it would be more convenient for participants to choose the most successful strategy of fully preparing for the earliest FP on each trial and then initiating the repreparation cycle if the IS does not occur. Moreover, from an empirical point of view, it has been demonstrated that people tend to consciously expect an alternation rather than a repetition of events (Hale, 1967; Soetens, Boer, & Hueting, 1985) as illustrated, for instance, by the gambler's fallacy. For these reasons, Los and van den Heuvel (2001) proposed an alternative account, which would also integrate both the FP and the sequential effects in the same theoretical framework. The starting point of their theory is that there is a similarity between the basic FP design and that used in trace conditioning with animal models (Gallistel & Gibbon, 2000; Machado, 1997). They therefore state that it is plausible that similar underlying mechanisms could also apply to the FP effect (Los, Knol, & Boers, 2001). Los and co-workers suggest that, for each FP, a state of conditioning is adjusted in a way that obeys the learning rules of trace conditioning (Machado, 1997). They assumed that to each possible FP there corresponds a conditioned strength of activation, and that during a trial the participants' readiness to respond tracks these strengths. They further assume that, on any trial, the conditioned strength corresponding to a FP is: 1) increased if that FP occurs, 2) unchanged if a shorter FP occurs; 3) decreased if a longer FP occurs. This final assumption is motivated by a supposed need to reduce the tendency to respond ahead of time; this is held to be strong when the current FP is longer than the preceding one (Los & van den Heuvel, 2001, p. 372; see also Ollman & Billington, 1972). Indeed, Näätänen (1971, p. 324) wrote that "to restrain the intensive cumulative tendency of motor readiness from flowing over into motor action, with a resulting relief from tension, is both exhaustive and provocative of aversion". It follows that the conditioned strength of activation corresponding to the longest FPs can never decrease as no even longer FP can occur. Hence, the sequential effects, if present, should be asymmetrically biased towards the shortest FP. This single-process view has the advantage of making the FP effect a direct consequence of the sequential effects, because the RT on trial n is a function of the conditioning influences produced on trial n-1.

Los and colleagues also challenged the strategic positions on the basis of findings obtained using valid and invalid temporal cues with variable FP tasks (e.g., Los & van den Heuvel, 2001; Los et al., 2001). Several studies using a temporal cueing paradigm initially supported the strategic accounts of preparation over time. This paradigm is built using a temporal version of the Posner's spatial cueing procedure (Posner, 1980). In a typical temporal cueing paradigm, the warning stimulus could be either a neutral cue providing no information, or a symbolic cue providing information about the duration of the forthcoming FP. This information could be either valid or invalid. By increasing the frequency of valid cues with respect to invalid ones, participants are encouraged to exploit the information provided by the cue. Cueing studies have shown that responding at short FPs is faster for valid cues than for neutral cues, and faster for neutral cues than for invalid cues. By contrast, responding at long FPs is not affected by the cue validity (e.g., Correa, Lupianez, & Tudela, 2006; Coull et al., 2000; Coull & Nobre, 1998; Griffin, Miniussi, & Nobre, 2002; Miniussi, Wilding, Coull, & Nobre, 1999). These findings are consistent with the view that temporal orienting is initially directed to the moment specified by the cue, and may be redirected if IS appears later than when specified, but not vice versa (e.g., Alegria, 1975; Coull & Nobre, 1998).

A shortcoming of these temporal cueing studies is that they have not usually investigated sequential effects of the FP, which are also obtained in the temporal cueing paradigm (but see Correa et al., 2006). On the other hand, Los & van den Heuvel (2001), focusing their attention on these effects, found a dissociation between effects due to temporal orienting and sequential effects, supposedly due to trace conditioning. In particular, they designed 3 experiments using a temporal cueing paradigm. The experimenters used FPs of 0.5, 1 and 1.5 sec, presented randomly in a rectangular distribution. Thus, in their experiment 2, they used valid (80%) and invalid (20%) signals to cue the FP interval. With a valid cue the sequential effects were drastically attenuated because participants could intentionally prepare for the cued FP. The most impressive results, however, were obtained with an invalid cue for the FP duration. In particular, when an invalid cue for a long FP preceded an actual current short FP, the cost of not having prepared in advance for that short FP was not constant. It varied as a function of the FP that occurred on the preceding trial (i.e., according to the sequential effects). Sequential effects were stronger as compared with those occurring after a validly cued FP. If sequential effects were fully strategic in nature, as some traditional accounts claim (e.g., Alegria, 1975; Karlin, 1959), there would be no reason for them to influence costs after invalid cues. Corroborating these findings, other recent studies also revealed that validity effects, which are supposed to reflect intentional preparation processes, do not interact with sequential effects, which are supposed to be more automatic in nature (e.g., Correa, Lupiáñez, Milliken, & Tudela, 2004; Correa et al., 2006).

In conclusion, the work by Los and colleagues demonstrates a dissociation between intentional processes (valid cue-related effects of accelerating RTs) and unintentional ones (stronger invalid cue-related sequential effects) to non-specific response preparation, in the context of temporal cueing paradigms. In the next chapter, we will try to address the issue of the relative contribution of intentional and unintentional mechanisms in the context of more basic variable FP paradigms without temporal cueing. The prediction of the Los & van den Heuvel's (2001) model would be that in such situation, conditioning mechanisms alone would suffice to explain the effects found. We tried to investigate whether, even in such situations, other mechanisms, such as intentional or strategic ones, may also play a role.

1.3. The present project

The aim of cognitive neuroscience, as suggested by its name, is essentially twofold. From the 'cognitive' point of view, scientists in this field try to uncover and identify the elementary processes that may contribute to the overt behaviour (e.g., Gazzaniga, Ivry, & Mangun, 2002; Sternberg, 2001). From the 'neuroscientific' point of view, the aim of cognitive neuroscience is to find the neural mechanisms that underlie these processes. Noticeably, as it will be shown in the current research project, the two aims are strictly interrelated and one can benefit from the other (cf., Shallice, 1988; Umiltà, 2006).

The specific aim of this thesis mirrors to some extent the general aim of cognitive neuroscience. In the limits of a 3-years PhD project, we chose to study a specific function of a particular PFC area. This area is the right DLPFC. Specifically, we were interested to explore implications of findings of Stuss and colleagues (Stuss et al., 2005), who found that lesions to this area result in a selective deficit in the performance of RT tests using a variable FP paradigm. At the same time, from the cognitive point of view, we were interested in finding out which processes are involved in this paradigm. As already shown, in order to explain performance on this task, contrasting views in the literature have invoked either strategic multi-process accounts (see Niemi & Näätänen, 1981, for a review), or a single-process account derived from the trace conditioning tradition (e.g., Los & van den Heuvel, 2001).

These contrasting theories have been tested here using different approaches. The phenomena involved in the variable FP task were first investigated through behavioural studies (experiments 1, 2, 5 and 6, chapter 2). Localization of functions in the brain by means of Transcranial Magnetic Stimulation (TMS) and neuropsychology were then used, with the aim of disentangling these two theories by means of the dissociation logic (e.g., Shallice, 1988; experiments 7, 8 and 9, chapter 3). These methods are indeed useful for discriminating between contrasting psychological theories, as stated elsewhere (e.g., Jones, 1983; Pascual-Leone, Walsh, & Rothwell, 2000; Sack, 2006; Shallice, 1988). With a similar aim, we conducted 3 experiments on children, using a dissociative method which we called developmental dissociation, in analogy to the neuropsychological dissociations (experiments 3a, 3b and 4, chapter 2).

Starting from a related but independent scientific question, that is the role of explicit temporal judgment on the FP phenomena, we conducted a series of behavioural experiments using a modified version of the variable FP paradigm (experiments 10-14, chapter 4). These experiments did not show a clear modulation of the FP phenomena by an explicit temporal judgment, at odds with the initial prediction. However, they produced a new stimulus-response compatibility effect, relevant to infer how temporal information is cognitively represented.

As will be shown later, results of experiments on the variable FP paradigm, especially those adopting TMS and neuropsychological methods, support the involvement of right PFC in strategic processes, and particularly monitoring processes, at least in the domain of temporal preparation. Therefore, we were also interested in extending these results in a different domain. To this aim, we conducted 2 additional experiments in the source memory domain, this time using the technique of Event-related Potentials (ERPs). Results of these 2 experiments will be exposed in chapter 5.

Finally, in chapter 6 conclusions will be drawn about the overall study, exposing the methodological, empirical and theoretical considerations which can be derived from this project.

Chapter 2

In this chapter the cognitive aspects of the FP phenomena will be investigated and characterized better. In the first 2 experiments, 2 groups of adults were given a variable FP paradigm using different ranges and lengths of FPs, in order to test the hypothesis that the sequential effects and the FP effect derive from a common mechanism, as follows from the Los and van den Heuvel's theory (2001; discussed in paragraph 1.2.1.2., chapter 1) but not from traditional views assuming different underlying mechanisms (paragraph 1.2.1.1., chapter 1). In a second set of experiments (experiments 3a, 3b and 4), the aim was to investigate the developmental time-course of those two effects, under the assumption that, if they derive from independent underlying processes, there is no need for them to develop with the same trajectory. The hypothesis that a monitoring process is responsible for the appearance of the FP effect was tested in the experiment 5. In this experiment, the conditional probability of stimulus occurrence was kept constant to remove a possible influence of the monitoring process on the FP effect. In experiment 6, an n-back task has been adopted in the context of a variable FP paradigm, in order to functionally dissociate the FP and the sequential effects. The rationale of this experiment consists of testing the hypothesis that the sequential effects are more automatic than the FP effect. If this is the case, increasing the working memory load should influence the latter but not the former (cf. Shiffrin & Schneider, 1977a).

2.1. Testing the conditioning view of the FP phenomena: a behavioural study

The general aim of the experiments 1 and 2 is to investigate the feasibility of the conditioning model by testing predictions derived from it. Specifically, a first purpose of the next 2 experiments is to assess the existence of an intra-experimental learning period for the FP phenomena. Even if the conditioning model per se is agnostic about the existence of a learning phase (Los & van den Heuvel, 2001), the more general conditioning framework from which it originates is not (e.g., Machado, 1997). Both the classical and the operant conditioning theories entail a learning period during which associations between the unconditioned and the conditioned stimuli and/or responses are gradually established through extinction and reinforcement (Ferster & Skinner, 1957; Pavlov, 1927; Watson & Rayner, 1920). For instance, in animal studies of time-based conditioning schedules, it is usually possible to detect a developing behavioural trajectory followed by the subject before the achievement of a steady state (e.g., Machado, 1997; see also Gallistel & Gibbon, 2000; Miller & Barnet, 1993).

For this reason, the existence of a learning period would provide evidence in favour of the conditioning model (Los & van den Heuvel, 2001), basically supporting its derivation from the trace conditioning theoretical framework. On the other hand, absence of a long-term learning phase, even if not directly in conflict with the conditioning model, would take the phenomenon away from the tradition of the trace conditioning, or at least would require further explicit assumptions and detailed adjustments. The strategic views are instead more agnostic with respect to the existence of a learning phase.

However, a more crucial purpose of the experiments 1 and 2 is the assessment of the within-subject correlation between the sequential effects and the FP effect. The prediction of a positive correlation between the two effects derives from the assumption of the conditioning model that the FP effect is a side effect of the sequential effects. On that model, indeed, the FP effect originates from the interplay between the processes of extinction and reinforcement taking place before the current trial (Los & van den Heuvel, 2001). On the contrary, from the strategic positions it does not follow that there should be any correlation between the sequential effects and the FP effect, as it is assumed that the two effects originate from different, albeit interacting, processes. A lack of a correlation would thus indirectly support the strategic model.

2.1.1. Experiment 1

The experiment 1 was designed to be as similar as possible as far as material and timing are concerned to those in the Los and van den Heuvel's study (2001). However, it had a simpler design, in order to study the FP phenomena in their simplest context, without other (possibly) confounding variables. Thus, a simple RT task was used instead of a choice RT task. In addition, no temporal cue or feedback was employed, as FP phenomena were to be studied in a standard WS-IS paradigm.

Method

Participants

Fifteen volunteer participants took part in the experiment. They were 26 years old on average (range = 19-30); 7 were males and 9 females; 14 were right- and 2 left-handed (writing hand). All had normal or corrected-to-normal vision, no auditory impairment, and were in apparent good health. Approval from the local ethical committee was obtained for the study.

Apparatus and Materials

The experiment was conducted on a PC, with responses collected from a keyboard. Participants viewed the display at a distance of about 50-60 cm from the centre of the computer screen, with the index finger of their dominant hand resting on the spacebar. They wore headphones (Sony, MDR-CD280) over which the auditory WS was repeatedly presented at a comfortable level (constant across participants) during the whole experiment. All visual stimuli were presented on a black background. A centrally presented cross, consisting of two yellow crossed bars 1.0 x 0.5 cm in size, served as fixation stimulus. The WS was a 1500 Hz pure tone, presented for 50 ms. The IS was a downward pointing white arrow 2 cm long that consisted of a 1.5 x 1 cm bar attached to a 0.5 cm arrowhead with a maximum width of 2 cm. Four different quasi-random lists of 360 trials were prepared to have a large enough number of trials per condition. Each list was presented to 1/4 of the participants. In each list, three FPs of 0.5, 1.0 and 1.5 sec[1], respectively, were presented randomly on an equal number of trials (i.e. 120 trials each), drawn from a rectangular a priori probability distribution.

Procedure and Task

Participants were tested individually in a silent and dimly lit room. They received written instructions explaining both the course of events and the simple RT task. The experiment began only after the participant was confident that she/he understood the task. A trial started with the presentation of the fixation cross together with the WS. The onset of WS marked the beginning of the FP. When the FP ended, the fixation cross disappeared, and the IS appeared at the centre of the screen. Participants were instructed to respond as fast as possible to the IS only by pushing the spacebar with their writing hand. The IS was removed by the response key-press or after a deadline of 1.5 sec. After a blank interval of 2 sec, a new trial started. No practice trials were given because the task was very easy but

---

[1] Strictly speaking, the FP is a continuous variable. In the current study, we decided to treat the FP as a categorical variable, using only two or three discrete values of the FP. This choice was aimed to allow comparison with the existing literature on the FP effect, where this variable has been almost always treated as categorical (see Niemi and Näätänen 1981, for a review), apart from a few exceptions (e.g., Drazin, 1961).

above all because we were interested in the time course of the development of any FP effect from the beginning to the end of the experiment. The experiment consisted of 6 blocks of 60 trials each. At the end of each block, participants were encouraged to take a short break. They started a new block of trials by pushing the spacebar. The whole experimental session lasted about 25 minutes.

Design and Data Analysis

The within-subject independent variables considered in the experimental design included FP on the current trial (FP_n = 0.5, 1.0 and 1.5 sec), FP on the preceding trial *n-1* (FP_{n-1}), and experimental block (from 1 to 6).

Trials on which the RT was outside the 100-1000 ms range and trials where anticipated responses were made (viz. ones occurring before the IS) were discarded from further analyses. In addition, the first two trials of each block were eliminated. Mean RTs for each subject and condition were analysed by repeated measures ANOVAs. For the significant effects, post hoc Tukey honestly significant difference comparisons were performed, in order to see which comparisons accounted for the effects. An effect was defined as significant if its corresponding α-level was below .05. This criterion was chosen for all the experiments in the study.

Results

The first two trials of each block (3.3%), trials involving anticipated responses, that is RT before IS onset (2.7%), trials involving premature responses (RT < 100 ms: 1%), and trials with delayed responses (RT > 1000 ms) or without responses (0.3%), were discarded from further analyses. Less than 8% of trials were excluded.

Basic FP effect and sequential effects

In order to assess whether extinction and reinforcement were plausible processes underlying the RT differences in this FP design, we examined the FP effect and the sequential effects carrying out a 3x3 ANOVA, involving FP_n (0.5, 1.0, 1.5 sec) and FP_{n-1}. The following effects were significant (see Figure 1). First, the main effect of FP_n was obtained [$F(2, 28) = 39.1$, $p < .001$]. The post hoc Tukey tests indicated that RTs for the shortest FP were reliably longer than RTs for the other two FPs (for both, $p < .001$), but there was no difference between the RTs for the medium and longest FPs, replicating the typical negatively accelerating FP-RT function. Second, a significant main effect of FP_{n-1}

indicated that RT increased as a function of the length of the preceding FP [*F*(2, 28) = 48.8, $p < .001$], all the post hoc comparisons also being significant (for all, $p \leq .001$). More interestingly, there was a significant FP_n x FP_{n-1} interaction [*F*(4, 56) = 18.9, $p < .001$], which occurred because the effect of FP_{n-1} was strongest on the shortest FP_n (RT = 302, 341 and 364 ms for the FP_{n-1} of 0.5, 1 and 1.5 ms, respectively, for all, $p < .001$), attenuated on the medium FP_n (RT = 275, 288 and 304 ms; FP_{n-1} = 0.5 vs. 1.0, n.s.; 0.5 vs. 1.5, $p < .001$; 1.0 vs. 1.5, $p < .001$), and very small on the longest FP_n (275, 277 and 291 ms, FP_{n-1} = 0.5 vs. 1.0, n.s.; 0.5 vs. 1.5, $p < .01$; 1.0 vs. 1.5, $p < .05$).

In addition, the RT on the shortest FP_n was slower than the RT on the medium FP_n if they were each preceded by the shortest FP_{n-1} (302 vs. 275 ms, $p < .001$). The RT on the shortest FP_n was also slower than the RT on the longest FP_n if they were each preceded by the shortest FP_{n-1} (302 vs. 275 ms, $p < .001$). These effects are in conflict with predictions from the original theory of Los and van den Heuvel (2001) but not with their revised model (Los & van den Heuvel, 2001, p. 382-384, see discussion on page 41).

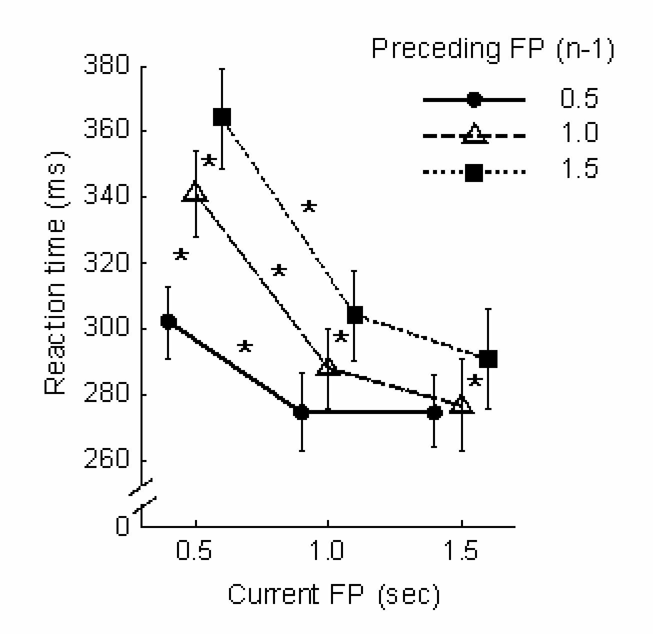

Figure 1. Mean reaction times as a function of current FP (x-axis) and preceding FP (lines), in experiment 1. FP = foreperiod. Vertical lines depict standard errors of the means; asterisks indicate significant post hoc Tukey comparisons (only for neighbours).

Long-term learning effects

A 6x3x3 repeated measures ANOVA was also performed with block, FP_n and FP_{n-1} as the within-subject variables, in order to see how the FP and sequential effects developed during the course of the experiment. The only significant effects were again those of FP_n

[$F(2, 28) = 37.2$, $p < .001$] and FP_{n-1} [$F(2, 28) = 38.3$, $p < .001$], while the main effects of block and the interactions involving it were far from significant (for all, $p > .8$, see Figure 2).

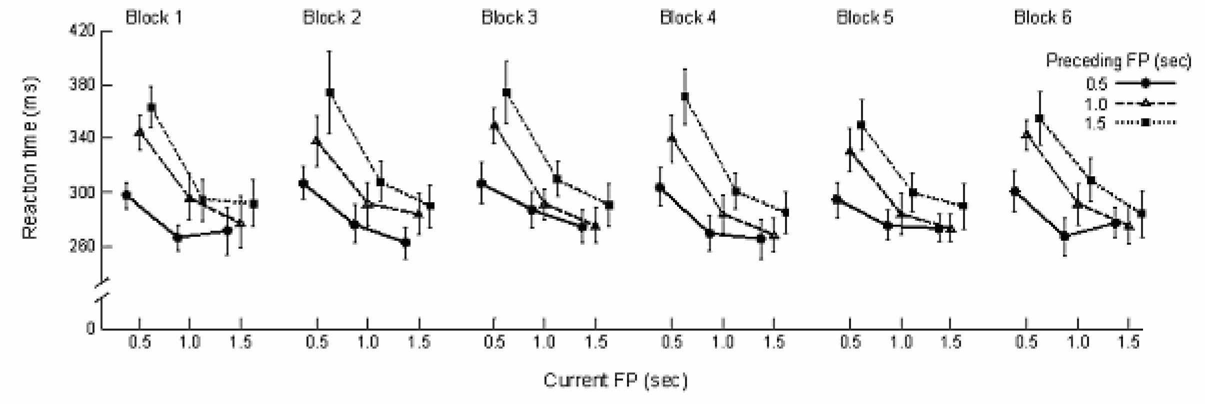

Figure 2. Mean reaction times as a function of current FP (x-axis), preceding FP (lines), and block (panels), in experiment 1. FP = foreperiod. Vertical lines indicate standard errors.

The lack of any interaction involving block demonstrates that sequential effects as well as the FP effect do not change during the course of the experiment. However, learning effects might have already occurred rapidly during the first block of 60 trials. Unfortunately, further dividing the first block into smaller blocks with a roughly equal number for each of the 3 FP_n x 3 FP_{n-1} conditions was not planned in advance. For this reason, when the first block was divided into two mini-blocks of 30 trials each, a full factorial 2 mini-block x 3 FP_n x 3 FP_{n-1} ANOVA could not be conducted because some participants had not an adequate number of trials per condition. We therefore conducted two separate ANOVAs: one with a 2 mini-block x 3 FP_n design and another with a 2 mini-block x 3 FP_{n-1} design, in order to check if learning effects occurred in the first block. These two ANOVAs produced a main effect of FP_n [$F(2, 28) = 9.9$, $p < .001$] and FP_{n-1} [$F(2, 28) = 10.4$, $p < .001$], respectively and no other effect. Thus, the absence of a learning phase, at least for the main effects of FP_n and FP_{n-1}, was demonstrated even considering such a small amount of trials as 30.

Correlational analysis

In order to assess the correlation between FP and sequential effects, the following formula was used as a comprehensive measure of the sequential effects:

$$A = [(RT \mid FP_n = 0.5 \wedge FP_{n-1} = 1.5) - (RT \mid FP_n = 0.5 \wedge FP_{n-1} = 0.5)]$$

$$B = [(RT \mid FP_n = 1.5 \wedge FP_{n-1} = 0.5) - (RT \mid FP_n = 1.5 \wedge FP_{n-1} = 1.5)]$$

$$C = A - B$$

where A is a measure of ‘extinction’ during the shortest FP, B is a measure of ‘reinforcement’ during the longest FP, and C is a measure of the difference between the first two, that is a measure of the sequential effects calculated from the point of view of the conditioning model (all the values are expressed in seconds). FP effect was defined as the difference between mean RT after the shortest FP_n and mean RT after the longest one[2]. A product-moment correlation coefficient, Pearson r, was calculated between the FP effect and the sequential effects computed as above for each participant. As results showed (see Figure 3, left panel), correlation coefficient was negative and not significant (*r* = -.27).

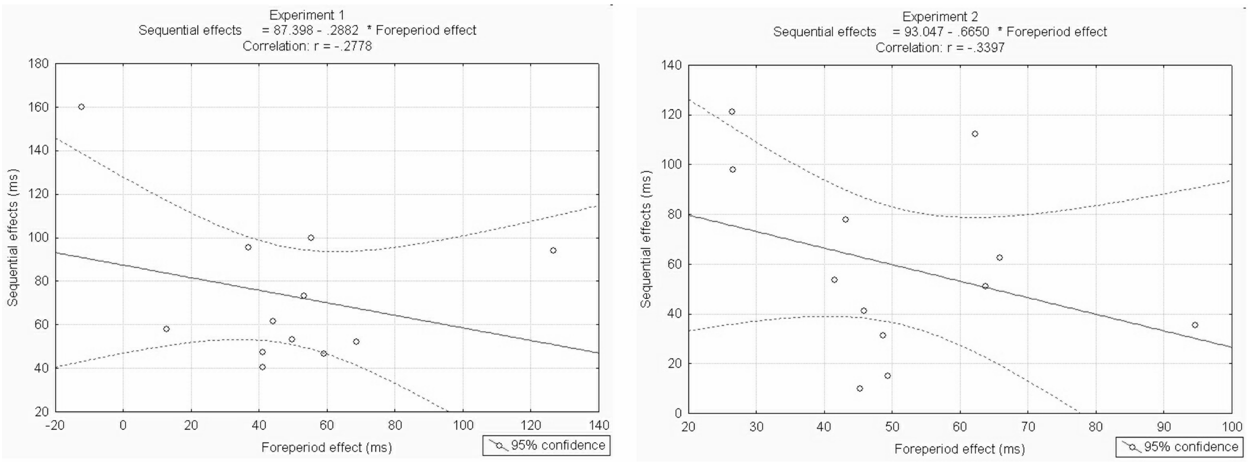

Figure 3. Results of the correlational analysis between FP effect (x-axis) and sequential effects (y-axis), in experiments 1 (left) and 2 (right).

2.1.2. Experiment 2

In experiment 2, three FPs longer than those employed in experiment 1 were used, in order to investigate whether the relationship between the FP effect and the sequential effects, and the supposed underlying conditioning processes, are stronger with relatively longer FPs. It is obvious that, with a longer average FP, temporal difference between one FP and another must be enough wide to permit discrimination among the various FPs, despite the increase in time uncertainty due to longer intervals used (Näätänen, Muranen,

---

[2] To calculate the FP effect using only the same trials as the sequential effects, trials with the shortest and longest FPs_n preceded by a medium FP_{n-1} were not included in the calculation of the FP effect. However, results did not change when these further trials were included.

& Merisalo, 1974). Therefore a wider FP range was used in experiment 2. The three FPs were 3, 5 and 7 sec, respectively. A second reason for using this FP range was to compare our results with the neuropsychological study by Stuss and colleagues (2005), which used a similar FP range.

Method

Participants

There were 12 participants, all different from those who carried out experiment 1. They were 24 years old on average (range = 20-32); 6 were males and 6 females, 10 were right- and 2 left-handed (writing hand). All had normal or corrected-to-normal vision and no auditory impairment, and all were in apparent good health. They participated in the experiment as volunteers.

Apparatus and Materials

The apparatus and stimuli were the same as in the Experiment 1. As in Experiment 1, four different quasi-random lists of trials were prepared to have enough trials to analyse sequential effects. Each list was presented to 25% of the participants.

Procedure and Task

The task and procedure were the same as in Experiment 1. As a consequence of the longer FP intervals used, the experimental session lasted about 35 instead of 25 minutes.

Design and Data Analysis

The experimental design was the same as in Experiment 1, except that the FPs had durations of 3, 5 and 7 sec. To compensate for the longer duration there was a reduction in the number of trials (300 instead of 360) and so in the number of blocks (5 instead of 6). Thus, the within-subject variables were FP_n (3, 5 or 7 sec), FP_{n-1}, and block (from 1 to 5).

The same procedure used in the analyses of the experiment 1 was also applied to the results obtained in the experiment 2.

Results

The first two trials of each block (3.3%), trials involving anticipated responses, that is the response being made before the onset of the IS (0.7%), trials involving premature responses (RT < 100 ms: 0.25%), and trials with delayed responses (RT > 1000 ms) or without responses (0.6%), were discarded from further analyses. In total, less than 5% of trials were excluded.

Basic FP effect and sequential effects

As in the previous study, we performed a 3 (FP_n) x 3 (FP_{n-1}) ANOVA. First, a significant main effect of the FP_n was obtained [$F(2, 22) = 39.3$, $p < .001$]. As in experiment 1, post hoc Tukey tests demonstrated that RTs after the shortest FP were significantly slower compared with RTs after the medium and longest FP (for both, $p < .001$), while there was no difference between RTs after the medium and the longest FPs. Also the main effect of the FP_{n-1} was replicated [$F(2, 22) = 24.3$, $p < .001$], indicating that RTs increased as a function of the length of the preceding FP, all the post hoc comparisons being significant (for all, $p < .05$). The FP_n x FP_{n-1} interaction [$F(4, 44) = 3.9$, $p < .01$] was principally due to the fact that sequential effects became weaker as the current FP duration increased. With the shortest current FP (3 sec), RTs were slower when the preceding FP was the longest (7 sec) than when it was the same shortest FP ($p < .001$). When the current FP was the medium one (5 sec), there was a trend for RTs to be slower if the preceding FP was the longest one rather than the shortest one ($p < .07$). However, for the longest current FP (7 sec), there was no effect of the preceding FP at all (for all, $p > 0.9$). As in experiment 1, the RT on the current shortest FP is slower than the RT on the current medium FP if they are each preceded by the shortest FP_{n-1} ($p < .01$).

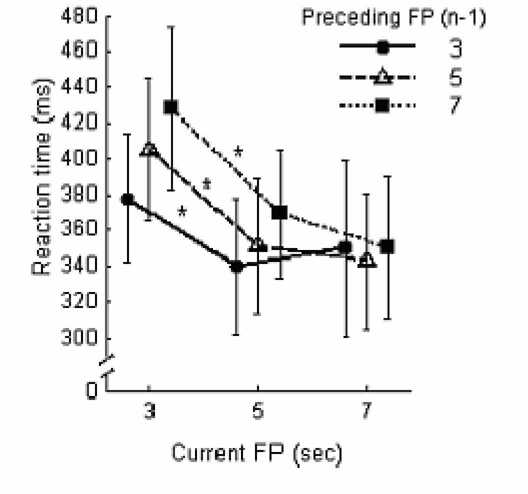

Figure 4. Mean reaction times as a function of current FP (x-axis) and preceding FP (lines), in experiment 2. Details as in *Figure 1.*

Long-term learning effects

The same type of analysis over blocks as in experiment 1 was carried out, using a 5x3x3 repeated measures ANOVA with block (from 1 to 5), FP_n (3, 5 and 7 sec), and FP_{n-1} (3, 5 and 7 sec) as the within-subject variables. Apart from the not surprising main effects of FP_n and FP_{n-1}, and their interaction (already shown in the previous analysis), this analysis revealed a significant main effect of block [$F(4, 44) = 4.5$, $p < .01$], reflecting the fact that RTs slowed from the first to the last block. Post hoc tests demonstrated that this effect was mainly due to differences between the first block on the one hand, and the 3rd, 4th and 5th blocks on the other (for all, $p < .05$). As in the first experiment, the block factor did not interact either with FP_n ($p = .9$) or with FP_{n-1} ($p = .08$), and there was no 3-way interaction ($p = .2$, see Figure 5).

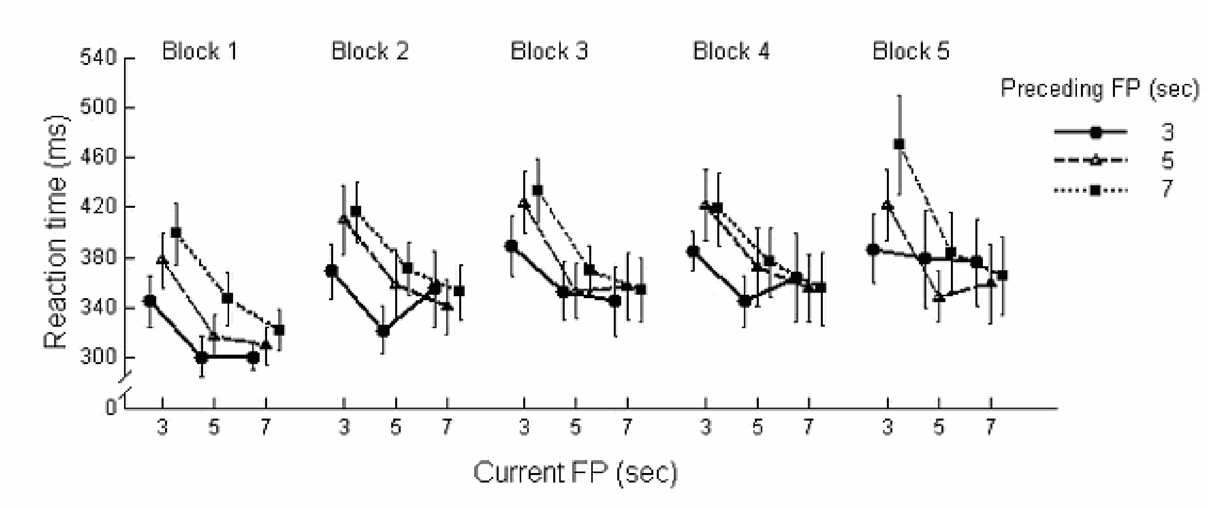

Figure 5. Mean reaction times as a function of current FP (x-axis), preceding FP (lines), and block (panels), in experiment 2. Details as in Figure 2.

Two similar ANOVAs as in the experiment 1 were conducted also here in order to check if learning effects occurred within the first block of trials. A 2 mini-block x 3 FP_n and a 2 mini-block x 3 FP_{n-1} ANOVAs were conducted. As in experiment 1, these two ANOVAs produced only a main effect of FP_n [$F(2, 22) = 20.2$, $p < .001$] and FP_{n-1} [$F(2, 22) = 11.2$, $p < .001$]. The main effect of mini-block was also significant [$F(1, 11) = 6.7$, $p < .05$], due to RTs increasing from the first 30 trials to the subsequent ones. Importantly, no interaction was observed in either ANOVA, again demonstrating no learning phase even with such a small amount of trials as 30.

Correlational analysis

The same formula as in experiment 1 was used as a comprehensive measure of the sequential effects for each participant. The correlation between FP and sequential effects was non-significant also in the experiment 2, with a slope that, if anything, was negative ($r = -.34$; see Figure 3, right panel).

Discussion: experiments 1 and 2

The present study aimed to assess whether the conditioning account, as proposed by Los and co-workers (Los et al., 2001; Los & van den Heuvel, 2001), is likely to underlie the FP phenomena. In 2 experiments employing two different FP ranges (i.e., 0.5, 1, 1.5 sec and 3, 5 and 7 sec, respectively) with a variable FP paradigm, we replicated the variable FP effect as it is known from the early literature (e.g., Niemi & Näätänen, 1981; Woodrow, 1914). Sequential effects, consisting of a lengthening of the RT as the preceding FP_{n-1} increases, were also replicated. As expected from the literature, these effects are asymmetrically biased towards the shortest current FP, because they become increasingly small as the current FP duration increases.

The pattern of sequential effects predicted in the original version of Los and van den Heuvel's theory (2001; Los et al., 2001) has been only partially obtained. First, on this model RTs should be relatively slow when FP_{n-1} is longer than FP_n, as extinction would be occurring in this condition; this is indeed found in the current experiments. Second, to account for the finding that RTs on the shortest FP_n are slower when they are preceded by the longest FP_{n-1} than by the medium one, a further assumption was put forward that the conditioning processes have a gradual effect across the time-scale (Los & van den Heuvel, 2001). With this assumption, the sequential effects, especially those obtained in experiment 1, are not incompatible with the conditioning model, albeit with some adjustments. However, no result supports the presence of reinforcement. The conditioning model, in fact, would also predict that RT should be relatively fast when the same FP is repeated as compared with the condition in which a shorter FP is presented before, as reinforcement should be occurring in the former case, and neither reinforcement nor extinction should occur in the latter. In the current experiments, as well as in Los and van den Heuvel's experiments (2001), this prediction is not supported: current RTs following preceding trials with shorter FPs are equally fast or faster than RTs after trials with equal FPs. In their revised model, Los and van den Heuvel (2001, p. 384) explain this finding by assuming that when a short FP occurs on trial *n-1*, subsequent reinforcement also extends to the adjacent longer FP. Then, if this longer FP occurs on trial *n*, RT will be faster than if a longer FP had occurred on trial *n-1*. In the latter case, extinction of the state of activation associated with shorter FP, still acting during the final phase of the current longer FP, may outweigh the advantage of stronger subsequent reinforcement associated to this FP. However, even with such theoretical adjustment, it is noteworthy that if there are conditioning processes, their overt effect on RTs is observed only or mostly in the negative direction (extinction) and not in the positive one (reinforcement).

Two aspects of experiments 1 and 2 give new insights to the understanding of the FP phenomena, namely, the lack of a long-term learning phase for the FP and the sequential effects, and the lack of a within-subject correlation between them. The lack of learning effects represents an additional finding that does not fit with some predictions of the trace conditioning framework from which the theory of Los and colleagues derives. Animal conditioning models generally assume, either explicitly or implicitly, the existence of an acquisition phase, in which the consolidation of the associations into long-term memory structures occurs (Gallistel et al., 2000; Machado, 1997; Pavlov, 1927). In fact, the trajectory of the acquisition phase can usually be empirically observed (e.g., Ferster & Skinner, 1957). A simple way of assessing if the acquisition phase also occurs in human subjects performing the variable FP paradigm is to examine the time-course of the FP phenomena over the experiment. As the results of experiments 1 and 2 show, the magnitude of the FP and the sequential effects does not change during the experiment.

However this observation, even if still theoretically interesting, is not crucially problematic from the point of view of the conditioning account. This is because the learning phase may have occurred during a smaller number of trials than those considered here (i.e., before the first 30 trials). This possibility was not tested as current experiments were not designed to analyse such a few trials. Moreover, absence of an acquisition phase, even if unusual, has been observed in some ‘trace conditioning’ experiments with animals. For instance, in some circumstances of high motivation, pigeons adjust virtually immediately to changes in inter-reinforcement intervals (Higa, Wynne, & Staddon, 1991). If a learning phase for the appearance of the FP and sequential effects does not exist or is too short to be detected, the conditioning model needs to account for this feature, for instance by explicitly assuming that. Further studies should test if the conditioning laws act in a very rapid time-window, without evolving during the experiment or, alternatively, if the conditioned associations are already present from the subject’s history.

A more problematic result to account for from the point of view of the conditioning model is the lack of a correlation between sequential effects and FP effect. The conditioning view predicts a strong positive correlation between the FP effect and the sequential effects, as both arise from common conditioning processes (Los et al., 2001; Los & van den Heuvel, 2001). The lack of a significant correlation between the FP and the sequential effects suggests instead that what produces the decreasing slope of the FP-RT function is not, or not mainly, the magnitude of the supposed conditioning effects occurring on the preceding trial, as reflected by the sequential effects. This evidence is in contrast with the conditioning view, while it suggests that the FP effect (and the underlying processes) is at least partially independent from the sequential effects, as expected by the strategic accounts.

Experiments 1 and 2, despite the different FP ranges and values used, produced patterns of results which were quite similar, with some minor differences. For instance, unlike experiment 1, there was an increase in the RTs in experiment 2 as a function of the block, which could be easily interpreted as a consequence of the decrease in the subjects' vigilance, due both to the longer FPs on each trial and the longer overall duration of the experimental session. However, this result is not relevant to the main purpose of this study, which is concerned with evaluating the conditioning account of the FP effect and the sequential effects. Importantly, increasing the absolute difference between FPs in the experiment 2, did not influence the (non-significant) correlation between FP effect and sequential effects.

A longer interval is available in experiment 2 than in experiment 1 for participants to reach an acceptable level of preparation at the shortest FP. However, despite this, sequential effects seem to be ubiquitous. These findings document that sequential effects hold as the available time for the minimum FP increases, at least for the FP range considered here, although for yet greater average FP values it is known that both FP and sequential effects can be attenuated and even disappear (Drazin, 1961; Elliott, 1973; Requin & Granjon, 1969).

In conclusion, the first two experiments bring evidence against a single-process, conditioning account of the FP phenomena. Contrary to what it is predicted by the conditioning view, the FP effect and the sequential effects seem to be two rather independent phenomena. However, the results of these experiments are not useful to understand the nature of the processes underlying the two effects. In particular they are not relevant for evaluating strategic accounts, as the latter are basically agnostic about the effects found in this study. The following experiments will address more directly this issue.

2.2. Developmental dissociations in preparation: deconstructing variable foreperiod phenomena

In cognitive research, neuropsychological dissociations can be useful in providing evidence on the functional architecture of normal cognition, given that the effects involved do not differ in the quantitative levels of the cognitive resources needed to produce them (Shallice, 1988). An analogous logic could apply to dissociations observed in the developmental time-course. In the present study, such a developmental perspective has been adopted in order to disentangle different accounts of the variable FP effect, a well-known phenomenon which has traditionally been studied in adults.

A recent neuropsychological study (Stuss et al., 2005; see paragraph 1.1.2.3., chapter 1) shows that the FP effect depends upon the functioning of the rDLPFC. Other imaging studies have documented that this area also has a more general role in time processing (e.g., Lewis & Miall, 2003a) and in attention to time (e.g., Coull, Frackowiak, & Frith, 1998; Coull et al., 2000; Coull, 2004). Hence, the FP effect might be expected to follow the neuro-developmental curve of the rDLPFC. It is known that this region myelinates and its number of synapses decreases in an accelerated fashion from 6-7 years of age (Delalle, Evers, Kostovic, & Uylinghs, 1997; Huttenlocher & Dabholkar, 1997). Moreover, a number of tasks which rely on frontally located processes begin to be performed well at this age (e.g., Archibald & Kerns, 1999; Davidson, Amso, Anderson, & Diamond, 2006; Drummey & Newcombe, 2002). On the other hand, little is known about the anatomical basis of the sequential effects.

From a functional point of view, if the same process underlies the two different behavioural effects in this paradigm, then they would be expected to show the same developmental trajectory. If instead two different processes underlie them, then there is no reason why they should develop in a parallel fashion. More specifically, by exploring the ontogenetic development of the FP phenomena, the current study assessed the viability of the conditioning view as opposed to strategic models. The conditioning view of Los and van den Heuvel (2001), indeed, predicts a parallel ontogenetic development of the sequential effects with respect to the FP effect as, on this account, the FP effect occurs as a *side effect* of the interplay between reinforcement and extinction which gives rise to the *asymmetric* sequential effects. According to this view, therefore, if no FP effect is shown by the youngest children, no sequential effects should be observed either.

On the traditional strategic accounts, a different prediction can be made. If no FP effect is observed in a group of children, that might indicate that the repreparation/maintenance process (e.g., Alegria, 1975) does not fully operate. On these dual-process accounts, there is no need for the FP effect to follow the same developmental trajectory of the sequential effects, as they rely upon different processes. However, if the sequential effects are observed without the FP effect, the FP repetition expectancy account (e.g., Drazin, 1961) would predict faster RTs for short-short and long-long FP sequences rather than for long-short and even short-long ones (namely, a crossover FP_n x FP_{n-1} interaction).

2.2.1. Experiment 3a

A few studies in the literature have examined the FP effect in children, usually showing a slightly smaller FP effect than adults (e.g., Adams & Lambos, 1986; Ozmun, Surburg, & Cleland, 1989). To our knowledge, the only study to investigate sequential effects in children is one by Elliott (1970). The results of that study failed to show any modulation of the FP phenomena as a function of age. However, the youngest group of children in that study were 6 year old on average. Therefore, studying the FP phenomena from a younger age could reveal more about their ontogenetic time-courses. Experiment 3a was designed to investigate the ontogenetic time-course of the FP effect and the sequential effects in young children from 4 years of age on. This has been done by administering a variable FP paradigm to children from 4 to 11 years of age as well as to a control group of adults.

Method

Participants

Children (4-11 years) were mainly recruited in a summer camp and grouped into 4 age groups, with each group comprising two years (see Table 1). A control group of adults was also enrolled. A total of 106 participants took part in the experiment. Parents had previously signed informed consent for all the children participating in the study. The study was previously approved by the SISSA Ethical Committee

Apparatus and Materials

Each participant was tested individually in a silent and dimly lit room. Participants viewed a 17” computer monitor at a distance of ~60 cm. The index finger of their writing/drawing hand rested on the keyboard spacebar. Materials were the same as in the experiment 1, apart from the following exceptions. The chosen FP range lay between those used in the earlier two experiments, namely FP durations of 1, 3 or 5 sec. This choice was made to avoid, on the one hand, children not having enough time to prepare for the shortest FP (0.5 sec in experiment 1) because of an immature perceptual-motor system and, on the other hand, becoming distracted though waiting too long for the longest FP (7 sec in Experiment 2). Only a single block of 60 trials was used, in order to prevent the children from becoming tired or bored, and as no change was observed across the blocks of trials in the previous 2 experiments.

Table 1

Main demographical characteristics of the five age groups in experiment 1a

		Gender[a]		Handedness		
Group[b]	Mean Age (min-max)	Females	Males	Left	Right	N
4-5[c]	61 months (48-71)	11	10	1	20	21
6-7[d]	83 months (72-94)	10	12	2	20	22
8-9	107 months (96-119)	10	15	1	24	25
10-11	130 months (120-142)	5	12	1	16	17
Adults	25 years (19-30)	7	14	1	20	21

Notes. [a]Initial ANOVAs did not reveal any significant effect of gender. Therefore, the results were collapsed across gender. [b]Each age group, apart from adults, is defined by the range of years spanned. [c]Three children from this groups refused to participate. [d]One child from this group refused to participate.

Procedure and Task

Children were accompanied by the experimenter one at a time, from their playing place to the experimental room. On the way, the experimenter spoke for a few minutes with each child to obtain her/his collaboration and to avoid fear and shyness. When a friendly atmosphere had been established, the experimenter asked if she/he would take part in the experiment. If she/he agreed, he explained the task, consisting of pressing the spacebar when an arrow appeared. This task was presented as a ‘velocity game’, but the need to avoid anticipations was also highlighted. Apart from this initial phase, the experimental conditions were completely comparable for children and adults. Preceding the 60 test trials, 3 learning trials were run and repeated until the participant performed the warm-up without errors or hesitation. However no more than 2-3 learning cycles were necessary for any participant.

Data Analysis

The familiarization trials and the first test trial were not analysed. Trials were treated as errors and discarded from the RT analyses if a response was made during the FP or the first 100 ms after IS onset (anticipated responses), or if the RT was slower than 1500 ms or no response was detected (delayed and null responses). For the RT analyses, the within-subject independent variables included FP_n (1, 3, or 5 sec) and FP_{n-1}. The between-subjects variable involved 5 age groups: 4-5, 6-7, 8-9, 10-11 and adults. The dependent variable chosen was the median RT[3]. The RT data were normally distributed but the ANOVA assumption of homoschedasticity was occasionally violated (significant Levene test). For that reason, a log-transformation was applied to make the variances more homogeneous. After applying this transformation, the assumption of homoschedasticity was always achieved. Greenhouse-Geisser ε corrections were used when appropriate. Post-hoc Tukey’s HSD comparisons were performed to evaluate pairwise differences among the means.

Results

Accuracy

Table 2 shows the error percentages for each group. For the accuracy analysis, non-parametric tests were used because the distributions of most variables were non-Gaussian by the Kolmogorov-Smirnov test and because some participants did not make any error.

Overall anticipated responses decreased as a function of age [Kruskal-Wallis test: H (4, N=106)=17.8, $p < .01$]. Anticipated responses increased significantly as a function of FP_n in the 4-5 year old children [Page’s L = 266, $p < .05$] and, as a tendency, in the 6-7 year old ones [Page’s L = 274.5, critical L for $p < .05$ = 275]. Anticipated responses decreased significantly as a function of the previous FP_{n-1} in 4-5 year old children [Page’s

---

[3] Median RTs (instead of mean RTs) were used here, in the two subsequent experiments 3b and 4, and also in the patient study presented in chapter 3 (experiment 9), in order to reduce the intra-subject variability (Keppel, Saufley, & Tokunaga, 1992), which was due to the low number of trials per condition used with these special populations (young children and patients).

L = 264, *p* .05], and also in 6-7 and 8-9 year old ones [Page's L = 280 and 319, respectively, for both, *p* < .01].

Overall delayed and null responses decreased as a function of age [Kruskal-Wallis test: H (4, N=106) = 37.7, *p* < .001]. Delayed and null responses generally decreased as a function of FP_n and increased as a function of FP_{n-3b}ut these tendencies, although constant, never reached significance for any group with the Page's L test.

Table 2

Mean error percentages (+ SE) as a function of type of error, current foreperiod (in seconds), preceding foreperiod (in seconds) and group of age (in years) in experiment 3a (above) and in experiment 3b (below, see page 52, for details).

Age	Foreperiod n						Foreperiod n-1					
	1	3	5	1	3	5	1	3	5	1	3	5
	Anticipated Responses			Delayed + Null Responses			Anticipated Responses			Delayed + Null Responses		
Exp. 3a												
4-5	5.3 (1.3)	9.2 (1.7)	11.2 (2.4)	7.3 (1.8)	7.9 (2.1)	6 (1.4)	10.6 (2.3)	9.7 (2.3)	5.5 (1.2)	5.2 (1.8)	5.9 (1.3)	10.2 (2.5)
6-7	6.7 (1.5)	9.9 (1.4)	10.5 (2.2)	2.5 (0.7)	3.8 (1.1)	3 (1.1)	10.8 (2.3)	10.4 (2.1)	5.9 (1.5)	2.8 (0.7)	1.9 (0.5)	4.5 (1.2)
8-9	4.8 (1.4)	4.1 (0.9)	6.2 (1.6)	2.1 (0.9)	0.4 (0.4)	0.4 (0.3)	8.5 (2.1)	4.7 (1.1)	2 (0.9)	0.2 (0.2)	0.4 (0.3)	2.2 (0.9)
10-11	3.6 (1.5)	5.2 (1.6)	7.4 (2.3)	0.6 (0.4)	0 (0)	0.3 (0.3)	7.4 (2.3)	4.6 (1.9)	4.1 (1.5)	0.3 (0.3)	0.6 (0.4)	0 (0)
Adults	1.7 (0.5)	2.6 (1.0)	4.3 (1.3)	1 (0.5)	0 (0)	0 (0)	3.4 (1.3)	3.1 (0.9)	2.1 (0.7)	0 (0)	0.3 (0.3)	0.7 (0.4)
Exp. 3b												
Age												
4-5	4.6 (2)	10.4 (2.3)	12.9 (3.8)	12.1 (3.1)	13.8 (4.4)	12.1 (3.2)	10.8 (3.2)	11.3 (3.4)	5.8 (1.8)	9.2 (2.7)	13.8 (3.5)	15 (3.9)
5-6	1.7 (0.9)	5.4 (1.9)	9.2 (1.9)	4.2 (1.5)	4.2 (2.1)	5 (2.5)	4.6 (1.1)	5 (1.6)	6.7 (1.7)	5.4 (2.9)	2.1 (1)	5.8 (2.6)

Reaction Times

A 3x3x5 mixed ANOVA was performed with FP_n and FP_{n-1} as the within-subject variables and age as the between-subjects variable (see Figure 6). This produced a significant main effect of age [*F*(4, 101) = 83.7, *p* < .001]. Tukey tests demonstrated that for any two groups, responding was faster in the older group, except for the comparison between the 8-9 and 10-11 groups, which was non-significant (for all the other comparisons, $p < .05$).

FP effect and Sequential effects

The main effect of FP_n was significant [$F(1.7, 169.8) = 95.48$, corrected $p < .001$]. Tukey comparisons showed that RTs were slowest for the shortest FP of 1 sec as compared to the medium ($p < .001$) and longest FPs ($p < .001$), but there was no difference between the RTs for FPs of 3 and 5 sec. Critically, a significant age x FP_n interaction was present [$F(6.7, 169.8) = 9.67$, corrected $p < .001$]. A FP effect (i.e., RTs slower for the shortest FP than for the longest one) was present in all groups apart from the 4-5 year old one. For this group, the difference between the mean RT on shortest and longest FPs_n was non-significant (Tukey $p > .99$, for all the other groups, $p < .01$).

To evaluate the difference in the magnitude of the FP effect across groups, *planned comparisons* were performed contrasting RTs on FPs of 1 sec with those on FPs of 5 sec for each age group and for each pair of age groups. The FP effect found in the 4-5 year old children (-13 ms) was significantly smaller than in all the other groups (for all planned comparisons between 4-5 years group and each other group: $p < .001$). The 6-7 year old group had a smaller FP effect compared with the 10-11 year old ($p < .05$) and the adults ($p < .001$). No other difference was found. Additionally, *polynomial contrasts* were used to obtain an overall picture after exclusion of the qualitatively different 4-5 year old group: the linear model contrasting the RTs on FP_n of 1 vs. 5 sec, for the other four groups, fitted the results well [$F(1, 81) = 17.87$, $p < .001$], indicating that the FP effect grows linearly as a function of age from 6-7 years to adulthood.

The main effect of FP_{n-1} was significant [$F(2, 202) = 103.86$, $p < .001$]. Current RT was slower following a longest FP_{n-1} trial than a medium FP_{n-1} trial (Tukey, $p < .001$). This, in turn, was slower than RT following a shortest FP_{n-1} trial ($p < .01$). The FP_n x FP_{n-1} interaction was also significant [$F(3.7, 371.5) = 13.88$, corrected $p < .001$], replicating results concerning the asymmetry of the sequential effects known from the literature. This interaction indicates that the effect of FP_{n-1} was greatest for the shortest FP_n and smallest for the longest FP_n. When the FP_n was the shortest one (1 sec), RTs were slower if the FP_{n-1} was the longest (5 sec) than if it was the medium one (3 sec; Tukey, $p < .001$). In turn, RTs were slower when the FP_{n-1} was the medium one than when it was the shortest one ($p < .001$). When the current FP_n was the medium one (3 sec), the same pattern was observed but to a more minor extent (for both 5 vs. 3 sec FPs_{n-1} and 3 vs. 1 sec FPs_{n-1}, Tukey $p < .05$). Finally, for the longest FP_n (5 sec), no modulation by FP_{n-1} was observed. Most critically, no sequential effect involving the FP_{n-1} was significantly different between any of the groups (see Figure 6). This demonstrates that sequential effects are present with the same relative magnitude in adults at least by 4-5 years of age. The age x FP_n x FP_{n-1} interaction was not significant. However, visual inspection of the Figure 6 suggests that the youngest children did not produce asymmetric sequential effects.

