When Time Shapes Behavior: fMRI Evidence of Brain Correlates of Temporal Monitoring

Antonino Vallesi[1], Anthony R. McIntosh[1,2], Tim Shallice[3,4], and Donald T. Stuss[1,2]

Abstract

■ Time processing may shape behavior in several ways, although the underlying neural correlates are still poorly understood. When preparatory intervals between stimuli vary randomly in a block, for instance, responses are faster as the interval gets longer. This effect, known as variable foreperiod (FP) effect, has been attributed to a process monitoring the conditional probability of stimulus occurrence as the interval increases. Previous evidence points to the right dorsolateral prefrontal cortex (DLPFC) as a possible node for this time-monitoring process. The present study addresses this hypothesis with functional magnetic resonance imaging (fMRI). Block-design fMRI was used on 14 young participants while they performed a visual discrimination task with fixed and variable preparatory intervals (FPs) of 1 and 3 sec. In the variable versus fixed FP contrast, the right DLPFC and a visual area were more activated in the subgroup of participants who showed a reliable variable FP effect than in another subgroup who did not show that effect. Only the activation in the right DLPFC was supported by a significant interaction between FP condition (variable vs. fixed) and group. This finding may reflect possible differences in the strategy adopted by the two subgroups of participants while performing the task. Although results suggest that many brain areas may be involved in preparation over time, the role of the right DLPFC is critical to observe the strategically mediated behavioral effects in the variable FP paradigm. ■

INTRODUCTION

When preparing a response to forthcoming environmental stimuli, the cognitive system tries to anticipate their occurrence in time and to fine-tune the processes necessary for perceiving, processing, and responding to them (Brunia & van Boxtel, 2001; Niemi & Näätänen, 1981). This preparatory ability is likely to require, among other processes, estimation of the temporal interval between stimuli.

Sub- and perisecond intervals are usually processed more efficiently and automatically than suprasecond ones (e.g., scalar theory of time perception; Gibbon, Church, & Meck, 1984). When participants are required to synchronize (e.g., tapping) and continue to reproduce regular intervals with a movement of an effector, variability increases as a function of the interval length (e.g., Madison, 2001; Michon & van der Valk, 1967; Klemmer, 1957). Moreover, time affects behavior also when elapsing time is not task-relevant, such as in simple and choice reaction time (RT) tasks. In such tasks, if the interval between a warning and a target stimulus (i.e., foreperiod, FP) is kept fixed across trials, RTs are typically shorter with relatively short intervals than with long ones (fixed FP effect; e.g., Mattes & Ulrich, 1997; Simon & Slaviero, 1975; Teichner, 1954). This finding is traditionally interpreted as due to increasing time uncertainty as the FP increases (e.g., Gottsdanker, 1970; Klemmer, 1957).

However, behavioral effects change dramatically not only as a function of the FP range employed (sub- and suprasecond) but also as a function of the mode of administration of the different FPs in the block (fixed vs. variable). Events occurring at variable intervals are more frequent in real life than those occurring at a fixed rate. When stimuli occur at random temporal intervals, it is impossible to know a priori when the next stimulus will be presented. However, the elapsing time itself may provide information about the forthcoming presentation of the stimulus (Elithorn & Lawrence, 1955). As time runs without the stimulus being shown, indeed, the conditional probability of its occurrence in the next interval increases. It is supposed that the cognitive system monitors this changing conditional probability in order to endogenously increase response preparation (e.g., Stilitz, 1972; Näätänen, 1970; Baumeister & Joubert, 1969; Requin & Granjon, 1969). As a result, RTs are shorter for longer FPs than for shorter ones, in contrast to what happens with the fixed FP paradigm. This robust behavioral phenomenon is known as the variable FP effect

[1]Rotman Research Institute at Baycrest, Toronto, Ontario, Canada, [2]University of Toronto, Toronto, Ontario, Canada, [3]SISSA-ISAS, Trieste, Italy, [4]University College London, UK

(Elliott, 1970; Requin & Granjon, 1969; Woodrow, 1914; see Niemi & Näätänen, 1981, for a review).