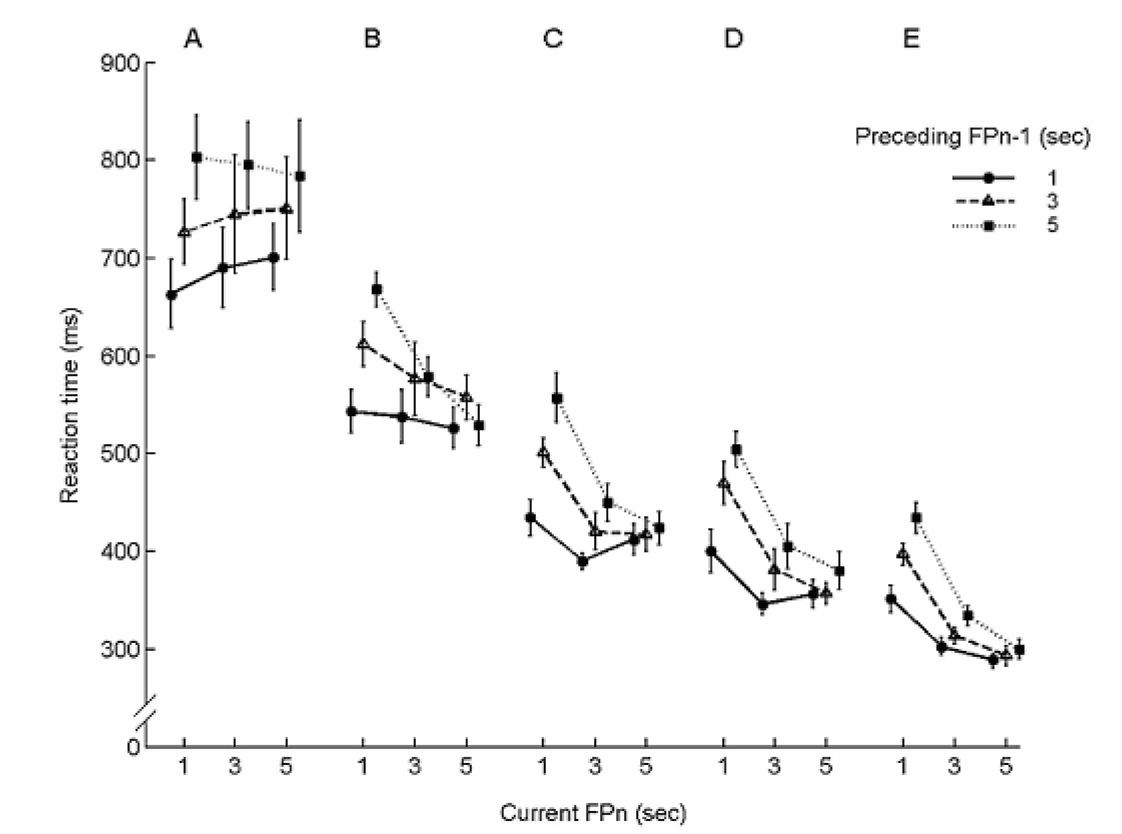

Figure 6. Median reaction times as a function of the current FP (x-axis) and preceding FP (lines) in Experiment 3a. Vertical lines indicate standard errors of the mean. FP = foreperiod. Panels from A to E show the raw data separately for each Group of Age = A: 4-5 year old children; B: 6-7; C: 8-9; D: 10-11; E: Adults. Note that the ANOVAs reported in the text and in Table 3 were performed using log-transformed data while the figure shows raw data for reasons of clarity.

To statistically corroborate this observation, subsequent 3x3 repeated measures ANOVAs were performed separately on each group, with FP_n and FP_{n-1} as the within-subject variables. For all groups, apart from the 4-5 year old one, these analyses confirmed results from the previous analysis, as all of them showed a significant main effect of FP_n, FP_{n-1}, and the FP_n x FP_{n-1} interaction (see Table 3). It is noteworthy that only 4-5 year old children completely failed to show the FP_n effect and, as critically, there was absolutely no

FP_n x FP_{n-1} interaction. On the other hand, they showed significant sequential effects at the .001 α level (i.e., main effect of FP_{n-1}; see Table 3).

The lack of FP_n x FP_{n-1} interaction for this group was due to RTs being exclusively modulated by the previous FP_{n-1} with no effect of the current FP_n, even when the latter was the longest one (Figure 1, Panel A).

Table 3

Outputs of the separate ANOVAs for each of the 5 age groups of experiment 1a. SS = Sum of Squares; df = Degrees of Freedom; MSE = Mean Square Error.

Group	Effect	SS	df	MSE	*F*	*p* <
4-5	FPn	0.001	2; 40	0	.07	.93
	FPn-1	0.124	1.5; 30.8	.062	13.46	*(Adj.p)* .001*
	FPn*FPn-1	0.011	2.6; 52.5	.003	.65	*(Adj.p)* .57
6-7	FPn	0.098	1.5; 32.4	.049	8.49	*(Adj.p)* .01*
	FPn-1	0.072	2; 42	.036	16.97	.001*
	FPn*FPn-1	0.05	4; 84	.013	3.33	.05*
8-9	FPn	0.26	1.5; 35.3	.13	31.59	*(Adj.p)* .001*
	FPn-1	0.137	2; 48	.068	38.85	.001*
	FPn*FPn-1	0.063	3; 72.5	.016	5.45	*(Adj.p)* .01*
10-11	FPn	0.275	2; 32	.138	28.84	.001*
	FPn-1	0.109	2; 32	.054	29.54	.001*
	FPn*FPn-1	0.032	4; 64	.008	3.58	.01*
Adults	FPn	0.519	2; 40	.26	107.9	.001*
	FPn-1	0.079	2; 40	.04	21.7	.001*
	FPn*FPn-1	0.035	4; 80	.009	5.4	.001*

Note. For each age group, a 3 (FPn = foreperiod on the trial n) x 3 (FPn-1 = foreperiod on the trial n-1) Repeated measures ANOVA was performed. Greenhouse-Geisser corrections were applied when appropriate.

Discussion

In the present experiment, a variable FP paradigm was administered to a developmental population with the aim of exploring the ontogenetic time-course followed by the FP and the sequential effects. The results show a general reduction of the RTs with age, which can be ascribed to the fact that processing speed is slower in young children and progressively increases during development (e.g., Salthouse & Kail, 1983). More relevant for the present purposes, a developmental dissociation has been observed between the two effects: sequential effects are already present at least from 4-5 years of age, while the FP effect appears gradually from 6-7 years on. The different developmental trajectories followed by the two effects already provide evidence in favour of a dual-process account and are difficult to explain on a single-process account. A potentially useful additional result, in order to understand which mechanism underlies the sequential effects, is the observation that, in the 4-5 years children, these effects were symmetrical across all the 3 current FPs_n[4]. However, this observation is weakened by a lack of age x FP_n x FP_{n-1} three-way interaction.

2.2.2. Experiment 3b

A possible reason for the lack of the age x FP_n x FP_{n-1} 3-way interaction, which would demonstrate qualitative differences in the shape of the sequential effects in youngest children with respect to older, could be the variability across and within groups in experiment 3a. A within-subject approach would be of use in order to reduce the variability across groups. To that purpose, a follow-up approach was adopted in the experiment 3b. To our knowledge, no other developmental study has previously investigated the FP phenomena longitudinally.

Method

Participants

Twelve participants from the 4-5 year old group of the experiment 3a (9 females, 1 left-handed) were retested 14 months after the first study. In the first session, children were 61 months old on average (range: 50-71).

Apparatus and Procedure

The apparatus and procedure of the second session were kept as similar as possible as those in the first session (see method session of experiment 3a), apart from the fact that now children were tested in their homes instead of in the summer camp.

Data Analysis

The same criteria were adopted as in experiment 3a for the accuracy and RTs here. For RT analyses, a 2x3x3 within-subject ANOVA was employed with test session (first vs. second session), FP_n (1, 3, or 5 sec) and FP_{n-1} as the independent variables. The ANOVA

---

[4] We use the expression symmetric sequential effects here and hereafter, meaning that there is a symmetric influence of the FP_{n-1} on the RTs whatever FP_n has occurred. This influence consists of RT being slower as the preceding FP_{n-1} gets longer. Strictly speaking, also a cross-over FP_n x FP_{n-1} interaction would be symmetric, but not in the sense explained above.

assumption of normality was not violated by the median RT data, which were then used as the dependent variable.

Results

Accuracy

The accuracy results for experiment 3b are presented in the second part of the Table 2. There was a tendency for a reduction of the overall percentage of anticipations from the first to the second session [Wilcoxon: $Z > 1.73$, $p = .08$]. The rate of anticipations increased as a function of FP_n, both in the first session [Page's $L = 154$, $p < .05$] and in the second one [Page's $L = 157$, $p < .01$]. The number of anticipations did not change significantly as a function of FP_{n-1} in either session. The rate of overall delayed and null responses decreased from the first to the second session [Wilcoxon: $Z > 2.49$, $p < .05$]. The number of such responses did not vary significantly as a function of FP_n in either session. This type of error increased significantly as a function of FP_{n-1} in the first session only [Page's $L = 153.5$, $p < .05$].

Reaction Times

The main effect of session [$F(1, 11) = 4.9$, $p < .05$] demonstrated that median RTs were slower in the first session than in the second one (770 vs. 670 ms). There was a main effect of FP_n [$F(2, 22) = 3.5$, $p < .05$] but it was qualified by a FP_n x session interaction [$F(2, 22) = 3.8$, $p < .05$]. The latter was in accordance with that FP_n effect being present in the second session but absent in the first one. Subsequent planned comparisons contrasting RTs for the shortest FP_n of 1 sec and for the longest FP_n of 5 sec were not significant in the first session ($p > .7$) but were significant in the second session ($p < .01$). As far as sequential effects were concerned, the main effect of FP_{n-1} was significant [$F(2, 22) = 11.4$, $p < .001$], indicating that RT was faster as FP_{n-1} was shorter. No other effect reached significance. However, when data from the 2 testing sessions were analysed separately, the FP_n x FP_{n-1} interaction showed a tendency towards significance in the second session only [$F(4, 44) = 2.3$, $p < .07$; for the first session, $p = .46$], suggesting the presence of asymmetric sequential effects at 5-6 years of age.

In order to control for possible learning effects, the results from the 12 children of the second session of the longitudinal study (5-6 years old) were compared with those of 5 and 6 years old children of experiment 3a (considered as a single group). After the exclusion of the children participating in the longitudinal study from the latter group, a 2x3x3 mixed

ANOVA was performed with group as the between-subjects variable (21 children of experiment 3a vs. 12 children of experiment 3b, second session), and FP_n and FP_{n-1} as the repeated measures variables. This analysis did not show a significant main effect or any interaction concerning the group factor, indicating that no learning effects had occurred for the children re-tested in the second session of experiment 3b.

Discussion

The experiment 3b confirmed results of experiment 3a from a longitudinal point of view, by demonstrating that a population of young children did not show the FP effect when they were 4-5 years old, but showed the effect 14 months after the first test. Moreover, no difference was observed between sequential effects in the two sessions. Sequential effects were basically symmetric in this population, as no FP_n by FP_{n-1} interaction was observed at either session. A limit of experiments 3a and 3b was that the difference between the symmetric sequential effects in 4-5 year old children and the asymmetric sequential effects in older children and adults was not statistically corroborated. This may be due to a lack of power in the experiment 3b, in which it was possible to re-test only 12 participants in the second session. As far as experiment 3a is concerned, detailed analyses of RT data performed on the 4 and 5 year old children (N = 8 and 13, respectively) as separate groups, demonstrated that 4 year old showed symmetric sequential effects whereas 5 year old did not [age x FP_n x FP_{n-1} interaction: $F(4, 76) = 2.8$, $p < .05$]. In addition, within each age group, a Pearson correlation analysis was carried out between months of age and an index of asymmetry of sequential effects. This index was obtained for each participant as follows. First, sequential effects on the shortest FP_n were calculated through the RT difference between the shortest FP_n given a longest FP_{n-1} and given a shortest FP_{n-1}. Then, sequential effects on the longest FP_n were calculated through the RT difference between the longest FP_n given a longest FP_{n-1} and given a shortest FP_{n-1}. To estimate the degree of asymmetry of the sequential effects, the difference between the two RT differences was calculated. A positive value would indicate asymmetry towards the shortest FP_n, a negative one would indicate asymmetry towards the longest FP_n, with values near to 0 indicating symmetric sequential effects. A positive correlation was obtained between the asymmetry index and months of age within the 4-5 years old children only (Pearson’s $r = .63$, $p < .05$), suggesting that sequential effects became gradually more asymmetric from 4 to 5 years of age. This suggested that the 4-5 year old group consisted of two heterogeneous populations, which would be worthwhile to consider separately. However, given the small number of 4 year old children (i.e., 8), we replicated the experiment with a new and larger sample size for each group, considering 4 and 5 year old children as two separate groups.

2.2.3. Experiment 4

In the experiment 4, we concentrated on the most sensitive ages of 4, 5 and 6 years old, both because the main developmental changes in the FP effect found in previous experiments were observed during this critical period, and because this permitted us to reduce the variability across-ages in the magnitude of the absolute RTs, which is observed when older groups are also included. In addition, a more fine-grained approach was adopted in this experiment, in that 4 and 5 year old children were treated as separate groups.

A limit of experiments 3a and 3b was the small number of trials used. The choice of 60 trials, although sufficiently small in number to avoid distraction and tiredness in children as young as 4 years old, was not optimal from the statistical point of view, given the high number of conditions involved in the analysis. For this reason, we doubled the number of trials in the experiment 2 (120 vs. 60). However, in order to run more trials roughly in the same time, the range of FPs used was narrowed to 1, 2 and 3 sec instead of 1, 3 and 5 sec, a manipulation which, if one extrapolates from the literature on adults (e.g., Niemi & Näätänen, 1981), should not qualitatively affect the occurrence of the basic FP phenomena.

Method

Participants

Sixty-eight children were recruited for experiment 4, mostly in a kindergarten. They belonged to 3 age groups: 4 year old (N = 26, 9 Females, 1 left-handed, mean age: 55 months), 5 year old (N = 24, 12 Females, 1 left-handed, mean age: 65 months), and 6 year old (N = 18, 7 Females, 2 left-handed, mean age: 76 months). Parents had previously signed informed consent for all the children participating in the study. Two other 4 year old children refused to participate. One further 4 year old child refused to complete the test.

Apparatus and Materials

The apparatus and materials were the same as in the experiment 3a, apart from a few exceptions. Children were tested in a quite room of a kindergarten and not of a summer camp. The FPs employed were 1, 2 and 3 sec instead of 1, 3 and 5 sec.

Procedure and Task

Procedure and task were the same as in the experiment 3a, except that 120 test trials were administered to each participant instead of 60. A short rest was given after the first block of 60 trials.

Data Analysis

The same criteria were adopted to analyse data in the experiment 4 as in experiment 3a, apart from the following exceptions. For the RT analyses, a 3x3x3 mixed design ANOVA was used, with FP_n (1, 2, 3 sec) and FP_{n-1} as the within-subject independent variables and age group (4, 5 and 6 year old children) as the between-subjects variable. No assumptions underlying ANOVA was violated. This permitted the use of median RTs as the dependent variable.

Results

Accuracy

The percentage of errors in experiment 2 is shown in the Table 4. The rate of overall anticipated responses was comparable across age groups [Kruskal-Wallis test: H (2, N=68) = 4.1, $p = .13$]. The rate of anticipated responses increased significantly as a function of the FP_n for the 4 and 5 year old groups [Page's L = 386.5 and 348.5, respectively, for both, $p > .001$], but this tendency was not significant for the 6 year old group. Anticipated responses decreased significantly as a function of the FP_{n-1} in the 4 and 5 year old groups [Page's L = 332, $p > .01$ and Page's L = 350, $p > .001$, respectively], and there was a similar tendency in the 6 year old group [Page's L = 226.5, critical L for $p < .05$ = 227].

The rate of overall delayed and null responses decreased as a function of age [Kruskal-Wallis test: H (2, N=68) > 15.8, $p < .001$]. Delayed and null responses decreased significantly as a function of FP_n in the 4 and 5 year old groups [Page's L = 392, $p > .001$ and Page's L = 305, $p = .01$, respectively], and there was a similar tendency in the 6 year old ones [Page's L = 225.5, critical L for $p < .05$ = 227]. Delayed and null responses increased reliably as a function of FP_{n-1} in the 4 and 5 year old groups [Page's L = 336.5, $p < .001$ and Page's L = 302, $p < .05$, respectively] but this tendency was not significant in the 6 year old group.

Table 4

Mean error percentages (+ SE) as a function of type of error, current foreperiod n (in seconds), preceding foreperiod n-1 (in seconds), and group of age (in years), in experiment 4.

	Foreperiod n						Foreperiod n-1					
	1	2	3	1	2	3	1	2	3	1	2	3
Age	Anticipated Responses			Delayed + Null Responses			Anticipated Responses			Delayed + Null Responses		
4	3.2 (0.8)	10.3 (1.6)	12.7 (1.6)	18.4 (2.5)	18.9 (2.7)	16.5 (2.5)	11.6 (1.4)	8.6 (1.3)	6 (0.9)	14.3 (2.7)	18.5 (2.2)	21 (2.8)
5	4.5 (1.6)	8.8 (2)	13.4 (2.1)	13.3 (2.7)	12.4 (2.4)	9.5 (2.3)	13.1 (2.3)	8.3 (1.6)	5.3 (1.5)	9.5 (2.1)	11.9 (2.5)	13.8 (2.7)
6	4.9 (0.9)	5.4 (1.2)	6.9 (1.5)	8.1 (2)	4.2 (1.3)	3.2 (1.2)	8.5 (1.4)	4.2 (1.1)	4.6 (1)	4.2 (1.3)	5 (1.2)	6.3 (1.9)

Reaction Times

The median RTs in experiment 4 are shown in Figure 7. A significant main effect of age was obtained [$F(2, 65) = 17.4$, $p < .001$]. Tukey tests demonstrated that, for any 2 age groups, responding was faster in the older group (for all comparisons, $p < .01$).

FP effect and Sequential effects

The main effect of FP$_n$ was significant [$F(1.9, 124.3) = 24.1$, corrected $p < .001$]. Critically, also a significant age x FP interaction was present [$F(3.8, 124.3) = 3$, $p < .05$]. Post-hoc comparisons demonstrated that the FP effect (i.e., RTs slower for the 1 sec FP than for the 3 sec FP) was present in the 5 and 6 year old group only (for both, $p < .01$).

The main effect of FP$_{n-1}$ was significant [$F(1.8, 119.3) = 46.6$, corrected $p < .001$]. RTs were slower following a longest FP$_{n-1}$ or a medium FP$_{n-1}$ than a shortest FP$_{n-1}$ (for both, $p < .01$). The FP$_n$ x FP$_{n-1}$ interaction was also significant [$F(3.6, 231.8) = 4.1$, $p < .01$], indicating that the effect of FP$_{n-1}$ was greatest for the shortest FP$_n$ and smallest for the longest FP$_n$. However, this interaction was qualified by an age x FP$_n$ x FP$_{n-1}$ interaction [$F(8, 260) = 2$, $p < .05$]. This last finding fitted with sequential effects being symmetric in the 4 year old children and asymmetric in the older groups. This was supported by subsequent ANOVAs (3 FP$_n$ x 3 FP$_{n-1}$) performed separately on each group. The 4 year old children did not show a significant FP$_n$ x FP$_{n-1}$ interaction ($p = .49$), whereas this interaction was significant in older children [for the 5 years old, $F(3.5, 81.6) = 3.7$, corrected $p < .01$; for the 6 years old, $F(4, 68) = 6.3$, $p < .001$][5].

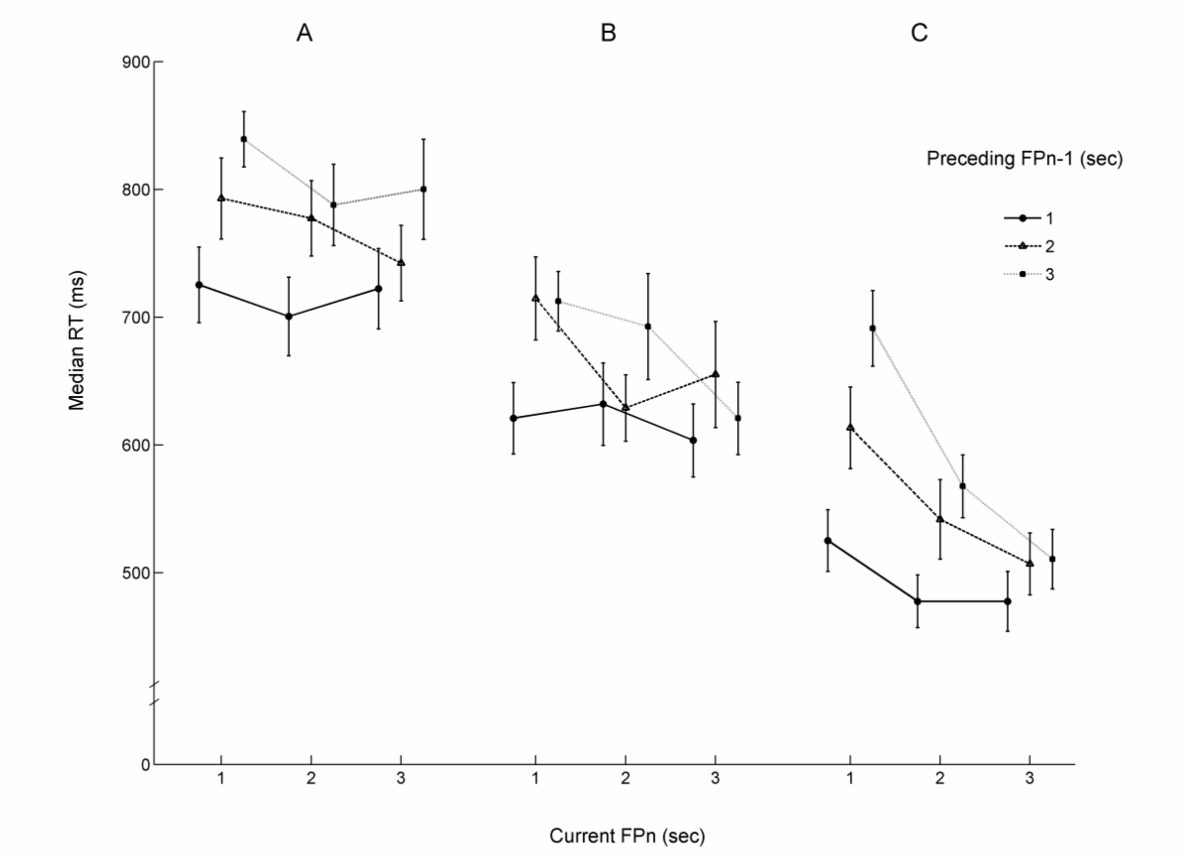

Figure 7. Median reaction times as a function of the current FP (x-axis) and preceding FP (lines) in Experiment 2. Vertical lines indicate standard errors of the mean. FP = foreperiod. Panels from A to C show data of the 4, 5 and 6 year old groups, respectively.

Discussion

The results of experiment 4 basically confirm those of experiment 3a and 3b with respect to the developmental curve shown by the FP effect. The 4 year old children again do not show the FP effect, whereas this effect is fully present in the 6 year old group, with the 5 year old one in between. More interestingly, the picture of the sequential effects obtained in this experiment is clearer than that obtained in the experiment 3a, as the significant age x FP_n x FP_{n-1} 3-way interaction obtained here reveals that sequential effects

---

[5] We wanted to further check if the performance of 4 year old children, who made more errors with respect to the other two groups, could be explained by speed-accuracy trade-off. Due to the relatively high number of errors made by the youngest children (normally distributed), it was possible to perform two 3 FPn x 3 FPn-1 full factorial ANOVAs on the percentage of their anticipations and delayed and null responses, respectively. These ANOVAs did not show any FPn x FPn-1 interaction [anticipated responses: $F(4, 100) = 1.3$, $p = .26$; delayed and null responses: $F(4, 100) = 2.1$, $p = .09$], mirroring the RT analysis. This result clearly discards the possibility that symmetric sequential effects found in the RT data of youngest children are an artefact of errors, as their performance cannot be attributed to speed-accuracy trade-off.

change qualitatively with age. The sequential effects are symmetrically present across all the 3 FPs_n in the 4 year old children, while they become asymmetrically biased towards the shortest FP_n in 5 and 6 year old ones. This could explain the lack of 3-way interaction when 4 and 5 year old children are considered as a single group, as they seem to belong to 2 different populations, as far as the pattern of their sequential effects is concerned.

General Discussion: experiments 3a, 3b and 4

The present set of developmental experiments reveals for the first time a dissociation between the FP effect and the sequential effects from an ontogenetic perspective. As shown consistently in all the 3 experiments (3a, 3b and 4), the ontogenetic time-course of the FP effect gradually develops as one goes from 4 or 4-5 years of age to older ages, whereas sequential effects are already present in their typical magnitude even in the youngest children considered here.

In the literature, a study by Elliott (1970) has already investigated the sequential effects together with the FP effect in children. As for our findings, the results of that study showed the presence of sequential effects in children, but, unlike our study, there was only a slight and non-significant modulation of the FP effect as a function of age. The difference in results between the two studies can be attributed to the different ages of the youngest groups of children tested (5-7 year old in the Elliott's study vs. 4-5 year old here). However, even when comparable age groups are considered, the results still remain partially incongruent. It is possible that the differences in a number of experimental details could explain the remaining differences across studies. These include the use of different stimulus modalities (auditory, in Elliott's study vs. visual, here), different social backgrounds (upper middle-class children with parents in academic and medical occupations, there vs. children chosen randomly from a wider range of social contexts, here) and, probably most important, the different ranges of FPs used (1-16 sec, with an exponential distribution, in Elliott's case, vs. 1-5 sec and 1-3 sec, with a rectangular distribution, here). In particular, a possible influence of different FP ranges and distribution on the developmental time-course of the FP phenomena needs further investigation.

A closer examination of the sequential effects showed by the youngest children in the current study can help to clarify their nature further, and to discriminate between different existing accounts of these phenomena. Despite the usual pattern of asymmetric sequential effects found in adults, sequential effects were symmetric for the youngest children in all the 3 experiments of the study. In other words, the RTs become slower when the previous FP_{n-1} is increasingly long, whatever the current FP_n is. However, the pattern of sequential effects observed in the youngest children was significantly different from that found in older children in the experiment 4 only, when the 4 year old were considered separately from the 5 year old children. This discrepancy suggests that the mechanism responsible for an *asymmetrization* of the sequential effects, whatever it is, begins to mature between 4 and 5 years of age. As a further support for this hypothesis, even in the experiment 3a, when performance of 4 year old children was compared to that of 5 year old children, a significant difference in the pattern of sequential effects (i.e., age x FP_n x FP_{n-1} interaction) was obtained (see discussion of experiment 3b).

On the traditional view (e.g., Drazin, 1961), the sequential effects per se are due to an expectation of FP repetition being carried over from one trial to the next. Their asymmetry is due to a complementary repreparation/maintenance mechanism operating when this expected repetition does not occur for short FP_{n-1}-long FP_n sequences (e.g., Alegria, 1975). It follows that if the latter process does not work, no FP_n effect should occur, whereas a FP_n x FP_{n-1} crossover interaction should emerge. That is, RTs should be faster when FP_n is the same as FP_{n-1} than when it is longer or shorter. Contrary to this prediction, although youngest children did not show a FP_n effect, they did not show any interaction either, but a significant main effect of FP_{n-1} only.

Symmetric sequential effects would also not be expected on the conditioning view (Los & van den Heuvel, 2001). On this single-process account, the FP effect should have occurred together with the sequential effects in ontogenetic development, as both are held to originate from common conditioning processes. In other words, if no FP_n effect occurs, neither a FP_{n-1} effect nor a FP_{n-1} x FP_n interaction are to be expected. No interaction was actually obtained but the FP_{n-1} did modulate RTs even in the youngest children considered here. The presence of sequential effects without a FP effect suggests that they have at least partially different functional origins. This makes it unlikely that conditioning mechanisms alone could explain the empirical results of the present study.

There is recent evidence in support of a dual-process interpretation of the FP phenomena. Los and Agter (2005), for instance, obtained changes in the slope of the FP-RT function by contrasting different distributions of FPs within blocks of trials (i.e., uniform, exponential, and peaked). According to a pure conditioning model, the shape of the FP-RT function, obtained under a given distribution of FPs, might be predicted by re-weighting sequential effects as a function of the different frequency of occurrence of the various FP sequences under the other distributions. However, this was shown not to be a critical factor, as re-weighting sequential effects accounted for little variance of the difference between the FP-RT functions obtained in the three distributions, suggesting that processes other than conditioning ones could have been also engaged with the various distributions. As the authors suggested, these critical processes are likely to be intentional ones.

Therefore, the sequential effects found in the youngest children are theoretically relevant. As an alternative to the previous accounts, they can be better explained by assuming an enhancement in arousal following a short FP_{n-1} and a decrease in arousal following a long FP_{n-1}, independently of the current FP_n. It is as if the preparation process benefits if the previous preparation has been maintained for only a short interval, but becomes refractory when preparation has previously been maintained over a long time-interval. This may be because to keep prepared for a long interval is cognitively expensive and exhausts processing resources (see Näätänen, 1971). This account is also supported by the accuracy data of experiment 4. In that experiment, children (especially 4 and 5 years old) were more likely to give a very slow response (i.e., > 1500 ms), or even not to respond, as the FP_{n-1} gets longer, suggesting a long-lasting inhibitory effect of long FPs_{n-1} on the preparation level during the current trial. The fact that a similar pattern of errors was not statistically corroborated in older children and adults may well be attributed to ceiling effects derived by the ease of the task. Moreover, all children performing experiment 4 (i.e., 4-6 years old) were more likely to give anticipated responses as the FP_{n-1} gets shorter, suggesting a facilitation on their preparation level after a short FP_{n-1}. It is notable that the trend in the accuracy data for the youngest groups of the experiment 3a and 3b (sometimes even for older children) goes in the same direction (see Table 2), even if this is not always statistically detectable.

There is recent electrophysiological evidence which may be interpreted in favour of this hypothesis of preparation modulation by the previous FP. Using temporal cueing paradigms with variable FPs on adults, Los and Heslenfeld (2005) found symmetric sequential effects in the Contingent Negative Variation (CNV), a negative ERP component whose amplitude is considered a marker of non-specific preparation and is known to be modulated by arousal level (e.g., Kamijo et al., 2004). Specifically, when the FP_{n-1} was short, the CNV amplitude was tonically greater throughout the FP_n than when the FP_{n-1} was long. Moreover, the effect of FP_{n-1} did not interact with the effect of cueing. In other words, the effect of FP_{n-1} on the CNV was additive with effects of the status of the cue (valid vs. neutral) and of the information provided by a valid cue (short vs. long). Moreover, at least one electrophysiological effect found by Los and Heslenfeld (2005) does not fit the conditioning model of the sequential effects in its first version (Los et al., 2001; Los & van den Heuvel, 2001). According to the conditioning model, there is no reason for the preparation to be lower when a long FP_n follows an equally long FP_{n-1}. In this case reinforcement should act enhancing, and not tonically diminishing, the non-specific preparation reflected by the CNV amplitude. This should be especially the case with a neutral cue condition when the effect of conditioning mechanisms, if present, should be observed more clearly without interfering effects of informative cueing.

The sequential effects observed in older children and adults in the present study and in the literature would seem to require an additional process of endogenous preparation, analogous to that already described by some traditional accounts (e.g., Coull & Nobre, 1998; Miniussi et al., 1999; Niemi & Näätänen, 1981). In a variable FP task, this process checks for the non-occurrence of the imperative stimulus; in this case it uses the increasing conditional probability of the imperative stimulus occurring as time elapses to enhance preparation (Näätänen, 1970). In this way, it would partially compensate for and attenuate the process of tonic arousal modulation producing the sequential effects at longer FPs, thus generating sequential effects asymmetrically biased towards the shortest FPs. With respect to the previous versions of the conditional probability checking account, this explanation emphasizes more the role of this process, by relating it with the sequential effects. On this account, indeed, the conditional probability monitoring, not only determines the FP effect, but does it also by contrasting the negative influence of a previous long FP on RTs.

In an analogous fashion to findings in neurological patients after lesions to the rDLPFC (Stuss et al., 2005), this checking process would be assumed not to work in the youngest children. The reason would be that the rDLPFC region controlling such a process is damaged in right frontal patients and not yet adequately mature in 4 year old children.

However, the occurrence of this endogenous process, although it may attenuate the influence of FP_{n-1} at longer $FPs_{n,}$ does not eliminate such influence. Indeed, in studies employing variable FP paradigms with catch trials (i.e., when no imperative stimulus appears across the trial), RTs at the longest FP_n are slower after a catch trial than after a respond trial (e.g., Correa, et al., 2004; Correa, et al., 2006; Los & Agter, 2005), demonstrating an effect of the events occurring during the preceding trial.

From a broader point of view, the results of the current study may be interpreted in the context of other studies of executive functioning in childhood. There is evidence showing that the executive processes supposed to underlie the tasks at study, and not task difficulty or complexity per se, may explain the developmental dissociations found in children (e.g., Davidson et al., 2006). A prediction derived from the supervisory attention system model (Norman & Shallice, 1986) is that known as age-of-acquisition principle, according to which processes involved in lower-level systems, such as automatic processes (i.e., contention scheduling, in Norman & Shallice’s terminology) are acquired before processes belonging to the higher-level supervisory system (e.g., Shallice, 2004; see also Karmiloff-Smith, 1994; Zelazo et al., 1996), as the latter are mainly localized in the prefrontal cortex, which is known to mature at a slower rate with respect to other portions of the brain (e.g., Delalle, et al., 1997; Huttenlocher & Dabholkar, 1997). On this view, the fact that sequential effects are acquired before the FP effect suggests that underlying processes are more automatic than those involved in the FP effect (see Houdé, Angard, Pillon, & Dubois, 2001, for a similar approach).

In conclusion, the present results suggest that the process of endogenous preparation, thought to produce the FP effect, appears later in cognitive development than the processes underlying the sequential effects. The observation that FP and sequential effects can be dissociated across different ages, both between- and within-subjects, demonstrates that at least partially different processes underlie the two FP phenomena.

2.3. FP phenomena with equal conditional probability for each FP

The results of the developmental experiments already described are useful for understanding the processes underlying the FP phenomena. In particular, they support the hypothesis that the processes underlying the sequential effects consist of automatic influences from the preceding trials (see also Los & van den Heuvel, 2001). On the other hand, the mechanism responsible for the FP effect would appear to work on a higher cognitive level (possibly a strategic one), because it obeys the age-of-acquisition principle typical of SAS processes (Shallice, 2004). Even if evidence provided by the developmental study is useful for discarding single-process accounts, this study does not help explain what specific mechanism causes the FP effect. Nevertheless, other studies in the literature have shed some light on these processes, suggesting that they are likely to be monitoring processes (see Niemi & Näätänen, 1981, for a review; see paragraph 1.2.1.1., chapter 1).

One influential explanation of the FP effect is the strategic account, which basically suggests that non-specific preparation develops in accordance with the conditional probability of IS occurrence (e.g., Elithorn et al., 1955; Jurkowski, Stepp, & Hackley, 2005; Luce, 1986; Näätänen, 1970; Sperling & Dosher, 1986). With a rectangular FP distribution, this conditional probability is low immediately after the warning signal, increases as possible short FPs are bypassed without an IS occurring, and is maximal just prior to the last FP. Under the assumption that increased preparation is reflected by decreased RT, as preparation increases with the lengthening of the FP, RTs become faster giving rise to the classical FP effect.

The manipulation of the FP distribution has effects on the rate of increase of conditional probability of stimulus occurrence during a FP. If one assumes that what is critical for the generation of the FP effect is the process checking for the non-occurrence of the imperative stimulus along the FP, and the consequent increase in subjective expectancy of its forthcoming occurrence as the conditional probability of this event increases (see paragraph 1.2.1.1., chapter 1), then the typical shape of the FP-RT function should be also modified. This seems to be the case (e.g., Baumeister & Joubert, 1969; Los & Agter, 2006).

For instance, if the frequency of the shortest FPs is increased (i.e., positively skewed distribution), the conditional probability of stimulus occurrence is kept constant because the a priori probability of shorter FPs is higher than that of longer ones. Such a priori distribution is called a ‘non-aging’ distribution (Nickerson & Burnham, 1969) because the corresponding subjective FP distribution is supposed to become rectangular (Niemi & Näätänen, 1981). In other words, a high probability of short FPs induces an early expectancy, so that the preparation process is already at its maximum even for short FPs (Zahn & Rosenthal, 1966). As a consequence, a flat FP-RT function is usually observed (e.g., Baumeister & Joubert, 1969; Trillenberg, Verleger, Wascher, Wauschkuhn, & Wessel, 2000). If instead the frequency of the longest FPs is increased (i.e., negatively skewed distribution), a steeper FP-RT function is produced (Baumeister & Joubert, 1969; Griffin et al., 2002; Zahn & Rosenthal, 1966).

An implementation of this procedure is to program the time at which the stimulus may occur according to a Bernoulli process, so that the probability of stimulus occurrence at a given FP is not influenced by what has happened in the preceding FPs. In other words, the FPs employed are distributed according to a negative power (see Näätänen, 1971, for details). In such conditions, the time after the warning stimulus no longer carries any information about the probability of the upcoming stimulus. Experiments using such a paradigm showed that RT either slowly increases or remains constant with increasing FPs (Granjon, Requin, Durup, & Reynard, 1973; Näätänen, 1971; Nickerson & Burnham, 1969). All these results are taken as evidence in favour of the monitoring account of the FP effect (e.g., Näätänen, 1970; Niemi & Näätänen, 1981).

Another method of keeping the conditional probability constant across each FP is to space FP values so that the interval between two consecutive possible FPs is exponentially delayed towards the longest FP in the range. In this way, once more, the conditional probability of stimulus occurrence is non-aging across FPs. The typical result of this paradigm is again a slightly increasing mean RT as FP increases (e.g., Green & Luce, 1971; Hermelin, 1964).

In the following experiment, we tried to further test whether a monitoring process is responsible of the FP effect, in order to corroborate the literature briefly reviewed above. For this reason, we used a procedure in which the imperative stimulus could occur with the same a priori probability at each of two possible FPs within a trial. Moreover, the probability of occurrence of the stimulus at the late FP did not change according to whether it had already occurred at the early FP or not. In other words, IS could appear never, once (during either the short or the long FP), or even twice in a single trial. The rationale of such a paradigm is that monitoring of the conditional probability of stimulus occurrence would be useless here, as this probability is kept constant. Under the assumption that this monitoring process is critical for occurrence of the typical FP effect, the prediction is made the FP-RT function obtained with this procedure will have a nearly flat shape.

The procedure employed in this study is different from that used in previous studies manipulating the conditional probability of stimulus occurrence. The earlier experiments reported here and in the literature showed that the sequential effects are an important factor influencing the RT in variable FP paradigms. Hence, as a secondary aim, the sequential effects produced in this new paradigm were also explored.

2.3.1. Experiment 5

Method

Participants

Fourteen healthy volunteers (9 females and 5 males) took part in the experiment in return for payment. They were 25 years old on average (range = 19-29). Apart from 2 left-handed participants, all the others were right-handed (writing hand). All of them were naïve to the purpose of the experiment.

Apparatus and Materials

An E-prime PST Serial Response Box was used to collect responses. At the beginning of each trial, an auditory warning stimulus (a 1500 Hz pure tone) was presented for 50 ms through speakers. The visual stimuli were presented on a black background. A centrally presented cross (as in the previous experiments), which appeared together with the warning, served as fixation stimulus. The fixation lasted 500 ms and was replaced by a blank screen for other 500 ms. The IS was an arrow (as in the previous experiments). There were 4 equiprobable conditions (see Figure 8):

(i) IS appeared after a short FP of 1000 ms only (present-absent, PA); (1)
(ii) IS appeared after a long FP of 3000 ms only (AP);
(iii) IS appeared twice in a trial, after a short FP of 1000 ms (PP1) and then after a long one of 3000 ms (PP2);
(iv) catch trials: IS never appeared for all the duration of the trial (i.e., 4500 ms; AA).

Whenever the arrow appeared, it then disappeared after 500 ms, and was replaced by the blank until the next event would occur. The time limit for the response was 1500 ms after the arrow onset. Four white circles (visual angle: 1°) presented in each corner of the screen constantly marked the duration of a trial from the warning onset to the end of the second FP (i.e., 4500 ms). An ITI of 1000 ms separated one trial from one other. During the ITI, a blank screen (without the four circles) appeared.

Procedure and Task

Each participant was tested individually in a silent and dimly lit room. Participants viewed a 17” computer monitor at a distance of ~60 cm. A trial started with the central fixation cross, replaced after 500 ms by a blank screen and possibly by 1 or 2 subsequent arrows. Four FP conditions as specified in (1) alternated in a random fashion, on an equal number of trials. The task was to press the middle button (out of 5) of the response box with the index finger of the writing hand as soon as an arrow was seen. There was a short familiarization phase with 8 trials at the beginning of the experiment. Two blocks of 100 trials each (1/4 per each condition) were then administered for the test phase. A short break separated one block from the other.

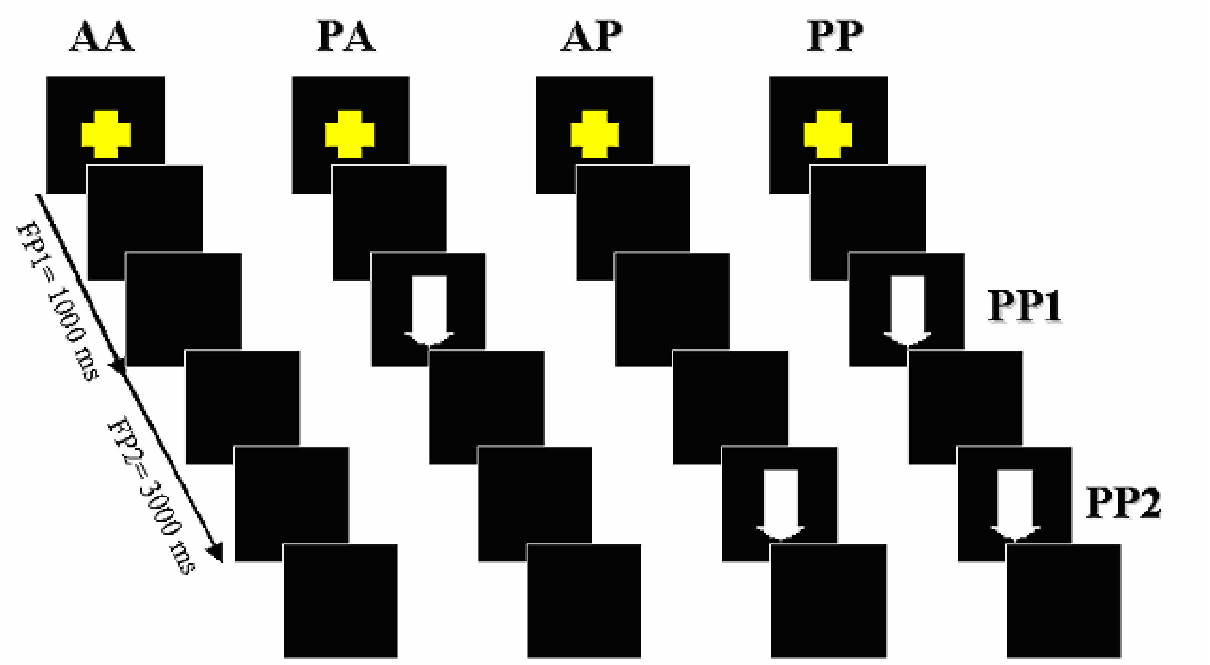

Figure 8. A representation of the 4 possible event flows in each trial of experiment 5 (see text, for details). FP = foreperiod. AA = target absent; AP = target presented after the long FP of 3 sec; PA = target presented after the short FP of 1 sec; PP = repetition trial, with the target presented after both the short and the long FPs; PP = repetition trial where: PP1 indicates the target presented after the short FP and PP2 indicates the target presented after the long FP.

Data Analysis

Trials were treated as errors and discarded from the RT analyses if a response was made during the FP or the first 100 ms after imperative stimulus onset (anticipated responses), if the RT was slower than 1500 ms or absent (delayed and null responses). Four FP_n conditions were included in the design: PA, PP1, AP, PP2 (PP1 and PP2 denote a stimulus presented during a repetition trial PP, in the short FP and in the long one, respectively). However, for the analyses PP1 and PA were collapsed, as they are equivalent from the participant's point of view. The AA condition was not considered among the levels of the variable FP_n because no response was required on that condition. Thus, a 3 FP_n condition (PP1+PA, AP, PP2) x 4 FP_{n-1} condition (AA, PA, AP, PP) repeated measures ANOVA was employed, with RTs as the dependent variable.

Results

Accuracy

Anticipated responses were 1.13% for the short FP and absent for the long one. The low percentage of anticipated responses may be due to the presence of catch trials (e.g., Correa et al., 2006). Delayed responses were 0.69 and 0.38% for the short and the long FPs, respectively. These data were discarded from further analyses.

Reaction Times

Reaction times are displayed in Figure 9. The main effect of the FP_n showed a small tendency [$F(2, 26) = 2.6$, $p = .089$], suggesting that RTs were slightly slower for a PP2 condition than for the other two FP_n conditions. There was a significant effect of the preceding FP_{n-1} condition [$F(3, 39) = 6.4$, $p = .001$], because RTs were faster after a PP condition than after all the other conditions, as demonstrated by a t-test contrasting RTs in the PP condition with the average of the three other conditions ($p < .01$). Moreover, the FP_n x FP_{n-1} interaction was significant [$F(6, 78) = 9.4$, $p <.001$]. Post-hoc Tukey tests revealed that responding to the current PP1+PA conditions was slower after an AP condition than after PA and PP conditions (for both, $p < .05$). Noteworthy, this effect resembles the classical sequential effects on the short FP. Moreover, responding to a current PP2 condition was faster after a PP condition than after all the other conditions (for all, $p < .001$).

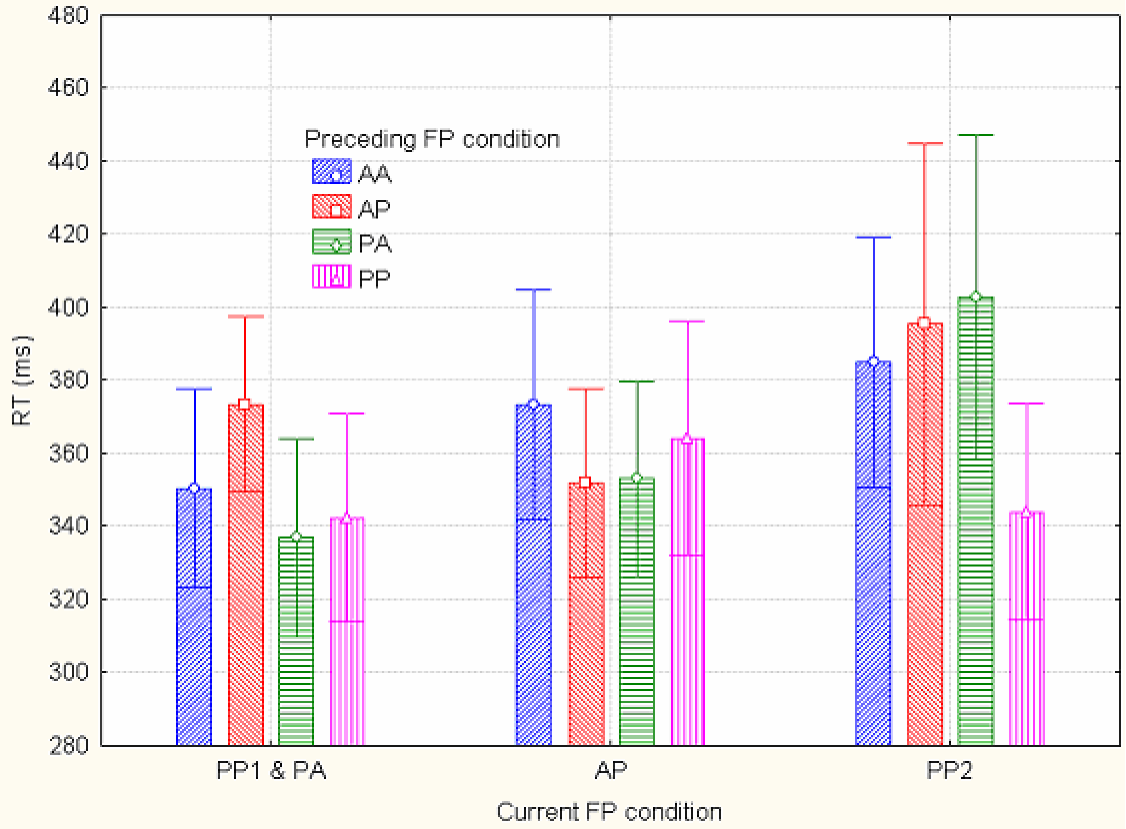

Figure 9. Mean reaction times as a function of the current FP condition (x-axis) and preceding FP condition (histograms) in Experiment 5. Vertical lines indicate confidence intervals. Labels as in figure 8.

Discussion

The current experiment replicates results known from the literature with respect to the disappearance of the FP effect when the conditional probability of stimulus occurrence is kept constant across the trials (e.g., Baumeister & Joubert, 1969; Näätänen, 1971; Nickerson & Burnham, 1969). This pattern demonstrates once again that the conditional probability of stimulus occurrence is a critical variable for the FP effect. With a rectangular FP distribution, a monitoring process is supposed to operate, which checks the conditional probability of stimulus occurrence as time elapses, so as to increase the level of preparation and to produce the FP effect (e.g., Näätänen, 1970). If the conditional probability is kept constant, the process cannot be effective, leading to the disappearance of the FP effect as observed here and elsewhere (Granjon et al., 1973; Green et al., 1971; Hermelin, 1964; Näätänen, 1971; Nickerson et al., 1969).

Moreover, a new effect has been found in this study as far as the sequential effects are concerned. This consists of a RT cost paid when the current FP condition is a repetition of the target stimulus in the 2 possible FPs within the same trials (PP2 condition). This effect is however abolished if a PP condition has just occurred in the preceding trial, as RTs are faster in this condition with respect to conditions in which a single target or a catch trial has been presented.

A phenomenon which could be a candidate for an analogy with the repetition costs found here is the attentional inhibition of return (Posner & Cohen, 1984), even if the theoretical backgrounds are very different. RTs to targets appearing at previously (>300 ms) attended locations are longer than to targets appearing at new locations. However, inhibition of return manifests itself with exogenous (e.g., peripheral) cueing of spatial attention, and it is usually reported as a phenomenon of shifting attention (e.g., Hooge, Over, van Wezel, & Frens, 2005), whereas here spatial attention if kept constant on the fovea.

A further possible explanation could be derived from the reasoning literature. The cognitive system is held to use inferential processes in order to keep representations isomorphic with environmental contingencies (Newell, 1990). In our paradigm, a repetition of targets within a single trial is a relatively infrequent phenomenon, as it occurs in only ¼ of the trials. In such a situation, the inferential system was not prepared to expect a repetition of targets, so that a slowing in the response is observed as a consequence of this ‘surprise effect’ (see Cherubini, Burigo, & Bricolo, 2006, for somewhat similar RT repetition costs with visuo-spatial and numerical material). Only when a PP condition has just occurred on the previous trial, the surprise effect is suppressed, as if the inferential system temporarily becomes more aware of the possibility that a repetition event may occur. To test this hypothesis, one could increase the probability of occurrence of a repetition trial. If this probability is a critical factor, one should observe a decrease of the costs along with the increasing probability. Therefore, the interpretation of the repetition costs is worthwhile being addressed by further ad hoc studies.

A possible criticism of the novelty of this paradigm could be that it resembles paradigms employing positively skewed FP distributions. Indeed, when a repetition trial occurs, it is as if there are two relatively short FPs which are occurring one after the other, so increasing the conditional probability of stimulus occurrence at short FPs. However, in order to avoid this problem, each trial was marked by circles appearing after the ITI in the four corners of the screen. With such trial markers, it is more likely that each target in a repetition trial is perceived as occurring in the short or in the long FP of that precise trial.

In conclusion, this study supports accounts of the FP effect concerning monitoring of the conditional probability of stimulus occurrence, as it shows that keeping it constant within the trial, the FP effect is nullified. The pattern of sequential effects in repetition trials represents another key finding of this study, which is worthwhile to be investigated in more detail by future studies.

2.4. A functional dissociation between the FP and the sequential effects

In the developmental study (experiments 3a, 3b and 4), a dissociation between the FP effect and the sequential effects has been obtained in children. In the present study, a different approach has been adopted in order to test whether the FP and the sequential effects can also be dissociated in healthy adults. The basic variable FP paradigm has been modified by embedding a spatial n-back task, with the following rationale.

In the developmental study, a dual-process model of the FP phenomena has been put forward. On this model, the sequential effects are held to be more automatic than the FP effect. If this is the case, then interference by a secondary task, obtained by increasing the working memory load in the n-back paradigm, should modulate the FP effect and should not alter the sequential effects (cf. Shiffrin & Schneider, 1977a; see paragraph 1.1.1., chapter 1).

A relationship was expected between the magnitude of the FP effect and the working memory load. First, the hypothesis that the FP effect should interfere with the n-back condition is anatomically plausible. In the n-back paradigm load-sensitive activity has been found in the rDLPFC (Casey et al., 1998; see also Braver et al., 1997; Jansma, Ramsey, Coppola, & Kahn, 2000). The rDLPFC seems also to be involved in the FP effect (Stuss et al., 2005).

Moreover, from a cognitive point of view, the relationship between size of the FP effect and the n-back condition could take one of two opposite directions. The FP effect could decrease if similar (monitoring) processes are responsible for the performance on the n-back task and for the speeding up of the RTs on the longest FP_n. In contrast, the size of the FP effect could be expected to increase if the optimal preparation level reached in the longest FP_n can be used cognitively to carry over the processes underlying the spatial n-back task, on the one hand, whereas the effort to reach this preparation level on the shortest FP_n does not allow the efficient completion of the n-back task in such a short time, on the other hand.

A reason for choosing the spatial n-back paradigm was to manipulate working memory load without altering the general response preparation level according to the conditions of this task. In contrast to other non-spatial variants of the n-back task, only in the spatial version of the task error rate is a measure of workload or performance. On the other hand, RTs remain constant because in all levels, except for the 0-back level, participants know what the next response will be before the next IS is presented, as it is determined by preceding stimuli (e.g., Gevins & Cutillo, 1993; see Procedure and Task). This choice was made in order to avoid difficulty in the interpretation of possible effects on RT.

2.4.1. Experiment 6

Method

Participants

Fifteen healthy volunteers (8 females and 7 males) took part in the experiment in return for payment. They were 26 years old on average (range = 20-35). Apart from one left-handed participant, all the others were right-handed (writing hand). All of them were naïve to the purpose of the experiment.

Apparatus and Materials

Participants viewed the screen at a distance of about 60 cm. There were four possible positions where the IS could appear (see Figure 10). These positions were marked by 4 white squares (each side: 3.5 cm) placed horizontally in the middle of the screen at a distance of 2 cm from each other. The extreme sides of the leftmost and rightmost squares were 10 cm distant from the center. A central fixation cross (each bar: 1 cm) and the 4 squares remained in a black background during all the trials. Layout of the four response-keys (from left to right: the keys ‘V’, ‘B’, ‘N’, and ‘M’ of the computer keyboard) corresponded spatially to the four possible positions in which the IS could appear. The IS was a white circle (diameter: 1.5 cm, thickness: 0.3 cm) appearing in the center of one of the squares.

Procedure and Task

A trial started with the 4 white squares and the fixation cross on a black background. After the FP elapsed (FPs: 1000 vs. 2000 ms, random presentation), a circle was displayed randomly but equiprobably in the middle of one of the 4 squares, provided that the position of the circle was not repeated at least before 1, 2 or 3 trials in the 0-, 1- and 2-back conditions, respectively.

The instruction of the spatial n-back task (3 levels: 0-, 1- and 2-back) were as follows (see Figure 10). In all the n-back conditions the task was to press one of the 4 keys spatially corresponding to the location of the circle in a given trial. More specifically, participants had to press the key corresponding to the spatial position occupied by the circle on the current trial n, on the preceding trial n-1, and on the trial n-2, in the 0-, 1-, and 2-back conditions, respectively.

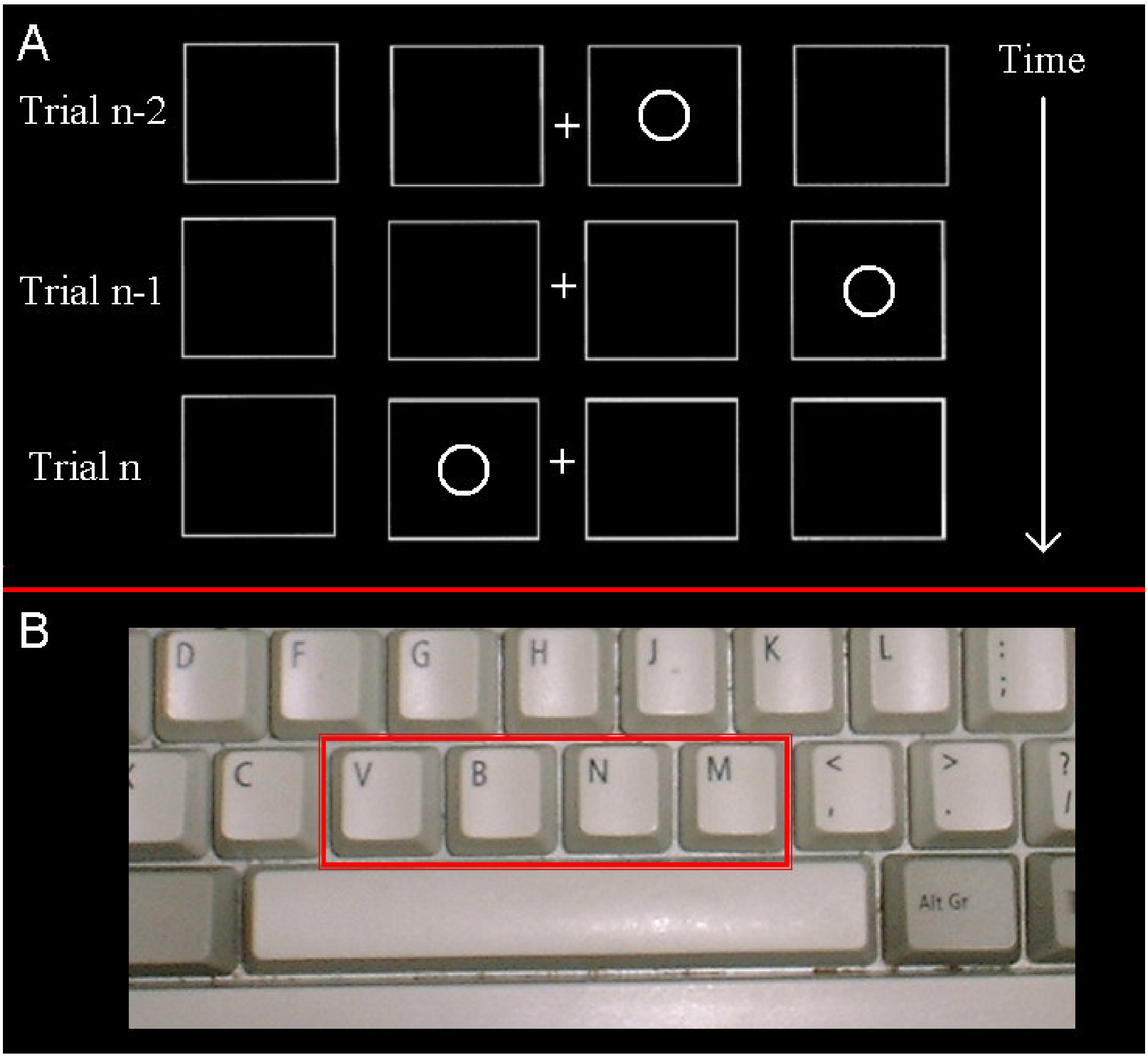

Figure 10. Illustration of the spatial n-back paradigm (Panel A). In this paradigm, a circle was randomly presented in one of four adjacent box locations. Participants were required to perform a spatial compatibility task. The possible keys used for the response were, from left to right, the letters ‘V’, ‘B’, ‘N’ and ‘M’, from the computer keyboard (Panel B). With a 0-back condition, the response should have been as follows. Trial n-2: ‘N’, trial n-1: ‘M’, trial n: ‘B’. With a 1-back condition, participants should respond by pressing ‘N’ on the trial n-1, and ‘M’ on the trial n (according to the position occupied by the circle on the trial before). With a 2-back condition, participants had to press ‘N’ on trial n (according to the position occupied by the circle on the trial n-2).

All participants were instructed to maintain their gaze at the fixation cross on the middle of the screen during performance of the task. A trial ended with the participant’s keypress or after 2000 ms had elapsed without response. No response was required on the first trial for the 1-back condition, and on the first 2 trials for the 2-back condition.

Each n-back condition consisted of a block of 164 trials. A practice phase of 10 trials was administered before each test block. The order of presentation of the 3 n-back conditions was counterbalanced across participants.

Data Analysis

Trials with the RT outside the 100-1500 ms range and with anticipated responses (viz. ones occurring before the IS) were discarded from further analyses. In addition, the first 1, 2 or 3 trials of each block were eliminated for the 0-, 1- and 2-back conditions, respectively. For the RT analysis, also errors were discarded. For both mean RTs and accuracy analyses, a 3x2x2 within-subject ANOVA was employed with n-back condition (0-back, 1-back, 2-back), FP_n (1000 vs 2000 ms)[6] and FP_{n-1} (1000 vs 2000 ms) as the independent variables.

Results

Accuracy

The only significant effect concerning the accuracy was the main effect of n-back condition [$F(2, 28) = 5.9$, $p < .01$]. As planned comparisons showed, accuracy was lower for the 2-back condition than for the 0- and for 1-back conditions ($p < .01$ and $p < .05$, respectively), with no difference between the 0- and 1-back conditions.

Reaction Times

Mean RTs are displayed in the Figure 11. The main effect of n-back condition was significant [$F(2, 28) = 8.8$, $p < .01$]. Post hoc tests were not significant. Less conservative paired t-tests showed that mean RT was faster for the 1-back condition than for the 0-back ($p < .05$) and for the 1-back condition than for the 2-back one ($p < .01$). The main effect of the FP_n [$F(1, 14) = 46.3$, $p < .001$] was due to RT being slower on a short FP_n than on a long one. The effect of the FP_{n-1} [$F(1, 14) = 10.2$, $p < .01$] indicated that mean RT was faster after a short FP_{n-1} than after a long one. The classical FP_n x FP_{n-1} interaction was also significant [$F(1, 14) = 18.3$, $p < .001$]. For the short FP_n, RT was slower after a long FP_{n-1}

---

[6] Only two FPs were employed here. Medium FPs have been previously included in order to explore gradient effects in the RT function. Thus, medium FPs were not included as they were not relevant for the aim of the present study.

than after a short one (planned comparison, $p < 001$). As expected, this sequential effect was asymmetric as it was not observed for the long FP_n.

Critically there was a significant FP_n x n-back condition interaction [$F(2, 28) = 21.9$, $p < .001$]. Post-hoc Tukey comparisons demonstrated that RT on the short FP_n was slower for the 2-back condition than for the 0- and 1-back conditions (for both, $p < .001$). Moreover, RT on the long FP_n was slower on the 0- and the 2-back conditions than on the 1-back condition (for both, $p \geq .01$). Interestingly, the FP effect (i.e., the difference between the short FP_n and the long one) was present for the 1- and 2-back conditions (for both, $p < .01$) and virtually absent for the 0-back condition ($p = .89$).

No other effect was significant. In particular, the sequential effects were not modulated by the n-back condition (n-back condition x FP_{n-1}, $p = .53$; n-back condition x FP_n x FP_{n-1}, $p = .13$).

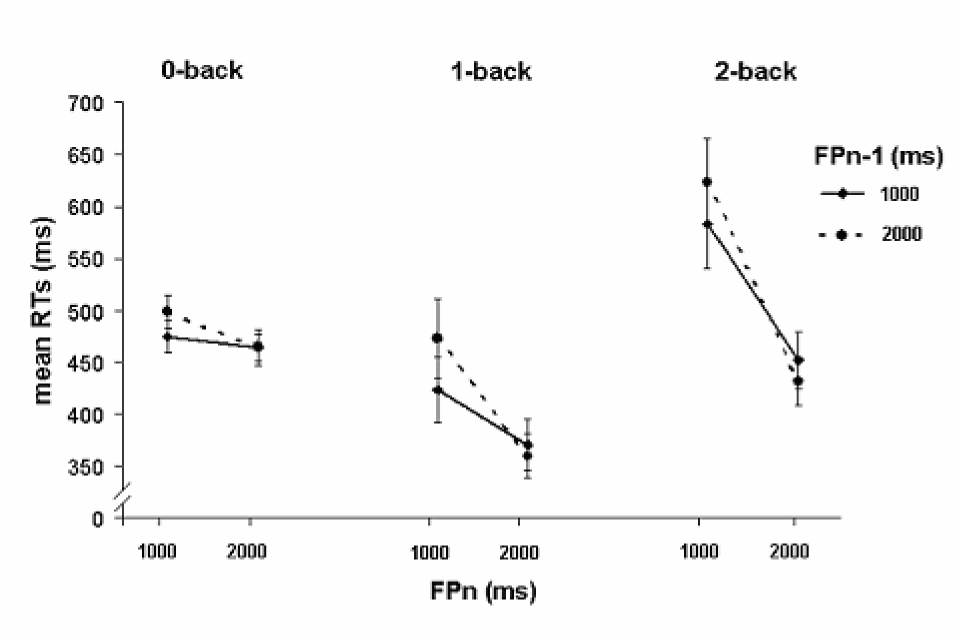

Figure 11. Mean reaction times as a function of the current FPn (x-axis), the preceding FPn-1 (lines), and the n-back condition (panels) in Experiment 6. Vertical lines indicate standard errors of the mean.

Discussion

Contrary to other studies using the spatial n-back task (e.g., Gevins & Cutillo, 1993), in this experiment we obtained a modulation of basic RTs by the n-back condition: RTs were slower in the 2-back condition than in the other 2 conditions. This may be due to the embedment of this task in a variable FP paradigm, which may have made the task more difficult, especially for the 2-back condition. This could be taken as a suggestion that the processes underlying the FP phenomena interfere with those underlying the spatial n-back task. This is anatomically plausible, given that both are known to involve the same brain area, namely the rDLPFC.

The absence of FP effect for the 0-back condition was not predicted. It could however be tentatively interpreted as due to the difficulty of the response selection stage in a 4-choice RT task, which may have absorbed the advantage of being more prepared on the long FP in the stage preceding IS onset. Additionally, participants may have decided not to prepare optimally during the longest FP in order to avoid the execution of wrong responses.

More relevant for the purposes of the study, the FP effect was modulated by the task demands as it increased more with the working memory load. The influence of the n-back condition on the FP effect manifests itself mainly by increasing RTs on the short FP in the 2-back condition with respect to the other two conditions. This result may be interpreted as an indication that, in a variable FP paradigm, reaching an appropriate level of preparation on the short FP is demanding, especially in a situation where processing resources have to be devoted to another challenging process.

More critically, a dissociation has been found between the FP and the sequential effects. As already discussed, the FP effect was modulated by the n-back condition, whereas the sequential effects remained constant independently of the n-back condition. This pattern of results confirms that sequential effects are a robust phenomenon, as they remain virtually unchanged independently of task demands. This can be also taken as evidence of the unintentional nature of processes underlying them (cf., Los & van den Heuvel, 2001). Moreover, this finding demonstrates once again that processes underlying FP and sequential effects are not the same, and they are dissociable not only ontogenetically (see experiments 3a, 3b and 4) but also functionally in adult participants.

Chapter 3

In the previous chapter, processes underlying the FP effect and the sequential effects have been investigated in detail. Evidence provided both in chapter 2 and in the literature suggests a dual-process account: an automatic priming effect from the FP occurring on the previous trial seems to be the basis for the sequential effects of the FP, whereas a process monitoring the conditional probability of stimulus onset on the current trial seems more appropriate to account for the occurrence of the FP effect.

Besides of an enduring interest of cognitive psychology in investigating the nature of the processes underlying preparation over time (e.g., Correa et al., 2006; Los & van den Heuvel, 2001; Los & Agter, 2005; Niemi & Näätänen, 1981), there is a renewed interest in elucidating which brain areas may be responsible for such processes (e.g., Coull & Nobre, 1998; Janssen & Shadlen, 2005; Lewis & Miall, 2003a; Stuss et al., 2005).

The aim of the studies reported in the current chapter is twofold. A first purpose is to contribute to the investigation of the brain sources of preparation over time. A second aim is to further corroborate the dual-process account by means of neuropsychological tools. Neuropsychological dissociations found on the behavioural level can be taken as a proof for the existence of different processes underlying overt performance (e.g., Shallice, 1988). Evidence from both healthy participants undergoing TMS, as a technique to transiently interfere with localized neural activity (experiments 7 and 8), and tumor patients, undergoing a surgical removal of the tumoral brain tissue (experiment 9), will be used to infer the nature of the processes responsible of the FP phenomena produced during the performance of a variable FP task. A more general aim of these studies is to test directly the viability of the fractionation approach in the study of PFC functionality (e.g., Stuss et al., 2005) as opposed to the equipotentiality approach (e.g., Duncan, 2005), by using TMS and neuropsychology as tools to achieve the localization of functions within PFC.

3.1. Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation

As shown in a recent neuropsychological study (Stuss et al., 2005, paragraph 1.1.2.3., chapter 1), patients with lesions in the rDLPFC fail to show the typical FP effect, unlike both control participants and other subgroups of prefrontal patients. Stuss and colleagues suggest that the rDLPFC is likely to be the region responsible for the strategic process producing the FP effect, which controls the state of preparedness by checking the conditional probability of IS occurrence. This account fits a range of studies which attribute a monitoring role to the rDLPFC (Coull et al., 1998; see Fletcher & Henson, 2001; Shallice, 2004, for reviews). Unfortunately, the sequential effects were not considered in Stuss and colleagues' (2005) study. Hence, without an additional investigation of the sequential effects produced by the patients, the lack of FP effect shown can alternatively be interpreted as a failure in the conditioning processes, according to the conditioning view (Los & van den Heuvel, 2001).

The aim of the present study is twofold, concerning both the anatomical and the functional bases of the FP phenomena. From an anatomical point of view, the aim was to investigate whether the neuropsychological results (Stuss et al., 2005) could be reproduced in healthy adults by means of TMS. In addition, however, the study could allow one to establish the role of the rDLPFC not only in the FP effect, but also with respect to the sequential effects, which have not been investigated neuropsychologically. In addition, the role of the right angular gyrus (AG) in the FP phenomena was investigated here, since this area is often associated with temporal processing found in fMRI and TMS studies (Coull et al., 1998; Rao, Mayer, & Harrington, 2001; Lewis & Miall, 2003a; Alexander, Cowey, & Walsh, 2005). It can be argued that these studies utilize tasks which require explicit time processing while the time processing required in a FP paradigm is implicit. However, a recent study has also demonstrated anticipatory activity revealing an internal representation of both elapsed time and the probability of the stimulus occurrence in the macaque parietal lobe during an implicit time processing task similar to the variable FP paradigm (Janssen & Shadlen, 2005; see also Onoe et al., 2001).

From the functional point of view, TMS can provide a strong test of the various cognitive models of the FP phenomena. If both the FP and the sequential effects are influenced by the TMS on rDLPFC, a common mechanism is likely to underlie them, as predicted by the conditioning view (e.g., Los et al., 2001). If instead the FP effect only is modulated by the TMS on this area, this would be evidence for a dual-process theory of the FP phenomena (see paragraph 2.2., chapter 2). In order to test these possibilities, 2 experiments were designed with a simple and a choice RT task (experiments 7 and 8, respectively) and a theta burst stimulation (TBS) off-line paradigm of repetitive TMS, which has been demonstrated to transiently reduce cortical activity in the stimulated area (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Moreover, the range of FPs used in Stuss and colleagues' (2005) study (i.e., 3-7 seconds), might suggest the alternative explanation of a deficit of the vigilance system in maintaining attention over a long period of time, instead of a monitoring process, in the case of right prefrontal lesions. For this reason, a much shorter FP range was used (i.e., 0.5, 1 and 1.5 sec), to discard vigilance-related accounts of a possible modulation of the FP effect.

3.1.1. Experiment 7

In experiment 7 a simple RT task was used in order to study the FP phenomena in their simplest form. For this purpose, a range of FPs (i.e. 0.5, 1.0 and 1.5 sec) was employed in a standard variable FP paradigm. A repetitive TMS paradigm was adopted to investigate the role of the rDLPFC in the FP phenomena. In order to control the specificity of any effect obtained to the rDLPFC, two additional areas were stimulated during different sessions, namely a site in the left DLPFC and another in the right AG.

Method

Participants

Nine volunteer participants, 3 females and 6 males, took part in the experiment. They were 31 years old on average (range = 24-43). All of them were right-handed with an average score of 92 on the Edinburgh Handedness Inventory (EHI, Oldfield 1971). All had normal or corrected-to-normal vision, and no auditory or neurological impairment. This study was approved by the UCL Committee on the Ethics of Human Research.

Apparatus and Materials

The experiment was conducted on a PC. Stimuli were presented on a 19” monitor with a 100-Hz refresh rate. Participants viewed the display at a distance of about 60 cm from the centre of the monitor, with the index finger of their dominant hand resting on the keyboard spacebar. Stimuli were the same as those used in the experiment 1 (paragraph 2.1.1. chapter 2). Two blocks were presented during each session to each participant, one before and the other after TMS. In each block, 3 FPs of 0.5, 1.0 and 1.5 sec, respectively, were presented for an equal number of trials (i.e. 48 trials each), randomly drawn from a rectangular probability distribution. Each FP was preceded with the same probability by a FP of 0.5, 1.0 and 1.5 sec.

Procedure and Task

Figure 11 displays the hierarchical organization of the experiment 7. The experiment consisted of 3 sessions performed in 3 different days within one week, one for each area stimulated (see below). Each session consisted of 2 blocks of 144 trials each. The first block was run before the TMS to measure the baseline performance. The second block was run after the TMS to measure its effects on the behavioural performance. Experiments 1 and 2 (chapter 2) have shown that the learning period for the FP phenomena, if any, is very brief, as after an initial block of 60 trials the FP and sequential effects are already present with the same magnitude as in subsequent blocks. For this reason, we could be confident that the performance of the baseline block would not influence the performance on the post-TMS block.

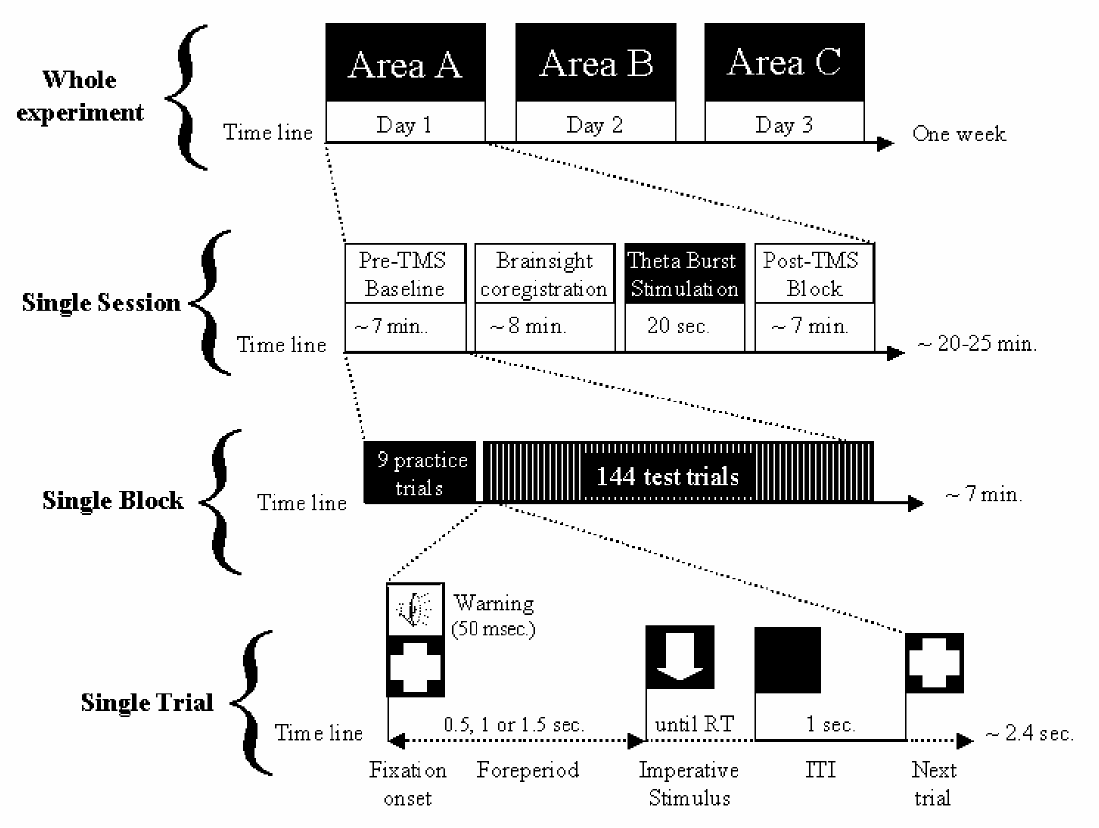

Figure 1. Hierarchical organization of experiment 7. See the Method section for details.

Participants were tested individually in a silent and dimly lit room. They received written instructions explaining the simple RT task. Within each block, the procedure and task were the same as in the experiment 1 (chapter 2). Nine practice trials were given at the beginning of the test. An experimental session lasted about 25 minutes each day (i.e., 6-7 minutes per block plus some minutes after the baseline block needed to find the site coordinates in the brain).

TMS protocol

Locations for TMS were determined using the Brainsight TMS-MRI co-registration system (Rogue Research, Montreal, Canada), through conversion of the MNI stereotaxic coordinates to participant's normalised brain using the software SPM2. For each session, participants underwent the co-registration in the interval between the 2 pre- and post-TMS blocks, in order to find the coordinates of the area of interest in their real brain. These coordinates were taken from an fMRI study by Lewis and Miall (2003b), in which activation of the right and left DLPFC and of the right AG was found during a temporal discrimination task for both sub- and supra-second intervals. For each participant and session, one area was stimulated after the performance of the pre-TMS baseline block. The areas to be stimulated were located in the rDLPFC (MNI stereotaxic coordinates: 48, 42, 24), in a control area on the left DLPFC (the mirrored contralateral site, i.e., -48, 42, 24) and in the right AG (48, -45, 48), respectively (see Figure 12). The order in which the 3 areas were stimulated was counterbalanced across participants, such that each area was stimulated in the first day session on an equal number of participants.

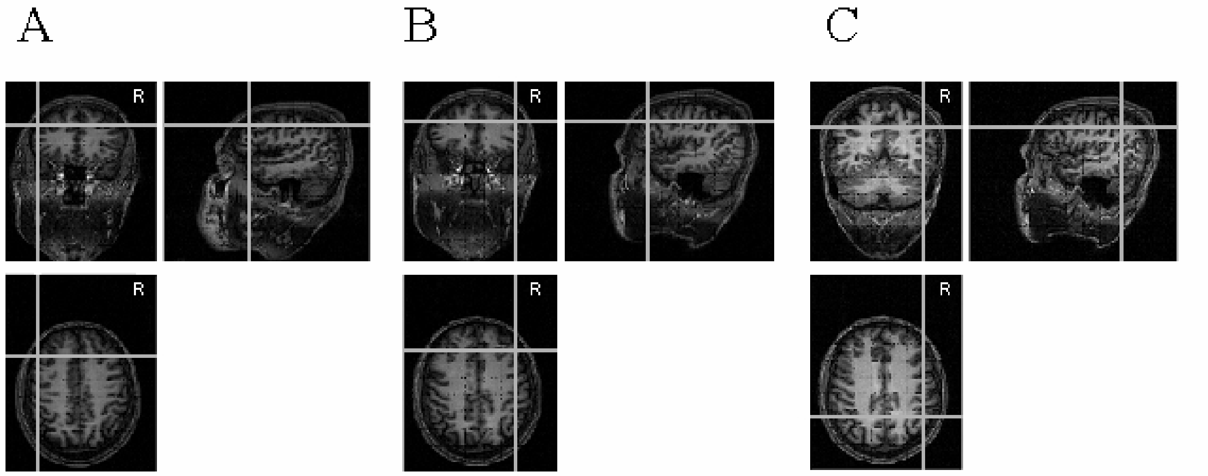

Figure 12. Brainsight localizations showing stimulation sites of the brain of a single participant, identified in co-registration with the TMS coil position. Panels A, B and C show the targeted sites in the right DLPFC, left DLPFC and right AG, respectively. In each panel, the regions in the crosshairs of the coronal, sagittal and axial views are based on the coordinates reported in Lewis and Miall (2003b) (48, 42, 24 for the right DLPFC; the mirrored contralateral coordinates -48, 42 24 for the left DLPFC; 48 -45 48 for the right AG).

Participants wore a latex swimming cap on which the location found in the co-registration procedure was marked with a phosphorescent spot. Stimulation was produced through a MagStim Super Rapid stimulator with 4 external boosters with a maximum output of approximately 2 Tesla (MagStim, Whitland, UK). A figure-of-eight 50-mm coil was used for the stimulation with the center of the coil positioned over the marked spot such that the windings were at 90° to the scalp and the handle pointed vertically.

An offline TMS paradigm was chosen rather than an on-line one to prevent any exogenous influence of the sound and the proprioceptive sensation given by the TMS on the RTs (e.g., Terao et al., 1997) and hence on the FP phenomena. In each session, the TMS parameters were those of the continuous TBS, consisting of a burst of 3 pulses at 50 Hz (i.e., 20 ms between each stimulus), which was repeated at intervals of 200 ms for 20 seconds (giving a total of 300 pulses). The output strength of the TMS was set to 80% of the participant’s active motor threshold, defined as the minimal intensity of stimulation capable of inducing a visible twitch of the contralateral first dorsal interosseus in at least 6 trials out of 10, by means of a single pulse delivered at the best scalp position over motor cortex. During the calculation of the active motor threshold, the participant’s dominant hand was in a moderately contracted position and the thumb and index fingers were in opposition. Previous studies (Di Lazzaro et al., 2005; Huang et al., 2005) have demonstrated that this TBS protocol temporarily produces reduced excitability of motor cortex outlasting the period of actual TMS. With 20 seconds stimulation, the time window of reduced excitability was estimated to last up to 20 minutes (see also paragraph 6.3., chapter 6).

Data Analysis

Trials on which the RT was outside the 100-1000 ms range and trials where anticipated responses were made (viz. ones occurring before the IS) were discarded from further analyses. In addition, the first trial of each block was eliminated. Mean RTs for each participant and condition were analysed by repeated-measures ANOVAs.

As a first step, three separate repeated-measures ANOVAs have been conducted contrasting baseline against post-TMS blocks separately for each site stimulated during each session (right DLPFC, left DLPFC, right AG). The within-subject independent variables considered in these preliminary analyses included FP on the current trial (FP_n = 0.5, 1.0 and 1.5 sec), FP on the preceding trial *n-1* (FP_{n-1}) and the TMS block (baseline vs post-TMS). The dependent measure was the mean RT.

In order to investigate differences across TMS sessions, a subsequent overall repeated-measures ANOVA was then performed with FP_n, FP_{n-1}, and TMS site (right DLPFC, left DLPFC and right AG) as the within-subjects variables. The dependent variable chosen in this overall ANOVA was the degree of change in mean RTs as a result of stimulation at each site compared with the mean RTs of the pre-TMS baseline block of the same session (with 100% representing no RT change, a value >100% representing a slowing down, and one <100% indicating a speeding up)[7].

For the significant effects, post-hoc Tukey honestly significant difference comparisons were performed, in order to see which comparisons accounted for the effects. An effect was defined as significant if its corresponding α-level was below .05. The F-test was adjusted by the Greenhouse-Geisser ε correction when the Mauchley sphericity test was significant.

Results

The first trial of each block (0.7 %), trials involving anticipated responses (RT before IS onset: 1.9 %), trials involving premature responses (RT < 100 ms: 0.5 %), and trials with delayed responses (RT > 1000 ms) or without responses (0.03 %), were discarded from further analyses. Fewer than 3.2 % of trials were excluded, with no difference across conditions.

Behavioural Results

The FP and sequential results were produced as expected. The following effects were significant in ANOVAs conducted on the 3 sessions separately (see Figure 13). First, the main effect of FP_n was obtained [$F(2, 16) = 28.7$, $p < .001$; $F(1.1, 9.1) = 40.1$, *Adj.* $p < .001$; $F(2, 16) = 34.1$, $p < .001$, for right DLPFC, left DLPFC and right AG, respectively]. Post-hoc Tukey HSD comparisons showed that RTs were slowest for the shortest FP of 0.5 sec as compared to the medium and longest FPs (for all, $p < .001$), but there was no difference between the RTs for FPs of 1.0 and 1.5 sec in any session. The main effect of

---

[7] We chose this dependent variable as it directly estimates the direction of any change of the post-TMS RTs with respect to the baseline RTs (i.e., slowing or speeding). However, alternative ANOVAs were also conducted on the raw RTs, with FP_n, FP_{n-1}, TMS site (right and left DLPFC and right AG) and block (baseline and post-TMS block in experiment 7; baseline, first and second post-TMS blocks in experiment 8). These ANOVAs gave exactly the same results as those reported here, in both experiments. Specifically, the FP_n x TMS site x block interaction was significant [$F(4, 32)=3.4$, $p < .05$; $F(8, 64) = 2.3$, $p < .05$, for the experiments 7 and 8, respectively], confirming the selective reduction of the FP effect after stimulation of the right DLPFC.

FP_{n-1} also reached significance [$F(1.1, 8.8) = 5.5$, *Adj.* $p < .05$; $F(1.2, 9.9) = 15.3$, *Adj.* $p < .01$; $F(1.3, 10.1) = 17.2$, *Adj.* $p = .001$, for right DLPFC, left DLPFC and right AG, respectively]. The post-hoc comparisons showed that current RTs were slower following a longest FP_{n-1} trial than a shortest FP_{n-1} trial (for all, $p \leq .01$). The FP_n x FP_{n-1} interaction, concerning asymmetry of sequential effects, was also significant [$F(4, 32) = 23.6$, $p < .001$; $F(4, 32) = 11.4$, $p < .001$; $F(2.4, 19.6) = 6.5$, *Adj.* $p < .01$, for right DLPFC, left DLPFC and right AG, respectively]. This effect was primarily due to the differential contribution of the FP_{n-1} to the RT at each of the 3 current FPs, being greatest for the shortest FP_n and smallest, virtually absent, for the longest FP_n, as confirmed by post-hoc comparisons.

TMS effects: separate ANOVAs for each TMS site

No TMS block main effect was observed for any site of stimulation, indicating that RTs were not non-specifically modified by the TBS. More critically, the TMS block x FP_n interaction was significant only for the right DLPFC session [$F(2, 16) = 7.2$, $p < .01$], indicating that the FP effect was reduced in the post-TMS block as compared with the baseline block during the right DLPFC session. This conclusion was corroborated contrasting the RT difference between the shortest and the longest FP_n in the baseline block (43 ms) and the same RT difference in the post-TMS (26 ms) by means of planned comparisons ($p < .001$). In addition, there was a tendency for a TMS x FP_{n-1} interaction in the right DLPFC session [$F(2, 16) = 3.5$, $p = .054$], suggesting that the effect of the FP_{n-1} was slightly reduced after TMS with respect to the baseline block. However, the TMS block x FP_n x FP_{n-1} three-way interaction was not significant in any session (for all, $p > .3$), indicating that the sequential effects were not significantly modulated by the TMS.

TMS effects: overall ANOVA

The only significant effect obtained in the overall ANOVA was the interaction between TMS site and FP_n [$F(4, 32) = 2.8$, $p < .05$], indicating that the FP effect was selectively modulated after TMS over the right DLPFC (see Figure 14). In this case only, indeed, the RTs on the longest FP_n were slower with respect to the baseline (104%) while the RTs on the shortest FP_n were faster (97%), the difference between these two values being significant following post-hoc Tukey comparisons ($p < .01$). It is noteworthy that this modulation goes in the opposite direction with respect to the FP effect itself, slowing RTs down on the longest FP_n and speeding them up on the shortest FP_n. Notably, no TMS modulation was found for the sequential effects, as indicated by the lack of significance for the TMS site x FP_n x FP_{n-1} three-way interaction (p = .45).

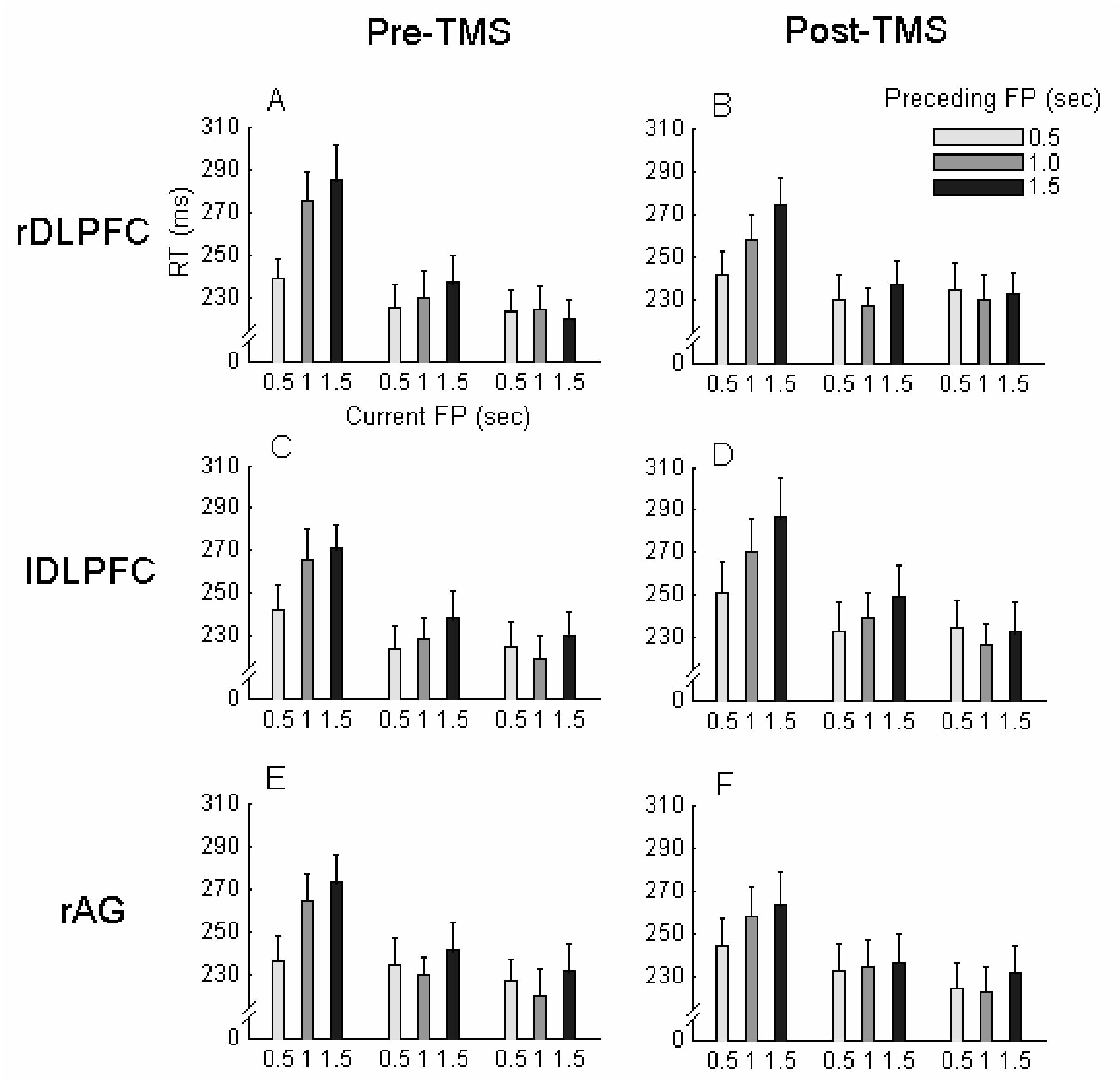

Figure 13. Mean RTs (and standard errors) in experiment 7, as a function of FP on the current trial (x-axis), FP on the preceding trial (parameter), and experimental block (panels). Panels A, C and E refer to the baseline blocks before TMS on the right DLPFC, left DLPFC and right AG, respectively. Panels B, D and F refer to the blocks after TMS on the right DLPFC, left DLPFC and right AG, respectively.

Discussion

The FP effect and the asymmetric sequential effects, usually found in a variable FP paradigm, were replicated in experiment 7. Moreover, a role of the right DLPFC was demonstrated for the FP effect. Following TMS over the left DLPFC and the right AG, no significant changes were observed with respect to the baseline. On the other hand, after

TMS over the right DLPFC, a reduction in the FP effect was observed, confirming the role of this area in the occurrence of this effect, as already shown by a recent neuropsychological study (Stuss et al., 2005). This result is interesting per se but cannot be used to corroborate any dual-process model of the FP phenomena. A dissociation between the FP and the sequential effects was not clearly obtained in this experiment, because the effect of the FP_{n-1} also showed a tendency towards being reduced after the TMS over the right DLPFC, even if the critical FP_n x FP_{n-1} x TMS interaction was far from significance.

As the reduction of the cortical excitability of the motor cortex reaches a maximum from 7 to 14 min after TBS (Di Lazzaro et al., 2005; Huang et al., 2005), a similar time course can be expected in the case of the right DLPFC. For this reason, in the second experiment two blocks of trials were performed by participants in order to cover, apart from an initial 6 min period similar to experiment 7, an additional subsequent period when the stimulation effects are supposed to be at their greatest.

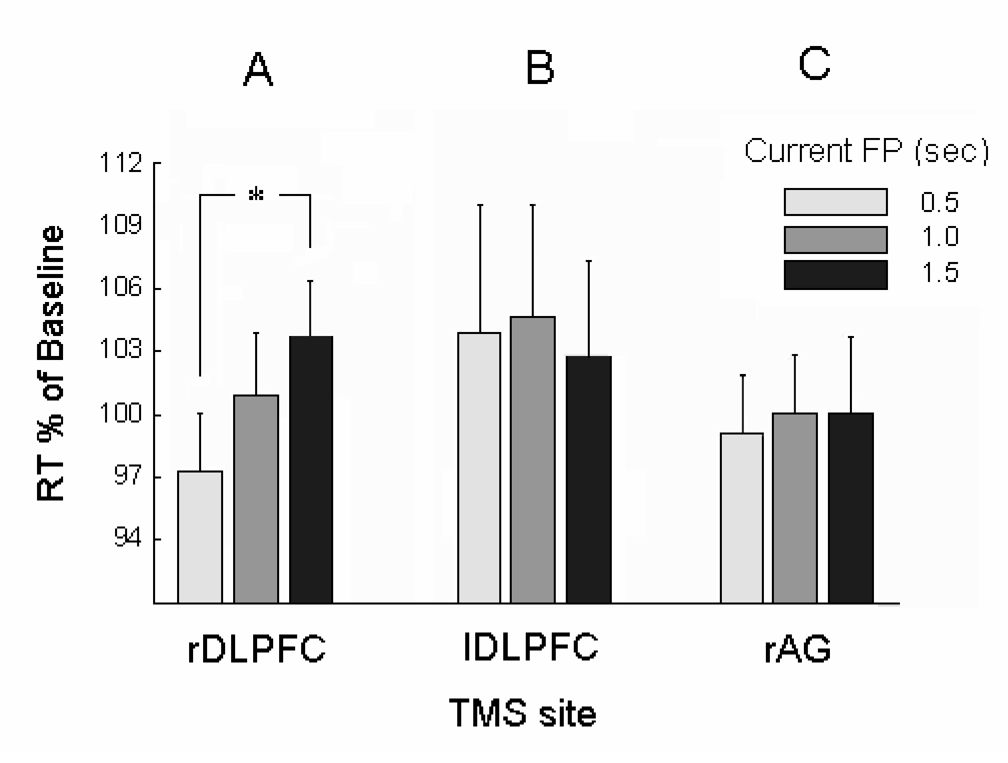

Figure 14. Degree of change (in percentage) in mean RTs collected during the post-TMS block with respect to RTs collected during the pre-TMS baseline block (i.e., post-TMS RT/baseline RT x 100), in experiment 7. Bars indicate standard errors of the mean. Data are plotted as a function of the stimulation site (x-axis) and of the current FP (parameter). Panels A, B and C refer to the blocks after TMS on the right DLPFC, left DLPFC, and right AG, respectively. **p* < .01.

3.1.2. Experiment 8

Experiment 8 was designed to be similar to experiment 7, with two exceptions. First, there were two blocks of trials instead of one after the TMS. This change was made in order to cover the whole period in which the long-lasting effects of TBS operate, including the most critical interval of 7-14 min post-TMS, possibly increasing the sensitivity of experiment. Second, a two-choice RT paradigm was chosen in order to avoid anticipation and ceiling effects which might occur during a simple RT task, such as that used in experiment 7; such effects could have partially obscured any TMS effects. It should be noted that, although the additional stage of response selection is required by a choice RT task, FP effect is held to involve *non-specific* preparation processes only. Indeed, the typical FP phenomena are basically similar for both simple and choice RT tasks (e.g., Los & van den Heuvel, 2001), and the right prefrontal lesion effect is found for both paradigms (Stuss et al., 2005).

Method

Participants

Nine volunteer participants, 4 females and 5 males, took part in experiment 8. They were 30 years old on average (range = 22-43). All of them were right-handed (with an average score of 83 at the EHI). All had normal or corrected-to-normal vision, and no auditory or neurological impairment. Three of them had participated in the experiment 7 (at least one month before).

Apparatus and Materials

The apparatus and materials were the same as in experiment 7 except that, on each trial, the IS appeared with the same probability to the right or left of the fixation cross at a distance of 7.5 cm (center to center).

Procedure and Task

The task was to perform a spatially compatible response to the IS by pressing a right or left key on the computer keyboard (‘F’ or ‘J’, respectively) as fast as possible. The experiment consisted of 3 sessions performed on 3 different days within a maximum period of a week. Each session consisted of 3 blocks of 144 trials each. During each session, the first block was run before the TMS to measure the baseline performance and the second and third blocks were run consecutively after the TMS. A whole experimental session lasted about 35-40 minutes.

Data Analysis

The same criteria as in experiment 7 were used for the analysis of the data obtained in experiment 8. In addition, only trials with correct (spatially compatible) responses to the imperative stimulus were considered for the RT analyses. Moreover, preliminary analyses including the spatial position of the IS (and of the response) did not give rise to any interaction between this factor and that of the TMS site factor. For this reason, the spatial position factor was collapsed in the following analyses.

As a first step, 3 separate repeated-measures ANOVAs were conducted, one for each stimulated site (right DLPFC, left DLPFC and right AG). The within-subject independent variables considered in these preliminary analyses included FP on the current trial (FP_n = 0.5, 1.0 and 1.5 sec), FP on the preceding trial *n-1* (FP_{n-1}) and the TMS block (Baseline, first and second post-TMS blocks). The dependent measure was the mean RT.

A subsequent overall repeated-measures 3x3x2x3 ANOVA was also performed with FP_n, FP_{n-1}, TMS block (first and second post-TMS blocks) and TMS site (right DLPFC, left DLPFC, right AG) as the within-subjects variables. The dependent variable chosen in this overall ANOVA was the percentage of change of mean RTs collected after the first and second post-TMS blocks in each session compared to the mean RTs of the pre-TMS baseline of the same session. As in the experiment 7, the F-test was adjusted by the Greenhouse-Geisser procedure when appropriate.

Results

The first trial of each block (0.7 %), trials involving anticipated responses (RT before IS onset: 0.08 %), trials involving premature responses (RT < 100 ms: 0.02 %), and trials with delayed responses (RT > 1000 ms) or without responses (0.02 %), and trials with an incorrect response on the spatial compatibility task (0.8 %) were discarded from further analyses. Fewer than 1.8 % of trials were excluded.

Behavioural Results

The following effects were significant in ANOVAs conducted on the 3 sessions separately (see Figure 15). A main effect of FP_n was obtained [$F(2,16) = 10.1$, $p = .001$;

F(1.3, 10.1) = 15.8, *Adj.* $p < .01$; *F*(2, 16) = 17.3, $p < .001$, for the right DLPFC, left DLPFC and right AG, respectively]. Post-hoc comparisons showed that RTs were slowest for the shortest FP of 0.5 sec as compared to the medium and longest FPs (for all, $p < .01$). Moreover, the main effect of FP_{n-1} was also significant [*F*(2,16) = 16, $p < .001$]. The post-hoc comparisons showed that current RTs were slower following a middle FP_{n-1} trial than a shortest FP_{n-1} trial and, in turn, following a longest FP_{n-1} trial than a middle one (for the right AG, the difference between the middle FP_{n-1} and the longest one was not significant, for all the other comparisons, $p < .05$). The FP_n x FP_{n-1} interaction, concerning the asymmetric sequential effects, was also significant [*F*(1.8, 14.8) = 5.1, *Adj.* $p = .02$; *F*(4, 32) = 12.7, $p < .001$, for the right DLPFC and left DLPFC, respectively; and a tendency for the right AG, *F*(1.5, 12) = 3.9, *Adj.* $p = .059$]. This effect was principally due to the differential contribution of the FP_{n-1} to the RT on each of the three current FPs, being greatest for the shortest FP_n and smallest for the longest FP_n, as confirmed by post-hoc comparisons.

TMS effects: separate ANOVAs for each TMS site

No TMS block main effect was observed for any site of stimulation, indicating that RTs were not non-specifically modified by the TBS. As for experiment 7, the TMS block x FP_n interaction was significant for the right DLPFC session only [*F*(4, 32) = 4.5, $p < .01$]. The FP effect was reduced in the first and second post-TMS block with respect to the baseline, as demonstrated by subsequent planned comparisons. Significant planned comparisons were obtained contrasting the RT difference between the shortest and the longest FPs in the baseline condition and the same RT difference in the first and in the second blocks post-TMS of the right DLPFC (for all, $p < .001$). However, post-hoc comparisons indicated that the differences between RTs in any of the FPs in the baseline contrasted with the same FPs in the post-TMS blocks were not significant (for all, $p > .1$). As in experiment 7, this pattern indicates that the reduction of the FP effect was not due to a specific effect on RTs for the shortest, medium or longest FP, but instead to an overall effect which acts by attenuating the FP effect as a whole. Thus, the difference between the RT on the shortest FP_n and on the longest FP_n decreased from 33 ms in the baseline block to 22 ms in the first post-TMS block, to reach 15 ms in the last post-TMS block. No other effect was significant. In particular a lack for a three-way TMS block x FP_n x FP_{n-1} interaction in all the 3 sessions (for the left DLPFC, $p > .8$; for the right AG, $p > .6$; for the right DLPFC, $p > .2$) suggested that TMS did not modulate sequential effects.

Although no three-way interaction was observed in any analysis, visual inspection of Figure 15 suggests, for the right DLFPC session, the presence of more symmetric sequential effects in the last TMS block with respect to the baseline. The three-way interaction may be hidden by the number of conditions introduced in the ANOVA. To statistically assess this possibility, a subsequent 3x3x2 ANOVA was performed for the right DLPFC session, with FP_n, FP_{n-1} and TMS block as within-subjects variables, contrasting the baseline block with the second TMS block only. This analysis was justified by the fact that the TMS effect was expected to reach a maximum during this second block (i.e., from 7 to 14 minutes post-TMS; cf. Huang et al., 2005).

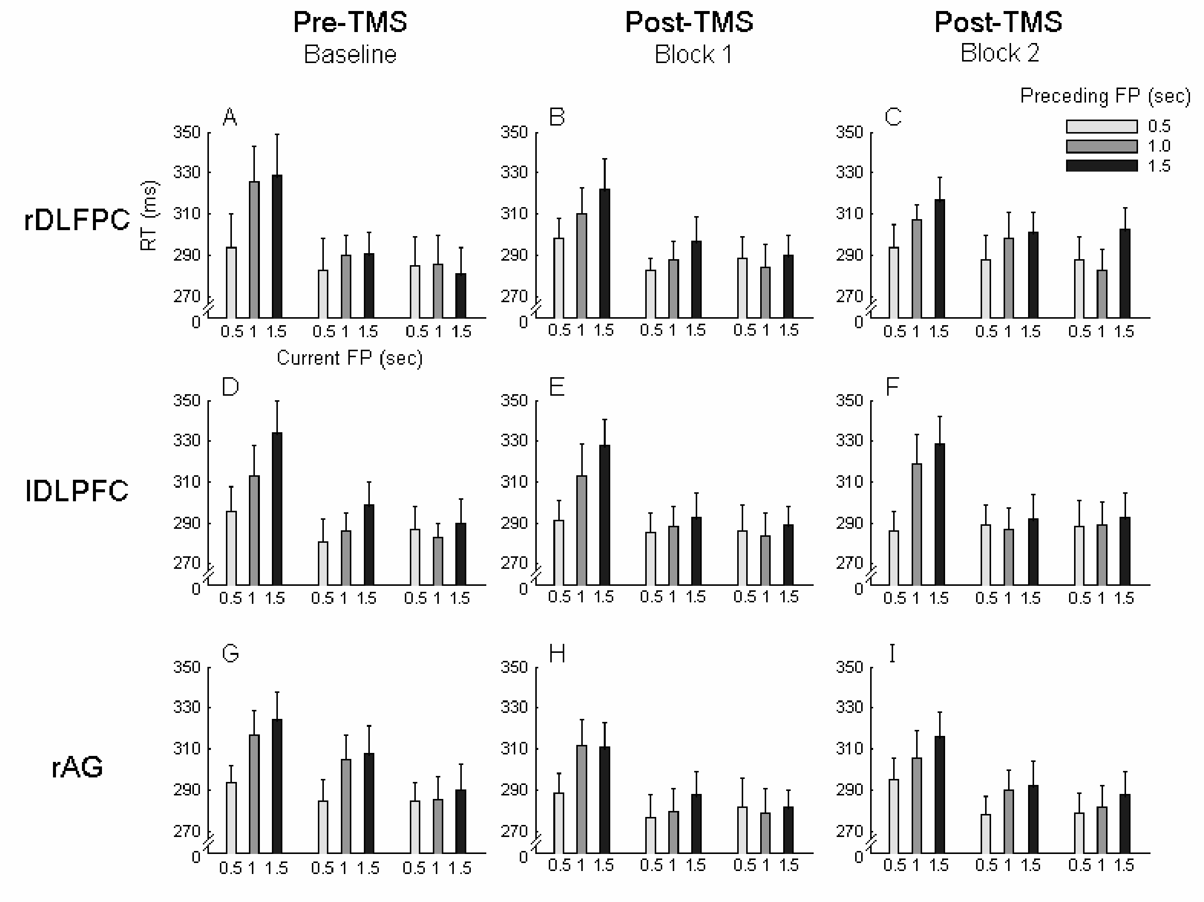

Figure 15. Mean RTs (and standard errors) in experiment 8, as a function of FP on the current trial (x-axis), FP on the preceding trial (parameter) and experimental block (panels). Panels A, B and C refer to baseline, first and second blocks after TMS on the right DLPFC. Panels D, E and F refer to baseline, first and second blocks after TMS on the left DLPFC. Panels G, H and I refer to baseline, first and second blocks after TMS on the right AG.

Apart from the main effects of FP_n and FP_{n-1} and the interaction between these two factors, which confirm the previous analysis, this analysis produced a significant three-way interaction [$F(4, 32) = 2.7$, $p < .05$]. To confirm that the difference was due to the presence of symmetric sequential effects in the second post-TMS block, further planned comparisons have been carried out. Specifically, these comparisons contrasted the difference between the RT on the longest FP_n preceded by the longest FP_{n-1} and the RT on the same longest FP_n preceded by the shortest FP_{n-1} in the baseline with the same difference in the second post-TMS block. This analysis was significant ($F(1, 8) = 13.9$, $p < .01$), confirming that, in the second post-TMS block, sequential effects were basically symmetric, as they were also present on the longest FP_n.

TMS effects: overall ANOVA

The main effect of the FP_n was significant [$F(2, 16) = 5.1$, $p < .05$]. Post-hoc comparisons indicated that post-TMS RTs were slower after a long FP_n and faster after a short FP_n with respect to the baseline values (101% vs. 99%; $p < .05$). More importantly, an interaction between TMS site and FP_n was obtained [$F(4, 32) = 3.5$, $p < .05$], indicating that the FP effect was selectively attenuated after TMS on the right DLPFC (see Figure 16). In this case only, the RTs on the longest FP_n were slower with respect to the baseline block (103%) while the RTs on the shortest FP_n were slightly faster (99%), the difference between these two values being significant on post-hoc Tukey comparisons ($p < .05$). This effect demonstrates a reduction of the FP effect selectively after the TMS to the right DLPFC, replicating the results of experiment 7. No other effect was significant. As in that experiment, the left DLPFC and the right AG turned out to act as TMS control sites because no effect involving TMS was observed in these analyses.

Discussion

The results of experiment 8 confirm those of experiment 7. In particular, the reduction of the FP effect as a consequence of TMS acting specifically on the right DLPFC was replicated while no TMS effect was obtained on the left DPLFC and the right AG. This result confirms the role of the rDLPFC for the occurrence of the FP effect (see Stuss et al., 2005).

On the other hand, the sequential effects were not reduced by the TMS in the rDLPFC, clearly suggesting that the non-significant tendency found in experiment 7 was likely to be due to noise. As a dissociation between the two effects has been obtained, the hypothesis of a common mechanism underlying both effects is not supported. Interestingly, the sequential effects become more symmetric during the second post-TMS block of trials on the same area. This was confirmed by the presence of a significant FP_n x FP_{n-1} x TMS block interaction, although this was obtained only for a direct comparison between the baseline block and the second post-TMS one, namely the block in which the effects of the TBS would be expected to be stronger (see Huang et al., 2005). Such evidence, although not confirmed by the analysis across TMS sessions, corroborates the pattern found in the developmental study of the FP phenomena (see Experiments 3a, 3b and 4, chapter 2; see also general discussion below). As in the youngest children of that study (i.e., 4-5 years old), whose DLPFC is presumably not yet mature, after 6-7 minutes from TMS of the rDLPFC the sequential effects become more symmetric while the FP effect decreases.