Research focusing on the anatomical substrates of temporal processing has increased in the last few years (Nobre, Correa, & Coull, 2007). Within this literature, recent work has begun to specifically elucidate the neural bases of preparation over variable time intervals, as reflected by the variable FP effect. Converging evidence points to the right dorsolateral prefrontal cortex (DLPFC) as a key area in this effect. In a recent neuropsychological study (Stuss et al., 2005), for instance, patients with lesions in that region did not show the variable FP effect (see Vallesi, Shallice, & Walsh, 2007, for similar TMS evidence). Worth mentioning, in contrast to patients with superior medial prefrontal lesions, these patients were not impaired in similar RT tasks with a fixed FP presentation. In light of the classical account concerning conditional probability monitoring (Näätänen, 1970; Nickerson, 1967; Thomas, 1967; Sanders, 1966; Elithorn & Lawrence, 1955), these results have been interpreted as an indication that the right lateral prefrontal cortex is a key region for checking whether a stimulus has occurred over time, and increasing readiness as time passes.

However, a possible confound of this account derives from the fact that the shape of the FP effect depends, at least in part, on sequential FP effects: RTs on the current trial are longer for long FPs on the previous trial than for short ones (e.g., Baumeister & Joubert, 1969; Karlin, 1959; Woodrow, 1914). Such effects are usually asymmetric, being mainly present with the shortest current FP in the range.

Traditional explanations hypothesize that the sequential effects originate from strategic processes. One of these accounts, for instance, proposes that participants strategically expect an FP repetition from one trial to the next (Alegria, 1975; Thomas, 1967; Karlin, 1959). These strategic accounts have been challenged by behavioral evidence showing that these effects persist after invalid temporal cues (Los & van den Heuvel, 2001). 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 varied according to the sequential effects. If sequential effects were fully strategic in nature, there would be no reason for them to influence costs after invalid cues (i.e., when ''strategic'' preparation was diverted toward a different FP).

Moreover, the sequential FP effects appear at an earlier developmental stage than the current FP effect, that is at least at 4 years of age, when strategically mediated behavior is unlikely to occur (Vallesi & Shallice, 2007). The diverging developmental trajectories followed by the sequential effects and by the current FP effect, as found in the latter study, suggest a possible dissociation of processes and neural mechanisms involved in the two effects: a prefrontally based strategic mechanism of conditional probability monitoring (e.g., Stuss et al., 2005) and a more automatic process of regulation of the preparation level according to the length of the preceding FP, whose neural bases have started to be investigated only recently. In another neuropsychological study (Vallesi, Mussoni, et al., 2007), a variable FP paradigm was administered to patients with unilateral tumors located in different brain regions (i.e., prefrontal, premotor, parietal) both a few days before and a few days after tumor surgical removal. A reduced variable FP effect, with no significant changes in the sequential effects, was observed after excision of tumors located in the right lateral prefrontal region only.

The aim of this study is to confirm, by means of fMRI, the involvement of the right DLPFC during a variable FP paradigm, and to extend these findings by investigating which other brain regions are associated with the performance of this paradigm. A block fMRI experiment with a 2 FP (1 vs. 3 sec) by 2 Paradigm (fixed vs. variable) factorial design was administered to 14 healthy subjects. A block design was used in order to avoid any confound due to the influence of the different time intervals on the trial-averaged BOLD response. This influence could occur independently of the cognitive demands required by FPs of different length, for instance, because of the intrinsic temporal constrains of the BOLD response development.