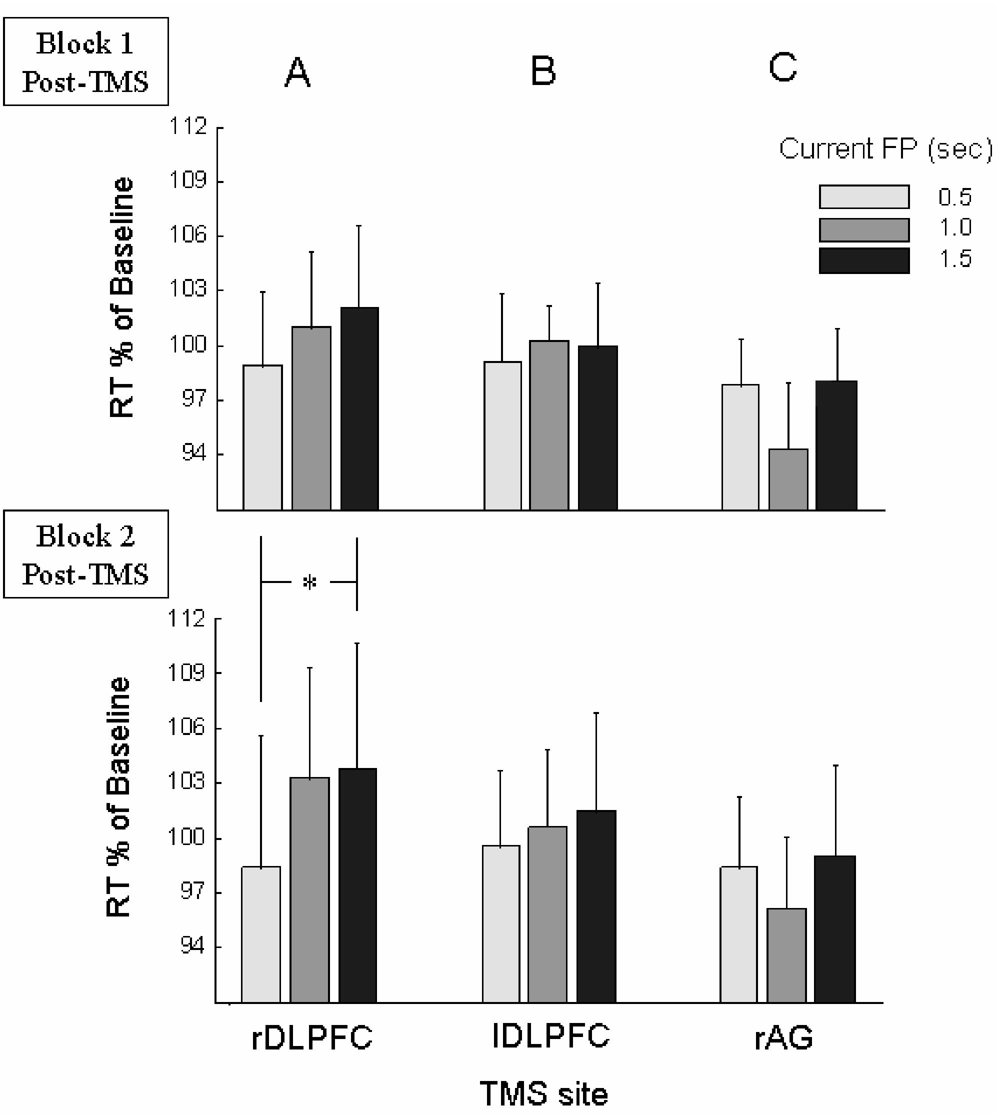

Figure 16. Degree of change (in percentage) in mean RTs collected during the two post-TMS blocks with respect to RTs collected during the pre-TMS baseline block, in experiment 8. Data are plotted as a function of the stimulation site (x-axis) and of the current FP (parameter). Bars indicate standard errors of the mean. Upper and lower panels indicate results of the first and second post-TMS sessions, respectively. Panels A, B and C refer to the blocks after TMS on the right DLPFC, left DLPFC, and right AG, respectively. *$p < .05$.

General discussion

The FP effect can be briefly described as a negatively accelerating FP-RT function, obtained when a range of FPs is randomly administered with the same a priori probability in simple or choice RT tasks. The present study was primarily designed to investigate the anatomical basis of the FP effect by means of TMS. To this purpose, in the experiment 7 a variable FP paradigm with a simple RT task was performed by 9 volunteers in two blocks, before and after TMS of three sites, right DLPFC, left DLPFC and right AG (one per each session day). A possible limitation of experiment 7 was that testing did not take place in the most critical period of the TMS effect when the TBS is employed (i.e., 7-14 min, see Huang et al., 2005). This limitation was overcome in the second experiment, where 9 participants carried out two experimental blocks following TMS. Stuss and colleagues (2005) found a right frontal lesion effect on variable FP paradigms using choice RTs as well as simple RTs. So, another change introduced in the second experiment was the use of a choice RT task instead of the simple RT task used in the experiment 7.

Both experiments of the present study provide clear evidence for a role of the rDLPFC in the production of the FP effect. Specifically, a 20 sec off-line repetitive TMS (i.e., TBS) over this area, compared to the pre-TMS baseline level and to an analogous stimulation on two other sites (i.e., left DLPFC and right AG), is enough to significantly reduce the size of the FP effect for the post-TMS period investigated. This period was about 6 minutes long for the simple RT task in experiment 7, and 15 minutes long for the choice RT task in experiment 8. These results fit well with existing neuropsychological literature. As suggested by Stuss and colleagues (2005), the rDLPFC seems to be the location of a process critical for the FP effect, because patients with lesions of this region do not show the typical FP effect. Moreover, a link between the FP effect and dopaminergic activity has been demonstrated in neuropsychological studies. The dopaminergic system is a neurotransmitter system massively present within the DLPFC. Drug-free schizophrenic patients, for example, who have increased levels of dopamine (see Kapur, 2003, for a review), show an exaggerated variable FP effect (Zahn, Rosenthal, & Shakow, 1963), whereas Parkinsonian patients, who suffer from deficiencies in dopamine levels (e.g., Rakshi et al., 1999), have a reduction of this effect (Jurkowski et al., 2005).

The short FP range used in the present study (i.e., 0.5, 1 and 1.5 sec) allows us to discard accounts relating the reduction of FP effect after TMS of the rDLPFC to vigilance or alertness (e.g., see Posner & Petersen, 1990), such as a deficit in maintaining a high level of preparation for a long time interval. This account would be also in contrast to the results obtained by Stuss and colleagues (2005) on prefrontal patients. In that study, indeed, right frontal patients showed no FP effect with a variable FP paradigm. Noteworthy, with a fixed FP paradigm, their performance was comparable, even for the longest FPs in the range, to that of other frontal patients, apart from medial frontal ones.

The FP effect is probably due to a process of endogenous preparation, analogous to that already described by some traditional accounts (e.g., Näätänen 1970). This process checks the non-occurrence of the IS, using the information derived from the increasing conditional probability of the IS occurrence as time elapses in order to enhance preparation. As in right lateral prefrontal patients (Stuss et al., 2005), it is likely that this checking process does not operate efficiently after TMS over this area. The rDLPFC region controlling such process would be permanently damaged in the neuropsychological patients studied by Stuss and colleagues and compromised transiently in the present study using TMS.

In partial support of this view, activation of the rDLPFC has already been demonstrated in a number of brain imaging and TMS studies during tasks dealing with temporal processing, such as time discrimination tasks (e.g. Rao et al., 2001; Lewis & Miall, 2003b) and time reproduction tasks (e.g. Basso, Nichelli, Wharton, Peterson, & Grafman, 2003; Koch, Oliveri, Torriero, & Caltagirone, 2003; Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004). It can be argued that these tasks are different in nature from the variable FP task, in that the former overtly require temporal processing while the latter do not. However, what the two kinds of tasks may have in common is the monitoring of temporal information, which is explicitly required by time reproduction and discrimination tasks, and implicitly exploited during the variable FP paradigm in order to reach an optimal level of preparation (Näätänen 1970). As the results of the present study and of the literature empirically suggest, this monitoring process is conceivably subserved by the rDLPFC.

The present study also investigated the role of the rDLPFC in the sequential FP effects. These well-known effects consist of an increase in RT as the preceding FP becomes longer. The sequential effects are usually asymmetrically more pronounced for the shortest FPs in the range employed, while they are virtually absent for the longest FPs. A tendency ($p = .054$) for a reduction of the effect of FP_{n-1} was found after stimulation of the rDLPFC in the experiment 7, which used a simple RT task. This tendency was, however, not different following TMS of rDLPFC from that of the other two sites employed (see results of the overall ANOVA). Moreover, in the experiment 8, a dissociation between the FP effect and the sequential effects was obtained after stimulating the rDLPFC: the FP effect was significantly reduced while the sequential effects were not influenced in magnitude. Thus, we obtained site controls (i.e., rDLPFC vs. all other sites and no TMS) and a task control for our effects (i.e., FP vs. sequential effects dissociation).

In addition, in the second block after TMS of the rDLPFC, when the TMS effects are supposed to be at their strongest (Huang et al., 2005), the sequential effects were more symmetric with respect to the baseline block, as confirmed by a subsequent ANOVA. Symmetric sequential effects would not be expected according to the conditioning view (Los & van den Heuvel, 2001). This account predicts that the sequential effects, if present, must inevitably be asymmetric, due to a main role of extinction on the activation strength of the shortest FPs, and of reinforcement on the activation strength of longest FPs. The observation of symmetric sequential effects when the FP is attenuated may be tentatively accounted for by the dual-process model proposed in the general discussion of the developmental study (paragraph 2.2., chapter 2). According to this model, the sequential effects per se can be explained by assuming an enhancement in arousal following a short FP_{n-1} and a decrease following a long FP_{n-1}, whatever the current FP_n (cf., Los & Heslenfeld, 2005). It is likely that sequential effects are usually compensated for during long FPs by the processes underlying the FP effect, thus accounting for their asymmetry. However, given the lack of a significant interaction between the sequential effects and the TMS site, further investigation is required to test the relationship between FP effect size and degree of symmetry of the sequential effects suggested by the pattern of the present results.

To the best of our knowledge, this was the first study in which an effect of the TBS parameters was demonstrated on behavioural variables (i.e., RTs) not directly linked to the measure of the motor cortex excitability, indicating its usefulness in cognitive neuroscience, as a feasible alternative to other kinds of off-line stimulation (see also paragraph 6.3., chapter 6).

In conclusion, the present study demonstrated that the rDLPFC is a critical locus of the FP effect, as a reduction in this effect is obtained after TMS over that area. Moreover, the dissociation between the FP effect and the sequential effects produced by TMS of the rDLPFC, especially in experiment 8, suggests a dual-process account, according to which the two (usually interacting) effects are likely to be dissociable both functionally and anatomically.

3.2. The neural basis of the foreperiod phenomena: insights from brain tumor patients

The recent neuropsychological study by Stuss and colleagues (Stuss et al., 2005) found that right lateral prefrontal patients were selectively impaired in a variable FP task, as they did not show the classical FP effect. According to the traditional account concerning conditional probability monitoring (e.g., Näätänen, 1970; Niemi & Näätänen, 1981), right prefrontal patients fail to check whether a stimulus has occurred over a few seconds, and are not able to increase their readiness to respond as time goes on (Stuss et al., 2005). This account fits a range of neuropsychological (e.g., Rueckert & Grafman, 1996; Wilkins, Shallice, & McCarthy, 1987) and functional imaging studies (e.g., Coull et al., 2000; Henson, Shallice, & Dolan, 1999), which assign a monitoring role to the rDLPFC (see Fletcher & Henson, 2001; Shallice, 2002; 2004 for reviews; cf. Posner & Peterson, 1990).

Another possible explanation for the deficit of right frontal patients, however, may be that the FP effect vanishes as a consequence of reduced or absent sequential effects. The conditioning single-process account, indeed, would predict this possibility (Los & van den Heuvel, 2001). On this view, the FP effect is entirely a side effect of the conditioning mechanisms operating on the preceding trial and generating the sequential effects. Unfortunately, sequential effects were not investigated in Stuss and colleagues' study (Stuss et al., 2005; but see our TMS study, paragraphs 3.1.). Therefore, it is not possible to disentangle this possibility directly from the data reported in that study.

TMS experiments 7 and 8 replicate the neuropsychological finding (Stuss et al., 2005) on healthy participants. As results showed, when rDLPFC was temporarily inhibited by the TMS, a reduction in the FP effect was observed with respect to a pre-TMS baseline and with the stimulation of other control areas, such as the left DLPFC and the right angular gyrus. Fortunately enough, that study also checked the sequential effects, which were however not influenced in magnitude by the TMS of any of the three areas under study. In other words, the FP effect was reduced in the presence of normal size sequential effects. To our knowledge, no study has found the opposite dissociation, namely reduced or absent sequential effects in the presence of an unchanged FP effect. Thus, it is not possible to know from that study whether the two effects derive from entirely independent processes, as the possibility exists that the sequential effects are a necessary but not sufficient condition for the occurrence of a normal-size FP effect. In other words, the FP effect may have been reduced because of the impairment of an unknown process, whose contribution to the FP effect may be additional to that made by the sequential effects. On the other hand, the presence of a normal FP effect in the absence of sequential effects, if found, could be taken as evidence for the complete independence of the processes underlying the two effects, according to the logic of double dissociations (Shallice, 1988).

In this study, an approach similar to that developed by Stuss and colleagues (e.g., Stuss et al., 1995; Stuss et al, 2005) was adopted to analyse attentional deficits derived from lesions in different cortical areas. On this approach, a careful task analysis may provide valuable insights about the fractionation of cognitive functions (Stuss, 2006). This approach was specifically employed here on a cohort of patients with unilateral brain tumors performing a variable FP task. An anatomically-driven analysis was performed on patients grouped into different anatomical regions, according to the tumor location. As it arises from the brief review above, an open issue, which still remains to be investigated, is the neural locus of the sequential effects. For this reason, investigation of the neural bases of the FP phenomena has been extended, in this study, to lesions outside the prefrontal cortex. Therefore, the six tumor locations of patients tested here were: right and left prefrontal, right and left premotor, right and left parietal. Prefrontal patients have been tested with the specific purpose of replicating previous neuropsychological and TMS studies on the role of lateral PFC in the variable FP effect (Stuss et al., 2005; see also our TMS study, paragraph 3.1.). The investigation of patients with tumors in premotor and parietal regions was justified by the fact that several fMRI studies on temporal preparation or temporal processing have consistently shown activations of areas within these regions (e.g., Basso et al., 2003; Coull et al., 2000; Lewis & Miall, 2003a; Macar et al., 2002).

A clear advantage of the study of tumor patients with respect to other categories of neuropsychological patients is that baseline performance may be measured within-subject before tumor resection. As it is still unclear whether and to what extent tumors, especially high-grade ones, have deleterious effects on the cognitive system, we also investigated whether the baseline performance of tumor patients on the variable FP paradigm was already defective, due to the tumor per se, by comparing it with the performance of a control group of hospitalized (orthopaedic) patients without any cerebral disease.

3.2.1. Experiment 9

Method

Assignment to patient group

The pre-operative location of the tumor was determined using a digital format T1-weighted MRI scan obtained 1-2 days before surgery. The post-operative MR scans were available 3-4 months after surgery, about one month from the end of the radiotherapy. As by this time the area of removed brain tissue was partially replaced by healthy brain, pre-operative MR scans have been used for localization purposes. Each patient's lesion was referred to an anatomical template image AAL (automated anatomical labeling; Tzourio-Mazoyer et al., 2002), that is a macroscopic anatomical partition of Montreal Neurological Institute (MNI) volume (Collins et al., 1998). MRIcro software was used to extrapolate a 3D representation of the lesion from digital MR scans (Rorden & Brett, 2000). The tumor contour was drawn as a region of interest (ROI) on each sagittal slide. Afterwards, the scans and ROIs were normalised using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) with a human-assisted process. In collaboration with the neurosurgeon and, for low grade tumors, also with the neuroradiologist, who did not know the behavioral results, the tumor boundary was limited to the brain tissue effectively removed during the surgical operation, therefore excluding the oedema.

Patients were assigned to the parietal group if the tumor involved the parietal and occipito-parietal cortices or posterior temporal cortex (posterior to BA 4). Patients with tumors in either or both the motor and premotor areas (BA 4 and 6) have been included in the premotor group. Patients with tumors involving areas anterior to BA 6 have been included in the prefrontal group. Patients with tumors located in the anterior portion of Sylvian fissure, fronto-insular and fronto-temporal areas have been excluded.

Patient selection

One-hundred and eleven patients had initially been tested with tumors of the following types: gliomas, mav, meningiomas and metastases. Fifty-three patients have been excluded from the analysis reported in the current study for the following reasons: they were left-handed (2 cases), the operation was for a recurrence of the tumor (4 cases), they were only available for testing in one of the two sessions (11 cases), they had multiple metastatic lesions (2 cases), or the lesions involved white matter almost entirely (2 cases) or were intra-ventricular (2 case), bilateral (8 cases), predominantly insular with frontal-temporal involvement (11 cases), involved roughly equally two of the three brain regions under study (7 cases), because of marked diffused cognitive deficits (1 case), because of the absence of a 3D scan (1 case), because the patient suffered from alcoholism (1 case) or mental retardation (1 case).

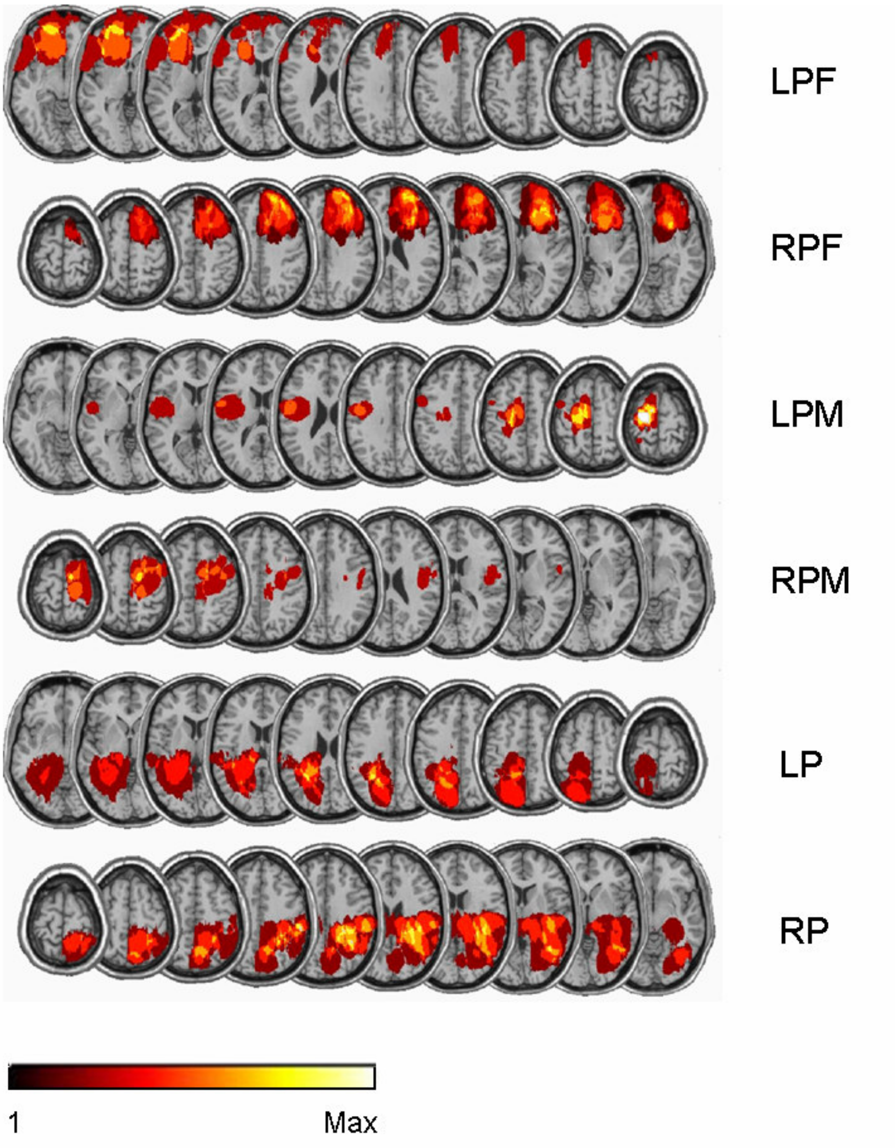

Figure 17. Display of the tumor overlap for the 6 groups of tumor patients. The percentage of overlapping tumors in each voxel is illustrated using a grey-scale within the region of interest: the lighter is a point on that scale, the higher the percentage of patients within that group with that voxel damaged. The white colour indicates voxels with maximal percentage of tumors within each patient group. Maximal percentage of overlap was 67, 43, 63, 43, 56, 36, for the left and right prefrontal, left and right premotor and left and right parietal groups, respectively. The z-coordinates of each transversal section in Montreal Neurological Institute space are -8, 0, 8, 16, 24, 32, 40, 50, 60, 70. LPF = left prefrontal; RPF = right prefrontal; LPM = left premotor; RPM = right premotor; LP = left parietal; RP = right parietal.

The remaining 58 patients were divided into 6 groups with the following sample sizes: 6 left prefrontal, 14 right prefrontal, 8 left premotor, 7 right premotor, 9 left parietal, 14 right parietal (see Figure 17). The histological examination of the tumors of the included patients were: 20 high grade gliomas, 20 low grade gliomas, 15 meningiomas, 3 metastasis. Mean tumor volume was 36.4 ml (on a total of 1352 ml), SD 29.8 ml.

Patients having tumors which show pronounced involvement of a defined region but a small involvement of other critical regions have been included in the study. This was the case for the 8 following patients: tumors of 3 right prefrontal patients extended to right premotor regions; tumor of another right prefrontal patient extended to the anterior portion of Sylvian fissure; one left prefrontal patient had an involvement of the anterior portion of Sylvian fissure; tumor of another left prefrontal patient had compressive effects on a small portion of the right hemisphere (however, only the tumor in the left hemisphere was surgically removed); tumors of 2 premotor patients, one left and one right, involved a small amount of left and right prefrontal cortex, respectively. Occasionally patients had oedema involving other critical brain regions under study: two right parietal patients had oedema in the premotor and motor areas; one right premotor patient had an involvement of parietal and prefrontal cortex; two right prefrontal patients had oedema involving premotor areas.

A control group of 12 hospitalized orthopedic patients without neurological problems or cognitive impairment (Corrected Mini-Mental State Examination > 24) was also tested in order to check for learning effects, and for the baseline performance of tumor patients on the pre-surgery session. The demographic characteristics of each patient group are reported in Table 5.

When the 7 groups were compared in one-way ANOVAs, there were no significant differences between the groups with respect to age [$F(6, 63) = 1.38$, $p = .23$] and to years of education [$F(6, 63) = 1$, $p = .4$]. Among the 6 groups of tumor patients there was a tendency towards significance for location on lesion volume [$F(5, 52) = 2.19$, $p = .07$]. The lesion volume for the premotor groups tended to be smaller than that for the parietal and prefrontal groups. Forty participants underwent surgery under general anesthesia, whereas the other 18 were awake during operation. Preliminary analyses did not reveal any effect of interaction between gender, volume size or anesthesia, on the one side, and the variable FP phenomena and the testing session, on the other side. Therefore, data were collapsed with respect to these factors. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and was previously approved by SISSA ethical committee.

Table 5

Main demographical characteristics of the seven patient groups included in the experiment 9.

	Mean Age[a]	Mean Education[a]	Gender		Anaesthesia		Tumor Volume[b]	Sample size
Group	(min-max)	(SD)	F	M	G	L	(SD)	
Left Parietal	53 (31-70)	9 (3)	3	6	6	3	40 (32)	9
Right Parietal	54 (30-70)	10 (4)	6	8	13	1	40 (37)	14
Left Premotor	45 (31-60)	11 (3)	5	3	2	6	15 (11)	8
Right Premotor	39 (18-58)	12 (3)	2	5	2	5	18 (14)	7
Left Prefrontal	45 (33-62)	11 (4)	3	3	5	1	45 (20)	6
Right Prefrontal	45 (23-72)	12 (4)	5	9	12	2	48 (30)	14
Controls	47 (23-73)	11 (4)	6	6	----	----	--------	12

Notes. [a]In years. [b]In millilitres (total volume: 1352 ml). SD = standard deviation; F = female; M = male; G = general; L = local.

Stimuli and Procedure

Each patient was tested individually with her/his gaze ~55 cm from the screen. Patients were tested twice: 1-3 days before operation and 2-6 days after it. The control participants were also tested twice with a comparable time-range between the two testing sessions (i.e., 4-8 days) but without any surgical intervention in between. In addition to the test reported here, tumor patients carried out 20 other neuropsychological tests: 5 on perception, 5 on praxis and 8 on executive functions and working memory, 1 on optic ataxia, and 1 on neglect. For the variable FP task, participants are required to fixate a cross in the centre of a 15” VGA monitor (composed by 2 black lines, 4 cm each). The onset of the fixation cross served as a warning signal. The cross was displayed on the screen until the FP expired. The imperative stimulus was a central yellow rectangle (width: 5.5, height: 4 cm). Participants were instructed to press the spacebar as soon as they would see the rectangle. The imperative stimulus disappeared when the response was detected. The FPs between the cross onset and the rectangle onset were: 3, 4, 6 and 7 sec, respectively. These relatively long FPs were chosen in order to use similar experimental conditions as those used by Stuss and colleagues (Stuss et al., 2005), who administered a very similar FP range to the frontal patients. The 4 FPs were administered randomly and equiprobably across trials. The inter-trial interval between the response detection and the next fixation onset was 1 sec. All the stimuli were presented against a white background. During each session, the experiment consisted of 36 trials (9 per each FP) presented in a different pseudo-random order for each patient. A familiarization phase with 4 trials (one per each FP) preceded the test phase. The recorded variable was the RT.

Data Analysis

RTs outside the 100-3000 ms range, the first trial of the test block and data from the initial familiarization phase were excluded from analyses. Initial analyses comprehend all the 7 groups, typically using a 7x2x2x2 mixed ANOVA. This ANOVA involved patient group as the only between-subject factor (left and right prefrontal, left and right premotor, left and right parietal, and controls), and 3 within-subject factors: FP_n (short vs. long, i.e., 3-4 vs. 6-7 sec), FP_{n-1} (3-4 sec vs. 6-7 sec), and testing session (first and second session, which means pre- vs. post-surgery for tumor patients).

Results

Accuracy

Less than 0.6% of trials were discarded because of RTs being outside the 100-3000 ms range. This percentage tended to be significantly different across patient groups, as demonstrated by a non-parametric Kruskal-Wallis test [$H(6, N: 70) = 12.4$, $p = .054$]. This could be due to the fact that virtually no trial was excluded for the controls and the premotor groups. However, the percentage of excluded trials was low also in the other 4 groups (0.7, 0.6, 1.3 and 1.5%, for the left and right parietal, and left and right prefrontal groups, respectively).

Reaction Times

The results are presented in Figures 18 and 19. The overall ANOVA produced the following significant effects. The main effect of FP_n was significant [$F(1, 63) = 87.2$, $p < .001$], indicating that RTs were slower on the short FP_n than on the long one (i.e., the classical FP effect). The main effect of FP_{n-1} was also significant [$F(1, 63) = 47.5$, $p < .001$]: RTs were slower after a long FP_{n-1} than after a short one. The effect of FP_{n-1} was modulated by the testing session [$F(1, 63) = 6.9$, $p = .01$], being stronger in the first testing session than in the second one. The sequential effects were asymmetric as indicated by the significant FP_n x FP_{n-1} interaction [$F(1, 63) = 5$, $p < .05$]. However, the latter two interactions were better qualified by a tendency toward significance of the testing session x FP_n x FP_{n-1} interaction [$F(1, 63) = 3.7$, $p < .056$]. This tendency suggested that sequential effects were present in the first session, but absent in the second session, a pattern mainly observed on the short FP_n.

More critically, the patient group x testing session x FP_n interaction was also significant [$F(6, 63) = 2.5$, $p < .05$]. Visual inspection of Figure 18 suggests that this interaction was due to a reduction of the FP effect selectively after removal of tumoral tissue in right lateral PFC. In order to statistically corroborate this observation, separate ANOVAs for each group were conducted with testing session, FP_n and FP_{n-1}, as repeated measures. As predicted (cf. Stuss et al., 2005), the testing session x FP_n interaction was significant for the right prefrontal patients only [$F(1, 13) = 8.2$, $p = .01$], due to a reduction of the FP effect after surgery (12 ms) with respect to the pre-surgery effect (57 ms). We further checked if there was a correlation between this effect and lesion extension. Neither the pre- nor the post-surgery FP effect in right prefrontal patients correlated with lesion size.

These separate ANOVAs had also been carried out to find the source of the testing session x FP_{n-1} and testing session x FP_n x FP_{n-1} interactions in the overall ANOVA. Although these interactions are not significantly modulated by the patient group in the overall ANOVA, visual inspection of Figure 19 suggests that the premotor and prefrontal groups are principally responsible for these effects. This was only partially confirmed as the testing session x FP_{n-1} interaction was a tendency for the right prefrontal group ($p = .06$) and for the left premotor group ($p = .08$).

To find the source of the testing session x FP_n x FP_{n-1} interaction, we chose a Bonferroni correction of a critical significance level of .0083, as this 3-way interaction was only a trend in the overall ANOVA. The only individual patient group showing a significant testing session x FP_n x FP_{n-1} interaction, when analyzed separately from the other groups, was the left premotor one [session x FP_n x FP_{n-1} 3-way interaction: $F(1, 7) = 22.1$, $p = .002$], indicating that the sequential effects, which were present before surgery mainly on the short FP_n, had disappeared after it. This was observed in this patient group despite the standard FP effect being present with the same magnitude before and after the operation, as shown by a significant main effect of FP_n [$F(1, 7) = 55.4$, $p < .001$], which was not modulated by the testing session (session x FP_n interaction, $p = .36$).

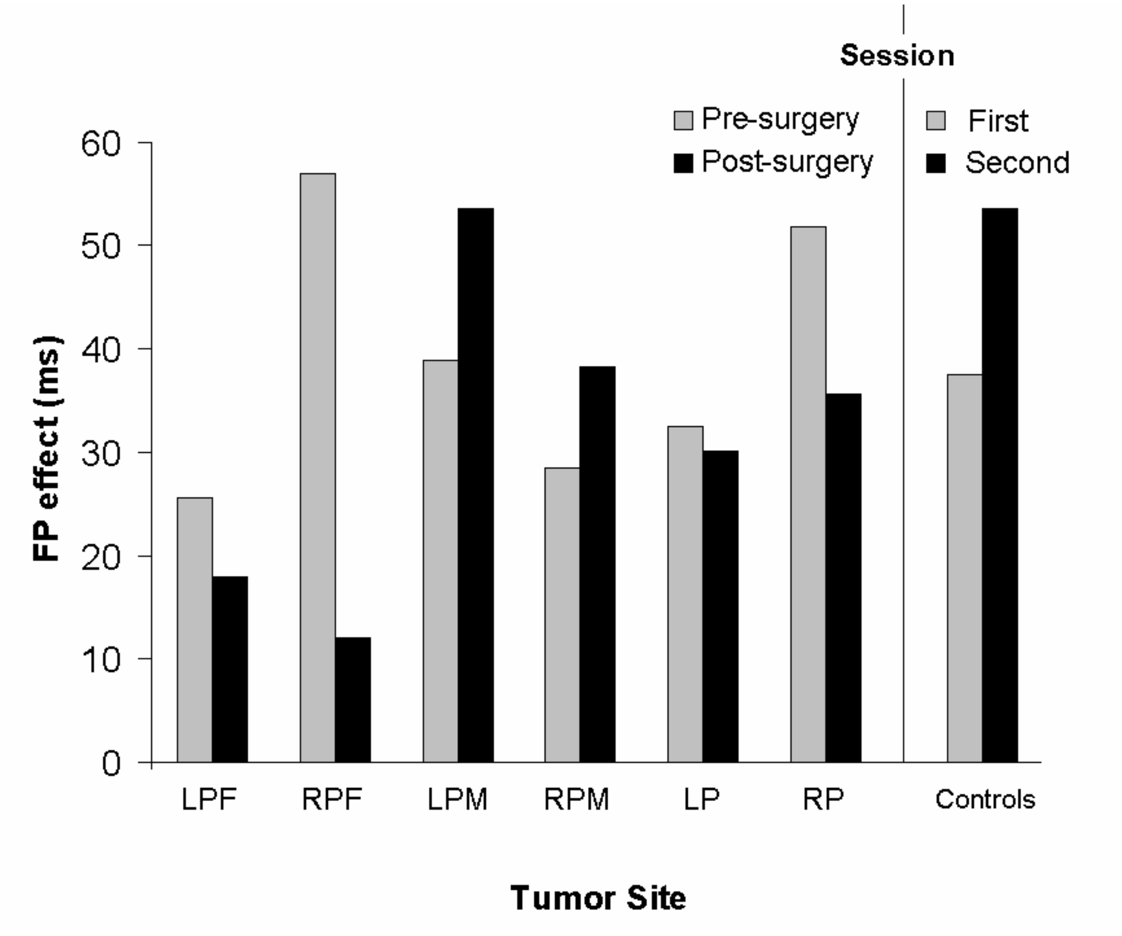

Figure 18. The foreperiod effect (reaction time difference between foreperiods of 3-4 and 6-7 seconds) as a function of patient group and testing session, experiment 9. FP = foreperiod. Tumor group labels as for figure 17.

The main effect of testing session was also reliable in this group [$F(1, 7) = 31.7$, $p < .001$], due to RTs being slower after the operation than before, which could conceivably arise from a motor effect, given that these patients were all right-handed.

Discussion

In this study, we aimed to investigate the variable FP phenomena on tumor patients, when tested before and after surgical removal of the tumor located in different cortical areas. The most important finding was a reduction of the FP effect after surgical removal of tumoral portions of the right prefrontal cortex. This finding corroborates recent studies on FP phenomena obtained in chronic patients with predominantly other etiologies such as stroke (Stuss et al., 2005), and in healthy participants undergoing inhibitory TMS over rDLPFC (experiments 7 and 8).

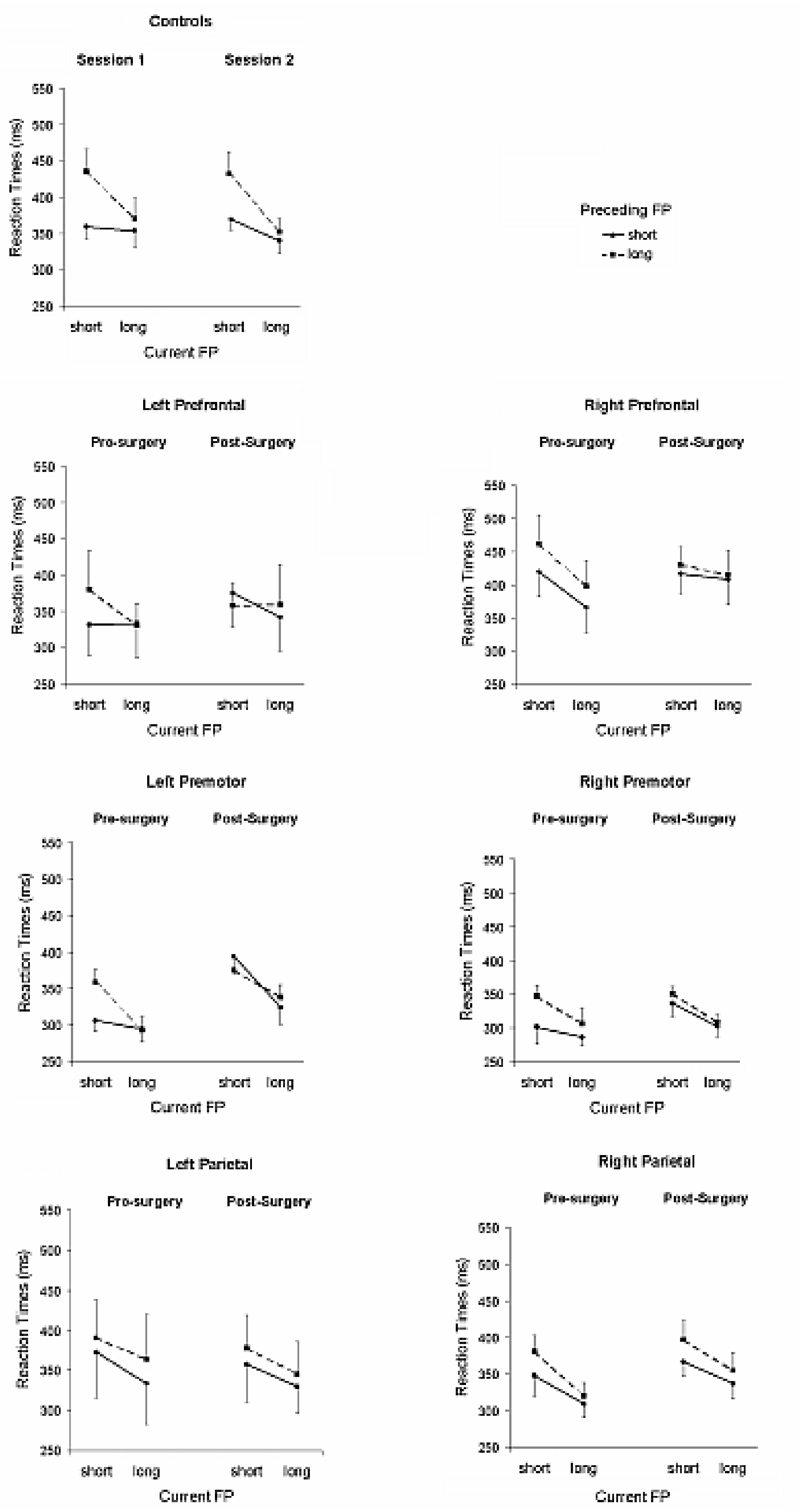

Figure 19. The sequential effects as a function of patient group and testing session, experiment 9. Short = 3-4 seconds. Long = 6-7 seconds.

Although obtained in such a simple experimental task, the FP effect is generally considered as a marker of high-level monitoring processes (e.g., Näätänen, 1970; Niemi & Näätänen, 1981; Stuss et al., 2005; but see Los & van den Heuvel, 2001). On this view, this result supports the hypothesis that right lateral PFC is the seat of the critical process producing the FP effect, that is monitoring of the increasing conditional probability of stimulus occurrence along the FP (e.g., Näätänen, 1970).

Unlike the previous neuropsychological work (Stuss et al., 2005), the current study additionally investigated the effect of the preceding FP, which is known to generate asymmetric sequential effects: RTs are slower for long FP_{n-1} than for short ones, but only when the current FP is a short one. In the overall ANOVA, there was a reduced effect of the FP occurring on the preceding trial, when performance in the second session was compared to that in the first session. This effect is difficult to interpret from the localizational point of view, as we did not found clear statistical evidence for the specificity of the tumor site.

More critically, a zoom on the behavior of the left premotor group could give some additional clue about the localization of the sequential effects and their underlying cognitive mechanisms. Despite the presence of an unchanged FP effect, sequential effects disappeared after operation when performance was compared within-group with the pre-surgery performance, as indicated by the significant session x FP_n x FP_{n-1} interaction in this group only. Specifically, there was no RT reduction after a short FP_{n-1} in the post-surgery session. This result may be interpreted suggesting a pre-motoric/motoric locus of a facilitatory effect carried over when a short FP had occurred in the previous trial. Left premotor areas are directly involved in the preparation of the manual key-press, which is the response required in this task. Supporting this hypothesis, an electrophysiological study on monkey premotor and motor cortex (Riehle & Requin, 1993) revealed that activity of neurons within this region may be predictive for performance speed in tasks were a preparation period was administered. During the delay period of a delayed-reach task, moreover, micro-stimulation of neurons within premotor cortex lead to a highly-specific lengthening in reach RT (Churchland & Shenoy, 2007). Nevertheless, prudence regarding localizational conclusions is imposed by the lack of interaction with the other patient groups in the overall ANOVA. Thus, this finding should be seen as a suggestion for further studies rather than as evidence fully supported by the current data.

However, functional conclusions can be drawn even in the absence of strong anatomical localization. Indeed, this finding represents the second component of a double dissociation between FP and sequential effects. On the one hand, we found a reduction in the FP effect as an effect of inhibitory TMS on the rDLPFC in the absence of a modulation in the sequential effects (see experiments 7 and 8). On the other hand, here it has been shown that sequential effects disappear after surgery in left premotor patients despite an intact FP effect. This pattern supports dual-process accounts of the FP phenomena (e.g., experiments 3a, 3b and 4, chapter 2; see also Los & Agter, 2005), and is much difficult to account for in single-process accounts (e.g., Los & van den Heuvel, 2001).

The functional meaning of sequential effects, therefore, needs to be revised. According to the dual-process account put forward in chapter 2 (experiments 3a, 3b and 4), the sequential effects may be due to a tonic arousal modulation by the FP_{n-1}. As maintaining a high level of preparation for a long FP is effortful, a long FP_{n-1} decreases arousal (refractoriness) and lengthens RTs on trial n, whereas a short FP_{n-1} increases arousal (facilitation) and produces relatively faster RTs on trial n (see Los & Heslenfeld, 2005, for electrophysiological evidence). This arousal modulation is especially detectable on the shortest current FP, when the compensatory effect of the conditional probability monitoring cannot take place. After tumor removal in frontal patients here, and especially left premotor patients, the second process (facilitation) seems to be impaired, so that RTs on a short FP_n do not benefit from a short FP_{n-1}, conceivably because the brain area where this arousal modulation should produce its effects (i.e., left premotor cortex) is not working properly due to the surgical lesion.

The effects of tumor per se on cerebral functionality are still almost unknown. However, there are a few studies investigating cognitive functioning of brain tumor patients before any treatment and surgical intervention, which found cognitive deficits caused by the presence of tumor (e.g., Rabbitt & Page, 1998; Tucha, Smely, Preier, & Lange, 2000). Therefore, a baseline evaluation of cognitive abilities before surgery is methodologically desirable in any study of tumor patients undergoing surgery. To that purpose, the use of a matched control group of orthopedic patients allowed us to exclude, at least before surgery, any particular deficit of our sample of tumor patients in performing the variable FP paradigm.

A critical aspect of the present results is that the effects found are selective and are generally robust across etiologies. Indeed, resection of a right prefrontal tumour gives the same reduction in the FP effect as in a cohort of patients primarily suffering from stroke in the same region (Stuss et al., 2005). From a methodological point of view, this study supports the one by Shallice and colleagues on optic ataxia (Shallice, Mussoni, D'Agostini,

& Skrap, submitted), demonstrating that the effects of operation for resection of tumors can be a valuable method for localizing cognitive processes.

In conclusion, the present findings confirm the studies on the anatomical basis of the FP effect (Stuss et al., 2005) and additionally provide surprising new neuropsychological results on the sequential effects. The latter are best explained by a dual-process account of the FP phenomena. Finally the findings strongly support the utility of using acute tumor patients as a source of evidence about the localisation and fractionation of cognitive functions.

Chapter 4

4.1. Spatial-temporal association of response codes (STARCO): a new stimulus-response compatibility effect

In a variable FP paradigm, FP duration is a task-irrelevant feature, because the participant is not explicitly required to attend to it in order to perform the task. When validly cued by an external signal for a short FP, participants do not produce sequential effects (e.g., Los & Heslenfeld, 2005; Los & van den Heuvel, 2001, see paragraph 1.2.1.2., Chapter 1). This shows that attention to the time in which a stimulus will occur may enhance the process of getting prepared and compensate for the sequential effects that typically occur after a short FP. In the first experiment of the study presented in this chapter (experiment 10), we wanted to test whether the explicit requirement of monitoring the FP length could produce a similar disappearance of the sequential effects as that obtained with cueing paradigms. The assumed reason for the disappearance of the sequential effects after valid cues is that participants know in advance the duration of the forthcoming FP, and they intentionally get prepared for it. In this way, they can compensate for the influences from the preceding FP. In a similar manner, we expected that, if participants would be required to respond according to the length of the FP, as a task-relevant feature, they would compensate for the influence of the preceding FP, not only on long current FPs but also on short ones (i.e., no FP_n x FP_{n-1} interaction). Although in this case participants are not explicitly cued by an external signal occurring at the beginning of each trial, they are implicitly cued by the initial task instructions symmetrically towards both the short and the long FPs.

4.1.1. Experiment 10

Experiment 10 was specifically intended to test whether, in a situation where elapsing time is task-relevant, the costs of not being fully prepared for the short FPs (i.e., the sequential effects) would be attenuated. To that purpose, a modified version of the variable FP task was designed, in which the participant was explicitly required to judge the FP duration.

Method

Participants

Twenty healthy volunteers (11 females and 9 males) took part in experiment 10. They were 25 years old on average (range = 18-32). All the participants were right-handed. The average score on the EHI (Oldfield, 1971) was 82 (range: 55-100). All participants volunteering in the whole study were Italian-speakers (mother tongue) and had a medium-high educational level (years of education ≥ 13). All of them were naïve to the purpose of the experiment and were paid 6 euros per hour.

Apparatus and Materials

Participants were tested individually in a quiet and normally illuminated room. A personal computer was used for stimulus presentation and response sampling. Visual stimuli were presented through a 19-inch VGA-display at a distance of ~60 cm. A central cross (2 yellow crossed bars, 1.0 x 0.5 cm) was used as fixation. The imperative stimulus consisted of a downward pointing white arrow (a 1.5 x 1 cm bar attached to a 0.5 cm arrowhead with a maximum width of 2 cm).

Procedure and Task

Before beginning the experiment, each participant was required to fill the Edinburgh Handedness Inventory (EHI). A trial started with the central fixation cross, lasting for a FP of 1 or 3 sec. The 2 values of the FP were presented randomly on an equal number of trials. After the FP elapsed, the arrow requiring a response was presented. The task consisted of pressing ‘Z’ for a short cross duration (i.e., 1 sec) and ‘/’ for a long cross duration (i.e., 3 sec). The stimulus duration/response key assignment was inverted after 160 trials. The order of presentation of the 2 possible S-R mappings was counterbalanced across participants. After a response was detected, a 1 sec blank separated one trial from the other. A familiarization block, consisting of 20 trials, preceded each experimental block with opposite S-R mappings (160 trials each). During this phase, a visual feedback was displayed for 1 second soon after the response. The feedback provided during the initial practice phases consisted of the green string (in Italian): “good! Go on with the next trial!”, for correct responses, the red string: “wrong response, be careful!” plus a sound (a 1500 Hz pure tone lasting 50 ms) for incorrect responses, and the red string: “too slow, try to be faster!” (plus the 1500 Hz sound) for slow responses (>1500 ms) or null responses. The familiarization phase was repeated until participants would make 2 errors or less. All participants, however, reached this criterion after 1-2 familiarization phases.

Data Analysis

Trials were treated as errors and discarded from the RT analyses if a response was made during the FP or the first 100 ms after the arrow onset (anticipated responses), if the RT was slower than 1500 ms or no response was detected (delayed and null responses), and if the FP judgment was incorrect. A preliminary 2x2 repeated measures ANOVA was performed both for accuracy and mean RTs of correct trials, with FP_n (1 vs. 3 sec) and FP_{n-1} as the within-subjects factors. As this interaction was significant in the initial analysis (contrary to the predictions), we introduced the factor of response side (left vs. right) as a new within-subjects factor for a 2 FP_n x 2 FP_{n-1} x 2 response side within-subject ANOVA, in order to check whether the FP effect and the sequential effects were differentially present in the two hands. Being the FP_n x response side cross-over interaction significant (see results), we wanted to test whether the opposite effects of response side on the short and long FPs_n correlated. To that purpose, the RT differences between left and right hand responses on the short and long FP durations were also analyzed by using a Pearson’s correlation.

Results

Accuracy

There were virtually no anticipated responses (0.1%) and delayed or null responses (0.7%). Moreover errors in judging the cross duration were less than 4.4%. No significant effect was observed in the ANOVA concerning accuracy.

Reaction Times

Reaction times are shown in Figure 20. The effect of FP_n (i.e., cross duration) was significant [$F(1, 19) = 182.6$, $p < .001$], indicating that RTs were faster for the long FP_n than for the short one (381 vs. 507 ms). The effect of FP_{n-1} was also significant [$F(1, 19) = 30.1$, $p < .001$], indicating that RTs were faster after a short FP_{n-1} than after a long one (426 vs. 462 ms). Critically, there was a significant FP_n x FP_{n-1} interaction [$F(1, 19) = 30.1$, $p < .001$, see Figure 20, panel A], demonstrating the classical sequential effect. RT was faster after a short FP_{n-1} than after a long one (476 vs. 541 ms; t-test, $p < .001$), but this difference was asymmetrically present only on the short FP_n and virtually absent on the long FP_n (376 vs. 384 ms). The FP x response side interaction was also significant [$F(1, 19) = 6.1$, $p < .05$; see Figure 20, panel B].

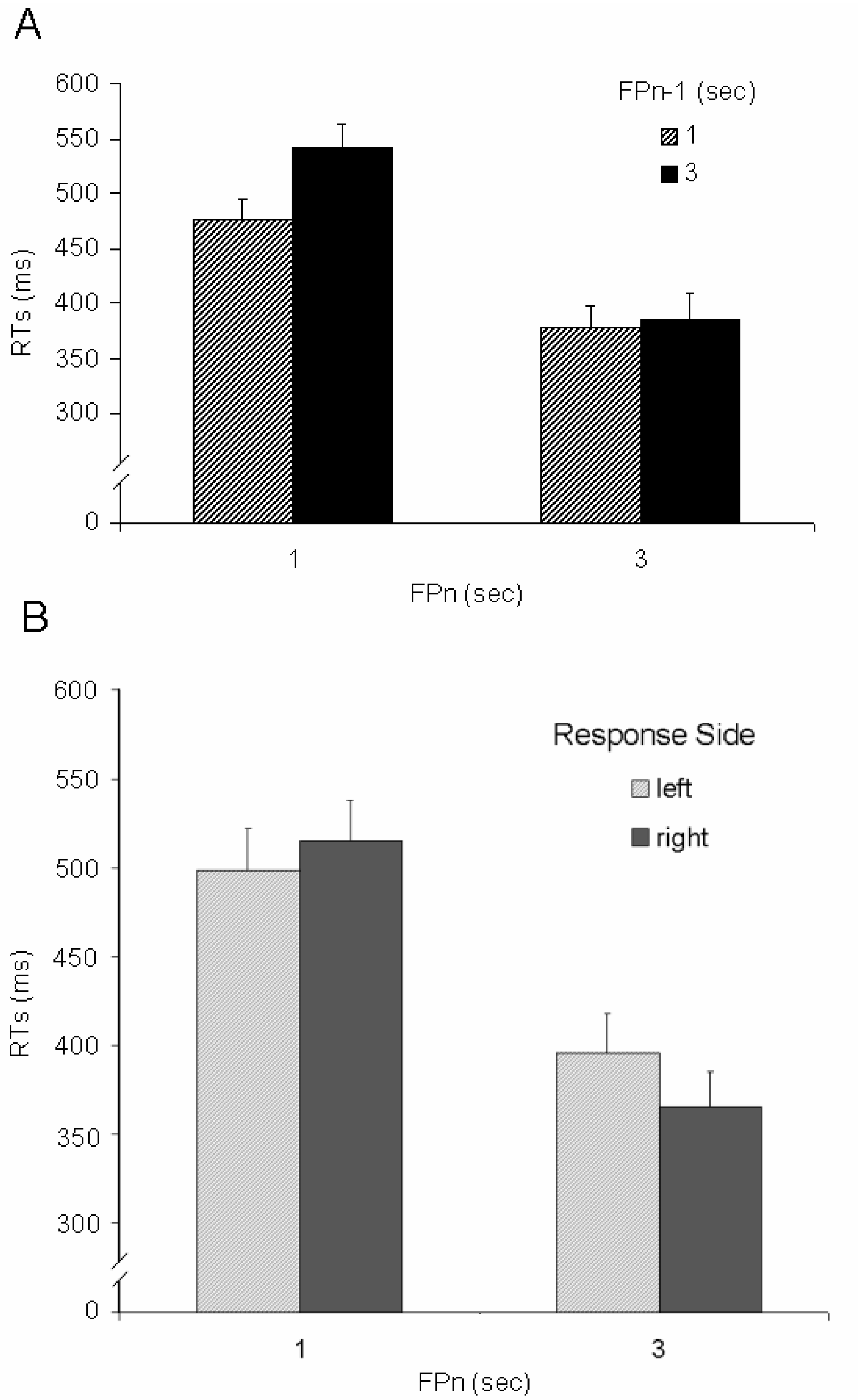

Figure 20. Mean reaction times in experiment 10. Panel A: mean reaction times shown as a function of the duration of the foreperiod occurring in the trial n (FPn, x-axis) and in the trial n-1 (FPn-1, histograms). Panel B: mean reaction times shown as a function of foreperiod duration in the trial n (x-axis) and of responding hand (histograms).

This interaction indicated that responding to the short FP was faster with the left hand than with the right one (499 vs. 516 ms), and responding to the long FP was faster with the right hand than with the left one (366 vs. 396 ms). T-tests comparing left vs. right hand RTs for the short duration and for the long duration were significant (for both, $p < .05$).

If the effects of response side on short and long FPs are due to different mechanisms, there is no reason why they should be correlated. On the other hand, if they are due to a common underlying mechanism, they should be correlated. To disentangle these hypotheses, a Pearson's correlation analysis was conducted between the effect size (i.e., RT difference between left and right response side) in the short and long duration conditions. This analysis showed a significant positive correlation ($r = .44$, $p < .05$, see Figure 21).

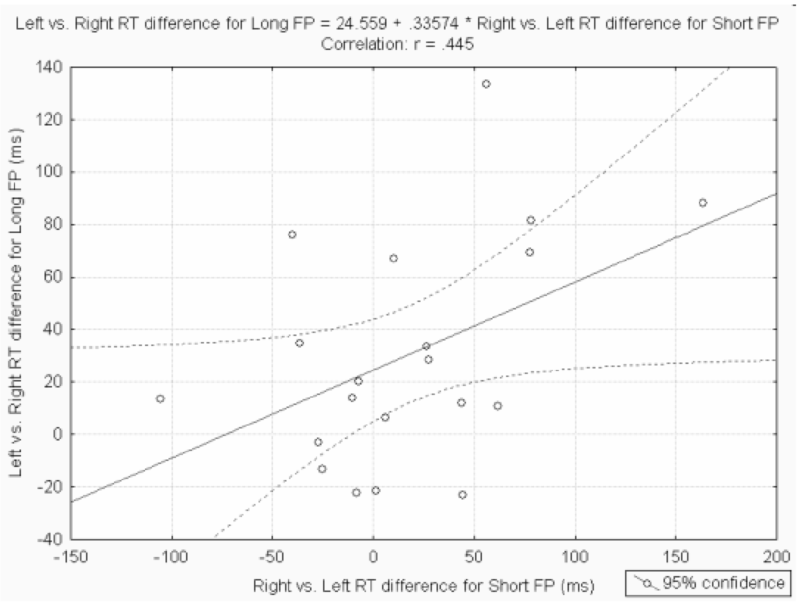

Figure 21. Pearson's correlation scatterplot (and confidence intervals) in experiment 1. Y-axis indicates Reaction Time differences between left and right responses for long foreperiods, whereas x-axis indicates Reaction Time differences between right and left responses for short foreperiods.