Fixed short and long FP paradigms collapsed were employed as a cognitive baseline for the variable FP paradigm. Fixed and random timing conditions share the same basic perceptual and motor demands. Moreover, preparation over time is also required by both conditions. However, if the FP is kept constant, such as in the fixed FP paradigm, conditional probability of stimulus occurrence also remains constant along the trial, and monitoring during the trial the elapsing time (i.e., monitoring changing conditional probability of stimulus occurrence) will not be useful for modulating the preparation level. The subjects might still monitor the passage of time, especially with the long fixed FP, but the RT literature suggests that, if they do so, this monitoring process is not as efficient as in the variable FP paradigm because RTs are longer with long fixed FPs than with short fixed FPs or with the same long FPs embedded in a variable paradigm (e.g., Niemi & Näätänen, 1981). In the variable paradigm, on the other hand, the FP varied randomly and usually equiprobably, allowing the monitoring process thought to underlie the variable FP effect to play a role (e.g., Näätänen, 1970; Elithorn & Lawrence, 1955). On the basis of previous neuropsychological (Vallesi, Mussoni, et al., 2007; Stuss et al., 2005) and TMS (Vallesi, Shallice, et al., 2007) evidence, we hypothesize greater activation of the right lateral prefrontal cortex with the variable FP paradigm than with the fixed one. This contrast would not concern areas involved in general temporal preparation, but more selectively, areas involved in monitoring changing probabilities over time on a trial-by-trial basis.

In order to disentangle effects of the current and preceding FP in the variable FP task, despite the fact that they are embedded in the same block design, we will correlate the magnitude of each of these two behavioral effects separately to the level of activation of the regions highlighted in the contrast between variable versus fixed FP paradigm. By adopting this approach, we will be able to estimate the relative strength of association between activation in these regions and the two behavioral effects.

Notably, for pragmatic purposes, participants performed two tasks in the scanner, with the order of administration of the two tasks counterbalanced across participants. One of them was the FP paradigm and the second was a Stroop-like task (Vallesi, McIntosh, Alexander, & Stuss, submitted) based on that described by Alexander, Stuss, Picton, Shallice, and Gillingham (2007). These two tasks were intended to be part of two independent studies. However, possible task order effects were assessed in terms of both behavioral measures and fMRI data.

METHODS

Participants

Fourteen healthy volunteers (8 women; mean age = 27 years, range = 20–34 years) took part in the study. All the participants had normal or corrected-to-normal vision and signed an informed consent that was previously approved by the Ethics Research Board of Baycrest. All of them were right-handed. The average score on the Edinburgh Handedness Inventory (Oldfield, 1971) was 87 (range = 69–100). Participants reported no history of psychiatric or neurological disorders, and no current use of any psychoactive drugs. Each participant received C$50 in compensation for her or his time.

Experimental Material and Design

A warning stimulus (an asterisk lasting 200 msec) was presented before the onset of the target stimulus. The target stimulus was either an empty square or an empty equilateral triangle (height = 4 cm), with a duration of 300 msec. The warning-to-target interval (FP) was kept constant to 1 sec in one run (short fixed FP paradigm), to 3 sec in another run (long fixed FP paradigm), and varied pseudorandomly and with the same probability between these two values in four consecutive runs (variable FP paradigm). Each run comprised 40 trials. In the variable FP paradigm, sequences of FPs were ordered so that every condition given by the factorial combination of 2 Current (1 vs. 3 sec) by 2 Preceding (1 vs. 3 sec) FP length was presented pseudorandomly and approximately with the same frequency (i.e., 9–11 times per run). Response times were recorded from the onset of the target stimulus. The response deadline was set at 2 sec after the onset of the target stimulus. The intertrial interval was jittered randomly and continuously between 0.5 and 2.5 sec after this deadline.

Participants performed a choice RT task. They were instructed to get prepared as soon as they saw the warning stimulus and to respond with either the index or the middle finger of their right hand according to the shape of the target stimulus. The correspondence between responding finger and target shape was counterbalanced across participants. The first two trials of each run were discarded from further analyses. The order of presentation of the three FP paradigms was counterbalanced across participants. Half of the participants performed this task before the acquisition of the structural scans (6.5 min) and the administration of another Stroop-like task inside the scanner (35 min). The Stroop-like task was an adapted version of the task used by Alexander et al. (2007). Data from the latter are not reported here. The other half performed the Stroop-like task and had their structural scans acquired before the performance of the FP task.