Discussion

The results of experiment 10 confirm the literature on the FP effect, and replicate this effect in a task where the FP duration is explicitly evaluated. This finding does not support our prediction that explicitly judging the FP could have had beneficial influences on the shortest FP_n. Specifically, we had predicted that, in a similar manner to when a valid temporal cue is used before the FP, sequential effects could disappear for the shortest FP_n if participants' attention had to be directed there because of the task demands (i.e., FP judgment). Critically, there was no influence of the task instructions on the sequential effects, as the FP_n x FP_{n-1} interaction was significant in the direction predicted by the null hypothesis (i.e., sequential effects asymmetrically biased towards the shortest FP_n with no effect of the task-relevant FP; see also Footnote 10, on page 131). Therefore, the alternative hypothesis of an influence of the explicit FP judgment on the sequential effects should be rejected. In other words, the information given by the initial instructions about the relevance of both the short and long FPs for the response was not sufficient to overcome the sequential effects. These effects, being a rather automatic and robust phenomenon (Los & van den Heuvel, 2001; see also experiment 6, paragraph 2.4.1.), did not disappear with the task-relevant FP length, probably because reaching an optimal preparation level for the shortest FP in the range is effortful (especially after a long FP in the preceding trial), and can be achieved only when participants are prompted to get prepared for the shortest FP, in a phasic fashion, at the beginning of each trial (and not tonically, through the initial task instructions). Indeed, a trial by trial temporal cueing procedure has been demonstrated to be more effective, for valid cue conditions, to reach a rather optimal preparation level even for short FPs (e.g., Coull & Nobre, 1998; Coull et al., 2000). In such a condition, sequential effects are significantly attenuated (Los & van den Heuvel, 2001).

An intriguing finding of this experiment is that the speed in judging the FP length (operationalized with the duration of the fixation cross) is not constant, but depends on the side of the response: responding to a short FP with the left key and to a long FP with the right key is faster than responding with the opposite S-R mapping. The opposite effects of using left and right hands on the short and long durations correlated across subjects, suggesting (although not demonstrating) a common underlying mechanism.

A possible interpretation of the S-R compatibility effect found here is that elapsing time is cognitively represented by a spatial vector running from left to right. Spatial attention would shift accordingly from left to right as time elapses, producing an ‘irrelevant’ response code, which develops continuously according to the spatially represented mental timeline, namely from left to right. This in turn may produce effects similar to some well-known spatial S-R compatibility effects, like the Simon effect (e.g., Hommel & Prinz, 1997). Thus, performance would be facilitated during the blocks in which the relevant response code (given by the instructions associating duration to a response) corresponds to the formally irrelevant directionality code, and delayed during the blocks in which the relevant and the irrelevant response codes go in opposite directions. In the latter case, indeed, the irrelevant response code would need to be inhibited before the ‘relevant’ correct response can be executed slowing RTs down. However, before developing this explanation further, alternative interpretations need to be carefully considered.

4.1.2. Experiment 11

A variable FP paradigm (e.g., Niemi & Näätänen, 1981) was used in the experiment 10. In this paradigm, different FPs (i.e., cross durations) alternate randomly and equiprobably across trials. As a result, RTs are faster for longer FPs than for shorter ones. This is the so-called FP effect (Woodrow, 1914). Therefore, an alternative explanation of a compatibility phenomenon between FP duration and response side found in experiment 10 could be due to the presence of a greater FP effect on either responding hand. This explanation would fit results of other compatibility effects, such as the Simon effect, which is known to be larger with the dominant hand than with the non-dominant one (e.g., Rubichi & Nicoletti, 2006). It is not possible to test this specific hypothesis directly from experiment 10 because, in each mapping, the FP effect was given by the combination of right and left hand responses within the same block. Experiment 11 directly investigated this explanation by using a variable FP paradigm embedded in a simple RT task, where only one hand had to respond in each block.

Method

Participants

Fourteen healthy participants (10 females and 4 males) volunteered in experiment 2. They were 26 years old on average (range = 21-35). Apart from 2 left-handed participants (EHI: -55 and -80, respectively), all the others were right-handed. The average score on the EHI was 63.6 (range from -80 to 100).

Apparatus and Materials

Apparatus and materials were basically the same as in the experiment 10. The only difference was that participants had to keep the index finger of the responding hand on the keyboard spacebar.

Procedure and Task

A trial started with the presentation of the fixation cross, which marked the beginning of the FP (i.e., 1 vs. 3 sec, 50% each, random presentation). When the FP ended, an arrow replaced the fixation. Participants were required to respond as fast as possible to the arrow by pressing the spacebar, with their right index finger in one block, and with their left index finger in the other block. The order of presentation of the 2 blocks was counterbalanced across participants. The arrow was removed by the response key press. After a blank interval of 1 sec, a new trial started. Two blocks of 80 trials (40 per each FP) were presented during each session to each participant. Ten practice trials preceded each experimental block.

Data Analysis

Trials were treated as errors and discarded from the RT analyses if a response was made during the FP or the first 100 ms after imperative stimulus onset (anticipated responses), or if the RT was slower than 1500 ms or no response was detected (delayed and null responses). Mean RTs were submitted to a 2 FP (1 vs. 3 sec) x 2 responding hand (left vs. right) repeated measures ANOVA[8].

Results

Accuracy

Anticipated and delayed responses were 1% and 0.14% of the total, respectively.

Reaction Times

The FP effect was the only significant effect found in the ANOVA concerning RTs [$F(1, 13) = 37.2$, $p < .001$, see Figure 22], due to RTs being faster for the long FP than for the short one (314 vs. 361 ms). In particular, the FP x responding hand interaction was far from significant [$F(1, 13) = .2$, $p > .88$]. After the exclusion of the 2 left handed participants, the pattern of ANOVA results was basically the same. Moreover, the EHI score did not correlate with the RT difference between the left and right hand responses for short and long FPs [r = -.37, $p = .2$; r = .49, $p = .08$, respectively].

Discussion

---

[8] Although the FP on the preceding trial is known to interact with FP on the current trial (i.e., sequential effects; e.g., Niemi & Näätänen, 1981), analyses of experiment 10 did not show any significant interaction between the FP on the preceding trial and response side, which is relevant for the present purposes. For this reason, the preceding FP factor was not included in the subsequent analyses (also in the next experiments).

Experiment 11 was designed to test whether the FP effect was greater when responding with the right hand than with the left one. No difference between hands was observed at all (even when the 2 left-handed participants were excluded) and the EHI score did not correlate with any between-hands RT difference either in the short or long FP condition. This pattern of results does not support the possibility that the FP by hand interaction found in the experiment 10 can be explained in terms of a greater FP effect with either hand. However, experiment 11 did not require competition between the 2 hands, as responses had to be given with one hand at a time in 2 separate blocks of a simple RT task.

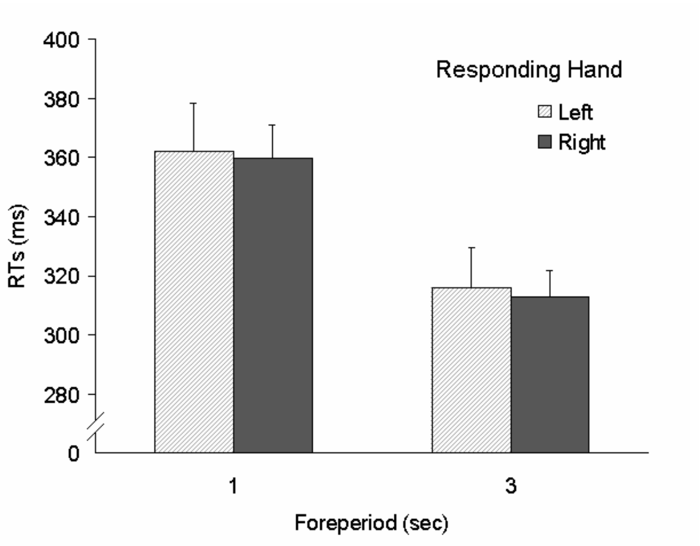

Figure 22. Mean reaction times (and standard errors) in experiment 11 as a function of foreperiod duration (x-axis) and responding hand (histograms).

4.1.3. Experiment 12

Results of experiment 11 excluded an account of the compatibility effect found between temporal duration and responding hand concerning a differential FP effect size in either hand. However, the possibility remains that the mechanism underlying the critical interaction in the experiment 10 derives from a within-trial competition between responding hands/hemispheres. For instance, it might be supposed that left hand/right hemisphere is better in responding to rapid temporal durations, and right hand/left hemisphere is better in responding to slower temporal durations, and that this differential ability would appear only when the selected response side switches within-trials.

In order to choose between an explanation of the superiority of the left-short/right-long mapping in terms of the response spatial position (i.e., left vs. right response key), and another in terms of the responding hand (i.e., right vs. left hand), in experiment 12 a manipulation was adopted, which is well-known in the spatial compatibility literature (e.g., Dehaene, Bossini, & Giraux, 1993; Rubichi & Nicoletti, 2006; Wallace, 1971): participants had to respond with their hands crossed, so that the right hand should press a left key and the left hand should press a right key. In this case, the response position and the anatomical identity of the effector do not correspond.

If the interaction observed in the experiment 1 arises from asymmetric proprioceptive or motor skills between the two hands/hemispheres, we should observe an inversion of the compatibility effect with respect to the keys. If the interaction is instead due to some preferred association between the left visual hemispace with short FP and the right visual hemispace with long FPs, no change should be observed in the interaction for the response keys compared to experiment 10.

Method

Participants

Seventeen healthy volunteers (11 females and 6 males) took part in experiment 12. A male participant was excluded because he did not follow the instructions throughout, as he used an anatomical hand position for one block (i.e., left hand on the left key and right hand on the right key). The final sample used for the analyses therefore consisted of 16 participants. They were 27 years old on average (range = 21-32). All participants apart from one were right-handed (mean EHI score: 65; range from -75 to 100).

Apparatus and Materials

The apparatus and materials were the same as in the experiment 1 apart from the following exception. For the responses, participants had to keep their hands crossed. The key located to the left of the body midline (‘Z’) was pressed by the right index finger, whereas the key located to the right (‘/’) was pressed by the left index finger.

Procedure and Task

Two blocks of 160 trials each were administered. In one block, the ‘Z’ key had to be pressed by the right hand after a short cross duration, and the ‘/’ key had to be pressed by the left hand after a long cross duration. The opposite S-R mapping was applied in the other block. The order of presentation of the 2 blocks was counterbalanced across participants. Half of each block was performed with the right hand standing on the top of the left one and the other half was performed with the left hand on the top of the right one. Half of the participants started each block with one position and then switched position after 80 trials. The opposite order was used for the other half of the participants. A practice phase with 20 trials (10 per each FP) was given at the beginning of each block. Similar feedback to that employed in experiment 1 was displayed at the end of each trial during the practice phase.

Data Analysis

The same criteria as in experiment 1 were used to exclude incorrect trials. Accuracy and mean RTs of correct trials were analysed by means of a 2 FPs (short vs. long) x 2 response side (left vs. right key) repeated measures ANOVA.

Results

Accuracy

There were virtually no anticipations during the FP. The FP x response side interaction was significant [$F(1, 15) = 8.4$, $p < .01$; see Figure 23]. Participants tended to make less errors when they had to respond to the short FP duration by pressing the key on the left side than by pressing the key on the right side (96.9 vs. 95.8 %, respectively; t-test n.s.), whereas the pattern was inverted when they had to respond to the long FP duration (98.2 vs. 96.2 %, with the right and left keys, respectively; t-test, $p < .05$).

Reaction Times

The FP effect was the only significant effect found in the ANOVA for RTs [$F(1, 15) = 67.6$, $p < .001$, see Figure 23], due to RTs being faster for the long FP than for the short one (348 vs. 471 ms). In particular, the interaction between FP and response side was far from significant [$F(1, 15) = .87$, $p = .37$].

Discussion

The only difference in the procedure with respect to experiment 10 was that in experiment 12 participants responded with crossed hands. Results showed a complete lack of interaction between responding hands (and response keys) and FP duration in terms of RTs, although an interaction was present in terms of accuracy. The RT null effect shows that, when hands are crossed, so that right hand is used with the left key and left hand with the right key, the S-R compatibility effect between response side and FP duration found in experiment 10 totally disappears, suggesting that this effect requires hands anatomically positioned on the spatially corresponding response key in order to occur in terms of speed. However, the null effect is uninformative about whether a key-related or a hand-related explanation applies to the compatibility effect found in experiment 10. Indeed, to be compatible with the first account, the results should have been the same as in experiment 10, when response keys are considered. Conversely, to be compatible with a hand-related account, the results should have been the opposite of those obtained in experiment 10, when response keys are considered.

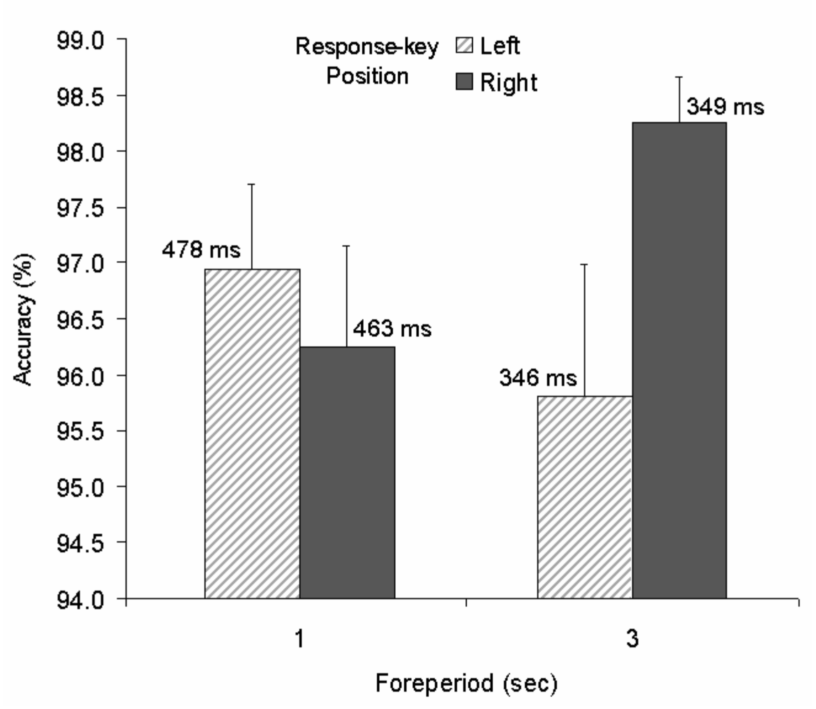

Figure 23. Mean percentage of correct responses (bars: standard errors) and reaction times in experiment 12 as a function of foreperiod duration (x-axis) and response-key position (histograms).

However, the compatibility effect was present here for accuracy, as responses to the short FP tended to be more accurate when the left key (right hand) was pressed rather than the right key (left hand), whereas responses to the long FP were significantly more accurate with a right key-press than with left one. The shift of the S-R compatibility effect from speed to accuracy could suggest a change in the task difficulty and especially in the participants' strategy. Specifically, participants may have decided to perform the ergonomically challenging task at a relatively high speed (409 ms here vs. 443 ms in experiment 10, where hands were anatomically positioned), with the result of making more errors in the more difficult conditions (i.e., left and right key-presses for long and short FPs, respectively). Notably, the direction of this interaction, although only partially supported by subsequent t-tests, is in line with an account relating the compatibility effect to the spatial position of the response target (i.e., keys) rather than of the responding effectors (i.e., hands), in analogy with other spatial compatibility effects (e.g., Riggio, Gawryszewski, & Umiltà, 1986).

4.1.4. Experiment 13

Experiment 12 tested whether asymmetries between hands/hemispheres could be responsible for the compatibility effect found in experiment 10 using crossed hands. This manipulation, however, failed to produce a clear compatibility effect between responding hands (or keys) and FP duration, at least in terms of RTs, such that it was impossible to choose between accounts related to manual/hemispheric asymmetries and accounts related to the spatial positions of the response keys. Following an analogue rationale, in experiment 13 two fingers of the dominant hand were used for the response, in order to check if there is a temporal S-R compatibility effect between temporal duration of the stimulus and spatial position of the response even within one hand. Thus, the index and middle fingers of the dominant hand were used to give the responses. If the response key relative positions (and not hands) matter, there should be a similar compatibility effect as that found in the experiment 10 even within a single hand. In other words, if the effect found in experiment 10 manifests itself even within one hand, any explanation concerning hemispheric asymmetries should be discarded.

Method

Participants

Eighteen healthy volunteers (11 females and 7 males) took part in experiment 13. They were 26 years old on average (range = 21-35). All participants were right-handed (EHI: 75; range 20-100). Two extra participants were previously discarded from the analyses because they declared to have systematically counted in order to estimate the cross duration (see Procedure).

Apparatus and Materials

The same apparatus and materials were used as in experiment 10, apart from the fact that responses were not bimanual but should be given using the index and middle fingers of the dominant hand.

Procedure and Task

The procedure and task were similar to those adopted in experiment 10. The only difference was that the response should be given by pressing a key (‘B’) with the index finger of the dominant hand and another key (‘N’) with the middle finger of the same hand. The ‘B’ and ‘N’ keys were labeled and referred to in the instructions with a red and green color, respectively, in order to avoid linguistic biases. Indeed, a couple of pilot participants reported that it was difficult to associate the ‘B’ label to a long duration because ‘B’ is the initial letter of the word ‘brief’ (in Italian: ‘breve’). The red and green keys were inverted for half of the participants (i.e., ‘N’ = red; ‘B’ = green). In one block, participants had to press the key labeled with one color for a short cross duration, and the key labeled with another color for a long cross duration. In another block, the key-duration associations were inverted. The order in which the 2 key-duration mappings were administered was counterbalanced across participants. A familiarization phase (20 trials) with a feedback procedure similar to that used in experiment 10 was adopted also here at the beginning of each block. After each familiarization phase, a test phase followed with 80 trials with a cross duration (i.e., FP) randomly varying between 1 and 3 seconds (50% each). Upon completion of the study, participants received a post-experimental questionnaire. In a first question, participants were asked if they had counted or used other strategies to perform the task. In a second multiple choice question, they were asked to choose a directionality for their representation of elapsing time. The available response choices were: left-right, right-left, top-down, bottom-up, clockwise, counterclockwise. The order with which these alternatives appeared varied randomly across participants. The option ‘other’ was also provided.

Data Analysis

Trials were treated as errors using the same criteria as in experiment 1. A 2 FP duration (1 vs. 3 sec) x 2 response side (left vs. right) ANOVA was employed for both accuracy and mean RTs on correct trials.

Results

Accuracy

Anticipated responses were the 0.13%, delayed and null responses were the 0.27%, incorrect FP judgments were the 5%. No effect was significant in the ANOVA concerning accuracy of the FP judgment.

Reaction Times

The main effect of FP was significant [*F*(1, 17) = 73.4, *p* < .001], due to RTs being faster for a long FP than for a short one (340 and 427 ms, respectively). Critically, the FP x response side interaction was also significant [*F*(1, 17) = 9.3, *p* < .01, see Figure 24]. This interaction was due to RTs being faster when the short FP (i.e., short cross duration) was responded to with the left key (i.e., 'B') rather than with the right key (411 vs. 443 ms, t-test, *p* = .01), and when the long FP was responded to with the right key (i.e., 'N') rather than with the left key (328 vs. 352 ms, t-test, *p* < .05).

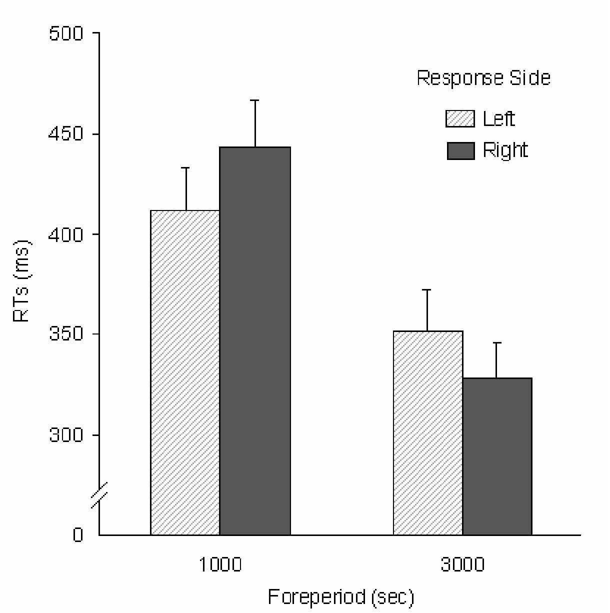

Figure 24. Mean reaction times (and standard errors) in experiment 13 as a function of foreperiod duration (x-axis) and response side (histograms).

As in experiment 10, a further Pearson's correlation analysis was conducted between the effect size (i.e., RT difference between left and right response side) in the short and long duration conditions. This analysis showed a trend for a positive correlation (r = .42, *p* = .078), partially confirming results of experiment 10.

Debriefing

As reported above, 2 participants out of 20 stated that they systematically used a strategy to give their response. This strategy consisted of counting how many seconds each FP lasted (sub-vocal pronunciation). More importantly, when asked to give a directionality to elapsing time by choosing one of 6 alternative answers, 18 participants chose the left-to-right option, 1 participant chose the clockwise option, and another participant chose the top-to-down option.

Discussion

The key result of experiment 13 was the response side by FP interaction, which showed that the compatibility effect found in experiment 10 using 2 hands can be also replicated when 2 fingers of only one hand are used for the response. Indeed, during the block in which the left key had to be pressed after a short cross duration and the right key had to be pressed after a long duration, RTs were faster than during the block in which the key-duration mapping was reversed (i.e., left key = long duration; right key = short duration). It should be noted that response keys were never labeled as ‘left’ and ‘right’ during the instructions given to the participants, but only through labels corresponding to their color (i.e., ‘red’ and ‘green’, assignment to the left and right response keys counterbalanced across participants).

The pattern of data obtained in the experiment 13 suggests that the compatibility effect between response keys and FP durations found in the experiment 10 cannot be accounted for with explanations concerning hemispheric asymmetries, competitions between hands, or handedness (all the participants were right-handed here). During the post-test questionnaire, 18/20 participants declared they represented elapsing time from left to right. Although the possibility exists that they developed this representation because it was suggested by the modality of response (left vs. right key), this result is in line with other studies (e.g., Traugott, 1975; Zwaan, 1965, quoted by Winn, 1994; Tversky, Kugelmass & Winter, 1991), where no analogous task was performed by participants before the questionnaire. Moreover, 3 participants spontaneously declared during the post-experimental debriefing to have had the subjective feeling that the short-left/long-right association was more natural and easier.

4.1.5. Experiment 14

Recently, Nuerk and colleagues (Nuerk, Iversen, & Willmes, 2004) showed that linguistic markedness may account for S-R compatibility effects in different domains. In many languages, there are pairs of complementary words one of which is marked and the other unmarked. Markedness may depend on lexical factors (Zimmer, 1964), such as the presence of prefixes (e.g., ‘clear’ vs. ‘un-clear’), or on so-called distributive and semantic factors (e.g., ‘right’ vs. ‘left’, Lyons, 1969). According to the linguistic markedness account, performance would be facilitated when the adjectives used to label the stimulus and the response have a congruent markedness status (i.e., both are marked or unmarked), and hindered when their markedness is incongruent (one is marked and the other unmarked). This hypothesis has been proposed for instance to explain the parity effects with numbers (Nuerk et al., 2004). As an example, in a parity judgment task, left hand responses are faster for odd numbers than for even ones because, according to the markedness account, ‘left’ and ‘odd’ are both marked linguistic labels; by contrast, right hand responses are faster for even numbers than for odd ones, as ‘right’ and ‘even’ are both unmarked. Incongruent combinations (marked-unmarked), instead, are held to lead to interference. It is possible that a similar account also applies for the S-R compatibility effect found in experiment 10. In other words, the linguistic label ‘short’ might be associated to the ‘left’ because both are marked, whereas the label ‘long’ might be associated to ‘right’, both being unmarked. If this linguistic explanation is the only factor accounting for the data, a categorical relationship should be predicted between ‘short’ durations and ‘left’ hand responses and ‘long’ durations and ‘right’ hand responses, even if the FP durations to be judged as ‘short’ and ‘long’ are not just two (categorical), but are parametrically varied along a continuum. On the other hand, if other factors influence this effect like, for instance, a continuous spatial representation of elapsing time from left to right, a gradual influence of the FP duration should be observed on the S-R compatibility effect found in the experiment 10, such that the RT difference between left and right hand responses should increase with duration. Experiment 14 aims to assess these alternative hypotheses.

Method

Participants

Data from 27 healthy volunteers (17 females and 10 males) were included in the analyses of experiment 14. These participants were 26 years old on average (range = 21-34). All were right-handed. The average score on the EHI was 78.2 (range: 30-100). One extra female participant was previously discarded from the analyses because she declared to have systematically counted in order to estimate the cross duration (see Procedure).

Apparatus and Materials

Apparatus and materials were the same as in experiment 10, with the following exception: the fixation cross lasted for a FP of 0.5, 1 or 1.5 sec (‘short’ duration) and for a FP of 2.5, 3 or 3.5 sec (‘long’ duration).

Procedure and Task

The procedure and task were basically similar to those used in the experiment 10, apart from the following exceptions. The 6 values of the FP (i.e., cross duration) were presented randomly on an equal number of trials (30 per each). The task consisted of pressing ‘Z’ for a short cross duration (i.e., 0.5, 1 and 1.5 sec), and ‘/’ for a long cross duration (i.e., 2.5, 3, and 3.5 sec). The stimulus duration/response key assignment was inverted after 180 trials. The order of presentation of the 2 possible S-R mappings was counterbalanced across participants. A familiarization block, consisting of 24 trials (4 per each cross duration), preceded each experimental block with opposite S-R mappings (180 trials each). During this practice block, similar feedback to that used in the previous experiments was provided at the end of each trial. The familiarization block was repeated until a criterion of 3 errors or less was reached. No more than 3 familiarization cycles were necessary for any participant. As for experiment 13, after the completion of the test, participants were asked whether they had counted or used other strategies in order to perform the task.

Data Analysis

The same criteria as in experiment 10 were used for the analysis of the errors. A 6x2 repeated measures ANOVA was performed both for accuracy and mean RTs of correct trials, with FP (0.5, 1, 1.5, 2.5, 3, and 3.5 sec) and response side (left vs. right) as the within-subject factors.

Results

Accuracy

Anticipated and delayed responses were 0.53% and 1.6%, respectively. Overall errors in judging the cross duration were 10.9%. The ANOVA concerning accuracy showed only the main effect of the FP duration [$F(5, 130) = 15.8$, $p < .001$]. Percentage of accurate trials was 96, 94, 84, 77, 89, 94, respectively, for the six FPs from 0.5 to 3.5 sec. Post-hoc Tukey tests indicated that accuracy was lower on the FP of 2.5 sec than on all the other FPs except for that of 1.5 sec (for all the other comparisons, $p < .05$). Moreover, accuracy was lower on the FP of 1.5 sec than on the FPs of 0.5 and 1 sec (for both, $p < .05$). No other effect was significant.

Reaction Times

There was a main effect of FP [$F(5, 130) = 39.4$, $p < .001$]. Subsequent planned comparisons showed that RTs were different for every two adjacent FPs apart from FPs of 0.5 and 1 sec (for all the other comparisons, $p < .05$). RTs were 552, 557, 602, 524, 461, and 425 ms, respectively, for each FP from 0.5 to 3.5. More relevant for the present purposes, there was a significant FP x response side interaction [$F(5, 130) = 6.7$, $p < .001$]. This interaction indicated that responding to the short FP was faster with the left hand than with the right one, while responding to a long FP was faster with the right hand than with the left one (see Figure 25).

In order to discriminate whether the RT difference between left and right hand responses varies as a stepwise or as a linear function of the FP duration, subsequent paired t-tests were carried out to evaluate the significance of this difference on each FP. These tests revealed that this difference was significant (with opposite directions) in the extreme FPs only (for the FP of 0.5 sec: $p < .05$; for the FP of 3 and 3.5 sec: $p < .01$ and .05, respectively). This pattern was compatible with a linear function[9]. However, in order to reject a description of the data in terms of a stepwise function, the between-hands RT difference within the 3 short FPs on one side, and within the 3 long FPs on the other, should show a significant increase within each FP subset as the FP gets longer. We

---

[9] A possible confound in the interpretation of these data is represented by the fact that judging intermediate FP durations was more difficult than judging extreme FP durations, as demonstrated by the fact that responses to a FP of 1.5 sec were the slowest and responses to a FP of 2.5 sec were the less accurate. This difficulty (i.e., floor effect) could partially explain why the RT difference between responding hands did not appear at intermediate FPs. Nonetheless, this explanation does not suffice to account for all the data, as it would not explain why the compatibility effect is absent even for the FP of 1 sec, where accuracy and RTs are perfectly comparable to those for the FP of 0.5 sec (where the effect is present).

performed two subsequent separate one-way ANOVAs to test this, with the FP as the only within-subject factor (3 levels: 0.5, 1 and 1.5 sec for the short FPs, and 2.5, 3, 3.5 sec for the long ones), and the between-hands RT difference as the dependent variable. Only the ANOVA for the long FPs showed a significant effect of the FP [$F(2, 52) = 5.8$, $p < .01$], which was due to a difference between the FP of 2.5 sec and that of 3 sec ($p < .01$; any other difference was not significant). On the other hand, the results of the ANOVA for the short FPs were far from significant ($p = .5$). Given this outcome, a stepwise function seems to better account for the present data.

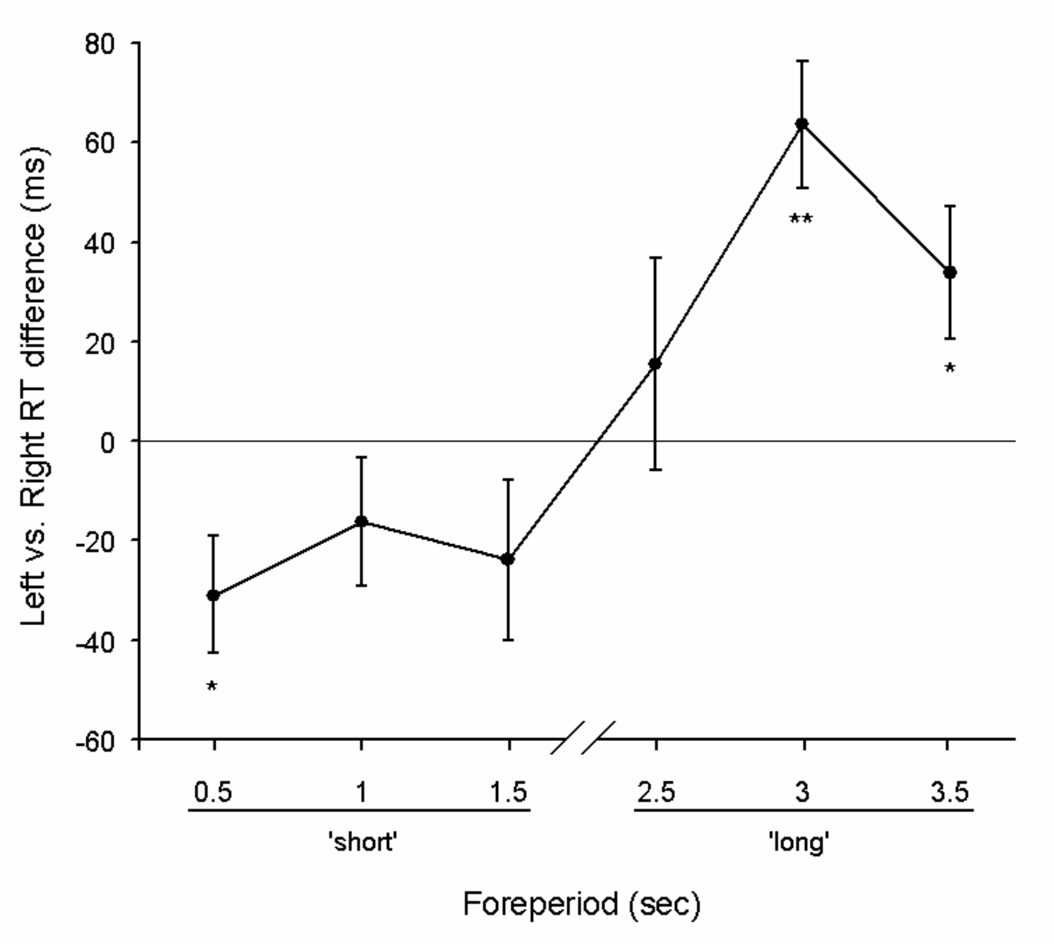

Figure 25. Mean reaction time difference between left and right hand responses (and standard errors) in experiment 14 as a function of foreperiod duration (x-axis). Reaction time differences between left and right hands for each foreperiod were evaluated by means of paired t-tests: * = t-test $p < .05$; ** = $p < .01$.

Discussion

Experiment 14 was designed to test whether the compatibility effect between responding hand and FP duration was present as a continuum when the FP length was parametrically varied, or it was categorical for ‘short’ vs. ‘long’ FP ranges. We found that the compatibility effect was present as an advantage of the left hand for the shortest FP and of the right hand for two longest FPs only, with similar effects being in the same direction but not significant for more intermediate FP values. This pattern cannot be accounted for by the linguistic markedness hypothesis, which instead predicts that the effect would follow a stepwise function of the FP: an advantage of ‘left’ hand responses for all the three ‘short’ FPs (0.5, 1, and 1.5 sec), and an advantage of ‘right’ hand responses for all the three ‘long’ FPs (2.5, 3, and 3.5 sec). More critically, however, the RT difference between the left and the right hand did not increase linearly along the 3 short and the 3 long FPs. This pattern is more in accord with the hypothesis that the compatibility effect follows a stepwise function.

Therefore, data of the present experiment support only partially our original hypothesis that elapsing time is progressively represented from left to right, and that this dynamic representation would be responsible of the S-R compatibility effect found in the experiment 10. On the contrary, the data of experiment 14 suggest that this compatibility effect is due to more categorical factors, as predicted, for instance, by the linguistic markedness hypothesis put forward in other domains (Nuerk et al., 2004; but see General Discussion).

General Discussion

This study started from the prediction that explicitly judging the FP could attenuate sequential effects on the shortest FP_n. According to this hypothesis, in a similar fashion to what happens when a valid temporal cue is used before the FP_n, sequential effects could disappear for the shortest FP_n. In a temporal cuing paradigm (with a higher rate of valid cues than of invalid ones), participants orient their attention on the shortest FP_n when they know in advance that the imperative stimulus will occur just after it (e.g., Los and van den Heuvel, 2001). In the current experiment, we expected that participants’ attention should be oriented already on the shortest FP, as the FP length is the feature critical for the response. The results did not fit with this hypothesis, as the FP_n x FP_{n-1} interaction was significant, indicating that sequential effects were not affected by the task demands[10].

---

[10] It could be that the sequential effects, even if present, were attenuated in this task. To test this possibility, experiment 11 provides a baseline condition (no explicit temporal judgment was required). It should be pointed out that the two experiments are not perfectly comparable, because also the task was different (choice vs. simple RT task). However, it is known that sequential effects are not influenced by the number of alternative responses (e.g., Los & van den Heuvel, 2001). Thus, we performed a 2x2x2 mixed ANOVA with

A new effect was found, instead, which can be ascribed to the S-R compatibility phenomena (e.g., Hommel & Prinz, 1997). In a series of experiments it has been shown that when a response is given according to the temporal duration of a stimulus, the response side affects performance. Specifically, participants are faster if they respond ‘short’ with the leftmost response and ‘long’ with the rightmost response than vice versa (e.g., experiment 10). This pattern suggests that elapsing time is internally mapped onto spatial representations.

The mechanism responsible for this phenomenon seems to be independent of asymmetries between hands in the magnitude of the variable FP effect, because when the responses are given by only one hand per block, the FP effect produced by the two hands was comparable (experiment 11). When participants cross their hands (experiment 12), the effect disappears in terms of speed, but manifests itself in terms of accuracy with respect to key position. In addition, any simple interpretation based on handedness or hemispheric asymmetries also has problems because the effect is also found (if response keys are considered) when two fingers of only one hand are used for the response (experiment 13).

Experiment 14 tested whether the RT difference between left and right hand responses varied categorically with the FP label (‘short’ vs. ‘long’) or parametrically with the FP effective duration (i.e., FPs from 0.5 to 3.5 sec). The results were only partially compatible with a parametric modulation of the S-R compatibility effect found (see Figure 25). On the one hand, the RT difference between left and right hand responses was significant only for extreme FP values, compatible with the hypothesis that passing time is continuously represented from left to right, at least in this task. On the other hand, this compatibility effect was not significantly different within the three short FPs, and the only difference found within the long FPs was that between the shortest and the medium one (i.e., 2.5 and 3 sec). This pattern is better fitted by a stepwise function between temporal duration and the between-hands RT difference. One way to account for this stepwise function is by attributing the compatibility effect to the linguistic categories used to label S-R features according to the linguistic markedness hypothesis (cf., Nuerk et al., 2004). On this hypothesis, ‘left’ and ‘short’ would be marked words (possibly at the semantic level), whereas ‘right’ and ‘long’ would not. That would explain why the left-short/right-long mapping is more advantageous than the opposite mapping (i.e., compatibility between the

---

FP_n and FP_{n-1} as repeated measures and experiment (experiment 10 vs. 11) as the between-subject factor. The results critically show a significant three-way interaction [$F(1, 36)=6.6$, $p < .01$], but in the opposite direction than that predicted: the sequential effects were greater in the experiment 10 (explicit temporal judgments) than in the experiment 11 (simple RT paradigm).

markedness status of stimulus and response categories). The reason why some words should be marked whereas others should not is however somewhat arbitrary (but see Lyons, 1969; Zimmer, 1964). Moreover, the alternative possibility still exists that elapsing time is represented from left to right progressively even if not linearly (but following a stepwise function), independently of the linguistic categories used to label stimuli and responses[11]. This could be due to the fact that the response is dichotomic (left vs right) whereas the stimulus is continuously varied (but again with the need of a categorical definition of the parametrically varied feature, i.e., 'short' vs. 'long' FPs). Thus, it could be that representing stimuli in a dichotomic way depends on the categorical nature of the response required. Further studies parametrically varying not only the stimulus duration but also the response required (e.g., using 4 response alternatives for 4 different FP durations) could be helpful in solving this issue.

The convention of representing time from left to right is likely to derive from the Roman writing system, which adopts a left-to-right directionality. Consistent with this hypothesis, Zwaan (1965) found that Dutch people, who read and write from left to right, associate the left side of the page with the idea of 'past'. In contrast, Israeli people, who read and write from right to left, relate this idea with the right side (see also Tversky et al.,1991, for developmental evidence).

The left-to-right directionality seems to be a consistent feature of how the cognitive system represents ordered material also in other domains. As an example, the cognitive representation of numbers has been shown to be to some extent spatial in nature (Dehaene et al., 1993). Even when number magnitude is irrelevant for the task (e.g., parity judgement), RTs tend to be faster when relatively small numbers are responded to with a left key, and large numbers are responded to with a right key, respectively, than vice versa, at least in cultures using the Roman writing system (Dehaene et al., 1993; Zebian, 2005). This is the so called Spatial Numerical Association of Response Codes (i.e., SNARC) effect (Dehaene, et al., 1993; see also Gevers, Verguts, Reynvoet, & Fias, 2006). According to the authors' interpretation, Arabic numerals automatically activate a magnitude code. This code is represented in terms of left and right parts of an analogical

---

[11] This possibility is currently under study in our laboratory. In a pilot experiment, the cross color changes from white to yellow during the short FP, and from yellow to red during the long FP. Participants are instructed to answer according to the final color of the cross (responding to 'yellow' with a 'left' key and to 'red' with a 'right' key). Preliminary data show that the same S-R compatibility effect as in experiment 10 is also found in this condition. Unless one supposes that participants use the (disadvantageous) strategy to re-label 'yellow' and 'red' as 'short' and 'long', these data suggest that the effect found is independent of the linguistic labels used for the stimulus features.

mental number line. The left and right codes generated by the representation of magnitudes cause facilitation in the case of compatible responses and interference in the case of incompatible ones (see Dehaene, 2003, for a review). Furthermore, other non-numerical materials with ordinal properties, such as sound pitches (Rusconi, Kwan, Giordano, Umiltà, & Butterworth, 2006), letters and months (Gevers, Reynvoet, & Fias, 2003; but see Dehaene et al., 1993, experiment 4), have also been demonstrated to have some form of spatially coded representation as, in some conditions, they show S-R compatibility effects similar to the SNARC effect.

Gevers and colleagues (2003) have argued that the convergence of evidence from such different domains suggests that the spatial representation of ordered information is a general feature of the cognitive system, rather than being specific for the number-domain, as previously supposed (Dehaene et al., 1993). The results reported in this paper add support to this view, extending it also to the temporal domain. However, the present study does not clearly determine whether temporal duration is spatially represented because of its special nature or because it is just an example of ordered information such as numbers, which the cognitive system organizes on a left-to-right mental line when particular task demands make it advantageous to do so. This issue needs to be investigated more thoroughly, for instance, by using different ordered materials (e.g., temporal and numerical) in the same task, and testing whether the compatibility effect obtained for the two domains is additive, suggesting different underlying processes, or interactive, suggesting a common mechanism (cf., Mapelli, Rusconi, & Umiltà, 2003).

From a functional point of view, in the temporal judgment task used in the experiments presented here (i.e., experiments 10, 12, 13 and 14), it is possible to know reasonably well in advance which response should be executed at the end of the short FP as well as at the end of the long one. Although this information is available in advance, however, interference on motor performance occurs anyway, suggesting that the locus of the effect should be somehow after response selection and during response preparation. A fruitful line of investigation of the functional locus of the phenomenon may be represented by the analysis of electrophysiological components, such as the Lateralized Readiness Potential, an index of covert response selection, preparation and execution, which has been successfully used to investigate processing stages involved in other S-R compatibility effects (e.g., Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988; Keus, Jenks, & Schwarz, 2005; Vallesi, Mapelli, Schiff, Amodio, & Umiltà, 2005).

We will refer to the behavioural effect found here as the Spatial-Temporal-Association-Between-Response-Codes (STARCO) effect, in analogy with similar compatibility effects found in other domains, like numbers (SNARC effect; e.g., Dehaene et al., 1993) or sound pitches (SMARC effect; Rusconi et al., 2006). It is worth noting that some differences already seem to exist from one domain to another. For instance, contrary to numbers, sound pitches, months or letters, which show the S-R compatibility effects even when the information presented is irrelevant for the task, the STARCO effect has never been observed when duration is not task-relevant; an example would be that of standard variable FP paradigms with bimanual responses (see experiment 8, chapter 3). This suggests that, although the mental representation of time can be spatially organized, this spatial representation, unlike for other ordered materials, is not accessed automatically, but rather requires awareness of the passage of time, which is task-relevant when the STARCO effect is observed (i.e., present experiments 10, 13 and 14)[12].

In conclusion, our approach indicates that it is possible to infer aspects of how the cognitive system represents a concept like time, by analyzing the costs paid when the incongruence between response tendencies triggered by such a representation and task-relevant responses has to be resolved. Specifically, the present study shows a new S-R compatibility effect, consisting of an improvement in performance when short and long durations have to be responded to on the left and right side of space, respectively, rather than when the association between temporal duration and response side is reversed. This effect suggests that one way in which the amount of elapsed time is cognitively represented is by the use of a spatial coordinate reference frame from left to right, in a similar fashion to other ordered material such as numbers, letters, months and pitches. However alternative explanations of the data such as the linguistic markedness cannot be excluded at present.

---

[12] This assertion is partially weakened by preliminary results of an experiment of our lab, which shows that the STARCO effect is also observed when the task-relevant feature is not time but a color continuously changing with time (see footnote 11). The condition in which the relevant and the irrelevant stimulus features co-vary together is however different from that of other S-R compatibility effects, such as the Simon effect and the SNARC effect, where the relevant and the irrelevant features vary orthogonally. Thus, whether time should be task-relevant (or co-vary with the task relevant feature) for the STARCO effect to occur is a point that deserves to be addressed by future research.

Chapter 5

The results of previous experiments on the variable FP paradigm, in particular those adopting TMS and neuropsychological approaches (experiments 7-9, chapter 3), support the involvement of right lateral (in particular dorsolateral) PFC in monitoring. The FP effect, which was reduced after TMS or surgical lesions on this region, is indeed considered as a marker of a monitoring process. In a typical variable FP task, the conditional probability of stimulus occurrence increases in the long FPs. The rDLPFC is supposed to be the seat of a process which basically checks the stimulus non-occurrence as time elapses in order to increase preparation over time (e.g., Stuss et al., 2005; Näätänen, 1970; see also experiment 5, chapter 2). These findings confirm that this region of the brain is involved in monitoring environmental contingencies in the time domain in order to optimize behaviour (e.g., Coull et al., 2000; cf., Fuster, 1990). Similar results have also been obtained in other domains (see paragraph 1.1.2.3., chapter 1).

The monitoring role of right lateral PFC has been documented, for instance, in the problem-solving domain. In a study by Reverberi and colleagues (Reverberi et al., 2005), various subgroups of prefrontal patients carried out the Brixton task, a visuo-spatial version of the WCST (Burgess & Shallice, 1996a). In the first part of the test, the participant was presented in each trial with a card containing a 2×5 matrix of circles, one of which was blue. The position of the blue circle changed from one trial to another, obeying a rule unknown to the participant. The participant had to discover this rule in order to predict where the blue circle would appear on the next card. In the second part, an interfering task was administered before the end of the blue series. A sequence of 4 cards with a red circle was presented, which always followed a rule different from that of the preceding blue series. Participants had to just touch the red circle until a blue circle would appear again. In this case, participants had to ignore the ‘red’ rule implicitly acquired, and redirect their attention to the last ‘blue’ rule which was active before the interfering task. The results of that study showed that acquiring an implicit rule in the blue series is more impaired in left lateral prefrontal patients, whereas checking that the most primed rule (the ‘red’ rule) is irrelevant for the current situation, in order to choose the less primed relevant rule (the previous ‘blue’ rule), is more impaired in the right lateral prefrontal patients.

Another example comes from the semantic domain. In a PET study, MacLeod and colleagues (MacLeod et al., 1998) scanned participants while they were listening to

English words and monitoring for the occurrence of names of dangerous animals in order to either estimate the percentage of occurrences or to report their number at the end. Although usually semantic tasks activate left prefrontal areas, in this particular task, relatively greater right prefrontal activation was obtained (BA 9 and 10) with respect to the baseline condition (i.e., passive word viewing), further supporting the role of this region in monitoring.

Domain-based approaches have been successfully applied to the study of the functionality of primary and secondary cortical areas, such as V1 and V2. In the light of the evidence briefly discussed above, one can conclude that a process-centred approach is instead more fruitful for the investigation of the PFC. The individuation of a specific process, with a good task analysis, is indeed more important than the use of a given task or domain in order to understand the role of a particular prefrontal area (see also paragraph 1.1.2.3., chapter 1). Specifically, the monitoring function, intended in a broad sense as the capacity to monitor internal and external contingencies, in order to check if they satisfy a given goal (e.g., Shallice, 2006), seems to be relatively more right-lateralized in the PFC independently of the task administered (e.g., Shallice, 2004; Stuss et al., 2002; Stuss et al., 2005; see also Petrides, 1994).

The current chapter aims to extend results showing a monitoring role of the rDLPFC (chapter 3), in a field different from that of attention and motor preparation over time. Among the literature investigating the role of the right PFC, the episodic memory domain (and in particular source memory) has traditionally received particular attention (e.g., Henson, Rugg, Shallice, & Dolan, 2000; Schacter, Curran, Galluccio, Milberg, & Bates, 1996; Tulving et al., 1994). Moreover, episodic memory is a domain where the conditions described by Shallice (2006) as critical for an involvement of right DLPFC are usually fulfilled (see paragraph 1.1.2.3., pages 21-22). Thus, the next 2 experiments will further investigate the role of PFC in monitoring endogenous events, such as the status of a mnemonic trace during source memory retrieval.

The methodological approach will also be different. The limited information offered by dependent variables such as response accuracy or speed makes it difficult to reveal the processing levels that are modulated. Hence, ERPs have been used in the 2 experiments reported below. Such technique offers the advantage of tracking covert cognitive processing with a high temporal resolution (virtually in real time), and provides at least a rough estimate of lateralization and localization of cortical activity[13]. Therefore, ERP technique is complementary to other methods, such as those adopted in the previous experiments, in order to infer functional dissociations among different cognitive processes (cf. Rugg & Coles, 1995).

5.1. Prefrontal involvement in source memory: an electrophysiological investigation of accounts concerning confidence and accuracy

The mapping of functionally distinct processes onto different neural substrates is a central objective for memory investigation. According to a commonly accepted neuropsychological model of episodic memory (Moscovitch, 1992), medial temporal/hippocampal areas mediate modular processes like encoding, storage and retrieval processes, while frontal areas mediate higher strategic and control functions. However, the specific roles the frontal lobes play in episodic memory is still a matter of debate. The issue has been addressed by means of various approaches.

Empirical background

In the neuropsychological domain, it has been reported that damage to the PFC can cause impairment in episodic memory tasks. With the exception of patients with lesions to the inferior medial regions (Gilboa & Moscovitch, 2002), the resulting impairment is usually mild and not as dramatic as that found in amnesic patients with temporal lesions. Patients with frontal lesions show mild deficits in item memory per se (Stuss et al., 1994), usually in the form of failures of organization at encoding (e.g., Mangels, 1997), or an increased probability of false alarms at retrieval (e.g., Curran, Schacter, Norman, & Galluccio, 1997; Swick & Knight, 1999), which suggests a deficit in the checking or monitoring processes (Shallice, 2002). Moreover, prefrontal patients perform poorly on tasks requiring retrieval of the memory context (source memory), such as memory for spatial position or temporal order (Janowsky, Shimamura, & Squire, 1989; Shimamura, Janowsky, & Squire, 2000). This may well be because these tasks greatly rely upon checking processes.

---

[13] However, the comparison with the TMS and neuropsychological studies would be limited from the localizational point of view, as the spatial resolution of the latter techniques is much higher than that offered by ERPs.

Another source of evidence comes from functional neuroimaging studies, which have consistently documented prefrontal activations during the performance of various memory tasks. In a review of PET studies, Tulving and colleagues proposed the Hemispheric Encoding/Retrieval Asymmetry (HERA) model (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; see also Shallice et al., 1994). According to this model, left and right prefrontal lobes have partially different functions in episodic memory. For verbal stimuli, left and right prefrontal cortical areas are differentially more involved in encoding and in retrieval, respectively.

In this study we will focus on the processes involved during retrieval. A theoretical model for the retrieval processes mediated by frontal lobes, based on the theory of Norman and Bobrow (1979), has been proposed by Burgess and Shallice (1996b; see also Moscovitch, 1992; Schacter, Norman, & Koutstaal, 1998, for related models). This model includes two main processes. The first process specifies search parameters and cues, and updates and maintains working memory contents. The second process manipulates and monitors the products of memory search. An fMRI study by Henson, Shallice and Dolan (1999b) brings anatomical evidence in favour of this model. In that study, the critical comparison was between two word recognition tasks that differed only in whether responses required retrieval of the spatiotemporal context of words at study (exclusion) or an old/new judgement only (inclusion). A right ventral prefrontal region (BA 47) was activated during retrieval without distinction between exclusion and inclusion conditions, consistent with the concept of search cues specification (see also Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998). The contrast between the exclusion and the inclusion conditions revealed activation in the left and right DLPFC (BA 46). According to the authors' interpretation, these areas are associated to monitoring demands, which are particularly heavy during the exclusion condition. That work, together with many others, shows that the left prefrontal areas can also be involved during retrieval and not only during encoding, contrary to the simplest form of the HERA model (e.g., Nolde, Johnson, & D'Esposito, 1998; Ranganath & Paller, 1999). The debate about right-left prefrontal asymmetry in episodic retrieval is far from resolved. Another open question concerns which specific products of memory search are the object of the monitoring processes associated to the prefrontal regions.

A promising line of evidence on this point comes from the electrophysiological domain. Some studies have shown a larger late prefrontal (more right) ERP positivity elicited by successful retrieval (e.g., Allan & Rugg, 1998; Donaldson & Rugg, 1998;

Graham & Cabeza, 2001; Wilding & Rugg, 1996; see Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996; Rugg, Henson & Robb, 2003, for neuroimaging related evidence), or by well-recollected test items rather than by items judged old on the basis of familiarity in the remember-know paradigm (e.g., Rugg, Schloerscheidt, & Mark, 1998). Wilding & Rugg (1996), for instance, recorded ERPs during the retrieval phase of a source memory task. Participants first made old/new judgements to visually presented words, and then, for words judged old, indicated in which of two voices (male vs. female) the words had been presented at study. ERPs were more positive for words correctly judged old (hits) than for correct rejections at the left parietal sites and also at the right frontal ones (old/new effect), where they were also more sustained over time. Importantly, the right frontal component was more positive for hits followed by a correct source judgement (hit/hit) than by incorrect ones (hit/miss). Consequently, the authors proposed a relationship between right frontal ERP effect and the monitoring of the products of successful retrieval.

Nevertheless, the results achieved in this field are rather controversial, as other studies fail to show any modulation of the prefrontal ERPs by successful recollection (e.g., Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Ranganath & Paller, 1999; Senkfor & Van Petten, 1998; for related neuroimaging evidence, see Kapur et al., 1995; Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998). As an example, in the study by Senkfor & Van Petten (1998) ERPs were recorded during recognition tasks for spoken words alone (items) or for both words and the voice of the speaker (sources). In both tasks, correctly recognized old words elicited more positive ERPs than new words. Only in the source task, old words also elicited a late prefrontal positivity. The prefrontal effect, however, did not differ between trials with accurate voice judgments and those with inaccurate ones. The discrepancy across studies in whether a modulation of the late prefrontal ERPs by retrieval accuracy occurs suggests that activity in these regions is not related to, or not restricted to, successful retrieval of the episodic information.

The current study

The present study aims to investigate which variables modulate the ERPs recorded over the prefrontal areas during memory retrieval, in order to better understand their role not only in episodic memory[14], but also and more generally in the cognitive system.

---

[14] We chose source memory tasks for a couple of reasons. First, we aimed to compare our results with the conflicting electrophysiological literature on the role of the successful source retrieval in influencing late prefrontal ERP components (e.g., Senkfor & Van Petten, 1998; Wilding & Rugg, 1996). Second, as pointed

In experiment 15, a design similar to that used in earlier ERP studies of source memory (e.g., Senkfor & Van Petten, 1998; Wilding & Rugg, 1996) was adopted in order to test a prediction derived from the retrieval success account by means of the ERPs. This account would predict that, in a task involving both item recognition and source judgements, hit/hit waves recorded in the right frontal sites should be more positive than hit/miss ones, since they would provide an electrophysiological correlate of the processes operating on successfully retrieved information. If this prediction could not be confirmed, another explanation, not dependent on the accuracy but linked to more subjective aspects of the memory retrieval, like confidence (e.g., Henson, Rugg, Shallice, & Dolan, 2000), is likely to account for the frontal ERP effects usually observed in source memory retrieval tasks. This hypothesis will be tested in the Experiment 16. The results of these experiments will then be discussed in comparison with results concerning the variable FP phenomena in order to detect communalities and differences between the two fields.

5.1.1. Experiment 15

Method

Participants

Sixteen volunteer participants took part in the experiment 15. They were 25.4 years old on average (range = 20-33); 8 were males and 8 females; all of them were right-handed. All had normal or corrected-to-normal vision, no auditory impairment, and had no history of neurological problems. Each participant gave written informed consent prior to participation in the study and received 10 euros at the end of the experimental session. Approval from the local ethical committee was obtained for the study.

Experimental Material

Stimuli at study consisted of 320 Italian words (low/middle frequency, length = 4-10 letters, mean = 7). The list contained words with either male or female semantic associations (50% of each), as indicated by a prior pilot study. For example, words with a male semantic meaning were ‘soccer’ and ‘plumber’; words with a female semantic meaning were ‘skirt’ and ‘jewel’. These 320 words were divided into two paired sub-lists of 160 different words, with comparable frequency, length and meanings.

---

out before, frontal activity is often held to be more related to the source memory than to item memory (e.g., Henson et al., 1999b; Janowsky et al., 1989) and this would increase the likelihood of obtaining a prefrontal engagement detectable with ERPs (e.g., Ranganath & Paller, 1999; Senkfor & Van Petten, 1998).

At study, words from one of the two sub-lists were presented, half pronounced by a male voice and half by a female voice. Of the words pronounced by each one of the voices, half had a congruent male meaning and half an incongruent female meaning. Study words were presented in 4 blocks of 40 items, with a pause of a few minutes between blocks. The order of presentation of items within each block was determined randomly.

The test list was formed by merging all 320 words of the initial database. This means that half of the test items were old, in that they had already been auditorily presented at study, and half were new. Of the 160 old words composing each test list, 80 had been spoken in the male voice and 80 in the female voice at study. Test words were presented in 5 sub-lists of 64 items each. The assignment of words to sub-list and the order of presentation of items within each block were determined randomly.

Test stimuli were presented visually on the center of a 17” monitor. Test words (12-point *Courier New* font) subtended approximate visual angles of 1.4° to 2.5° (horizontally) and 0.6° (vertically) from a viewing distance of 45 cm. Stimuli were exposed in white letters on a black background. The auditory study words were digitally recorded in two voices, male and female, at 22 kHz, 16-bit resolution, Stereo mode. They were edited so that the beginning of the stored sound segment corresponded to the onset of the spoken word. The mean duration of these stimuli was 815 ms, and did not differ significantly according to the gender of the voice. Auditory stimuli were presented binaurally at a comfortable hearing level through two earphones. Stimulus presentation was controlled by a PC. Responses were collected from an external four-button response box connected to the PC.

Procedure and Task

Participants were tested individually in a silent room. Each 1-hour experimental session began with instructions about the general aim of the experiment and some advice on how to avoid producing artefacts during the EEG recording. Participants were asked to relax, to avoid muscular and eye movements and blinks as much as possible, with the exception of when the fixation point was present on the screen. Following channel placement (*see* below) participants were seated in front of the stimulus presentation monitor. The index and middle fingers of their hands rested on each of the 4 buttons of a response box. The task in the study phase consisted of a gender voice judgement followed by a gender stereotype judgement in order to increase the depth of the encoding. In this first phase, a fixation point (an asterisk) appeared for 400 ms at the beginning of each trial, and was removed from the screen 100 ms prior to stimulus presentation. The word was auditorially presented with a blank screen appearing at the same time and lasting 1100 ms. A visually presented question ‘Voice?’ (in Italian: ‘Voce?’) lasting 1500 ms indicated to the participants the period in which they had to perform the decision on the gender of the voice. Another blank screen subsequently appeared for 400 ms. Then a second question ‘Stereotype?’ (in Italian: ‘Stereotipo?’) lasting 1500 ms indicated to the participants when to perform the judgement of the gender stereotype. A final blank of 400 ms separated the current trial from a new one. Each participant was instructed to press one of the two external buttons on which her/his index fingers rested, which depending upon whether the item was spoken in the male or the female voice. They then had to indicate, using the same buttons, whether its meaning was associated with the male or the female sphere. The finger to be used associated to the gender of the voice and of the stereotype was kept constant for each participant. The correspondence between hand and voice gender was counterbalanced across participants. Accuracy and speed were equally stressed for the voice judgement. Participants were instructed that there was no absolutely correct response for the stereotype judgement. Participants were aware that the subsequent task would be a memory task for the voice. A practice session consisting of 4 items preceded the study phase per se. The total duration of a study trial was 5400 ms. Responses faster than 200 ms, or slower than 2000 ms were treated as errors.

After a short pause of 5 minutes, during which the status of the net was checked and readjusted if needed, the test phase began. An asterisk lasting for 400 ms again preceded presentation of each word; it was removed 100 ms prior to stimulus onset. A test word appeared in the centre of the screen for 300 ms followed by the fixation point (asterisk) for 1700 ms. The onset of the word served as the cue for the first decision. This consisted of an old/new judgement. Participants had to press an external button with their left or right middle finger according to whether they remembered hearing the word at study or not. One index finger could be used to press a middle button when the participants were not sure about the old/new status of the word. The index finger used for the ‘don’t know’ response was the right one for half of the participants and the left one for the other half. This additional response alternative was introduced in order to obtain a cleaner separation between hits and misses (e.g., Wilding & Rugg, 1996), thereby reducing the possibility that some trials contributing to the hit ERPs could have been lucky guesses. Accuracy and speed were equally emphasized for this first decision. After a blank interval of 400 ms, a row of four question marks appeared on the screen for 2000 ms. For words judged old only, the question marks present during the 2000 ms interval were a cue to report the voice in which the word had been presented at study. The voice judgement was also made using the two external buttons on which the participants' middle fingers rested, with the option of pressing the 'don't know' middle button with one of the two index fingers (again counterbalanced across participants) in order to further separate trials on which study voice was successfully recollected and those on which it was not, by also reducing the number of lucky guesses for the source judgement. The association between hand and response for the two judgements was also counterbalanced across participants. A further blank interval of 400 ms separated the current trial from the following one. The total duration of a test trial was 5300 ms. A practice session consisting of 8 items preceded the test phase per se. Four of those practice items had already been auditorily presented at study and 4 were new. Initial old/new judgements quicker than 300 ms, or slower than 2000 ms were discarded from the analyses. Subsequent voice judgements slower than 2000 ms were also discarded.

EEG recordings

Scalp voltages were collected with a 128-channel Geodesic Sensor Net^{TM} (Tucker, 1993) connected to an AC-coupled, high input impedance amplifier (200 MΩ, Net Amps, Electrical Geodesics, Eugene, OR). Amplified analog voltages were filtered online (0.1-100 Hz band-pass) and digitalized at 250 Hz. Individual channels were adjusted until impedances were below 50 KΩ. Recording voltages were referenced online to a vertex channel but re-referenced after ERP extraction to the average voltage of all channels (see next section).

EEG Data Reduction and Analysis

The EEG was continuously recorded during the test phase. The ERPs were extracted off-line triggered by the test word onset and segmented for a temporal period extending from 100 ms pre-stimulus to 2200 ms post-stimulus. Trials were dropped from the analyses (i.e., automatically rejected prior to averaging) if they contained eye movements (eye channel differences greater than 50 μV) or more than 40% bad channels (fast average amplitude > 150 μV between samples, differential average amplitude > 150 μV, zero channel variance). Data from individual channels which were consistently bad for a given participant were replaced using a spherical interpolation algorithm if bad channels were less than 20% (Srinivasan, Nunez, Tucker, Silberstein, & Cadusch, 1996). The ERP data from 3 participants (out of 16) were discarded because of an insufficient number of artefact-free trials per condition (< 15).

The ERPs were baseline-corrected with respect to the 100 ms interval prior to word presentation and digitally band-pass filtered at 0.3-30 Hz. An average-reference transformation was used to minimize the effects of reference-site activity and to estimate accurately the scalp topography of the measured electrical fields (Dien, 1998; Picton, Lins, & Scherg, 1995). A spherical spline interpolation was also used to estimate the voltages of the scalp surface that was not covered by channels and to correct the polar average reference effect (Junghofer, Elbert, Tucker, & Braun, 1999).

On the basis of the literature and of preliminary analyses, eight regions were selected from the measured head space for analysis of the spatial scalp topography of the ERP effects (see figure 26).

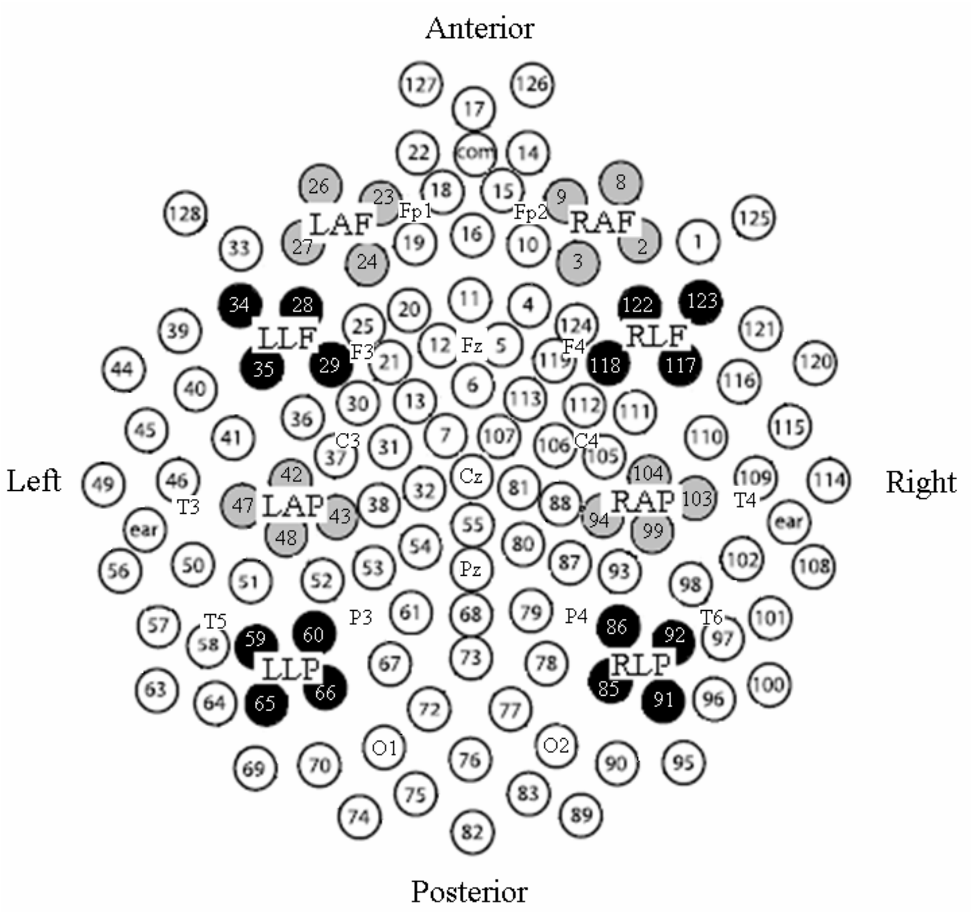

Figure 26. Approximate locations of the 128 channels in the Geodesic Sensor Net. Sets of Channels within anterior and lateral regions of the frontal and parietal lobes used in ANOVAs are shown in black and grey, respectively. LLF, LAF, RAF, RLF, LLP, LAP, RAP, RLP signify left lateral frontal, left anterior frontal, right anterior frontal, right lateral frontal, left lateral parietal, left anterior parietal, right anterior parietal, right lateral parietal. For purposes of comparison, also the approximate electrode location in the 10/20 system is shown.

The selected regions can be classified according to their topographical coordinates as follows: 2 hemisphere (left vs. right) x 2 lobe (frontal vs. parietal) x 2 regions within each lobe (anterior, lateral). Waveforms were obtained averaging ERPs from a pool of four adjacent channels for each region (see Curran, Schacter, Johnson, & Spinks, 2001, for a similar approach). Thus, the selected regions were the following: left anterior frontal (LAF, channels: 23, 24, 26, 27), right anterior frontal (RAF: 2, 3, 8, 9), left lateral frontal (LLF: 28, 29, 34, 35), right lateral frontal (RLF: 117, 118, 122, 123), left anterior parietal (LAP: 42, 43, 47, 48), right anterior parietal (RAP: 94, 99, 103, 104), left lateral parietal (LLP: 59, 60, 65, 66), right lateral parietal (RLP: 85, 86, 91, 92). The outcomes of analyses performed including the midline channel sites are not described unless they clearly conflict with the conclusions derived from analyses of the data concerning the lateral regions. In addition, ANOVAs focusing on a sub-set of regions are reported to corroborate and extend results from the overall ANOVAs. Main effects of ERP analyses for both experiments are not reported as they are not relevant for the purposes of the study. All the significant behavioural and electrophysiological effects were analysed further through post hoc comparisons if necessary (i.e., Tukey Honestly Significant Difference).

Results

Behavioural Data

Study Phase

Ninety-seven percent of the words were correctly judged according to the voice, with no difference between items spoken in the two voices. Mean reaction time (RT) for correct voice decisions was 497 ms, again with no difference between words pronounced by the two voices. Mean RT for the stereotype judgement was 431 ms. There was no difference according to the gender of the stereotype and of the voice.

Test Phase

Accuracy

Percentages of the various response categories for both the old/new judgement and the source one are displayed in the Table 6. The old and new items were initially classified as correct, incorrect and ‘don’t know’ according to the old/new judgement. A discrimination estimate of ‘$P_{\text{hit}} – (P_{\text{false alarm}} + P_{\text{don't know/new}})$’ was calculated for the recognition task (see Wilding and Rugg’s study, 1996). Discrimination was above chance for words spoken in each of the two voices [male: t(15) = 15.1, $p < 0.001$; female: t(15) = 12.7, $p < 0.001$] and the two indices for the two genders did not differ significantly. An ANOVA comparing the probabilities of incorrect responses to old male, old female and new words also revealed no significant differences.

Table 6

Percentages of response according to the accuracy of the response (correct, incorrect, and ‘don’t know’ responses) for the Old/New judgement and for the source judgement in the test phase of experiment 15.

	Voice		
Accuracy (%)	**Male**	**Female**	**New**
Old/New Judgement			
P (correct)	77.3	74.1	73.9
P (incorrect)	15.9	18.1	15.4
P (don't know)	2.6	2.8	4.8
Source Judgement **(for words judged old)**			
P (correct)	62.8	56.9	
P (incorrect)	29.4	34.9	13.2
P (don't know)	7.8	8.2	2.2

Note. Old words are separated according to study voice. The total percentage of old/new judgements for each voice category, collapsing accuracy, is always less than 100% because trials with no response and with reaction times out of the range 300-2000 ms have been discarded. Percentage of correct source judgement is not shown for new words because no voice had pronounced new words at study.

For words spoken in each of the two voices, the probability of a correct voice judgement was reliably higher than the probability of an incorrect judgement [male: t(15) = 5.64, $p < .001$; female: t(15) = 2.47, $p < .05$]. An ANOVA comparing the probability of a ‘don’t know’ response to correctly judged old words (male versus female voice) and to false alarms revealed a main effect of the type of initial response [$F(2, 30) = 6.6$, $p < .01$]: the probability of a ‘don’t know’ response to old words was significantly lower than the probability of a ‘don’t know’ response to false alarms (post hoc Tukey comparisons, $p < .05$; no difference between the two voices).

Reaction Times

The RTs for the various response categories in both the old/new judgement and the source one are presented in the Table 7. Given the low number of ‘don’t know’ responses, analysis of RTs is restricted to the correct and incorrect judgements. For the old/new judgements, an ANOVA was carried out with the factors of accuracy and word type (old male vs. old female vs. new). The only effect obtained was that RTs for correct judgements were reliably faster than RTs for incorrect judgements [$F(1, 15) = 26.7$, $p < .001$].

Table 7

Mean Reaction Times (in Milliseconds) of Response According to the Accuracy of the Response (Correct, Incorrect, and ‘don’t know’ Responses) for the Old/New Judgement and for the Source Judgement in the test phase of Experiment 15.

	Voice		
	Male	**Female**	**New**
RT (ms)			
Old/New Judg.			
RT (correct)	1154	1180	1218
RT (incorrect)	1300	1299	1296
RT (don't know)	1481	1667	1599
Source Judgement			
RT (correct)	642	632	
RT (incorrect)	665	728	736
RT (don't know)	853	779	794

Note. Old words are separated according to study voice. Mean reaction time of correct source judgement is not shown for new words because no voice had pronounced new words at study.

After re-classifying old words according to the subsequent voice judgement, an ANOVA involving the factors of voice judgement accuracy (hit/hit vs. hit/miss) and word type (male vs. female voice at study) gave only a main effect of accuracy [$F(1, 15) = 5.1$, $p < .05$], with RTs for later correct judgements being reliably faster than the RTs for later incorrect ones (hit/hit: 1145; hit/miss: 1174).

For the voice judgement, an ANOVA involving accuracy and word type (male vs. female) gave no significant effects (for all, $p > .15$), probably because participants withheld responses about voice judgements until the response cue '????' appeared. At test, no effect of the congruence between the voice at study and the gender meaning of the words was found.

Event-related Potentials

Only trials which resulted in hits for the old words and correct rejections for the new words were included in the ERP analyses. Trials associated with other categories of responses were discarded, due to insufficient trials for adequate analyses. The hits were re-classified a posteriori as hit/hit or hit/miss, depending upon the subsequent voice judgement. Only 13 participants contributed sufficient trials to permit the formation of reliable, artefact-free ERPs. As no behavioural difference had been observed between the two voices at study, the factor 'voice' was collapsed for the ERP averaging and analysis.

The mean number of trials entering into each participant's waveform analysis was 47, 24, and 77, for the hit/hit, hit/miss and correct rejection categories, respectively. ERPs concerning the test phase were averaged from 100 ms prior to the visual word onset to the occurrence of the 4 question marks, that is they included the time interval used for the old/new judgement before the voice judgement (2300 ms). As one can see from visual inspection of the grand average (see figure 27) and could be expected from the literature, the ERPs related to hit/hit and hit/miss show two positive-going modulations compared with the ERPs related to correct rejections: an early phasic left parietal one[15], and a late long-lasting right frontal one. As we were interested in the latter effect, the subsequent analyses will focus on mean amplitudes of ERPs from the eight chosen regions in two late consecutive latency-windows (i.e., 1400-1800 and 1800-2200 ms).

Middle and late frontal effects (1400-1800 and 1800-2200 ms latency-windows).

Two parallel 3x2x2x2 ANOVAs were conducted on the mean amplitudes obtained for the two middle and late subsequent latency-windows of 1400-1800 and 1800-2200 ms, respectively. Each ANOVA employed the factors of response category, hemisphere, lobe and regions.

---

[15] The analyses concerning parietal effects are reported in the Appendix, from page 121, as they are not relevant for the present purposes. The interested reader can also find a full report in Vallesi & Shallice (2006), *Brain Research, 1124(1),* 111-25.

The lobe x hemisphere interaction was significant only for the 1400-1800 ms latency-window [$F(1, 12) = 5.3$, $p < .05$]; this interaction derived from the right regions being more positive than left ones for the frontal lobes ($p < .001$), but not the parietal lobes ($p = .08$). Moreover, response category modulated this effect as the category x lobe x hemisphere interaction indicated [1400-1800 ms: $F(2, 24) = 7.5$, $p < .01$; 1800-2200 ms: $F(2, 24) = 5.7$, $p < .01$]. Indeed, the hit/miss waves were significantly more positive than correct rejection waves only in the right frontal regions (for both latency-windows, $p < .01$). No significant difference was obtained between the RAF and the RLF regions. The hit/hit waves too were more positive than correct rejections in the right frontal regions but the post hoc Tukey test gave a significant result for the latency-window of 1800-2200 ms only ($p < .01$). No difference at all was observed between the different conditions in the left hemisphere.

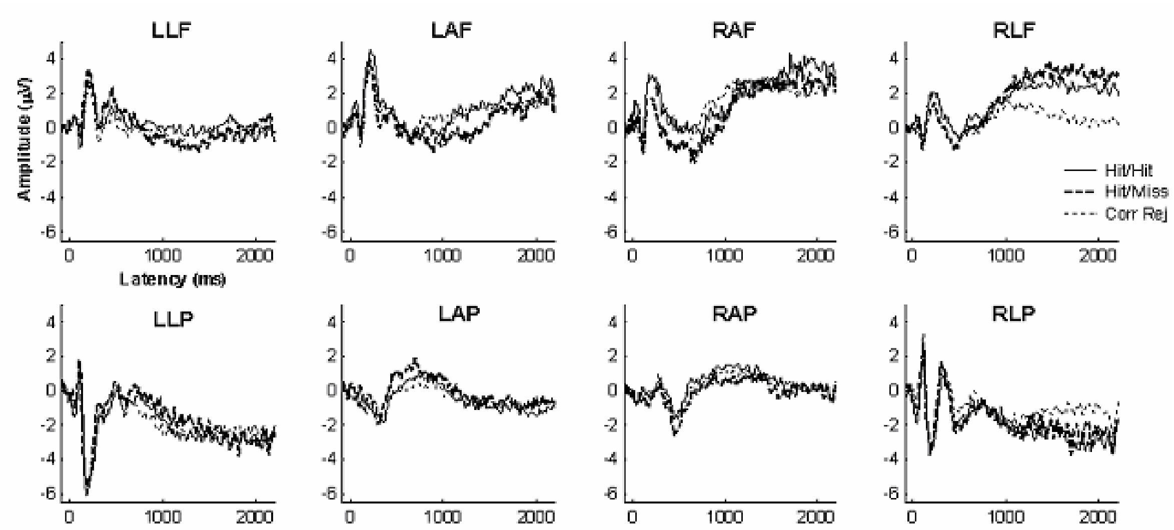

Figure 27. Grand average of ERPs associated with the hit/hit, hit/miss, and correct rejection response categories in Experiment 15 Labels of the Scalp Regions as for Figure 26.

Discussion

The results of experiment 15, apart from an early left parietal old/new effect (see Appendix, from page 121), replicate the late right frontal old/new effect (e.g., Donaldson & Rugg, 1998; Wilding & Rugg, 1996), with waves for hit/hit and hit/miss trials being more positive than those for correct rejections in two late latency-windows. However, the hit/miss waves were slightly, although not significantly, more positive than the hit/hit ones in the right prefrontal region. Hence, in the current experiment, the late positive frontal component is independent of the successful retrieval of a full memory trace. This pattern is in conflict with the retrieval success account of the late right frontal old/new effect (e.g., Wilding & Rugg, 1996). It is noteworthy that, in this experiment, RTs for old/new judgements were significantly slower for hit/miss than for hit/hit, while in the Wilding and Rugg's study (1996) there was no difference between RTs for the two types. Moreover, the percentage of correct source judgments was higher in our study than in their experiment 16, which was more similar to our design (60% vs. 50%), probably because our study involved a deeper encoding than their lexical decision.

Similar results to ours have been usually explained as reflecting monitoring of search operations in general (e.g., Kapur et al., 1995; Senkfor & Van Petten, 1998) rather than of the products of memory retrieval. A more specific interpretation of the prefrontal role in memory retrieval, which provides a clear alternative to the retrieval success accounts, is that this area is more involved when the response is less certain and hence needs additional monitoring (Henson et al., 1999a). In order to test this hypothesis more directly, an fMRI study by Henson and colleagues (Henson et al., 2000) adopted a procedure in which old/new judgements were required together with confidence ratings of these judgements. Results showed that correct low-confidence responses to old items activated DLPFC bilaterally. There is therefore enough evidence to suppose that the evaluation or checking of the response could be a good candidate for the modulation of the prefrontal ERP effects during source memory judgements (e.g., Shallice, 2002).

5.1.2. Experiment 16

The hypothesis of a possible influence of confidence on prefrontal ERPs during a source memory task was investigated directly in experiment 16. The ERP technique is a useful tool to temporally characterize an effect of retrieval confidence on the cortical electrical activity and to possibly dissociate it from the effect of retrieval accuracy. A procedure similar to that used in the fMRI study by Henson and colleagues (Henson et al., 2000) was therefore adopted in the present experiment.

Late ERP positivity is generally considered an electrophysiological hallmark of prefrontal engagement during retrieval (e.g., Wilding & Rugg, 1996). Thus, the prediction was made that late prefrontal waveforms associated with low-confidence judgments will be more positive than those associated with high-confidence ones, as the former are supposed to require more frontal-type processes (e.g., monitoring processes; see Henson et al., 2000, for fMRI evidence).

Method

Participants

Eighteen participants volunteered for experiment 16, all different from those who carried out experiment 16. They were 27 years old on average (range = 22-40); 12 were females and 6 males. All were right-handed, had normal or corrected-to-normal vision, no auditory impairment, and no history of neurological problems. Each participant gave written informed consent prior to participation in the study and received 10 euros at the end of the experimental session. One female participant was discarded from the analyses as she did not use some response categories at all (i.e., no ‘high-confidence’ responses).

Experimental Material

The stimuli were the same as in the experiment 15. The only difference was that the same 160 words auditorily presented at study were subsequently visually displayed at test, without new words. The 160 words presented were different for half of the participants.

Procedure and Task

The procedure was basically the same as in the experiment 15, apart from the following changes. Each experimental session lasted roughly 35-40 minutes. During the study phase, the task was limited to the gender stereotype judgement only, and so the time used for encoding of each word was decreased (a study trial lasted 4300 ms instead of 5400 ms). These manipulations were designed to increase the number of low-confidence judgements, in order to have enough trials per condition (i.e., > 15) to allow effective averaging of waves.

Following net placement, participants were seated in front of the stimulus presentation screen with the index fingers of each hand resting on a button. They wore earphones through which the auditory stimuli were presented binaurally. As a considerable number of trials had been discarded in experiment 15 because of ocular artefacts, a different procedure was adopted here. At study, an explicit request ‘Blink!’ (in Italian: ‘Ammicca!’) instead of the fixation asterisk appeared for 400 ms at the beginning of each trial, and was removed from the screen 400 ms prior to stimulus presentation. During that period participants had to blink if necessary. This procedure was adopted following guidelines by Picton and colleagues (Picton et al., 2000). Participants were required to maintain their gaze fixed on the centre of the screen and to avoid blinks for the rest of the trial. They were asked to relax and to avoid muscular movements as far as possible. Each word was auditorily presented and a blank screen appeared at the same time and lasted 1400 ms. Following the blank screen period, a question ‘Stereotype?’ (in Italian: ‘Stereotipo?’) appeared for 2000 ms. This question prompted the participants to perform the gender stereotype judgement. The instruction for this task were the same as in the experiment 15. After a further blank of 100 ms a new trial began. Participants were aware that all the test visual words would have already been presented auditorily at study. A practice session consisting of 8 items preceded the study phase per se. A short pause was given after each block of 40 trials both during the study phase and during the test phase.

After a short pause of 5 minutes, during which the status of the net was checked and readjusted if needed, the test phase began. The request ‘Blink!’ lasting for 400 ms preceded presentation of each word, and was removed 400 ms prior to stimulus onset. A test word appeared in the centre of the screen for 300 ms followed by the four letters ‘MmfF’ for 2000 ms. The onset of the word served as the cue for ‘voice retrieval’, namely the retrieval of the voice in which the word had been presented at study. The voice retrieval responses had to be made on a four-point confidence scale. If the participants were highly confident about their decision they had to press one of the two external buttons with a middle finger. Instead, if participants were less confident they had to press one of the two inner buttons using an index finger. In both cases, which button they should press depended on the voice in which they thought the word had been presented. The order of the responses associated with each of the four buttons from leftmost to rightmost was male/high-confidence, male/low-confidence, female/low-confidence, female/high-confidence (reversed for half of the participants). A further blank of 100 ms separated the current trial from the next one. A practice session consisting of 8 items (all old) preceded the test phase per se. The total duration of a test trial was 3200 ms. Voice judgements quicker than 300 ms, or slower than 2200 ms were excluded from analyses.

EEG recordings

The same settings were used as in the experiment 15 for the online recording of the EEG during task execution.

EEG Data Reduction and Analysis

The same criteria were adopted for the data reduction and analyses of the ERPs as in the experiment 15. Five participants did not reach the minimal criterion of 15 trials per category when 4 categories were created for a full 2 (confidence) x 2 (accuracy) factorial design. ERPs were therefore averaged twice, dividing trials according to confidence (high- vs. low-confidence) one time, and according to accuracy (hits vs. misses) the other time[16]. The mean numbers of trials used for the analyses of each subject's waveforms were 55, 58, 63 and 50, for the high-confidence responses, low-confidence responses, hits, and misses, respectively. The ERP latency windows analysed in the experiment 16 were different from those analysed in the experiment 15 as the procedure and task adopted were changed. As for experiment 15, the early parietal effects are reported in the Appendix (from page 121).

Results

Behavioural Data

Study Phase

The mean RTs for stereotype judgement were 622 ms, with no difference between words pronounced by the two voices (paired t-test: t(16) = 1.49, p = 0.15). There was no effect of congruence between voice and gender stereotype.

Test Phase

Accuracy

Percentages of responses classified according to response confidence, voice at study and accuracy are shown in the Table 8.

A 2x2x2 ANOVA was performed with accuracy, confidence and study voice as the within-subjects variables and the percentage of responses as the dependent variable. There were significantly more hits than misses [$F(1, 16) = 27.4$, $p < .001$]. The accuracy x confidence interaction was also significant [$F(1, 16) = 13.9$, $p < .01$], due to the percentage of highly confident responses being greater for hits than for misses (post-hoc, $p < .001$), while the percentage of low-confidence responses did not differ reliably between hits and misses ($p = .36$). A voice x accuracy interaction was also observed [$F(1, 16) = 9.7$, $p < .01$]. This was due to the difference between hits and misses being greater for words

---

[16] ERPs of the 12 participants with enough artefact-free trials per category were averaged according to a 2 confidence x 2 accuracy full factorial design. Five-way ANOVAs were conducted on these ERPs, with accuracy (hit vs. miss), confidence (high vs. low), lobe (frontal vs. parietal), side (left vs. right), and region (anterior vs. lateral) as the independent variable, and mean amplitude on selected time-windows (i.e., 500-700, 1000-1500 and 1500-2000 ms) as the dependent variable. These ANOVAs were more conservative than those conducted on ERPs of all the 17 participants averaged separately for confidence and accuracy and reported in the text (see Results), as some of the effects detected with the latter analyses were not significant with the full factorial ANOVAs. Moreover, the full factorial ANOVAs did not produce any additional interaction between confidence and accuracy. For these reasons, results of these ANOVAs will not be reported.

presented at study in the male voice than ones presented in the female voice. No other effects were significant.

Table 8

Mean Reaction Times (in Milliseconds) and Percentages of the Source Judgement Classified According to the Voice at Study (Male versus Female), Accuracy (Hit versus Miss) and Confidence (High- versus Low-Confidence) in the test phase of Experiment 16.

	Voice			
	Male		**Female**	
Percentage	**High Conf.**	**Low Conf.**	**High Conf.**	**Low Conf.**
Hit	1375	1459	1379	1484
	31%	25%	28%	22%
Miss	1464	1485	1412	1472
	16%	20%	21%	22%

Reaction Times

Mean RTs are presented in Table 8. The same 2x2x2 ANOVA as for accuracy was performed with the mean RT as the dependent variable. The RTs for hits were faster than the RTs for misses [$F(1, 16) = 5.7$, $p < .05$]. There was a main effect of confidence [$F(1, 16) = 7$, $p < .05$] with RTs for high-confidence responses being faster than for low-confidence ones. There was a significant accuracy x confidence interaction [$F(1, 16) = 5.6$, $p < .05$], through the RTs for highly confident judgements being faster for hits than for misses, with no such effect on RTs for low-confidence judgements. No effects involving voice were found.

Event-related Potentials

Confidence analysis

ERPs elicited by the high- versus low-confidence voice judgements are displayed in figure 28.

Middle and late Anterior Frontal effects (1000-1500 and 1500-2000 ms)

Two 2x2x2x2 ANOVAs (confidence, lobe, hemisphere and region) were performed on the mean amplitudes in the 1000-1500 and 1500-2000 ms latency-windows. A lobe x hemisphere interaction was observed principally in the middle latency-window [1000-1500 ms: $F(1, 16) = 7.3$, $p < .05$; 1500-2000 ms: $F(1, 16) = 3.1$, $p = .09$], due to more positive waves in the right frontal regions than in all the other regions (for all, $p < .001$). However, a lobe x region interaction was also obtained for the late 1500-2000 ms latency-window [$F(1, 16) = 5.8$, $p < .05$], due to there being more positive waves in the anterior frontal regions than elsewhere (for all, $p < .05$). The confidence x lobe x region interaction occurred in both time-windows [1000-1500 ms: $F(1, 16) = 9.5$, $p < .01$; 1500-2000 ms: $F(1, 16) = 7.9$, $p < .05$]. Post-hoc comparisons indicated that low-confidence responses elicited more positive waves than high-confidence responses selectively over the anterior frontal and the lateral parietal regions during the 1000-1500 ms time-window (for all, $p < .05$), with similar trends during the 1500-2000 ms time-window over the anterior frontal regions only ($p = .07$).

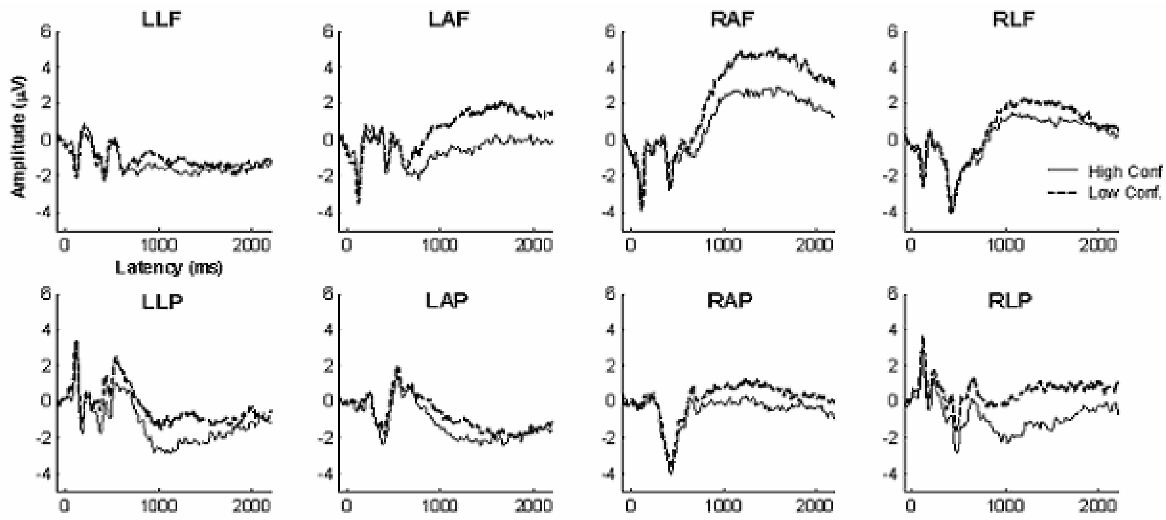

Figure 28. Grand average of ERPs associated with the High- and Low-confidence source judgments in experiment 16. Labels of the scalp regions as for Figure 26.

Given the results of the overall ANOVA and the existing literature on late prefrontal effects, two separate 2x2x2 ANOVAs were run, for the middle and the late latency-windows, respectively; they were restricted to the prefrontal regions only, involving the factors confidence (high- vs. low-confidence responses), hemisphere (left vs. right frontal) and region (anterior vs. lateral). These two analyses led to very similar findings. A main effect of hemisphere was obtained [1000-1500 ms: $F(1, 16) = 27.6$, $p < .001$; 1500-2000 ms: $F(1, 16) = 20$, $p < .001$], due to right frontal ERPs being more positive than left ones. The main effect of region was also significant [1000-1500 ms: $F(1, 16) = 4.4$, $p = .05$; 1500-2000 ms: $F(1, 16) = 6$, $p < .05$], due to there being more positive waves in the anterior prefrontal regions than in the lateral ones. The only significant interaction was the confidence x region one [1000-1500 ms: $F(1, 16) = 7$, $p < .05$; 1500-2000 ms: $F(1, 16) = 9$, $p < .01$]. ERPs for low-confidence judgements were more positive than those for high-confidence ones, this difference being more pronounced in the bilateral anterior frontal regions than in the lateral frontal ones, as planned comparisons demonstrated ($p < .05$ and $p < .01$ for the middle and late latency-windows, respectively). The results of the more specific analysis therefore confirmed those from the more general one.

Accuracy analysis

Similar ANOVAs were conducted replacing the factor confidence with that of accuracy. However, no effect of accuracy was observed in the ERPs, as can be seen in the figure 29.

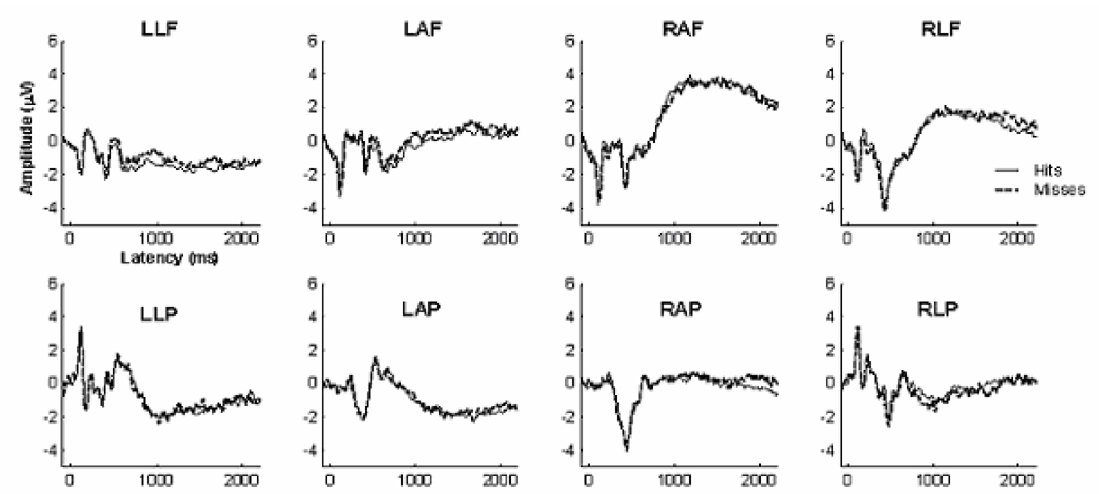

Figure 29. Grand average of ERPs associated with the correct versus incorrect source judgments (Hits versus Misses) in experiment 16. Labels of the scalp regions as for Figure 26.

Discussion

Experiment 16 confirms the general involvement of right frontal regions in two late time-windows during a source memory task already shown in previous memory studies (e.g., Wilding & Rugg, 1996) and in the experiment 15 of the present study. In particular, waves in the right frontal regions were the most positive in the subsequent latency-windows of 1000-1500 and 1500-2000 ms. However, the present results again do not corroborate the successful retrieval account of the prefrontal involvement during a source memory task. The accuracy of the source judgement did not influence ERPs at all (as shown in the figure 29), confirming the results of experiment 15, even though the paradigms adopted in the two experiments were different.

The aim of experiment 16 was primarily to evaluate the role of confidence in modulating late frontal ERPs during a source memory task. Previous ERP experiments requiring confidence rating of memory judgements did not examine late frontal effects in detail (Rugg & Doyle, 1992) and usually did not analyse low-confidence ERPs because of the low number of trials available for the averaging (Rubin, Van Petten, Glisky, & Newberg, 1999; Rugg, Cox, Doyle, & Wells, 1995). In the current study, the production of confidence ratings by the participants influenced their ERPs in two dissociable ways. First, ERPs are more positive for low-confidence ratings than for high-confidence ones. This pattern is observed over anterior prefrontal regions (i.e., 1000-2000 ms). It has been supposed that when low-confidence responses are given, more monitoring is dedicated to the retrieval processes before a decision is made (Henson et al., 2000), consistent with the longer RTs observed in the present experiment for low-confidence judgements. Our results would fit with such a long-lasting monitoring process occurring over the anterior prefrontal regions.

A second dissociable effect found in the present experiment consists of ERPs being specifically more positive over right prefrontal sites (i.e., anterior and lateral) than elsewhere in the middle latency-window (1000-1500 ms), during which participants were performing their judgement (mean RT = 1441 ms). This effect suggests that, in the present experiment, right prefrontal positivity is associated with the online confidence evaluation of the source judgement, independently of the accuracy and confidence of such judgement (but see General Discussion).

General Discussion

The specific aim of the present study was to elucidate the role of prefrontal areas in source memory retrieval and, specifically, to electrophysiologically dissociate the prefrontal ERP effects of the objective performance (viz., accuracy) from that of more subjective aspects of memory search processes (viz., confidence) during source retrieval. We tried to address these issues by means of ERPs measured with a high-density (128 channel) recording apparatus. By pursuing this specific purpose, we also wanted to bring evidence in favour of the hypothesis that the monitoring/checking function of right lateral prefrontal cortex is not only present in the temporal domain (FP effect) but also in other domains such as the source memory one.

In particular, our first interest was to test whether accuracy of source retrieval was linked to the frontal ERP old/new effect, as suggested by some ERP studies (e.g., Graham & Cabeza, 2001; Wilding & Rugg, 1996) but not confirmed by others (e.g., Senkfor & Van Petten, 1998; Ranganath & Paller, 1999). In the experiment 15, late ERPs evoked by hit/miss trials over the right frontal regions were if anything more positive, albeit not significantly, than ERPs evoked by hit/hit ones. In the light of the inconsistency of the effect of source retrieval accuracy on late frontal waves across studies (cf. Senkfor & Van Petten, 1998; Wilding & Rugg, 1996), this finding suggests that retrieval accuracy is not a critical variable influencing the late frontal ERPs. This is compatible with recent accounts ascribing the frontal contribution to memory to more general processing capacities which can be applied to non-memory tasks as well (e.g., Stuss & Alexander, 2005).

An issue then arises regarding the specific content of the monitoring processes supposed to occur during retrieval within the prefrontal areas (e.g., Burgess & Shallice, 1996b). A suggestion deriving from the fMRI study by Henson and colleagues (2000) is that prefrontal areas are modulated by variables which are more subjective than accuracy per se, such as the confidence level of the memory judgement. Experiment 16 aimed to extend these findings, investigating the electrophysiological correlates of confidence self-ratings during a source memory task. Specifically, in the retrieval phase of the second experiment, voice judgements were embedded together with response confidence evaluation.

According to a schematic analysis of this task, the following processes should occur, among others, during any trial in order to give an appropriate response: (a) After reading the test word, attention should be focused on memory products reactivated by this cue in order to start the memory search (attentional shift towards retrieval specification); (b) Attention needs to be maintained on these retrieval products so as to continue the memory search (maintenance of attention); (c) Memory retrieval products elicited by the cue are possibly brought to consciousness (ecphory); (d) To perform a correct source judgement, a further process is required which scans the products of memory search for information concerning voice. Accuracy of these products is then checked especially when the voice is not confidently recollected (monitoring process); (e) Finally, given the specific nature of this task, which additionally requires confidence judgements, another meta-level process is needed. This process is held to monitor the ongoing memory search itself, in order to evaluate the confidence status of the current source judgement (metamemory process).

Apart from a lack for any effect of accuracy on ERPs (process c, in our task analysis), which corroborates the results of experiment 15, the results of experiment 16 showed a number of specific ERP effects which might correspond to some of the processes already specified in the schematic task-analysis. Those effects can be distinguished on the basis of their temporal and topographical distribution, on the one hand, and of their sensitivity to the confidence level, on the other hand. Earlier parietal effects, which are relevant for processes a and b, have been discussed elsewhere (see footnote 15), whereas effects concerning later frontal waves will be discussed in detail in the following sections.

Anterior frontal effects: process (d)

An anterior-more-than-lateral prefrontal pattern was found in experiment 16 but not in experiment 15. In experiment 15, only one operation at a time had to be performed, namely an old/new judgement followed by a source judgement. Conversely, in experiment 16, two different operations had to be carried out rather simultaneously, namely a source judgement and a confidence evaluation, and the different processes underlying them had to be coordinated so as to give a response.

One possible explanation is suggested by the idea that a specific role for the anterior prefrontal region is to integrate the results of two or more separate cognitive operations in the pursuit of a more general behavioural goal (Ramnani & Owen, 2004; see also Reynolds, McDermott, & Braver, 2005). The electrophysiological dissociation between the two present experiments supports this model, if not strictly anatomically, due to the low-spatial resolution of the ERPs, at least functionally. However, in order to explain the effect of confidence on anterior prefrontal waves, this account needs to be extended by postulating further operations conceivably more engaged during a low-confidence judgement than during a high-confidence one. According to signal detection models of recognition in memory (Juola, Fischler, Wood, & Atkinson, 1971), low-confidence judgements are those in which the memory strength is close to the decision criterion. These situations are likely to involve more monitoring of the retrieved products, consistent with the longer RTs obtained here for low-confidence judgements. In the fMRI study by Henson and colleagues (2000), low-confidence responses selectively activated bilateral prefrontal cortex. In the present study, low-confidence responses evoked more positive waves on the bilateral anterior prefrontal scalp regions in a long-lasting fashion (i.e., middle and late time-windows). This ERP pattern might be considered as a marker of retrieval verification processes, which monitor the appropriateness of retrieved information, especially when the retrieval process is difficult (process d, in our task analysis; editing or mediator processes according to the model specified by Burgess & Shallice, 1996b; see also Henson et al., 1999b, 2000; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003). It would be difficult to interpret these findings from the point of view of alternative interpretations, such as the retrieval mode account (e.g., Kapur et al., 1995; Lepage, Ghaffar, Nyberg, & Tulving, 2000).

Right frontal effect: process (e)

Finally, another clearly localized electrophysiological effect was found in this study. ERPs were more positive over the right prefrontal sites (both anterior and lateral) than elsewhere, especially in the middle latency-window, independently of source memory accuracy (experiments 15 and 16) and confidence (experiment 16). It is possible to interpret this asymmetry in the light of our task demands. Noteworthy, during the latency-window in which the right prefrontal asymmetry is more evident (i.e., 1000-1500 ms), participants were actually performing the source-plus-confidence judgement. As pointed out in our previous task analysis, these task demands of the experiment 16 explicitly require a metamemory process monitoring the state of confidence of the response (process e). The right frontal ERP effect in this interval, thus, may be accounted for by attributing a role in metamemory evaluation of retrieval processes to the right prefrontal regions. This inference about possible brain sources of the right frontal ERP effect fits with the results of neuropsychological studies showing evidence for a possible metamemory role of the right PFC (e.g., Vilkki, Servo, & Surma-aho, 1998; Vilkki, Surma-aho, & Servo, 1999). However, the right-more-than-left effect was also found in our experiment 15 and in other ERP studies of episodic retrieval not requiring a confidence evaluation (e.g., Wilding and Rugg, 1996). This asymmetry also fits various functional imaging findings which widely document a right-more-than-left prefrontal involvement during retrieval (e.g., Lepage et al., 2000; Shallice et al., 1994; Tulving et al., 1994; but see Nolde et al., 1998). In recent fMRI studies, activity of right dorsolateral and fronto-polar prefrontal areas during retrieval has been linked to familiarity monitoring (e.g., Henson et al., 1999a; Dobbins, Rice, Wagner, & Schacter, 2003; Dobbins, Simons, & Schacter, 2004). On this account, the process thought to engage the right prefrontal regions consists of monitoring a familiarity signal in order to make a decision according to an internal criterion (cf. Banks, 1970). Assuming an anatomical correspondence between scalp potentials and sources, the latter interpretation seems more appropriate to account for the right frontal ERP effect found not only in our experiment 16, but also in the experiment 15 and in other studies of episodic memory which do not explicitly require metamemory processes. In our experiment 16, this familiarity monitoring could be functional not to achieve an old/new judgment (not required) but to decide how confidently one remembers the voice pronouncing the word.

Conclusions

The lack of any modulation of the ERPs throughout the scalp by accuracy of the source judgments, in both experiments of the current study, is very difficult to account for with the successful source retrieval hypothesis. The results of experiment 16 show a clear-cut dissociation among the prefrontal scalp regions of interest analyzed, along the anterior-lateral and left-right topographical dimensions, respectively. This pattern of results suggests a fractionation of memory functions within the underlying prefrontal areas. Anterior prefrontal ERPs were tonically modulated by the confidence rating of the source retrieval (i.e., more positivity for low- than for high- confidence ratings) during middle and late latency-windows. This pattern brings converging evidence for the role of confidence in modulating prefrontal involvement in memory retrieval and may well be ascribed to extra monitoring demands, necessary in order to achieve a source memory judgement during uncertain situations. On the other hand, the more general right-more-than-left prefrontal ERP positivity, also found in the experiment 15, could be attributed to the process of familiarity monitoring.

5.2. Monitoring in the FP and in the source memory domains: same or different processes?

With the source memory study we wanted to extend results about the monitoring role of right lateral PFC to a domain different from temporal preparation. Notwithstanding that a number of processes may differ between the two domains and tasks, some of the demands of these tasks are similar and may require some specific processes which are likely to be located in the rDLPFC.

One of the hypotheses regarding the role of right lateral PFC was that it is involved in non-evident error detection (Shallice, 2006; see also Petrides, 1994), that is “the process of detecting a discrepancy between the situation resulting from the implementation of the strategy and the requirements of satisfying a goal". One of the most important criteria which Shallice (2006) put forward in order to describe situations which are likely to involve such a process is uncertainty. Situations in which the information relevant for the task is not externally presented but should be internally recovered are likely to be uncertain. An example of uncertain situations where an involvement of the right DLPFC has been found is represented by tasks in which the task-relevant sensory information is presented in a degraded manner (e.g., Sharp, Scott, & Wise, 2004).

In the source memory tasks used in experiments 15 and 16, the task-relevant information was the source memory trace, a kind of information which does not have a link with the external environment, but should be internally checked once the memory trace has been reactivated (hence, the late time-window of the related prefrontal ERP effects). In the variable FP paradigm, the relevant information is the (uncertain) moment of occurrence of an imperative stimulus. In this case, what is likely to be checked is the non-occurrence of the stimulus as time elapses and the conditional probability of its forthcoming occurrence increases. The endogenous information should be continuously checked in order to satisfy a specific goal. This goal would be to establish its appropriateness for the response in the source memory task, and to increase preparation level in the variable FP task. In the light of what stated above, it is worthwhile testing if the process called non-evident 'error' detection in Shallice (2006) is part of a more general non-evident 'information' detection and checking function.

However, the disparity between the two domains (i.e., FP and source memory) and of the techniques of functional/anatomical investigation used here (TMS and neuropsychology, on the one side, and ERP, on the other side) makes it desirable to find other sources of evidence for the hypothesis that these tasks engage the same monitoring process in the same brain region.

A possible test of this hypothesis, at the behavioural level, could be a dual-task in which the two domains are combined. A suitable task can be a source memory retrieval test in which the period between the onset of the item of which the source (e.g., the voice gender of a word) should be retrieved and the appearance of the imperative stimulus (i.e., a go-signal such as an arrow) would be varied according to a variable FP design. The monitoring demands of the source retrieval could also be parametrically manipulated. However, a possible outcome of this task is an increased FP effect due to the fact that the time available for the source memory judgment would be less for the short FP than for the long one and, at least in some cases, participants could not have completed the retrieval when a short FP would occur, with a consequent RT lengthening on the short FP.

Alternatively, in order to avoid this possible drawback, an autobiographic task could be used, in which a word is presented at the beginning of each block (e.g., “Christmas”), as a cue for starting to mentally retrieve as many autobiographic details as possible concerning the event specified by the word. At the same time, participants could be required to perform a simple RT task with variable FPs. In this case, the probability that a given process related to the memory retrieval is engaged during a short or a long FP would be the same, as the participants have to spontaneously produce their own memories, without an externally given go-signal. After each block, a brief report of the autobiographic memory could be asked to the participants to check that they are actually performing the dual-task adequately. Moreover, at the end of all the blocks, participants may be required to sort the cue words initially provided according to some criteria which could be used as indirect measures of how much monitoring was required. Some criteria could be the quantity of the retrieved information, the precision of the perceptual details, the precision of the temporal context information, and the level of confidence. For the analysis, each word may receive a score according to its order in the classification for each parameter (for instance, a word receives a score of 1 when retrieved events evoked by that word were the most numerous, detailed, temporally precise, and retrieved with the highest confidence). The scores obtained by each word for each parameter might be summed together and used to classify the words according to a memory index (the higher the index, the more the monitoring conceivably required).

Whether the two monitoring processes required by the variable FP task and by the memory retrieval have same functional locus could be tested by applying the logic of the Additive Factor Method proposed by Sternberg (1969). According to this logic, two given task variables are held to affect different processing stages when their effects combine additively, whereas an interaction suggests that they affect a common processing stage. In other words, a common mechanism would be suggested if the magnitude of the FP effect interacts with the memory index calculated as described above.

Chapter 6

Concluding remarks

6.1. A brief historical overview

In the *Creation of Adam*, the marvellous Sistine Chapel painting by Michelangelo Buonarroti, God’s mantle and other background figures and shapes resemble an anatomical image of the human brain (Meshberger, 1990). God’s feet lay on the encephalic trunk, whereas his head is painted within the frontal lobe. God’s index finger, coming out of the PFC, points at Adam, and makes him human (Goldberg, 2001).

Although extremely amazing, the interpretation of this Michelangelo’s famous painting is likely to have been done only a posteriori. PFC was treated as the ‘silent’ portion of the brain until the mid-nineteenth century (e.g., Fritsch & Hitzig, 1870). The view according to which PFC is the seat of the typically human, high-level functions is indeed relatively recent, originating from pioneer clinical reports of patients with frontal lesions from the mid nineteenth century on (e.g., Bianchi, 1895; Donath, 1923; Ferrier & Yeo, 1884; Harlow, 1869; Welt, 1888).

The study of the specific functions of the PFC through more scientifically-based methodologies, however, started much more recently. As a consequence, a number of models in the eighties postulated the existence of a high-level cognitive system located in the PFC with a set of supervisory functions. However, in the first version of the SAS model (Norman & Shallice, 1980; 1986), but also in similar early models, such as the Central Executive (Baddeley, 1986), the central processor (Umiltà, 1988), the precise localization of functions within PFC was left undetermined, mainly because of a lack of detailed evidence at that time.

As empirical evidence accumulated over years, a more detailed view has emerged, which suggests a fractionation of these high-level functions within a network of different functional prefrontal areas (Shallice, 2004), even if the details of this view are far from being entirely specified (e.g., Smith & Jonides, 1999). A number of scientists, mainly on the basis of neuropsychological (Godefroy et al., 1999; Stuss et al., 2005) and brain imaging (e.g., Burgess, Simons, Dumontheil, & Gilbert, 2005) findings, have indeed hypothesized distinct localizations of different high-order functions within the PFC.

A particular role emerged for the DLPFC. Faw (2003), for instance, put forward a hierarchical model where PFC is metaphorically defined as the ‘five-member Executive Committee’. This organizational metaphor was aimed to highlight both the interactivity and the domain-specificity of different areas of the prefrontal lobes. This ‘committee’ represents the prefrontally-controlled expansion of five sub- and posterior-cortical systems. On this model, the DLPFC has the special status of a Coordinator (Faw, 2000a, 2000b), as it is dominant in directing attention, working memory, and willed action. A more specific monitoring role for the lateral PFC (especially right) has emerged from the work by Donald Stuss and his colleagues (e.g., Stuss et al., 1995; Stuss, Binns et al., 2002; Stuss et al., 2005).

However, according to an opposite view, each prefrontal area (right lateral PFC included) has an undifferentiated and equi-potential role, as different cognitive demands usually involve common, or at least overlapping, prefrontal regions, sometimes even at the single neuron level (e.g., Duncan & Owen, 2000). Based on a work by Stuss and colleagues (Stuss et al., 2005), in the present project we tried to provide a specific contribution to this more general debate, by investigating the prefrontal involvement in a basic cognitive capacity supposed to be seated in the rDLPFC, namely the monitoring of external and internal contingencies.

6.2. Summary of the current project

In the remainder of the chapter, the results of the project will be discussed in the light of their contribution to the understanding of the processes underlying the performance of some cognitive tasks and of the role that PFC seems to play in some of these processes. Specifically, in the following paragraphs, the main results of the project will be reviewed, following the order adopted in the experimental part of the thesis (chapters 2-5). We will start from the behavioural and developmental experiments on the basic FP phenomena (chapter 2). We will then discuss results of the TMS and neuropsychological studies (chapter 3). A paragraph will be dedicated to the STARCO effect (chapter 4). After that, results of the ERP study on source memory will be reviewed (chapter 5). Finally, the general implications of the overall project, the limits and the suggestions for future research will be discussed.

The FP phenomena: behavioural evidence

The first aim of this project was to better characterize the processes underlying the behavioural effects usually produced in a variable FP paradigm, starting from the neuropsychological finding that right lateral prefrontal patients are impaired in this task (Stuss et al., 2005). In a variable FP paradigm, the FP is defined as the waiting time between a warning and an imperative stimulus (i.e., the stimulus requiring a response). In a typical variable FP paradigm, a range of different FPs vary randomly but equiprobably across trials. In this paradigm, RT follows a negatively accelerating function of the FP (i.e., the variable FP effect). Another phenomenon, which was not investigated by Stuss and colleagues (2005), but which is however usually observed in a variable FP paradigm, are the sequential effects: RTs are slower when long FPs occur in the preceding trial than when short ones do (Drazin, 1961; Karlin, 1959). The sequential effects are usually asymmetric as they are mainly present with the shortest FPs in the range used.

Initially, we tried to obtain a fine-grained analysis of the task under study (i.e., the variable FP task). To that end, we investigated in detail which processes may be responsible of the FP and the sequential effects usually found in this task. Despite the simplicity of the variable FP paradigm, defining which processes underlie the behavioural effects obtained in this paradigm is puzzling. Contrasting views in the literature have proposed either multi-process strategic accounts (see Niemi & Näätänen, 1981, for a review), or a single-process account derived from the trace conditioning tradition (Los & van den Heuvel, 2001).

A strategic account attributes the FP effect to a process checking that the imperative stimulus has not occurred in order to increase the preparation level as time elapses and the conditional probability of stimulus occurrence increases (Näätänen, 1970). However, sequential effects are not explained by this account. A more detailed strategic account assumes that participants expect a repetition of the previous FP in the current trial, so that maximal preparation level is achieved at the same FP as occurred on the previous trial (e.g., Drazin, 1961). If FP_n is shorter than FP_{n-1}, then maximal preparation will not have been reached when the imperative stimulus occurs and a relatively slow RT will result. The asymmetry of the sequential effects is explained by postulating a strategic repreparation/maintenance process when the current FP is longer than the expected preceding FP (e.g., Alegria, 1975; Karlin, 1959). A disadvantage of these dual-process strategic accounts is that they propose two entirely different strategic processes to explain different aspects of the data. On the conditioning single-process account, instead, both the

FP and the sequential effects arise from the same conditioning laws which act on the preceding trial, basically by reinforcing FPs that occur on that trial and extinguishing shorter FPs (Los & van den Heuvel, 2001).

In the project, these divergent theories have been tested using different approaches. First, the phenomena involved in the variable FP task, and the underlying processes, were investigated through behavioural studies on adults. A prediction of the single-process conditioning view is that the FP and the sequential effects should correlate, as they derive from the basic conditioning mechanisms. Results of experiments 1 and 2 (chapter 2) show instead that the FP effect and the sequential effects do not correlate, independently of the FP range used.

To further investigate whether the FP and the sequential effects derive from a common mechanism or from different ones, a broader version of the dissociation logic (e.g., Shallice, 1988) was applied to children's data. A developmental approach was indeed used to track the ontogenetic time-course of the FP and sequential effects (experiments 3a, 3b and 4, chapter 2). If a common process underlies the FP and the sequential effects, as predicted by the conditioning view, a parallel ontogenetic time-course should have been observed. However, the results suggest different developmental trajectories for the two effects: the sequential effects are already present in the youngest group (especially 4 year old children) while the FP effect appears more gradually some years later. The pattern of sequential effects obtained on the RTs of the youngest children was also qualitatively different from the sequential effects obtained in older children and adults. For the latter, sequential effects are asymmetrically biased towards the shortest FP_n and disappear for the longest FP_n. For 4 year old children, instead, sequential effects were symmetrically present for every current FP.

Neither dual-process strategic accounts (e.g., Alegria, 1975) nor the conditioning view (e.g., Los & van den Heuvel, 2001) suffice to account for these observed data. Thus, a composite dual-process account, which shares some aspects with the previous accounts of the FP phenomena, was put forward to explain the data. For the sequential effects, an explanation concerning modulation of the arousal level by the preceding FP was proposed: arousal is enhanced following a short FP_{n-1} and decreased following a long FP_{n-1}. This explanation gains support from different sources. First, the accuracy pattern obtained from young children (mainly from the 4-5 year old ones) shows that delayed and null responses are more likely to occur after a long preceding FP, compatible with a decrease in the arousal level. On the other hand, anticipated responses mainly occur after a short preceding

FP, compatible with an increase in the arousal level. This result is not found in older children and in adults in terms of accuracy, probably because of the ceiling effects of the variable FP paradigm. However, when a covert measure of arousal such as the CNV electrophysiological component has been used, similar evidence is also found for adults (Los & Heslenfeld, 2005). As results of that study show, despite the fact that sequential effects are asymmetric at the RT level, the CNV amplitude is symmetrically modulated by the preceding FP, indirectly supporting our account of sequential effects in terms of arousal modulation.

This account, however, does not explain the FP effect. In order to account for the FP effect, we tested the traditional conditional probability monitoring explanation. On this account, the FP effect is the marker of a mechanism checking the stimulus non-occurrence as time elapses, and raising the level of preparation as the conditional probability of stimulus occurrence increases for the long FPs. Evidence for this account derives from various studies showing that changing the conditional probability of stimulus occurrence also changes the shape of the FP-RT function (e.g., Baumeister & Joubert, 1969; Nickerson & Burnham, 1969). We adopted a similar approach in the experiment 5 (chapter 2), where conditional probability of stimulus occurrence was kept equal along the FPs. No FP effect was observed in this condition. This finding confirms similar results in the literature and further supports the monitoring account of the FP effect.

An assumption of the dual-process explanation offered to account for the results of the developmental study is that the sequential effects and the FP effect are due to an automatic and to a controlled process, respectively. According to the traditional classification by Shiffrin and Schneider (1977a; see also Hasher & Zacks, 1979), automatic processes do not require attentive resources. Thus, they are not affected by interference from other processes (either automatic or voluntary), and do not change significantly with age. The idea here is that attentional resources require cortical maturation to be fully devoted to tasks. Thus, they are vulnerable to aging. This assumption, in turn, derives from the hypothesis that attentional resources are mainly located in the PFC (e.g., Posner & Peterson, 1990), which is the last region to mature and the first to decline on average. On this view, sequential effects are due to automatic processes, as they do not change quantitatively with age, whereas the FP effect should be instead considered as a controlled process, as it changes significantly with age.

Experiment 6 (chapter 2) aimed to further investigate the hypothesis that automatic and controlled processes may be responsible of the FP and the sequential effects, respectively.

In that study, a variable FP paradigm was embedded in a spatial n-back task. In this task, various levels of working memory load are administered in different blocks. The assumption was made that if a process is controlled in nature (and hence resource-demanding), it should be impaired when a concomitant process compete for the same resources, whereas if it is automatic (i.e., not resource-demanding), it should not be affected by the interference from another process. Results showed that the FP effect interacts with the difficulty of the task (with the increasing working memory load), whereas the sequential effects remain unchanged across the various conditions of working memory load (experiment 6, chapter 2).

Thus, the mechanism underlying sequential effects (the process of arousal modulation, in our dual-process account), can be considered essentially automatic, confirming results from cuing experiments (e.g., Los & van den Heuvel, 2001). These effects, indeed, are not subject to interference from another task (e.g., n-back task, experiment 6, chapter 2) and are relatively constant in size from 4 year of age to adulthood (e.g., developmental experiments 3-4, chapter 2). On the contrary, the FP effect seems to originate from a more controlled process (the conditional probability monitoring, in our dual-process account), since it is subject to interference from other processes and to ontogenetic maturation, as it is shown by the results of the n-back task and of the developmental study, respectively.

The FP phenomena: TMS and neuropsychological evidence

Studies on the variable FP paradigm were also carried out with more traditional dissociative methods, namely TMS and neuropsychology (chapter 3). The aim was twofold: further characterizing the cognitive processes underlying the variable FP phenomena, and finding the neural bases of these processes.

A recent neuropsychological study shows that the FP effect is impaired in patients with lesions in the right lateral PFC (Stuss et al., 2005). We conducted a TMS study (experiments 7 and 8, chapter 3) in order to test whether this finding could be also reproduced in healthy adults by means of TMS. In addition, we also studied the sequential effects, which have not been investigated neuropsychologically. We investigated these effects also for theoretical reasons. If the FP and the sequential effects arise from a common conditioning mechanism (Los & van den Heuvel, 2001), the disruption of the area responsible for this mechanism should affect both effects at the same time. If instead they originate from different processes, as predicted, for instance, by the dual-process account put forward in the developmental study, there is no reason to expect that disruption of the area responsible for one of these processes should affect both effects.

The TMS parameters used in the study were those of theta burst stimulation (TBS), an off-line stimulation paradigm which was demonstrated to temporarily depress cortical activity in the targeted area for 20-60 minutes after stimulation (depending on the TBS duration; Huang et al., 2005). Results of both experiments show that the FP effect is reduced after TBS of rDLPFC with respect to the pre-TMS baseline condition and to two control areas (i.e., left DLPFC and right angular gyrus). From a neuropsychological point of view, this finding confirms that the rDLPFC is responsible for the FP effect, whereas temporarily inhibiting this area with TMS does not affect quantitatively the sequential effects. From a cognitive perspective, these results cannot be explained by single-process accounts, whereas they are compatible with the dual-process explanation put forward to explain the developmental data (experiments 3a, 3b and 4, chapter 2). As a further support of this account, the pattern of sequential effects obtained in the block where TBS was supposed to be stronger (second TMS block, experiment 8, chapter 3) was analogous to that of youngest children: sequential effects were indeed basically symmetric while the FP effect was strongly reduced. This pattern was accounted for by supposing a compensatory effect of the process underlying the FP effect on the process underlying the sequential effects. In other words, the sequential effects do not usually appear for a long FP_n because the process of conditional probability monitoring accelerates RTs on this FP, even after a long FP_{n-1}, when a low level of arousal should occur. When the monitoring process is impaired because the brain area responsible for it is not yet mature or temporarily inhibited, the sequential effects appear also for long FPs.

The TMS results were complemented by those of a neuropsychological study on tumor patients (experiment 9, chapter 3). In that study, a variable FP paradigm was performed by patients with a tumor located in six different cortical regions and by a control group of orthopaedic patients. The six regions were: right and left prefrontal, right and left premotor, and right and left parietal cortices. Tumor patients performed the task both 1-3 days before surgical removal of tumoral tissue and 2-6 days after it. The control participants performed the task twice with the same temporal distance between the two sessions as the tumor patients, but without surgery in between. Results of that study show a significant reduction of the FP effect selectively after excision of tumors in right PFC. With respect to the sequential effects, results obtained with the right prefrontal tumor patients are more puzzling, as a certain degree of reduction was found for the sequential effect after excision of the right PFC. This reduction in the sequential effects, documented by a 2-way interaction between the FP_{n-1} and the testing session, was common to all the 4 frontal groups and was not present with the two parietal groups and the control group. The generality of this effect within all frontal lesions may be attributed to the fact that spatial localization in tumor studies is less selective as compared to TMS studies.

However, the sequential effects were reliably reduced after surgical removal of tumors located in the left premotor region (as documented by a 3-way FP_n x FP_{n-1} x testing session interaction, which was significant even after a Bonferroni correction). This reduction in the sequential effects was attributed to an impairment of the mechanism of arousal regulation by the length of the FP_{n-1}. Left premotor patients showed instead no change in the magnitude of the FP effect after the surgical operation. The dissociation between the two effects within the left premotor group has an opposite direction with respect to that found in young children and in healthy adults after TMS of rDLPFC, where the FP effect was reduced while the sequential effects were normal-sized. This pattern further supports the dual-process account of the variable FP phenomena.

The STARCO effect

FP phenomena have been traditionally studied with elapsing time (FP) as a task-irrelevant feature. In a typical variable FP task, indeed, participants have to detect or discriminate a target stimulus regardless of the length of the FP that precedes its occurrence. We wanted to explore whether the pattern of interaction between the current FP and the preceding one may change when the participant is explicitly required to monitor the FP. The specific hypothesis was made that when participants were explicitly asked to be aware of the FP length (also for the short FPs), they could compensate for the sequential effects, in a similar manner as it happens in validly cued short FPs (e.g., Los & van den Heuvel, 2001). To that purpose, a behavioural experiment was designed using a modified version of the variable FP paradigm, where an explicit temporal judgment was required (experiment 10, chapter 4). In the basic task, when the imperative stimulus appeared participants had to judge if the FP on that trial was short or long. The usual interaction between the current and the preceding FPs was found (i.e., asymmetric sequential effects), supporting the view that the sequential effects are a robust phenomenon which resists even to the fact that participants’ attention is oriented to the shortest FP, because it is a task-relevant feature.

Critically, this experiment produced a new S-R compatibility effect: RTs were shorter when short and long FPs had to be responded to with left and right hands (anatomically positioned), respectively, than with the opposite stimulus-response mapping. Control experiments (experiments 11-13) allowed us to exclude that hemispheric/manual asymmetries could explain the data. The compatibility effect found (i.e., STARCO effect) suggests that elapsing time is represented, in some circumstances, by means of spatial vectors, such as other ordered material (e.g., numbers and alphabetic letters). In view of the results of experiment 14, which show that the STARCO effect follows a stepwise function of the FP duration, explanations related to categorical factors (e.g., markedness hypothesis) cannot be excluded.

Prefrontal cortex involvement in source memory: electrophysiological evidence

From a general point of view, the last two experiments (experiment 15 and 16, chapter 5) aimed to extend results showing a monitoring role of the rDLPFC (chapter 3) beyond the domain of non-specific preparation. We chose the episodic memory retrieval domain (and in particular source memory), as it has been the focus of a number of studies investigating the role of the right PFC (e.g., Henson et al., 2000; Schacter et al., 1996a; Schacter et al., 1996b; Tulving et al., 1994), and it has been suggested to involve a monitoring process (e.g., Shallice, 2006).

The task was to retrieve the word and the voice of the speaker at study (experiment 15, chapter 5) or the voice of the speaker together with confidence ratings about the source judgement (experiment 16, chapter 5). ERPs were not modulated by the success of the voice retrieval, discarding accounts linked to retrieval success. Critically, a right-more-than-left late prefrontal positivity was found in both experiments. This late positivity has been attributed to a process monitoring the status of the source memory trace (i.e., familiarity monitoring). Moreover, results of experiment 16 show that confidence influences a neural circuit, presumably anteriorly located, as reflected by ERPs recorded from the bilateral anterior frontal sites: waves associated with low confidence judgments were more positive than those associated with high confidence ones. This pattern was interpreted as showing an engagement of anterior prefrontal regions when the source memory trace is weak and extra-monitoring is required to retrieve the item. Thus, the dissociable effects found within the prefrontal scalp regions, specifically along the anterior-posterior and right-left dimensions, are interpreted as markers of qualitatively different monitoring processes, probably subserved by different prefrontal circuits.

6.3. Methodological considerations

In the attempt to characterize the functions of different areas of PFC, the DLPFC has historically received relatively more attention (Shallice, 2004). This has not always corresponded to a linear progress in the understanding of its function. In brain imaging studies conducted in the early nineties, for instance, virtually every task was reported to activate left and/or right DLPFC. For instance, the rDLPFC was reported to be activated in tasks based on willed action (Frith, Friston, Liddle, & Frackowiak, 1991; Jahanshahi et al., 1995), working memory (Petrides et al., 1993), episodic memory retrieval (e.g., Tulving et al., 1994), classical conditioning extinction (Hugdahl et al., 1995) and so on. The tasks employed in these studies were multi-componential and it can be assumed that many processes underlie them.

To know which of these processes was critically associated to the DLPFC activation was rather arbitrary (Frith, 2000). A solution could be represented by the use of a fine-grained analysis of the task under study (cf. Stuss et al., 1995; 2005), with the aid of methods belonging to different disciplines, such as experimental psychology, developmental psychology and cognitive neuropsychology. Such analysis may reveal which cognitive processes are engaged during a task and permit a better localization of such processes in the brain. Once it is hypothesized that a cerebral area is critical for a given process, it is possible to devise a set of complementary experiments with different methods to test this hypothesis. To be completely process-driven, these experiments should employ various tasks in different domains, all of which are supposed to require the process under study.

The present project can be summarized in the way described above. The project, indeed, started from the purpose of testing the monitoring role of rDLPFC. To achieve this, a range of different methodologies and approaches have complemented each other, as described in the previous chapters. This multi-disciplinary approach, typical of cognitive neuroscience, has offered cumulative evidence in favour of the initial hypothesis, on the one side, and has contributed to better specify the processes underlying different tasks in two distinct domains, such as temporal preparation and source memory retrieval, on the other side. Thus, this approach demonstrates the heuristic value of a constant interaction between the neural level and the cognitive level of investigation.

Among the methodological approaches adopted in the project, three deserve further consideration here, not only because they have been quite recently introduced, but also for the potential value added to cognitive neuroscience by their use. These approaches are: developmental dissociations, TMS theta burst stimulation, and acute tumor patient studies. In the 3 sub-paragraphs below, we will discuss the methodological and theoretical implications of each of them.

Developmental Dissociations

Developmental dissociations occur when different effects produced in one or more tasks are shown to appear diachronically in cognitive development, as revealed either longitudinally in the same group of children, or across different age groups. The rationale underlying their use in cognitive neuroscience is analogous to that underlying dissociations in neuropsychology (e.g., Shallice, 1988). When two effects have different developmental trajectories, it may be provisionally assumed that they do not depend upon the same system. This assumption is subject to the same caveat as that applying to simple neuropsychological dissociations. Suppose that the onset of two behavioural effects A and B occurs at different ages, with effect A appearing some years before effect B. It is in fact possible to interpret this developmental dissociation as due to a resource artifact: the process underlying the two effects may be the same but the two effects need different levels of processing resources. The qualitatively equivalent processing resources of young children may suffice for the effect A to appear, but they may be insufficient for the effect B, which would appear when maturation will make more resources available. This caveat should be taken seriously when inferences are drawn from a developmental dissociation. One way to overcome this problem is to check whether there is a double dissociation with data obtained from adults. If the effect A is less pronounced than effect B in adults (contrary to what happens in children), the account in terms of artifact of resources is likely to be inappropriate. Davidson and colleagues (Davidson et al., 2006) found exactly this pattern. In that study, different tasks were administered to children from 4 to 13 years of age and to young adults. Young children and adults showed a double dissociation. In children, performance on a cognitive flexibility task (i.e., switching between rules) was more impaired than performance on a working memory task (with increasing working memory load). For adults, the working memory task was relatively more difficult than the cognitive flexibility task. In that case, it was not possible to interpret the impairment of children in the task dealing with cognitive flexibility as due to the fact that it was generally more difficult than the working memory task. This hypothesis is indeed disconfirmed by the fact that adults found the working memory task relatively more difficult. On the other hand, it is possible to assume that the cognitive flexibility task was more impaired in children because the prefrontal areas (and processes) critical for this task are not yet mature.

However, even when this fortunate pattern is not found in adults, the heuristic value of developmental dissociations in testing specific hypotheses still holds. In our developmental study (experiments 3a, 3b and 4, chapter 2), the specific hypotheses to be tested were the conditioning view (Los & van den Heuvel, 2001) and the strategic accounts (e.g., Alegria, 1975) of the FP and the sequential effects. It should be noted that neither of these accounts predicts that the FP effect and the sequential effects differ on the required resources. On the conditioning view, the resources necessary for the two effects should be identical, just because the two effects are due to the same conditioning process. Moreover, since the strategic views assume that the two processes underlying the FP phenomena are both strategic (FP repetition expectation and maintenance/repreparation), there is no evident reason for these two processes to differ in the amount of the resources required. Two specific predictions about the developmental time-course of the two effects could be derived from the two accounts: a parallel development of the two effects was expected by the conditioning view, whereas a crossover FP_n x FP_{n-1} interaction was predicted by the strategic views. Neither of them was confirmed by the pattern of symmetric sequential effects found in the 4 year old children. Therefore, the method of developmental dissociations was useful to disconfirm two hypotheses and to put forward a new testable hypothesis which was then corroborated by means of other more traditional dissociative methodologies such as TMS (experiments 7 and 8, chapter 3) and neuropsychological dissociations (experiment 9, chapter 3).

Theta Burst Stimulation (TBS)

In the TMS experiments (experiments 7 and 8, chapter 3), the new TBS technique was adopted (Huang et al., 2005). The TBS consists of a triplet of 3 pulses at 50 Hz which is repeatedly delivered at a frequency of 5 Hz (like the EEG ‘theta’ rhythm, hence its name).

The output strength of the TMS is usually set to 80% of the participant’s active motor threshold. This technique is an off-line TMS paradigm, as it is applied before the administration of a task in order to see the inhibitory effects of the stimulation on the performance, and not during the performance of a task (within-trials, on-line TMS stimulation). The depressing effect of 20 and 40 seconds of TBS has been demonstrated to last at least 20 and 60 minutes after stimulation, respectively, on the activity of the motor cortex (Huang et al., 2005).

A limit of the off-line stimulation with respect to other on-line stimulation parameters (above all, the single-pulse TMS) is the lack of temporal information. However, there are experimental paradigms, such as the variable FP paradigm, where it is not advisable to use on-line stimulation, because of the confounding interference produced by the auditory and proprioceptive TMS effects on arousal and RTs (e.g., Nikouline, Ruohonen, & Ilmoniemi, 1999).

TBS represents the last-generation of a set of possible TMS designs which have been used to temporarily inhibit a cortical area. For instance, low-frequency off-line TMS designs, such as stimulation at 0.9/1 Hz for 15 minutes, have also been proved to effectively inhibit the targeted area for 15 minutes after the end of the stimulation (e.g., Chen et al., 1997). These alternative methods have the disadvantage of being time-consuming and of producing effects lasting less than those produced by the TBS, so being no suitable for experiments which require a great number of trials (e.g., in ERP studies).

A shortcoming of the use of TBS, but also of the other stimulation designs, is that results concerning inhibitory or excitatory effects obtained in one area, such as the primary motor cortex, cannot be easily generalized to other brain areas. It should be pointed out that the TBS has different degrees of effectiveness even within the same Brodmann area. For instance, TBS has been demonstrated to be more effective for the primary motor cortex representing the first dorsal interosseus muscle than for that representing the biceps (Martin, Gandevia, Taylor, 2006). This problem is even more serious when the targeted areas are ‘silent’ (e.g., DLPFC), in the sense that their excitability cannot be assessed with a direct measure (e.g., the MEP for motor cortex) but only indirectly inferred from the behavioural outcomes. In our TMS study, we studied an effect (the FP effect), which was already neuropsychologically demonstrated to be located in this area (Stuss et al., 2005, as confirmed by experiment 9, chapter 3). We obtained exactly the result which is expected if the TBS is assumed to inhibit the functionality of the targeted area (i.e., a decrease in the FP effect). This study then supports the reliability of TBS inhibitory effects, even if indirectly, for the investigation of the cognitive functions of areas different from the originally assessed primary motor cortex.

Moreover, some ethical issues need to be raised. Stimulation intensity in TBS is usually kept 20-40% lower than in other more traditional stimulation parameters. No participant particularly complained about TBS and no side-effects were observed in our study or reported in the literature, to the best of our knowledge. Despite these considerations, having been only recently introduced, TBS is not among the parameters recommended by the conventional guidelines (Wassermann, 1998). Attention should then be devoted to its use in future research, for instance by means of studies combining TBS with EEG spectral analysis (e.g., Fuggetta & Walsh, in preparation), which could permit to assess the excitability (and to detect any possible epileptogenic activity) of different cortical areas as a function of changes in the parameters of the TBS applied (e.g., intensity and duration).

Tumor patient studies

The study of tumor patients in the neuropsychological research has been treated with a certain degree of scepticism from the scientific community. This scepticism derives from several sources (Shallice et al., subm.). It is not known, for instance, which is the effect of tumors per se on the cognitive system. Especially for high-grade gliomas, it is unclear whether the tumoral nervous tissue is fully functioning or not before the operation. As a further complication, low-grade gliomas, which grow slowly, may lead to reorganisation of function. Following the operation, there may be a certain amount of oedema, whose effects on the nervous tissue are in turn mostly unknown.

At least some of these concerns may be bypassed by adopting the approach that we used in our study (experiment 9, chapter 3). The use of a matched control group is effective in overcoming at least the criticism concerning the pre-operative baseline performance. Provided that no pre-surgery difference between the tumor patients and the control participants in a given task is documented, it can be assumed that the process under study is not affected by the tumor per se.

Moreover, the use of a within-subject approach, which is possible with tumor patients who are scheduled for a surgical operation, is not conceivable for other brain lesions such as brain trauma or stroke. The within-subject approach is more sensitive in detecting a cognitive deficit, provided that the following two conditions are observed: (i) the baseline performance should be a true baseline, which means that a pre-surgery deficit should not be present, as checked comparing tumor patients' data with those of a control group; (ii) the test under study is not subject to learning effects[17].

From a broader methodological point of view, this study demonstrates the usefulness of testing groups of acute brain tumor patients as an alternative neuropsychological method to obtain a picture of deconstruction and a localization of cognitive processes in the brain (see also Shallice et al., subm.).

6.4. Limits and suggestions for future research

"The scientist, by the very nature of his commitment, creates more and more questions, never fewer" (Allport, 1955). This is the case also with the present work. It would be hard to be exhaustive in exposing all the possible research avenues opened by the project, some of which would arise from the need to overcome the limits of the project itself. Some suggestions for future work have been already proposed in the previous chapters. Some other suggestions have not been reported within the discussion of each experiment for reasons of space. In the next paragraphs, these other suggestions will be presented schematically, roughly following the order of the experiments as they have been described earlier.

Suggestions for the project on the FP phenomena

A prediction can be derived straightforward from the developmental study on FP phenomena. It is known that PFC is the last part to reach maturity in childhood and undergoes an early deterioration in elderly people, particularly the DLPFC (Andrés, Parmentier, & Escera, 2006; Raz, Williamson, Gunning-Dixon, Head, & Acker, 2000; West, 1996). It should then be possible to detect an ontogenetic curve for the FP effect which spans all the life. In other words, it should be likely to find that the FP effect follows an inverted U-shaped function of age: increasing in young children, reaching a steady-state in adults, and then decreasing in elderly people. The sequential effects, if it is confirmed that they rely more on premotor than on PFC (see experiment 9, chapter 3), which is supposed to be less vulnerable to age (e.g., Shaw et al., 1984; Raz et al., 1997), should instead be less sensitive to age. This prediction is also supported by cognitive

---

[17] The occurrence of the latter condition in our study was also indirectly supported by results of experiments 1 and 2 of chapter 2, showing that there was no change in the FP phenomena from one block of trials to another.

considerations: if sequential effects are due to automatic processes, it is known that the latter are relatively insensitive to age (e.g., Hasher & Zacks, 1979).

Care should be taken about the choice of a correct FP range and, above all, the shortest FPs employed. It is possible that, for particularly short FPs (e.g., < 1000 ms), elderly people are less capable to reach an appropriate level of preparation due to the general slowing of their cognitive system (e.g., Der & Deary, 2006). In this case, an increase in the FP effect may be predicted in elderly people as a consequence of defective preparatory processes acting on the shorter FPs (with an RT increase). This increase of the FP effect by lengthening RTs on the short FP effect would be in contrast with a supposed decrease of the FP effect as a consequence of the defective process increasing RTs on the longer FPs (i.e., defective monitoring of the conditional probability). The result would be an unchanged FP effect despite of the fact that the underlying processes would be impaired. The use of different FP ranges may help in keeping the two kinds of processes separated.

Brain imaging techniques such as event-related fMRI could be useful to corroborate results linking the FP effect to functionality of rDLPFC, and to further test the suggestion derived from the study on tumor patients that left premotor cortex may be the locus of the sequential effects, at least in right-handers. In order to further test the latter hypothesis, TMS studies would also be useful as well as studies with single-neuron recordings in the premotor cortex of animals, such as monkeys or rats. It could be investigated whether, in a variable FP task, the activity of cells within the premotor cortex is modulated by the length of the FP occurring in the preceding trial, to further assess whether this brain area is part of a circuitry responsible for the sequential effects.

The explanation of the FP effect offered in the dual-process model (see chapters 2 and 3) relates this effect to the process checking the non-occurrence of the imperative stimulus during longer FPs. As already supposed (chapter 2), an additional process, following the detected absence of the imperative stimulus, is likely to endogenously tune the level of preparedness as a function of the conditional probability of its subsequent presentation. With respect to this account, a further issue needs to be discussed. The FP effect usually follows a negatively accelerating function (i.e., RTs on short FPs are slower than RTs on medium and long ones) while, if RTs linearly depended on the a posteriori conditional probability of stimulus occurrence, it would have to follow a positively accelerating function (i.e., RTs on short and medium FPs should be slower than RTs for long ones), because the conditional probability of stimulus occurrence varies as a positively accelerating function[18]. In other words, the RTs follow a non-linear function of the conditional probability of stimulus occurrence. A possibility is that this non-linearity could occur because other factors may interfere with the conditional probability monitoring. One may speculate that this could be because a ceiling effect is achieved after the medium FP. However, a ceiling effect account is not plausible as the negatively accelerating RT-FP function is also observed when RTs are relatively slow, as in the experiment 2 of chapter 2. Alternatively, it could be supposed that the process of enhancing preparation is compensated by a tendency to reduce the effortful holding of the preparedness state as time elapses; this tendency would play the main role, together with an increase in time uncertainty, when a blocked FP design is administered, when slower RTs correspond to longer FPs (Klemmer, 1956; Teichner, 1954; Woodrow, 1914). A further possibility is that the subjective FP distribution shows a strong tendency toward overrepresentation of the medium FP (cf., Näätänen, & Merisalo, 1977). Nonetheless, these possibilities cannot be disentangled by the present results and require further investigation.

An aim of the project concerning the FP phenomena was to test the hypothesis that a monitoring process underlies the FP effect. A possible drawback is represented by the fact that this aim was pursued directly only in experiment 5. However, there is already a rich literature, using complementary approaches, which strongly suggests that the size of the FP effect directly depends on the conditional probability of stimulus occurrence and thus on a process which monitors this information (Granjon, Requin, Durup, & Reynard, 1973; Green & Luce, 1971; Hermelin, 1964; Näätänen, 1970; 1971; Nickerson & Burnham, 1969). More effort was here devoted to test whether a recently proposed single-process model, according to which no monitoring process is required, such as the conditioning view (Los & van de Heuvel, 2001; Los et al., 2001), could explain all the effects found in a variable FP paradigm (FP effect included) without implying any monitoring process.

Suggestions for the project on the STARCO effect

As pointed out in chapter 4, there are a number of open issues which should be solved in order to better characterize the new STARCO effect. Among them, we can list: linguistic and cultural influences, functional locus of the effect in the processing stream, continuous vs. discrete nature of the FP-STARCO effect function, automatic vs. voluntary

---

[18] For instance, if there are 3 FPs of 1, 2, and 3 sec occurring randomly and equiprobably across trials, the conditional probability of stimulus occurrence on each of them is 0.33, 0.5, and 1, respectively.

access to the left-to-right spatial representation of time. Moreover, from this project and from evidence in the literature, a relationship can be predicted between rDLPFC and the STARCO effect found in the experiments exposed in the chapter 4. This project, indeed, supports the view that the rDLPFC is functionally linked to the monitoring of temporal information (at least implicitly) required in the variable FP task. On the other hand, the literature shows a clear role of this area also in explicit temporal estimation (e.g., Coull et al., 2000; Lewis & Miall, 2003b; Rao et al., 2001). If and how DLPFC modulates the STARCO effect should be addressed by further research, possibly by means of a TMS study. Results of such a study may be relevant to disentangle whether the STARCO effect is related to temporal estimation processes (in this case a reduction of the effect is predicted with inhibitory TMS on the rDLPFC; see, for instance, Lewis & Miall, 2003a) or to other factors such as linguistic markedness (which should not be affected by TMS on the rDLPFC).

Suggestions for the project on source memory

Among the questions still left open in the project on source memory (chapter 5), some will be briefly discussed here. The first three issues are cognitive, as they concern the functional meaning of the prefrontal ERP effects found in the study, whereas the last issue is more localizational.

An important effect found in that study was that low confidence ERPs were more positive than high confidence ones in the anterior prefrontal sites. Considering this finding, one may question whether the anterior prefrontal involvement in confidence is typical of source memory tasks or, as suggested by the process-based approach adopted here for the study of prefrontal functions, more domain-independent. To test this issue, it would be useful to design ERP studies which investigate the role of anterior prefrontal areas during low vs. high confidence judgments in domains different from the source memory retrieval, such as perception of peri-liminar stimuli or cognitive estimation tasks. If the involvement of anterior prefrontal regions during low confident judgments is domain-independent, the same ERP modulation should be observed in the anterior prefrontal sites even with different tasks and domains.

Another effect found in both experiments of the source memory study (chapter 5) was a right lateral ERP positivity during retrieval. This component has been attributed, among other processes, to the familiarity monitoring. To study this process, a judgment of frequency task has also been used (e.g., Dobbins et al., 2004). In this task, participants have to perform a judgement about the frequency of occurrence of a picture (2 vs. 6 times). This task is supposed to rely heavily on a process which monitors the familiarity of the items, and not on the recollection of contextual information alone. A recent fMRI study (Dobbins et al., 2004) found that, compared to an item memory task, the judgement of frequency was associated with more activation in the right but not in the left DLPFC. To explain their empirical results, authors of that study (Dobbins et al., 2004; see also Yonelinas, 1999; Ranganath, Johnson, & D'Esposito, 2000) proposed the so-called systematic/heuristic account. According to this account, left DLPFC is more likely to be activated when a contextual recollection is critical for the task. In this case a systematic processing, involving monitoring of more specific information, is held to occur. Conversely, rDLPFC activation is required when it is necessary just to monitor closely the familiarity of the item. In the latter case, a more heuristic processing is assumed to occur, that is relatively simple processes which suffice for tasks that do not have reflective demands, such as memory retrieval judgments based on familiarity (e.g., Nolde et al., 1998).

This is partially consistent with what we found in source memory experiments reported in chapter 5, where a right more than left prefrontal positivity was obtained independently of the accuracy of recollection. However, no left-more-than-right ERP component was found even with source judgments which were correct and confident. The latter situation is exactly that which, according to the model by Dobbins and colleagues (Dobbins et al., 2004), should involve systematic processing in the left prefrontal regions.

Future studies would be useful to further investigate the familiarity monitoring account of right prefrontal involvement in memory retrieval. A prediction derived from the literature is that a late right prefrontal ERP positivity would be also found in a judgment of frequency task, if the assumption that this task heavily relies on familiarity monitoring turns out to be true. The amplitude of this right prefrontal ERP component should be higher for the most difficult condition (i.e., judging the less frequent items as so) than for the easier one (i.e., judging the most frequent items as so). On the other hand, as already stated, a weak point of the study is that no ERP component was linked to accurate recollection, which according to the literature should have evoked a late (left) prefrontal effect (Ranganath & Paller, 1999; see also Dobbins et al., 2004). A possible reason for the lack of an accuracy effect is that the task was too difficult and pure recollection was not frequent. Further studies with easier recollection conditions (e.g., shorter and more structured encoding lists, simpler items) would help to clarify this issue.

An additional issue concerning localization of the ERP effects needs also to be considered. An apparent inconsistency exists between the confidence effect in the study by Henson and colleagues (2000) and in the current experiment 2 concerning the topographical locus of the effect. In the fMRI study by Henson and colleagues (2000), areas which showed a confidence effect were located bilaterally in the dorsolateral prefrontal regions, while in the present study this effect is picked up more by anterior frontal electrodes than by lateral frontal ones. However, anatomical inferences based on the ERPs recorded from the scalp need to be taken cautiously, because the localization of brain sources does not correspond directly to scalp potential topography. The application of a method of source analysis to the ERP data could help in clarifying the source of the components found[19]. If this source analysis were to confirm that the neural sources of the anterior ERP component modulated by confidence are located in the anterior PFC, an explanation for the discrepancy between the two studies should be found. The difference between the tasks adopted in the two studies might partly account for it. In the Henson and colleagues' study (2000), an old/new judgement was the object of the confidence evaluation, whereas in ours a voice retrieval was required. It could be that monitoring of source retrieval is located more anteriorly than item retrieval (e.g., Christoff & Gabrieli, 2000; Simons, Gilbert, Owen, Fletcher, & Burgess, 2005; but see Rugg et al., 2003).

6.5. Conclusions

This project aimed to investigate the feasibility of the fractionation view in the study of PFC function (e.g., Stuss et al., 1995; 2005). On this approach, starting from a detailed task analysis, it is possible to map various processes within different prefrontal areas, using various dissociative methods such as neuropsychological, TMS and developmental dissociations. A detailed task-analysis was performed and a functional decomposition was obtained by means of different methodologies for two distinct tasks, namely the variable FP paradigm and the source memory retrieval. Results of various sets of experiments complementarily support the hypothesis that a process (i.e., monitoring), usually attributed to the SAS (Norman & Shallice, 1980; 1986; Shallice, 2004), is implemented within a specific prefrontal area (i.e., the rDLPFC). This evidence is strengthened by the control

---

[19] This has not yet been done here because the resources available and the competence were not adequate.

offered by the dissociations obtained within-tasks. In particular, right prefrontal areas were involved in effects which have been proposed to rely upon monitoring function (e.g., FP effect), and not in other monitoring-independent effects which have been or could have been found within the same tasks (e.g., sequential FP effects). The present work demonstrates that the fractionating approach could be a solution to the ‘homunculus’ problem (Dennett, 1998). Deconstructing the ‘homunculus’ into small pieces is a fruitful approach in order to understand high-level functions and to map them within the PFC.

References

Adams, R. J. & Lambos, W. A. (1986). Developmental changes in response preparation to visual stimuli. *Perceptual & Motor Skills, 62,* 519-522.

Alegria, J. (1975). Sequential effects of foreperiod duration: some strategical factors in tasks involving time uncertainty. In P. Rabbit & S. Dornic (Eds.), *Attention and Performance V* (pp. 1-10). London: Academic Press.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu.Rev.Neurosci, 9,* 357-381.

Alexander, I., Cowey, A., & Walsh, V. (2005). The right parietal cortex and time perception: back to Critchley and the Zeitraffer phenomenon. *Cognitive Neuropsychology, 22,* 306-315.

Alexander, M. P. (2001). Chronic akinetic mutism after mesencephalic-diencephalic infarction: remediated with dopaminergic medications. *Neurorehabilitation and Neural Repair, 15,* 151-156.

Alexander, M. P., Stuss, D. T., & Fansabedian, N. (2003). California Verbal Learning Test: performance by patients with focal frontal and non-frontal lesions. *Brain, 126,* 1493-1503.

Alexander, M. P., Stuss, D. T., Shallice, T., Picton, T. W., & Gillingham, S. (2005). Impaired concentration due to frontal lobe damage from two distinct lesion sites. *Neurology, 65,* 572-579.

Allan, K. & Rugg, M. D. (1998). Neural correlates of cued recall with and without retrieval of source memory. *NeuroReport, 9,* 3463-3466.

Allport, G. W. (1955). *Becoming: Basic considerations for a psychology of personality.* New Haven: Yale University Press.

Amati, D. & Shallice, T. (in press). On the emergence of modern humans. *Cognition*.

Anderson, S. W., Damasio, H., Jones, R. D., & Tranel, D. (1991). Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. *J Clin Exp Neuropsychol, 13,* 909-922.

Andres, P. (2003). Frontal cortex as the central executive of working memory: time to revise our view. *Cortex, 39,* 871-895.

Andres, P., Parmentier, F. B., & Escera, C. (2006). The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. *Neuropsychologia, 44,* 2564-2568.

Andrés, P. & Van der Linden, M. (2001). Supervisory Attentional System in patients with focal frontal lesions. *Journal of clinical and experimental neuropsychology, 23,* 225-239.

Archibald, S. J. & Kerns, K. A. (1999). Identification and description of new tests of executive functioning in children. *Child Neuropsychology, 5,* 115-129.

Asaad, W. F., Rainer, G., & Miller, E. K. (2000). Task-specific neural activity in the primate prefrontal cortex. *J Neurophysiol., 84,* 451-459.

Baddeley, A. (1996). The fractionation of working memory. *Proc.Natl.Acad.Sci U.S.A, 93,* 13468-13472.

Baddeley, A., Emslie, H., Kolodny, J., & Duncan, J. (1998). Random generation and the executive control of working memory. *Q.J Exp Psychol A, 51,* 819-852.

Baddeley, A. D. (1986). *Working memory*. Oxford: Clarendon Press.

Baddeley, A. D. (1990). *Human memory: Theory and practice*. Oxford: Oxford University Press.

Banks, W. P. (1970). Signal detection theory and human memory. *Psychol.Bull., 74,* 81-99.

Basso, G., Nichelli, P., Wharton, C. M., Peterson, M., & Grafman, J. (2003). Distributed neural systems for temporal production: a functional MRI study. *Brain Res.Bull., 59,* 405-411.

Baumeister, A. & Joubert, C. (1969). Interactive effects of reaction time of preparatory interval length and preparatory interval frequency. *Journal of Experimental Psychology, 82,* 393-395.

Bertelson, P. & Boons, J. P. (1960). Time uncertainty and choice reaction time. *Nature, 187,* 531-532.

Bevan, W., Hardesty, D. L., & Avant, L. L. (1965). Response latency with constant and variable interval schedules. *Percept.Mot.Skills, 20,* 969-972.

Bianchi, L. (1895). The functions of the frontal lobes. *Brain, 18,* 497-522.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage, 5,* 49-62.

Brodmann, K. (1905). Beitrage zur histologischen lokalisation der grosshirnrinde. Dritte mitt eilusns: Die rindenfelder der niederen affen. *J.Psychol.Neurol., 4,* 177-224.

Brodmann, K. (1909). *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig: Barth.

Brunia, C. H. M. & Van Boxtel, G. J. M. (2000). Motor preparation. In Cacioppo J.T., L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (2nd ed., pp. 507-532). Cambridge, UK: Cambridge University Press.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Wagner, A. D., & Rosen, B. R. (1998). Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. *Neuroimage, 7,* 151-162.

Burgess, P. W. & Shallice, T. (1994). Fractionnement du syndrome frontal. *Revue de Neuropsychologie, 4,* 345-370.

Burgess, P. W. & Shallice, T. (1996a). Bizarre responses, rule detection and frontal lobe lesions. *Cortex, 32,* 241-259.

Burgess, P. W. & Shallice, T. (1996b). Confabulation and the control of recollection. *Memory, 4,* 359-411.

Burgess, P. W. & Shallice, T. (1996c). Response suppression, initiation and strategy use following frontal lobe lesions. *Neuropsychologia, 34,* 263-272.

Burgess, P. W., Simons, J. S., Dumontheil, I., & Gilbert, S. J. (2005). The gateway hypothesis of rostral prefrontal cortex (area 10) function. In J.Duncan, P. McLeod, & L. Phillips (Eds.), *Measuring the Mind: Speed, Control, and age* (pp. 215-246). Oxford: Oxford University Press.

Burgess, P. W., Veitch, E., de Lacy, C. A., & Shallice, T. (2000). The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia, 38,* 848-863.

Casey, B. J., Cohen, J. D., O'Craven, K., Davidson, R. J., Irwin, W., Nelson, C. A. et al. (1998). Reproducibility of fMRI results across four institutions using a spatial working memory task. *Neuroimage, 8,* 249-261.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M. et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology, 48,* 1398-1403.

Cherubini, P., Burigo, M., & Bricolo, E. (2006). Inference-driven attention in symbolic and perceptual tasks: biases toward expected and unexpected inputs. *Q.J Exp Psychol (Colchester.), 59,* 597-624.

Christoff, K. & Gabrieli, J. D. (2000). The Frontopolar Cortex and Human Cognition: Evidence for a Rostrocaudal Hierarchical Organization within the Human Prefrontal Cortex. *Psychobiology, 28,* 168-186.

Churchland, M. M. & Shenoy, K. V. (2007). Delay of movement caused by disruption of cortical preparatory activity. *J Neurophysiol., 97,* 348-359.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J. et al. (1997). Temporal dynamics of brain activation during a working memory task. *Nature, 386,* 604-608.

Collins, D. L., Zijdenbos, A. P., Kollokian, V., Sled, J. G., Kabani, N. J., Holmes, C. J. et al. (1998). Design and construction of a realistic digital brain phantom. *IEEE Trans.Med Imaging, 17,* 463-468.

Corcoran, R. & Upton, D. (1993). A role for the hippocampus in card sorting? *Cortex, 29,* 293-304.

Correa, A., Lupiáñez, J., Milliken, B., & Tudela, P. (2004). Endogenous temporal orienting of attention in detection and discrimination tasks. *Percept.Psychophys., 66,* 264-278.

Correa, A., Lupianez, J., & Tudela, P. (2006). The attentional mechanism of temporal orienting: determinants and attributes. *Exp Brain Res., 169,* 58-68.

Coull, J. T. (2004). fMRI studies of temporal attention: allocating attention within, or towards, time. *Brain Res Cogn Brain Res, 21,* 216-226.

Coull, J. T., Frackowiak, R. S., & Frith, C. D. (1998). Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. *Neuropsychologia, 36,* 1325-1334.

Coull, J. T., Frith, C. D., Buchel, C., & Nobre, A. C. (2000). Orienting attention in time: behavioural and neuroanatomical distinction between exogenous and endogenous shifts. *Neuropsychologia, 38,* 808-819.

Coull, J. T. & Nobre, A. C. (1998). Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *J Neurosci., 18,* 7426-7435.

Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G., & Haxby, J. V. (1998). An area specialized for spatial working memory in human frontal cortex. *Science, 279,* 1347-1351.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cereb.Cortex, 6,* 39-49.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature, 386,* 608-611.

Curran, T. (2004). Effects of attention and confidence on the hypothesized ERP correlates of recollection and familiarity. *Neuropsychologia, 42,* 1088-1106.

Curran, T., Schacter, D. L., Johnson, M. K., & Spinks, R. (2001). Brain potentials reflect behavioral differences in true and false recognition. *J Cogn Neurosci., 13,* 201-216.

Curran, T., Schacter, D. L., Norman, K. A., & Galluccio, L. (1997). False recognition after a right frontal lobe infarction: memory for general and specific information. *Neuropsychologia, 35,* 1035-1049.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K., & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Brain Res Cogn Brain Res, 7,* 1-13.

D'Esposito, M. & Postle, B. R. (2002). The organization of working memory function in lateral prefrontal cortex: evidence from event-related functional MRI. In D.T.Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 168-187). New York: Oxford University Press.

Daffner, K. R., Mesulam, M. M., Holcomb, P. J., Calvo, V., Acar, D., Chabrerie, A. et al. (2000). Disruption of attention to novel events after frontal lobe injury in humans. *J Neurol Neurosurg Psychiatry, 68,* 18-24.

Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science, 264,* 1102-1105.

Davidson, M. C., Amso, D., Anderson, L. C., & Diamond, A. (2006). Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia, 44,* 2037-2078.

Decary, A. & Richer, F. (1995). Response selection deficits in frontal excisions. *Neuropsychologia, 33,* 1243-1253.

Dehaene, S. (2003). The neural basis of the Weber-Fechner law: a logarithmic mental number line. *Trends in Cognitive Sciences, 7,* 145-147.

Dehaene, S., Bossini, S., & Giraux, P. (1993). The mental representation of parity and number magnitude. *Journal of Experimental Psychology: General, 122*, 371-396.

Delalle, I., Evers, P., Kostovic, I., & Uylings, H. B. (1997). Laminar distribution of neuropeptide Y-immunoreactive neurons in human prefrontal cortex during development. *J Comp Neurol, 379,* 515-522.

Della Malva, C. L., Stuss, D. T., D'Alton, J., & Willmer, J. (1993). Capture errors and sequencing after frontal brain lesions. *Neuropsychologia, 31,* 363-372.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J Neurosci, 15,* 5870-5878.

Dennett, D. C. (1998). Reflections on language and mind. In P.Carruthers & J. Boucher (Eds.), *Language and Thought – Interdisciplinary Themes* (pp. 284-294). Cambridge: Cambridge University Press.

Der, G. & Deary, I. J. (2006). Age and sex differences in reaction time in adulthood: results from the United Kingdom Health and Lifestyle Survey. *Psychol Aging, 21,* 62-73.

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P. et al. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *J Physiol, 565,* 945-950.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Primate analogue of the Wisconsin Card Sorting Test: effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behav Neurosci, 110,* 872-886.

Dias, R., Robbins, T. W., & Roberts, A. C. (1997). Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: restriction to novel situations and independence from "on-line" processing. *J Neurosci, 17,* 9285-9297.

Dien, J. (1998). Addressing misallocation of variance in principal components analysis of event-related potentials. *Brain Topogr., 11,* 43-55.

Dobbins, I. G., Rice, H. J., Wagner, A. D., & Schacter, D. L. (2003). Memory orientation and success: separable neurocognitive components underlying episodic recognition. *Neuropsychologia, 41,* 318-333.

Dobbins, I. G., Simons, J. S., & Schacter, D. L. (2004). fMRI evidence for separable and lateralized prefrontal memory monitoring processes. *J Cogn Neurosci., 16,* 908-920.

Donaldson, D. I. & Rugg, M. D. (1998). Recognition memory for new associations: electrophysiological evidence for the role of recollection. *Neuropsychologia, 36,* 377-395.

Donath, J. (1923). Die Bedeutung des Stirnhirns für die höheren seelischen Leistungen. *Dtsch Z Nervenheilkd, 23,* 282-306.

Drazin, D. H. (1961). Effects of foreperiod, foreperiod variability, and probability of stimulus occurrence on simple reaction time. *J Exp Psychol., 62,* 43-50.

Drewe, E. A. (1974). The effect of type and area of brain lesion on Wisconsin card sorting test performance. *Cortex, 10,* 159-170.

Drummey A.B. & Newcombe N.S. (2002). Developmental changes in source memory. *Developmental Science, 5,* 502-513.

Duncan, J. (1986). Disorganization of behavior after frontal lobe damage. *Cognitive Neuropsychology, 3,* 271-290.

Duncan, J. (2001). An adaptive coding model of neural function in prefrontal cortex. *Nat.Rev.Neurosci, 2,* 820-829.

Duncan, J. (2005). Frontal lobe function and general intelligence: why it matters. *Cortex, 41,* 215-217.

Duncan, J., Burgess, P., & Emslie, H. (1995). Fluid intelligence after frontal lobe lesions. *Neuropsychologia, 33,* 261-268.

Duncan, J. & Miller, E. K. (2002). Cognitive focus through adaptive neural coding in the primate prefrontal cortex. In D. T. Stuss & R. T. Knight (Eds.), *Principles of Frontal Lobe Function* (New York: Oxford University Press.

Duncan, J. & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci., 23,* 475-483.

Duzel, E., Cabeza, R., Picton, T. W., Yonelinas, A. P., Scheich, H., Heinze, H. J. et al. (1999). Task-related and item-related brain processes of memory retrieval. *Proc.Natl.Acad.Sci.U.S.A, 96,* 1794-1799.

Duzel, E., Yonelinas, A. P., Mangun, G. R., Heinze, H. J., & Tulving, E. (1997). Event-related brain potential correlates of two states of conscious awareness in memory. *Proc.Natl.Acad.Sci.U.S.A, 94,* 5973-5978.

Elithorn, A. & Lawrence, C. (1955). Central inhibition: Some refractory observations. *Quarterly Journal of Experimental Psychology, 11,* 211-220.

Elliott, R. (1970). Simple reaction time: effects associated with age, preparatory interval, incentive-shift, and mode of presentation. *J Exp Child Psychol., 9,* 86-107.

Elliott, R. (1973). Some confounding factors in the study of preparatory set in reaction time. *memory and cognition, 1,* 13-18.

Everling, S., Tinsley, C. J., Gaffan, D., & Duncan, J. (2002). Filtering of neural signals by focused attention in the monkey prefrontal cortex. *Nat. Neurosci, 5,* 671-676.

Fassbender, C., Simoes-Franklin, C., Murphy, K., Hester, R., Meaney, J., Robertson, I. H., & Garavan, H. (2006). The Role of a Right Fronto-Parietal Network in Cognitive Control Common Activations for "Cues-to-Attend" and Response Inhibition. *Journal of Psychophysiology, 20,* 286-296.

Faw, B. (2000a). Consciousness, motivation and emotion: Biopsychological reflections. In R.D.Ellis & N. Newton (Eds.), *Caldron of consciousness* (pp. 55-90). Amsterdam: John Benjamins Publishers.

Faw, B. (2000b). My amygdala-orbitofrontal-circuit made me do it. *Consciousness and Emotion, III,* 167-179.

Faw, B. (2003). Pre-frontal executive committee for perception, working memory, attention, long-term memory, motor control, and thinking: a tutorial review. *Conscious.Cogn, 12,* 83-139.

Ferrier, D. & Yeo, G. F. (1884). A record of experiments on the effects of lesion of different regions of the cerebral hemispheres. *Philos Trans R Lond B Biol Sci, 175B,* 479-564.

Ferster, C. & Skinner, B. F. (1957). *Schedules of reinforcement*. New York: Appleton-Century-Crofts.

Feuchtwanger, E. (1923). *Die Funktionen des Stirnhirns. Ihre Pathologie und Psychologie*. Berlin.

Fisher, C. M. (1983). Honored guest presentation: abulia minor vs. agitated behavior. *Clin Neurosurg, 31,* 9-31.

Fletcher, P. C. & Henson, R. N. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain, 124,* 849-881.

Fletcher, P. C., Shallice, T., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory. I. Encoding. *Brain, 121 (Pt 7),* 1239-1248.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1998). The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain, 121 (Pt 7),* 1249-1256.

Franz, S. I. (1907). On the functions of the cerebrum. The frontal lobes. *Arch Psychol, 2,* 1-64.

Freedman, D. J., Riesenhuber, M., Poggio, T., & Miller, E. K. (2001). Categorical representation of visual stimuli in the primate prefrontal cortex. *Science, 291,* 312-316.

Frith, C. D. (2000). The role of the dorsolateral prefrontal cortex in the selection of action as revealed by functional imaging. In S.Monsell & J. Driver (Eds.), *Control of cognitive processes: attention and performance XVIII* (pp. 549-565). Cambridge, MA: MIT Press.

Frith, C. D. & Done, D. J. (1986). Routes to action in reaction time tasks. *Psychol Res, 48,* 169-177.

Frith, C. D., Friston, K. J., Liddle, P. F., & Frackowiak, R. S. (1991). A PET study of word finding. *Neuropsychologia, 29,* 1137-1148.

Fritsch, G. & Hitzig, E. (1870). Über die elektrische Erregbarkeit des Grosshirns. *Archiv für Anatomie, Physiologie, und wissenscahftliche Medicin,* 300-332.

Fuster, J. M. (1990). Prefrontal cortex and the bridging of temporal gaps in the perception-action cycle. *Ann.N.Y.Acad.Sci, 608,* 318-329.

Fuster, J. M. (1997). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe*. (3rd ed.) Philadelphia: Lippincott-Raven.

Fuster, J. M. (1999). Cognitive functions of the frontal lobes. In B.L.Miller & J. L. Cummings (Eds.), *Human frontal lobes* (pp. 187-195). New York: Guildford.

Fuster, J. M. (2002). Physiology of executive functions: the perception-action cycle. In D.T.Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 96-108). Oxford: Oxford University Press.

Fuster, J. M. & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science Wash, DC 173,* 652-654.

Gallistel, C. R. & Gibbon, J. (2000). Time, rate, and conditioning. *Psychol.Rev., 107,* 289-344.

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). *Cognitive Neuroscience (*2nd Ed.). New York: Norton.

Gevers, W., Reynvoet, B., & Fias, W. (2003). The mental representation of ordinal sequences is spatially organized. *Cognition, 87,* B87-B95.

Gevers, W., Verguts, T., Reynvoet, B., Caessens, B., & Fias, W. (2006). Numbers and space: a computational model of the SNARC effect. *Journal of Experimental Psychology: Human Perception and Performance, 32,* 32-44.

Gevins, A. & Cutillo, B. (1993). Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr.Clin Neurophysiol., 87,* 128-143.

Gibbon, J., Church, R. M., & Meck, W. H. (1984). Scalar timing in memory. *Ann.N.Y.Acad.Sci, 423,* 52-77.

Gilboa, A. & Moscovitch, M. (2002). The cognitive neuroscience of confabulation: A review and a model. In A.D.Baddeley, M. D. Kopelman, & B. A. Wilson (Eds.), *Handbook of Memory Disorders* (2nd Ed., pp. 315-342). London: Wiley.

Ginsburg, N. & Karpiuk, P. (1994). Random generation: Analysis of the responses. *Perceptual and Motor Skills, 79,* 1059-1067.

Godefroy, O., Cabaret, M., Petit-Chenal, V., Pruvo, J. P., & Rousseaux, M. (1999). Control functions of the frontal lobes. Modularity of the central-supervisory system? *Cortex, 35,* 1-20.

Goldberg, E. (2001). *The Executive Brain: frontal lobes and the civilized mind*. New York: Oxford University Press.

Goldman-Rakic, P. S. (1987). Development of cortical circuitry and cognitive function. *Child Dev., 58,* 601-622.

Grafman, J., Jonas, B., & Salazar, A. (1990). Wisconsin Card Sorting Test performance based on location and size of neuroanatomical lesion in Vietnam veterans with penetrating head injury. *Percept.Mot.Skills, 71,* 1120-1122.

Graham, R. & Cabeza, R. (2001). Dissociating the neural correlates of item and context memory: an ERP study of face recognition. *Can.J Exp Psychol., 55,* 154-161.

Granjon, M., Requin, J., Durup, H., & Reynard, G. (1973). Effects of a timing signal on simple reaction time with "non-aging" foreperiods. *Journal of Experimental Psychology, 101,* 139-145.

Gratton, G., Coles, M. G. H., Sirevaag, E. J., Eriksen, C. W., & Donchin, E. (1988). Pre- and Post-stimulus activation of response channels: a psychophysiological analysis. *Journal of Experimental Psychology: Human Perception and Performance, 14,* 331-344.

Green, D. M. & Luce, R. D. (1971). Detection of auditory signals presented at random time: III. *Perception and Psychophysics, 9,* 257-268.

Griffin, I. C., Miniussi, C., & Nobre, A. C. (2002). Multiple mechanisms of selective attention: differential modulation of stimulus processing by attention to space or time. *Neuropsychologia, 40,* 2325-2340.

Gross, C. G. (1963). A comparison of the effects of partial and total lateral frontal lesions on test performance by monkeys. *Journal of Comparative and Physiological Psychology, 56,* 41-47.

Grotjahn, M. (1936). Klinik and bedeutung akinetischer zustande nach luftfullung des dritten ventrikels. *Monat.Psychiatr.Neurol., 93,* 121-139.

Hale, D. J. (1967). Sequential effects in a two-choice serial reaction task. *Q.J Exp Psychol., 19,* 133-141.

Happe, F., Booth, R., Charlton, R., & Hughes, C. (2006). Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. *Brain Cogn, 61,* 25-39.

Harlow, J. M. (1848). Passage of an iron rod through the head. *Boston Medical and Surgical Journal, 39,* 389-393.

Harlow, J. M. (1869). *Recovery from the passage of an iron bar through the head*. Boston: D. Clapp and Son.

Hasher, L. & Zacks, R. T. (1979). Automatic and effortful processes in memory. *Journal of Experimental Psychology: General, 108,* 356-388.

Henson, R. N., Rugg, M. D., Shallice, T., & Dolan, R. J. (2000). Confidence in recognition memory for words: dissociating right prefrontal roles in episodic retrieval. *J Cogn Neurosci., 12,* 913-923.

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999a). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *J Neurosci., 19,* 3962-3972.

Henson, R. N., Shallice, T., & Dolan, R. J. (1999b). Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain, 122 (Pt 7),* 1367-1381.

Henson, R. N., Shallice, T., Josephs, O., & Dolan, R.J. (2002). Functional magnetic resonance imaging of proactive interference during spoken recall. *NeuroImage, 17,* 543-558.

Hermelin, B. (1964). Effects of variation in the warning signal on reaction time of severe subnormals. *Quarterly Journal of ExperimentalPsychology, 16,* 241-249.

Higa, J. J., Wynne, C. D., & Staddon, J. E. (1991). Dynamics of time discrimination. *J Exp Psychol.Anim Behav.Process, 17,* 281-291.

Hommel, B., Daum, I., & Kluwe, R. H. (2004). Exorcizing the homunculus, phase two: editors' introduction. *Acta Psychologica, 115,* 99-104.

Hommel, B. & Prinz, W. (1997). *Theoretical issues in stimulus-response compatibility*. Amsterdam: North-Holland.

Hommel, B., Ridderinkhof, K. R., & Theeuwes, J. (2002). Cognitive control of attention and action: issues and trends. *Psychol Res, 66,* 215-219.

Hooge, I. T., Over, E. A., van Wezel, R. J., & Frens, M. A. (2005). Inhibition of return is not a foraging facilitator in saccadic search and free viewing. *Vision Res, 45*, 1901-1908.

Houdé, O., Angard, N., Pillon B., & Dubois, B. (2001). A new window on child prefrontal functions: inhibition of a non-strategic alternation-pointing scheme. *Current Psychology Letters, 5,* 49-63.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45,* 201-206.

Hugdahl, K., Berardi, A., Tompson, W. L., Kosslyn, S. M., Macy, R., Baker, D. P. et al. (1995). Brain mechanisms in human classical conditioning: a PET blood flow study. *NeuroReport, 6,* 1723-1728.

Huttenlocher, P. R. & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol, 387,* 167-178.

Jacobsen, C. F. (1936). Studies of cerebral function in primates. *Comp.Psychol.Monogr., 13,* 1-68.

Jahanshahi, M., Dirnberger, G., Fuller, R., & Frith, C. D. (2000). The role of the dorsolateral prefrontal cortex in random number generation: a study with positron emission tomography. *Neuroimage, 12,* 713-725.

Jahanshahi, M., Jenkins, I. H., Brown, R. G., Marsden, C. D., Passingham, R. E., & Brooks, D. J. (1995). Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain, 118 (Pt 4),* 913-933.

Jahanshahi, M., Profice, P., Brown, R. G., Ridding, M. C., Dirnberger, G., & Rothwell, J. C. (1998). The effects of transcranial magnetic stimulation over the dorsolateral prefrontal cortex on suppression of habitual counting during random number generation. *Brain, 121 (Pt 8),* 1533-1544.

Janowsky, J. S., Shimamura, A. P., & Squire, L. R. (1989). Source memory impairment in patients with frontal lobe lesions. *Neuropsychologia, 27,* 1043-1056.

Jansma, J. M., Ramsey, N. F., Coppola, R., & Kahn, R. S. (2000). Specific versus nonspecific brain activity in a parametric N-back task. *Neuroimage, 12,* 688-697.

Janssen, P. & Shadlen, M. N. (2005). A representation of the hazard rate of elapsed time in macaque area LIP. *Nat.Neurosci., 8,* 234-241.

Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S., & Passingham, R. E. (1994). Motor sequence learning: a study with positron emission tomography. *J Neurosci, 14,* 3775-3790.

Jha, A. P. & McCarthy, G. (2000). The influence of memory load upon delay-interval activity in a working-memory task: an event-related functional MRI study. *J Cogn Neurosci, 12 Suppl 2,* 90-105.

Jones, C. R., Rosenkranz, K., Rothwell, J. C., & Jahanshahi, M. (2004). The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation. *Exp.Brain Res., 158,* 366-372.

Jones, E. G. (1985). *The thalamus*. New York: Plenum Press.

Jones, G. V. (1983). On double dissociation of function. *Neuropsychologia, 21,* 397-400.

Jonides, J., Naveh-Benjamin, M., & Palmer, J. (1985). Assessing automaticity. *Acta Psychologica, 60,* 157-171.

Jueptner, M., Stephan, K. M., Frith, C. D., Brooks, D. J., Frackowiak, R. S., & Passingham, R. E. (1997). Anatomy of motor learning. I. Frontal cortex and attention to action. *J Neurophysiol., 77,* 1313-1324.

Junghofer, M., Elbert, T., Tucker, D. M., & Braun, C. (1999). The polar average reference effect: a bias in estimating the head surface integral in EEG recording. *Clin Neurophysiol., 110,* 1149-1155.

Juola, J. F., Fischler, I., Wood, C. T., & Atkinson, R. C. (1971). Recognition time for information stored in long-term memory. *Perception and Psychophysics, 10,* 8-14.

Jurkowski, A. J., Stepp, E., & Hackley, S. A. (2005). Variable foreperiod deficits in Parkinson's disease: dissociation across reflexive and voluntary behaviors. *Brain Cogn, 58,* 49-61.

Kahneman, D. & Treisman, A. (1984). Changing views of attention and automaticity. In R.Parasuraman & R. Davies (Eds.), *Varieties of Attention* (pp. 29-61). New York: Academic Press.

Kamijo, K., Nishihira, Y., Hatta, A., Kaneda, T., Kida, T., Higashiura, T. et al. (2004). Changes in arousal level by differential exercise intensity. *Clinical Neurophysiology, 115,* 2693-2698.

Kanwisher, N. & Potter, M. C. (1989). Repetition blindness: the effects of stimulus modality and spatial displacement. *Mem.Cognit., 17,* 117-124.

Kanwisher, N. G. (1987). Repetition blindness: type recognition without token individuation. *Cognition, 27,* 117-143.

Kanwisher, N. G. (1991). Repetition blindness and illusory conjunctions: Errors in binding visual types with visual tokens. *Journal of Experimental Psychology: Human Perception and Performance, 17,* 404-442.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry, 160,* 13-23.

Kapur, S., Craik, F. I., Jones, C., Brown, G. M., Houle, S., & Tulving, E. (1995). Functional role of the prefrontal cortex in retrieval of memories: a PET study. *NeuroReport, 6,* 1880-1884.

Karlin L. (1959). Reaction time as a function of foreperiod duration and variability. *J Exp Psychol., 58,* 185-191.

Karmiloff-Smith, A. (1992). *Beyond modularity: A developmental perspective on cognitive science*. Cambridge, MA: MIT press.

Karmiloff-Smith, A. (1994). Precis of Beyond Modularity: A developmental perspective on cognitive science. *Behavioral and Brain Sciences, 17,* 693-707.

Keppel, G., Saufley, W. H., & Tokunaga, H. (1992). *Introduction to Design and Analysis: A Student Handbook.* New York: Freeman. [Trad. Italiana: Disegno sperimentale e Analisi dei dati in Psicologia. (2001) Napoli: Edises].

Keus, I. M., Jenks, K. M., & Schwarz, W. (2005). Psychophysiological evidence that the SNARC effect has its functional locus in a response selection stage. *Brain Res Cogn Brain Res, 24,* 48-56.

Klemmer, E. T. (1956). Time uncertainty in simple reaction time. *J Exp Psychol., 51,* 179-184.

Koch, G., Oliveri, M., Torriero, S., & Caltagirone, C. (2003). Underestimation of time perception after repetitive transcranial magnetic stimulation. *Neurology, 60,* 1844-1846.

Krasnegor, N. A., Lyon, G. R., & Goldman-Rakic, P. S. (1997). *Development of the prefrontal cortex*. Baltimore: Paul Brooks.

Lepage, M., Ghaffar, O., Nyberg, L., & Tulving, E. (2000). Prefrontal cortex and episodic memory retrieval mode. *Proc.Natl.Acad.Sci.U.S.A, 97,* 506-511.

Levy, R. & Goldman-Rakic, P. S. (1999). Association of storage and processing functions in the dorsolateral prefrontal cortex of the nonhuman primate. *J Neurosci, 19,* 5149-5158.

Lewis, P. A. & Miall, R. C. (2003a). Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. *Curr.Opin.Neurobiol., 13,* 250-255.

Lewis, P. A. & Miall, R. C. (2003b). Brain activation patterns during measurement of sub- and supra-second intervals. *Neuropsychologia, 41,* 1583-92.

Lhermitte, F. (1983). 'Utilization behaviour' and its relation to lesions of the frontal lobes. *Brain, 106 (Pt 2),* 237-255.

Los, S. A. & Agter, F. (2005). Reweighting sequential effects across different distributions of foreperiods: segregating elementary contributions to nonspecific preparation. *Perception & Psychophysics, 67,* 1161-1170.

Los, S. A. & Heslenfeld, D. J. (2005). Intentional and unintentional contributions to nonspecific preparation: electrophysiological evidence. *J Exp Psychol.Gen., 134,* 52-72.

Los, S. A., Knol, D. L., & Boers, R. M. (2001a). The foreperiod effect revisited: conditioning as a basis for nonspecific preparation. *Acta Psychologica, 106,* 121-145.

Los, S. A. & van den Heuvel, C. E. (2001b). Intentional and unintentional contributions to nonspecific preparation during reaction time foreperiods. *J Exp Psychol.Hum.Percept.Perform., 27,* 370-386.

Luce, R. D. (1986). *Response times*. New York: Oxford University Press.

Luria, A. R. (1966). *Human brain and psychological processes*. New York: Harper & Row Publishers.

Lyons, J. (1969). *Semantics*. Cambridge: Cambridge University Press.

Macar, F., Lejeune, H., Bonnet, M., Ferrara, A., Pouthas, V., Vidal, F. et al. (2002). Activation of the supplementary motor area and of attentional networks during temporal processing. *Exp Brain Res., 142,* 475-485.

Machado, A. (1997). Learning the temporal dynamics of behavior. *Psychol.Rev., 104,* 241-265.

MacLeod, A. K., Buckner, R. L., Miezin, F. M., Petersen, S. E., & Raichle, M. E. (1998). Right anterior prefrontal cortex activation during semantic monitoring and working memory. *Neuroimage, 7,* 41-48.

Mangels, J. A. (1997). Strategic processing and memory for temporal order in patients with frontal lobe lesions. *Neuropsychology, 11,* 207-221.

Manoach, D. S., Schlaug, G., Siewert, B., Darby, D. G., Bly, B. M., Benfield, A. et al. (1997). Prefrontal cortex fMRI signal changes are correlated with working memory load. *NeuroReport, 8,* 545-549.

Mapelli, D., Rusconi, E., & Umiltà, C. (2003). The SNARC effect: an instance of the Simon effect? *Cognition, 88,* B1-10.

Martin, P. G., Gandevia, S. C., & Taylor, J. L. (2006). Theta burst stimulation does not reliably depress all regions of the human motor cortex. *Clin Neurophysiol., 117,* 2684-2690.

Mattes, S. & Ulrich, R. (1997). Response force is sensitive to the temporal uncertainty of response stimuli. *Percept.Psychophys., 59,* 1089-1097.

McCarthy, G., Puce, A., Constable, R. T., Krystal, J. H., Gore, J. C., & Goldman-Rakic, P. (1996). Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cereb.Cortex, 6,* 600-611.

McCloskey, M. (2003). Beyond task dissociation logic: a richer conception of cognitive neuropsychology. *Cortex, 39,* 196-202.

McElree, B. & Dosher, B. A. (1987). Serial position and set size in short-term memory: the time course of recognition. *J Exp Psychol, 118,* 346-373.

Mega, M. S. & Cohenour, R. C. (1997). Akinetic mutism: disconnection of frontal-subcortical circuits. *Neuropsychiatry Neuropsychol.Behav Neurol, 10,* 254-259.

Meshberger, F. L. (1990). An interpretation of Michelangelo's Creation of Adam based on neuroanatomy. *JAMA, 264,* 1837-1841.

Miller, E. K. & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu.Rev.Neurosci, 24,* 167-202.

Miller, R. R. & Barnet, R. C. (1993). The role of time in elementary associations. *Current Directions in Psychological Science, 2,* 106-111.

Milner, B. (1963). Some effects of frontal lobe lesions in man. In J.M.Warren & K. Akert (Eds.), *The Frontal Granular Cortex and Behavior* (pp. 313-331). New York: McGraw-Hill.

Milner, B. (1964). Some effects of frontal lobectomy in man. In J.M.Warren & K. Akert (Eds.), *The frontal granular cortex and behavior* (pp. 122-145). New York: McGraw-Hill.

Miniussi, C., Wilding, E. L., Coull, J. T., & Nobre, A. C. (1999). Orienting attention in time. Modulation of brain potentials. *Brain, 122 (Pt 8),* 1507-1518.

Mirsky, A. F. & Duncan, C. C. (2001). A nosology of disorders of attention. *Ann.N.Y.Acad.Sci, 931,* 17-32.

Mishkin, M. & Manning, F. J. (1978). Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Res, 143,* 313-323.

Monsell, S. & Driver, J. (2000). *Control of cognitive processes: Attention and performance XVIII*. Cambridge, MA: MIT Press.

Moscovitch, M. (1992). Memory and working with memory: A component process model based on modules and central systems. *Journal of cognitive neuroscience, 4,* 257-267.

Näätänen, R. (1970). The diminishing time-uncertainty with the lapse of time after the warning signal in reaction-time experiments with varying foreperiods. *Acta Psychologica, 34,* 399-419.

Näätänen, R. (1971). Nonaging foreperiod and simple reaction time. *Acta Psychologica, 35,* 316-327.

Näätänen, R. (1972). Time uncertainty and occurrence uncertainty of the stimulus in a simple reaction-time task. *Acta Psychologica, 36*, 492-503.

Näätänen, R., Merisalo, A. (1977). Expectancy and preparation in simple reaction time. In S. Dornic (Ed.), *Attention and Performance, VI.* Hillsdale, N. J.: Erlbaum.

Näätänen, R., Muranen, V., & Merisalo, A. (1974). Timing of expectancy peak in simple reaction time. *Acta Psychologica, 38,* 461-470.

Nagaratnam, N., Nagaratnam, K., Ng, K., & Diu, P. (2004). Akinetic mutism following stroke. *J Clin Neurosci, 11,* 25-30.

Naveh-Benjamin, M. (1987). Coding of spatial location information: an automatic process? *J Exp Psychol Learn.Mem.Cogn, 13,* 595-605.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex, 12,* 313-324.

Newell, A. (1990). *Unified theories of cognition.* Cambridge, MA: Harvard University Press.

Nickerson, R. S. (1967). Expectancy, waiting time and the psychological refractory period. *Acta Psychologica, 27,* 23-34.

Nickerson, R. S. & Burnham, D. W. (1969). Response times with nonaging foreperiods. *Journal of Experimental Psychology, 79,* 452-457.

Niemi, P. & Näätänen, R. (1981). Foreperiod and simple reaction time. *Psychological Bulletin, 89,* 133-162.

Nikouline, V., Ruohonen, J., & Ilmoniemi, R. J. (1999). The role of the coil click in TMS assessed with simultaneous EEG. *Clin Neurophysiol., 110,* 1325-1328.

Nobre, A. C. (2001). Orienting attention to instants in time. *Neuropsychologia, 39,* 1317-1328.

Nolde, S. F., Johnson, M. K., & D'Esposito, M. (1998). Left prefrontal activation during episodic remembering: an event-related fMRI study. *NeuroReport, 9,* 3509-3514.

Norman, D. A. & Bobrow, D. G. (1979). Descriptions: an intermediate stage in memory retrieval. *Cognitive Psychology, 11,* 107-123.

Norman, D. A. & Shallice, T. (1980). *Attention to action. Willed and automatic control of behavior.* CHIP Report 99: University of California, San Diego.

Norman, D. A. & Shallice, T. (1986). Attention to action: Willed and automatic control of behavior. In R.J.Davidson, G. E. Schwartz, & D. Shapiro (Eds.), *Consciousness and self regulation: Advances in research* (vol. 4, pp. 1-18). New York: Plenum Press.

Nuerk, H. C., Iversen, W., & Willmes, K. (2004). Notational modulation of the SNARC and the MARC (linguistic markedness of response codes) effect. *Q.J Exp Psychol.A, 57,* 835-863.

Ollman, R. T. & Billington, M. J. (1972). The deadline model for simple reaction times. *Cognitive Psychology, 3,* 311-336.

Onoe, H., Komori, M., Onoe, K., Takechi, H., Tsukada, H., & Watanabe, Y. (2001). Cortical networks recruited for time perception: a monkey positron emission tomography (PET) study. *Neuroimage, 13,* 37-45.

Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., & Petrides, M. (1998). Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proc.Natl.Acad.Sci U.S.A, 95,* 7721-7726.

Ozmun, J. C., Surburg, P. R., & Cleland, F. E. (1989). Effects of occurrence and time uncertainties on reaction and movement times of children. *Percept.Mot.Skills, 68,* 931-935.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Curr.Opin.Neurobiol., 10,* 232-237.

Passingham, R. E. (1975). *The brain and intelligence. Brain, Behavior, and Evolution, 11,* 1-15.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. (1993). The neural correlates of the verbal component of working memory. *Nature, 362,* 342-345.

Pavlov, I. P. (1927). *Conditioned reflexes*. London: Oxford University Press.

Petrides, M. (1994). Frontal lobes and behaviour. *Curr.Opin.Neurobiol., 4,* 207-211.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc.Natl.Acad.Sci U.S.A., 90,* 878-882.

Petrides, M. & Pandya, D. N. (1994). Comparative architectonic analysis of the human and the macaque frontal cortex. In F.Boller & H. Spinnler (Eds.), *The Frontal Lobes* (pp. 17-58). Amsterdam: Elsevier.

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., Jr. et al. (2000). Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology, 37,* 127-152.

Picton, T. W., Lins, O. G., & Scherg, M. (1995). The recording and analysis of event-related potentials. In F.Boller & J. Grafman (Eds.), *Handbook of Neuropsychology* (pp. 3-73). Amsterdam: Elsevier.

Picton, T. W., Stuss, D. T., Alexander, M. P., Shallice, T., Binns, M. A., & Gillingham, S. (in press). Effects of Focal Frontal Lesions on Response Inhibition. *Cereb.Cortex.*

Plum, F. & Posner, M. I. (1980). *The diagnosis of stupor and coma*. (3rd edition ed.) Philadelphia: F. A. Davis.

Posner, M. I. (1980). Orienting of attention. *Journal of Experimental Psychology, 32,* 3-25.

Posner, M. I. & Cohen, Y. (1984). Components of visual orienting. In H.Bouma & D. Bouwhuis (Eds.), *Attention and performance X* (pp. 531-556). London: Erlbaum.

Posner, M. I. & Petersen, S. E. (1990a). The attention system of the human brain. *Annu.Rev.Neurosci, 13,* 25-42.

Posner, M. I. & Peterson, S. E. (1990b). The attention system of the human brain. *Annu.Rev.Neurosci., 13,* 25-42.

Posner, M. I. & Snyder, C. R. R. (1975). Facilitation and inibition in the processing of signals. In P.M.A.Rabbit & S. Dornis (Eds.), *Attention and performance* (New York: Accademic press.

Postle, B. R., Berger, J. S., Taich, A. M., & D'Esposito, M. (2000). Activity in human frontal cortex associated with spatial working memory and saccadic behavior. *J Cogn Neurosci, 12 Suppl 2,* 2-14.

Postle, B. R., Stern, C. E., Rosen, B. R., & Corkin, S. (2000). An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. *Neuroimage, 11,* 409-423.

Preuss, T. M. & Goldman-Rakic, P. S. (1991). Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirhine primate Galago and the anthropoid primate Macaca. *J Comp Neurol, 310,* 429-474.

Pritchard, W. S. & Warm, J. S. (1983). Attentional processing and the subjective contour illusion. *J Exp Psychol Gen., 112,* 145-175.

Rabbitt, J. E. & Page, M. S. (1998). Selected complications in neuro-oncology patients. *Semin Oncol.Nurs., 14,* 53-60.

Rabbitt, P., Lowe, C., & Shilling, V. (2001). Frontal tests and models for cognitive ageing. *European Journal of CognitivePsychology, 13,* 5-28.

Rakshi, J. S., Uema, T., Ito, K., Bailey, D. L., Morrish, P. K., Ashburner, J. et al. (1999). Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. *Brain, 122 (Pt 9),* 1637-1650.

Ramnani, N. & Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nat.Rev.Neurosci., 5,* 184-194.

Ranganath, C., Johnson, M. K., & D'Esposito, M. (2000). Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J Neurosci., 20,* RC108.

Ranganath, C. & Paller, K. A. (1999). Frontal brain potentials during recognition are modulated by requirements to retrieve perceptual detail. *Neuron, 22,* 605-613.

Ranganath, C. & Paller, K. A. (2000). Neural correlates of memory retrieval and evaluation. *Brain Res.Cogn Brain Res., 9,* 209-222.

Rao, S. M., Mayer, A. R., & Harrington, D. L. (2001). The evolution of brain activation during temporal processing. *Nat.Neurosci., 4,* 317-323.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D. et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb.Cortex, 7,* 268-282.

Raz, N., Williamson, A., Gunning-Dixon, F., Head, D., & Acker, J. D. (2000). Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. *Microsc.Res Tech., 51,* 85-93.

Requin, J. & Granjon, M. (1969). The effect of conditional probability of the response signal on the simple reaction time. *Acta Psychologica, 31,* 129-144.

Reverberi, C., Lavaroni, A., Gigli, G. L., Skrap, M., & Shallice, T. (2005). Specific impairments of rule induction in different frontal lobe subgroups. *Neuropsychologia, 43,* 460-472.

Reynolds, J. R., McDermott, K. B., & Braver, T. S. (2005). A Direct Comparison of Anterior Prefrontal Cortex Involvement in Episodic Retrieval and Integration. *Cereb.Cortex, 16,* 519-528.

Riehle, A. & Requin, J. (1993). The predictive value for performance speed of preparatory changes in neuronal activity of the monkey motor and premotor cortex. *Behav.Brain Res., 53,* 35-49.

Riggio, L., Gawryszewski, L. G., & Umiltà, C. (1986). What is crossed in crossed-hand effects? *Acta Psychologica, 62,* 89-100.

Rorden, C. & Brett, M. (2000). Stereotaxic display of brain lesions. *Behav.Neurol, 12,* 191-200.

Rossi, A. F., Rotter, P. S., Desimone, R., & Ungerleiden, L. G. (1999). Prefrontal lesions produce impairments in feature-cued attention. *Soc.Neurosci.Abstr., 25,* 3.

Rossi, S., Cappa, S. F., Babiloni, C., Pasqualetti, P., Miniussi, C., Carducci, F. et al. (2001). Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation. *Nat.Neurosci., 4,* 948-952.

Rossi, S., Pasqualetti, P., Zito, G., Vecchio, F., Cappa, S. F., Miniussi, C., Babiloni, C., Rossigni, P. M. (2006). Prefrontal and parietal cortex in human episodic memory: an interference study by repetitive transcranial magnetic stimulation. *Eur.J Neurosci., 23,* 793-800.

Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S., & Passingham, R. E. (2000). The prefrontal cortex: response selection or maintenance within working memory? *Science, 288,* 1656-1660.

Rubichi, S. & Nicoletti, R. (2006). Simon effect and handedness: Evidence for a dominant-hand attentional bias in spatial coding. *Perception & Psychophysics, 68,* 1059-1069.

Rubin, S. R., Van Petten, C., Glisky, E. L., & Newberg, W. M. (1999). Memory conjunction errors in younger and older adults: Event-related potential and neuropsychological data. *Cognitive Neuropsychology, 16,* 459-488.

Rueckert, L. & Grafman, J. (1996). Sustained attention deficits in patients with right frontal lesions. *Neuropsychologia, 34,* 953-963.

Rugg, M. D. & Coles, M.G.H. (1995). *Electrophysiology of mind. Event-related brain potentials and cognition* (pp. 40-85). Oxford: Oxford University Press.

Rugg, M. D., Cox, C. J., Doyle, M. C., & Wells, T. (1995). Event-related potentials and the recollection of low and high frequency words. *Neuropsychologia, 33,* 471-484.

Rugg, M. D. & Doyle, M. C. (1992). Event-related potentials and recognition memory for low- and high-frequency words. *Journal of cognitive neuroscience, 4,* 69-79.

Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1996). Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain, 119 (Pt 6),* 2073-2083.

Rugg, M. D., Henson, R. N., & Robb, W. G. (2003). Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. *Neuropsychologia, 41,* 40-52.

Rugg, M. D., Schloerscheidt, A. M., & Mark, R. E. (1998). An electrophysiological comparison of two indices of recollection. *Journal of memory and language, 39,* 47-69.

Rusconi, E., Kwan, B., Giordano, B. L., Umiltà, C., & Butterworth, B. (2006). Spatial representation of pitch height: the SMARC effect. *Cognition, 99,* 113-129.

Rypma, B., Prabhakaran, V., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage, 9,* 216-226.

Sack, A. T. (2006). Transcranial magnetic stimulation, causal structure-function mapping and networks of functional relevance. *Curr.Opin.Neurobiol., 16,* 593-599.

Sakagami, M. & Niki, H. (1994). Encoding of behavioral significance of visual stimuli by primate prefrontal neurons: relation to relevant task conditions. *Exp Brain Res, 97,* 423-436.

Salthouse, T. A. & Kail, R. (1983). Memory development through the lifespan: The role of processing rate. In P.B.Baltes & O. G. Brim (Eds.), *Life-span development and behavior. Vol 5* (pp. 89-116). New York: Academic Press.

Sanders, A. F. (1966). Expectancy: application and measurement. *Acta Psychologica, 25,* 293-313.

Sanders, A. F. (1980). Stage analysis of reaction processes. In G.G.Stelmach & J. Requin (Eds.), *Tutorials in motor behavior* (pp. 331-354). Amsterdam: North-Holland Publishing Company.

Sanders, A. F. (1998). *Elements of human performance: Reaction processes and attention in human skill.* Mahwah, NJ: Lawrence Erlbaum.

Sandrini, M., Cappa, S. F., Rossi, S., Rossini, P. M., & Miniussi, C. (2003). The role of prefrontal cortex in verbal episodic memory: rTMS evidence. *J Cogn Neurosci., 15,* 855-861.

Schacter, D. L., Buckner, R. L., & Koutstaal, W. (1998). Memory, consciousness and neuroimaging. *Philos.Trans.R.Soc.Lond B Biol Sci., 353,* 1861-1878.

Schacter, D. L., Curran, T., Galluccio, L., Milberg, W. P., & Bates, J. F. (1996a). False recognition and the right frontal lobe: a case study. *Neuropsychologia, 34,* 793-808.

Schacter, D. L., Norman, K. A., & Koutstaal, W. (1998). The cognitive neuroscience of constructive memory. *Annu.Rev.Psychol., 49,* 289-318.

Schacter, D. L., Reiman, E., Curran, T., Yun, L. S., Bandy, D., McDermott, K. B., McDermott, K. B., Roediger, H. L. I. (1996b). Neuroanatomical correlates of veridical and illusory recognition memory: evidence from positron emission tomography. *Neuron, 17,* 267-274.

Schiltz, K., Szentkuti, A., Guderian, S., Kaufmann, J., Munte, T. F., Heinze, H. J. et al. (2006). Relationship between hippocampal structure and memory function in elderly humans. *J Cogn Neurosci., 18,* 990-1003.

Schmahmann, J. D. & Pandya, D. N. (1997). Anatomic organization of the basilar pontine projections from prefrontal cortices in rhesus monkey. *J Neurosci, 17,* 438-458.

Semendeferi, K. & Damasio, H. (2000). The brain and its main anatomical subdivisions in living hominoids using magnetic resonance imaging. *J Hum.Evol., 38,* 317-332.

Senkfor, A. J. & Van Petten, C. (1998). Who said what? An event-related potential investigation of source and item memory. *J Exp Psychol.Learn.Mem.Cogn, 24,* 1005-1025.

Shallice, T. (1982). Specific impairments of planning. *Philos Trans R Soc.Lond B Biol Sci, 298,* 199-209.

Shallice, T. (1988). *From Neuropsychology to Mental Structure*. Cambridge, UK: Cambridge University Press.

Shallice, T. (2001). 'Theory of mind' and the prefrontal cortex. *Brain, 124,* 247-248.

Shallice, T. (2002). Fractionation of the Supervisory System. In D.T.Stuss & R. T. Knight (Eds.), *Principles of Frontal Lobe Function* (pp. 261-277). Oxford: University Press.

Shallice, T. (2004). The fractionation of supervisory control. In M.S.Gazzaniga (Ed.), *The Cognitive Neurosciences* (III ed., Cambridge: Mass: MIT Press.

Shallice, T. (2006). Contrasting domains in the control of action: the routine and the non-routine. In M. Johnson, & Y. Munakata (Eds.), *Attention & Performance XXI Processes of Change in Brain and Cognitive Development*. New York: Oxford University Press.

Shallice, T. & Burgess, P. (1996). The domain of supervisory processes and temporal organization of behaviour. *PhilosophicalTransactions of the Royal Society of London, B, 351,* 1405-1412.

Shallice, T., Burgess, P. W., Schon, F., & Baxter, D. M. (1989). The origins of utilization behaviour. *Brain, 112 (Pt 6),* 1587-1598.

Shallice, T., Fletcher, P., Frith, C. D., Grasby, P., Frackowiak, R. S., & Dolan, R. J. (1994). Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature, 368,* 633-635.

Shallice, T., Marzocchi, G. M., Coser, S., Del Savio, M., Meuter, R. F., & Rumiati, R. I. (2002). Executive function profile of children with attention deficit hyperactivity disorder. *Dev.Neuropsychol., 21,* 43-71.

Shallice, T., Mussoni, A., D'Agostini, S., & Skrap, M. (subm.). Localisation through Operation for Cerebral Tumour: Optic Ataxia and Unilateral Neglect.

Shallice, T. & Vallar, G. (1990). The impairment of auditory–verbal shortterm storage. In G.Vallar & T. Shallice (Eds.), *Neuropsychological impairments of Short-Term Memory* (pp. 11-53). New York: Cambridge University Press.

Shammi, P. & Stuss, D. T. (1999). Humour appreciation: a role of the right frontal lobe. *Brain, 122 (Pt 4),* 657-666.

Sharp, D. J., Scott, S. K., & Wise, R. J. (2004). Monitoring and the controlled processing of meaning: distinct prefrontal systems. *Cereb.Cortex, 14,* 1-10.

Shaw, T. G., Mortel, K. F., Meyer, J. S., Rogers, R. L., Hardenberg, J., & Cutaia, M. M. (1984). Cerebral blood flow changes in benign aging and cerebrovascular disease. *Neurology, 34,* 855-862.

Shiffrin, R. M. & Schneider, W. (1977a). Controlled and automatic human information processing: I. Detection, search, and attention. *Psychological Review, 84,* 1-66.

Shiffrin, R. M. & Schneider, W. (1977b). Controlled and automatic human information processing: II. Perceptual learning, automatic attending and a general theory. Psychological Review, 84, 127-190.

Shimamura, A. P., Janowsky, J. S., & Squire, L. R. (2000). Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia, 28,* 803-813.

Simons, J. S., Gilbert, S. J., Owen, A. M., Fletcher, P. C., & Burgess, P. W. (2005). Distinct roles for lateral and medial anterior prefrontal cortex in contextual recollection. *J Neurophysiol., 94,* 813-820.

Smith, E. E. & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283,* 1657-1661.

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cereb.Cortex, 6,* 11-20.

Smith, E. E., Jonides, J., Koeppe, R. A., Awh, E., Shumacher, E. H., & Minoshima, S. (1995). Spatial versus object working memory: PET investigations. *Journal of cognitive neuroscience, 7,* 337-356.

Soetens, E., Boer, L. C., & Hueting, J. E. (1985). Expectancy or automatic facilitation? Separating sequential effects in two-choice reaction time. *J Exp Psychol.Hum.Percept.Perform., 11,* 598-616.

Spatt, J. & Goldenberg, G. (1993). Components of random generation by normal subjects and patients with dysexecutive syndrome. *Brain Cogn, 23,* 231-242.

Sperling, G. & Dosher, B. (1986). Strategy and optimization in human information processing. In K. R. Boff, L. Kaufman, & J. P. Thomas (Eds.), *Handbook of perception and human performance* (pp. 1-65). New York: Wiley.

Srinivasan, R., Nunez, P. L., Tucker, D. M., Silberstein, R. B., & Cadusch, P. J. (1996). Spatial sampling and filtering of EEG with spline laplacians to estimate cortical potentials. *Brain Topogr., 8,* 355-366.

Sternberg, S. (1969). The discovery of processing stages: Extensions of Donder’s method. In W. G. Koster (Ed.), *Attention and performance II: Acta Psychologica, 30* (pp. 276–315).

Sternberg, S. (1975). Memory scanning: New findings and current controversies. *Quarterly Journal of Experimental Psychology, 27A,* 1-32.

Sternberg, S. (2001). Separate modifiability, mental modules, and the use of pure and composite measures to reveal them. *Acta Psychologica, 106,* 147-246.

Stuss, D. T. (2006). Frontal lobes and attention: processes and networks, fractionation and integration. *J Int.Neuropsychol.Soc., 12,* 261-271.

Stuss, D. T. & Alexander, M. P. (2000). Executive functions and the frontal lobes: A conceptual view. *Psychol Res, 63,* 289-298.

Stuss, D. T. & Alexander, M. P. (2005). Does damage to the frontal lobes produce impairment in memory? *Current Directions in Psychological Science, 14,* 84-88.

Stuss, D. T., Alexander, M. P., Palumbo, C. L., Buckle, L., Sayer, L., & Pogue, J. (1994). Organizational strategies with unilateral or bilateral frontal lobe injury in word learning tasks. *Neuropsychology, 8,* 355-373.

Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R. et al. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia, 43,* 396-417.

Stuss, D. T. & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychol Bull., 95,* 3-28.

Stuss, D. T. & Benson, D. F. (1986). *The Frontal Lobes*. New York: Raven Press.

Stuss, D. T., Binns, M. A., Murphy, K. J., & Alexander, M. P. (2002). Dissociations within the anterior attentional system: effects of task complexity and irrelevant information on reaction time speed and accuracy. *Neuropsychology, 16,* 500-513.

Stuss, D. T., Floden, D., Alexander, M. P., Levine, B., & Katz, D. (2001). Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. *Neuropsychologia, 39,* 771-786.

Stuss, D. T. & Knight, R. T. (2002). Prefrontal cortex: the present and the future. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 573-597). Oxford: Oxford University Press.

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L. et al. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia, 38,* 388-402.

Stuss, D. T., Shallice, T., Alexander, M. P., & Picton, T. W. (1995). A multidisciplinary approach to anterior attentional functions. *Ann.N.Y.Acad.Sci., 769,* 191-211.

Stuss, D. T., Toth, J. P., Franchi, D., Alexander, M. P., Tipper, S., & Craik, F. I. (1999). Dissociation of attentional processes in patients with focal frontal and posterior lesions. *Neuropsychologia, 37,* 1005-1027.

Swick, D. & Knight, R. T. (1999). Contributions of prefrontal cortex to recognition memory: electrophysiological and behavioral evidence. *Neuropsychology, 13,* 155-170.

Teichner, W. H. (1954). Recent studies of simple reaction time. *Psychol.Bull., 51,* 128-149.

Tengvar, C., Johansson, B., & Sorensen, J. (2004). Frontal lobe and cingulate cortical metabolic dysfunction in acquired akinetic mutism: a PET study of the interval form of carbon monoxide poisoning. *Brain Inj., 18,* 615-625.

Terao, Y., Ugawa, Y., Suzuki, M., Sakai, K., Hanajima, R., Gemba-Shimizu, K. et al. (1997). Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. *Exp Brain Res., 115,* 541-545.

Thatcher, R. W. (1997). Human frontal lobe development: A theory of cyclical cortical reorganization. In G.R.Krasnegor, G. R. Lyon, & P. S. Goldman-Rakic (Eds.), (pp. 85-113). Baltimore: Paul Brooks.

Thomas, E. A. (1967). Reaction-time studies: the anticipation and interaction of responses. *Br J Math.Stat.Psychol., 20,* 1-29.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc.Natl.Acad.Sci U.S.A, 94,* 14792-14797.

Traugott, E.C. (1975). Spatial expressions of tense and temporal sequencing. *Semiotica 13,* 207-230.

Trillenberg, P., Verleger, R., Wascher, E., Wauschkuhn, B., & Wessel, K. (2000). CNV and temporal uncertainty with 'ageing' and 'non-ageing' S1-S2 intervals. *Clin Neurophysiol., 111,* 1216-1226.

Tucha, O., Smely, C., Preier, M., & Lange, K. W. (2000). Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery, 47,* 324-333.

Tucker, D. M. (1993). Spatial sampling of head electrical fields: the geodesic sensor net. *Electroencephalogr.Clin Neurophysiol., 87,* 154-163.

Tulving, E., Kapur, S., Craik, F. I., Moscovitch, M., & Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc.Natl.Acad.Sci.U.S.A, 91,* 2016-2020.

Tversky, B., Kugelmass, S., & Winter, A. (1991). Cross-Cultural and Developmental Trends in Graphic Productions. *Cognitive Psychology, 23,* 515-557.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N. et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15,* 273-289.

Umiltà, C. (1988). Orienting of attention. In F.Boller, J. Grafman, & et al. (Eds.), *Handbook of neuropsychology Vol 1* (pp. 175-193).

Umiltà, C. (2006). Localization of cognitive functions in the brain does allow one to distinguish between psychological theories. *Cortex, 42,* 399-401.

Ungerleider, L. G. & Mishkin, M. M. (1982). Two cortical visual systems. In D.I.Ingle, M. A. Goodale, & R. J. W. Mamsfield (Eds.), *Analysis of visual behavior* (pp. 549-586). Cambrige: MIT Press.

Upton, D. & Corcoran, R. (1995). The role of the right temporal lobe in card sorting: a case study. *Cortex, 31,* 405-409.

Vallesi, A., Mapelli, D., Schiff, S., Amodio, P., & Umiltà, C. (2005). Horizontal and vertical Simon effect: different underlying mechanisms? *Cognition, 96,* B33-B43.

Verin, M., Partiot, A., Pillon, B., Malapani, C., Agid, Y., & Dubois, B. (1993). Delayed response tasks and prefrontal lesions in man--evidence for self generated patterns of behaviour with poor environmental modulation. *Neuropsychologia, 31,* 1379-1396.

Vilkki, J., Servo, A., & Surma-aho, O. (1998). Word list learning and prediction of recall after frontal lobe lesions. *Neuropsychology, 12,* 268-277.

Vilkki, J., Surma-aho, O., & Servo, A. (1999). Inaccurate prediction of retrieval in a face matrix learning task after right frontal lobe lesions. *Neuropsychology, 13,* 298-305.

Von Economo, C. (1926). Die pathologie des schlafes. In A.Bethe, G. von Bergmann, G. Eubden, & A. Ellinger (Eds.), *Handbuch der normalen und pathologischen physiologie* (pp. 609). Berlin: Springer-Verlag.

Wagner, A. D., Pare-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron, 31,* 329-338.

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci., 9,* 445-453.

Wallace, R. J. (1971). Stimulus-response compatibility and the idea of a response code. *Journal of Experimental Psychology, 88,* 354-360.

Wallis, J. D., Dias, R., Robbins, T. W., & Roberts, A. C. (2001). Dissociable contributions of the orbitofrontal and lateral prefrontal cortex of the marmoset to performance on a detour reaching task. *Eur.J Neurosci, 13,* 1797-1808.

Warren, J. M. & Akert, K. (1964). *The Frontal Granular Cortex and Behavior*. New York: McGraw-Hill Book Company.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr.Clin Neurophysiol., 108,* 1-16.

Watson, J. B. & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology, 3,* 1-14.

Waugh, N. C. & Norman, D. A. (1965). Primary memory. *Psychol Rev., 72,* 89-104.

Welt, L. (1888). Ueber Charakterveränderungen des Menschen infolge von Läsionen des Stirnhirns. *Dtsch Arch Klin Med, 42,* 339-390.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull., 120,* 272-292.

Wilding, E. L. & Rugg, M. D. (1996). An event-related potential study of recognition memory with and without retrieval of source. *Brain, 119 (Pt 3),* 889-905.

Wilkins, A. J., Shallice, T., & McCarthy, R. (1987). Frontal lesions and sustained attention. *Neuropsychologia, 25,* 359-365.

Wilson, F. A., Scalaidhe, S. P., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science, 260,* 1955-1958.

Winn, W. (1994). Contributions of Perceptual and Cognitive processes to the Comprehension of Graphics. In Schnotz, W. & Kulhavy, R. W. (Eds.) *Comprehension of Graphics.* (pp. 3-27), Amsterdam, The Netherlands: Elsevier Science BV.

Woodrow, H. (1914). The measurement of attention. *Psychological Monographs 5(76),* 1-158.

Yonelinas, A. P. (1999). The contribution of recollection and familiarity to recognition and source-memory judgments: a formal dual-process model and an analysis of receiver operating characteristics. *J Exp Psychol.Learn.Mem.Cogn, 25,* 1415-1434.

Zahn, T. P. & Rosenthal, D. (1966). Simple reaction time as a function of the relative frequency of the preparatory interval. *J Exp Psychol, 72,* 15-19.

Zahn, T. P., Rosenthal, D., & Shakow, D. (1963). Effects of irregular preparatory intervals on reaction time in schizophrenia. *Journal of abnormal and social psychology, 67,* 44-52.

Zarahn, E., Aguirre, G., & D'Esposito, M. (1997). A trial-based experimental design for fMRI. *Neuroimage, 6,* 122-138.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1999). Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. *Brain Res Cogn Brain Res, 7,* 255-268.

Zebian, S. (2005). Linkages between Number Concepts, Spatial Thinking, and Directionality of Writing: The SNARC Effect and the REVERSE SNARC Effect in English and Arabic Monoliterates, Biliterates, and Illiterate Arabic Speakers. *Journal of Cognition and Culture, 5,* 165-190.

Zelazo, P., Carter, S., Resnick, K., & Frye, C. (1996). The development of executive functions in children. *Review of General Psychology, 1,* 198–226.

Zimmer, K. (1964). Affixed negation in English and other languages: An investigation of restricted productivity. *Word, 20,* Monograph No. 5.

Zwaan, E. W. J. (1965). Links en rechts in waarneming en beleving. (Left and right in visual perception as a function of the direction of writing). Ph.D. diss, Rijksuniversiteit Utrecht. The Netherlands. (quoted by Winn, 1994).

Appendix

Parietal effects found in the source memory Experiments 15 and 16.

Parietal effects in Experiment 15 (time window: 500-800 ms)

In order to replicate the well-known old/new left parietal effect, a repeated measure 3x2x2x2 ANOVA was initially conducted with the following factorial analysis: response category (hit/hit, hit/miss, correct rejection) x hemisphere (left vs. right) x lobe (frontal vs. parietal) x regions (anterior vs. lateral). The dependent variable was mean amplitude in the 500-800 ms time-window.

This analysis yielded a significant category x hemisphere interaction [$F(2, 24) = 8.4$, $p < .01$], mainly due to waves for hit/misses being more positive in the left hemisphere than in the right one ($p < .001$); waves for the two other response categories did not differ between hemispheres. In addition, a lobe x region interaction was obtained [$F(1, 12) = 5$, $p < .05$]. In view of this interaction, a 3x2x2 ANOVA (response category, hemisphere, region) was conducted on the parietal regions only. The only significant effect was the response category x hemisphere interaction [$F(2, 24) = 11.3$, $p < .001$]. The post-hoc analysis revealed that hit/miss waves were more positive in the left than in the right parietal regions ($p < .001$). In addition, as planned comparisons showed, the waves for hit/hit as well as those for hit/miss were more positive than those for correct rejections in the left parietal region as compared to the right one ($p < .05$ and $p < .01$, respectively). No hemispheric asymmetry was found for the hit/hit vs. hit/miss comparison.

Similar ANOVAs were conducted replacing the factor confidence with that of accuracy. However, no effect of accuracy was observed in the parietal ERPs (see Figure 28).

Thus, experiment 15 replicates the basic old/new effects known from the literature. In keeping with previous findings (e.g., Donaldson & Rugg, 1998; Wilding & Rugg, 1996), the differences between the ERPs to correct memory judgments for old and new items were characterized by an early left parietal old/new effect, consisting of waves for hits being more positive than waves for correct rejections. However, unlike some studies (e.g., Wilding & Rugg, 1996), but similar to others (Cansino, Marquet, Dolan, & Rugg, 2002; Senkfor & Van Petten, 1998), parietal waves were not modulated by the accuracy of the subsequent source judgement (hit/hit vs. hit/miss). Moreover, the hemispheric asymmetry (left more than right) in the old/new parietal effect was detected for the hit/miss condition only and not for the hit/hit one.

Parietal effects in Experiment 16 (time window: 500-700 ms)

A 2x2x2x2 ANOVA was performed with the following factorial analysis: confidence (low vs. high), lobe (frontal vs. parietal), hemisphere (left vs. right) and region (anterior vs. lateral). The mean amplitude of the ERPs in the 500-700 ms post-word onset was used as the dependent variable.

The lobe x hemisphere interaction was significant [$F(1, 16) = 5.1$, $p < .05$], due to waves being more positive in the left parietal regions than elsewhere (for all, $p < .05$). As the confidence x lobe x region interaction was also significant [$F(1, 16) = 10.7$, $p < .01$], a 2x2x2 ANOVA (confidence, hemisphere and region) was carried out limited to the four parietal regions only. This analysis produced a main effect of hemisphere [$F(1, 16) = 8.3$, $p < .01$], left ERPs being more positive than right ones. More importantly, the confidence x region interaction [$F(1, 16) = 11$, $p < .01$] showed that waves for low-confidence responses were more positive than waves for high-confidence ones in the lateral parietal regions only.

Similar ANOVAs were conducted replacing the factor confidence with that of accuracy. However, no effect of accuracy was observed in the parietal ERPs (see Figure 29).

Experiment 16 confirms the general involvement of left parietal regions during a source memory task in a time-window different from that concerning the right prefrontal effect, as already shown in previous memory studies (e.g., Wilding & Rugg, 1996) and in the experiment 15 of the present study. In particular, ERPs in the left parietal regions were the most positive in the early latency-window of 500-700 ms, while ERPs in the right frontal regions were the most positive in the subsequent latency-windows of 1000-1500 and 1500-2000 ms. However, the present results again do not corroborate the successful retrieval account of the parietal and prefrontal involvements during a source memory task.

In the current study, the production of confidence ratings by the participants influenced their ERPs in two dissociable ways. First, ERPs are more positive for low-confidence ratings than for high-confidence ones. This pattern is observed earlier over lateral parietal regions (i.e., 500-700 ms and 1000-1500 ms) and later and more sustained in time also over anterior prefrontal ones (i.e., 1000-2000 ms). This different time-course suggests a different functional role of the two regions during this task.

ERP parietal effects in source memory experiments: a general discussion

As far as the ERP parietal effects during memory retrieval are concerned, recollection and retrieval quality accounts have been proposed in the literature (process c, in our task analysis proposed on page 160; e.g., Curran, 2004; Duzel et al., 1997; Rugg et al., 1995). Such accounts originate from the hypothesis that the parietal ERP effects reflect medial temporal lobe activity (Duzel et al., 1999) or cortico-hippocampal interactions (Wilding & Rugg, 1996). Medial temporal activity, when reported in functional imaging studies, has usually been related to retrieval success (see Schacter, Buckner, & Koutstaal, 1998, for a review). However, the present results are in conflict with these accounts, as no effect of accuracy was obtained on these sites in either experiment. On the other hand, an effect of confidence was observed, with low-confident responses evoking more positive ERPs. Responses to be rated low-confidence are less likely to be vividly retrieved or recollected (as demonstrated by the behavioural results of experiment 16). Thus, given the existing evidence, the finding of low-confidence ERPs being more positive than high-confidence ones over the lateral parietal regions in the experiment 16 was unexpected. However, in addition to the current study, other ERP studies also show findings somewhat in contrast with the recollection account of the parietal effects. In a face recognition task, for instance, Graham and Cabeza (2001) found similar parietal ERP amplitudes for hit-hits and hit-misses. In another ERP study of recognition (Curran, et al., 2001), participants were a posteriori separated into Good and Poor performers, according to their ability to discriminate studied target words from similar lures. Surprisingly, only poor performers, despite of their inability to discriminate between old targets and lures, showed a reliable parietal old/lure difference.

The gap observed in these studies between behavioural performance and the parietal ERP effects suggests that the latter may be independent of retrieval accuracy and vivid recollection (see also Rossi et al., 2006). Moreover, it should be pointed out that the link between the parietal ERP effects and the medial temporal lobe activity is very indirect. Indeed, there is recent evidence showing no consistent relationship between left parietal ERP correlates of source memory retrieval and hippocampal volume and diffusion (Schiltz et al., 2006). The same study showed no correlation between accuracy in source memory retrieval and these indices of hippocampal integrity.

An alternative hypothesis, among others, is that posterior parietal ERP effects might reflect the shifting of attention to, and the maintenance of attention on, internally produced mnestic representations (processes a and b, in our task analysis; Wagner, Shannon, Kahn,

& Buckner, 2005). This hypothesis derives from the observation that the confidence effect occurs over the lateral parietal regions in two different time-windows, a phasic early time-window (see page 222) and a middle tonic one (see page 157), probably associated to the two above-mentioned processes. Moreover, in some short-term memory models, the left inferior parietal region is thought to be the seat of the input phonological buffer (Paulesu, Frith, & Frackowiak, 1993; Shallice & Vallar, 1990). The maintenance of attention on memory retrieval products is therefore likely to be increased in order to achieve a source memory decision especially for weakly stored traces (low-confidence judgements), whereas it is not clear how confidence status can influence the earlier stage of attentional shift. However, these interpretations should be taken cautiously, as the opposite pattern (more positive parietal ERPs for the high- than for low-confidence judgements) was reported in earlier ERP studies of confidence (e.g., Curran, 2004; Rubin et al., 1999). Differences in the task demands (source vs. old/new judgements) might help to partially account for the discrepancies with previous findings.