Image Acquisition and Data Analysis

Images were acquired at the Baycrest Hospital on a 3-Tesla Siemens Magnetom Trio whole-body scanner with a matrix 12-channel head coil. Functional volumes were obtained using a whole-head T2*-weighted echo-planar image (EPI) sequence (repetition time [TR] = 2 sec, echo time [TE] = 30 msec, flip angle = 70°, 28 oblique axial slices with interleaved acquisition, 3.1 × 3.1 × 5 mm voxel resolution, field of view [FOV] = 20 cm, acquisition matrix = 64 × 64). The first 5 volumes were discarded to allow the magnetization to reach steady state. Physiological data (heart and respiration rate) were acquired during the scanning session. Anatomical images were acquired using an MP-RAGE sequence (TR = 2 sec, TE = 2.63 sec, 160 oblique axial slices, with a 1-mm^3 voxel size, FOV = 25.6 cm, acquisition matrix = 256 × 256), either before or after the functional images (counterbalanced across subjects). Stimuli were presented visually through a mirror mounted on the coil that reflected images from a projector located at the bottom of the scanner. Finger-press responses were recorded with an MRI-compatible response pad.

The fMRI data were processed using Analysis of Functional Neuroimages (AFNI, AFNI_2007_05_29_1644 release) software (http://afni.nimh.nih.gov/; Cox, 1996). EPI time-series data were corrected for cardiac and respiratory parameters (program 3dretroicor). Six-parameter rigid body inter- and intrarun motion correction was then performed by coregistering volumes in the EPI scans to a reference EPI volume of the run whose motion parameters were the less extreme with respect to

the other runs (program 3dvolreg). After normalizing each run based on the mean intensity of the signal, time series in each run were de-trended to correct for possible constant baseline drifts using a cubic polynomial.

Individual analysis was performed by generating the hemodynamic response function model for each FP condition based on the convolution of the time points when the warning stimulus was presented and a gamma function (Cox, 1996). Maps of brain activity were produced by fitting a general linear model to the measured fMRI time series at each voxel using the AFNI program 3dDeconvolve. The model contained six parameters, one for each run.

Prior to group analysis, the activation maps for each participant and each condition were spatially normalized to an average volume of 152 normal skull stripped brains (www.bic.mni.mcgill.ca) matching a Talairach and Tournoux (1988) template; data sets were resampled with a $4 \times 4 \times 4$ voxel dimension (program @auto_tlrc) and spatially smoothed with an 8-mm FWHM Gaussian kernel (program 3dmerge). Group-level analyses were carried out using a three-factor ANOVA (program 3dANOVA3). The factors were participant (7 levels), which was a random factor, and FP condition (6 levels: fixed FP 1, fixed FP 3, and each of the 4 variable FP runs) and task order, which were fixed factors. The latter factor (2 levels) was included in order to control for possible effects of order of task execution within the scanner (FP task performed before vs. after the Stroop-like task and anatomical scans). In addition to the main effects and interaction, the following contrasts of interest between conditions was specified within this analysis (t tests): variable FP paradigm (4 runs collapsed) versus fixed FP paradigm (short and long runs collapsed); first versus last two runs of the variable FP paradigm; first two runs of the variable FP paradigm versus fixed FP paradigm.

For the inferential statistical tests, a single voxel threshold was set at $p < .005$ to control for alpha error, and a minimum cluster size of 1280 mm^3 (i.e., 20 voxels) was used to correct for multiple comparisons. This combination of p value and cluster size was obtained by running a Monte Carlo simulation (program AlphaSim) with the following parameters: single-voxel uncorrected $p = .005$, FWHM = 8 mm, with whole-brain mask, yielding a corrected single-voxel threshold of $p < .00005$ (corresponding to a corrected $p < .05$ for a whole cluster with 20 voxels).

RESULTS

Excluded Trials

RTs from the first trial of each run (3%), RTs outside the 100–1500 msec range (2.3%), error trials (2%), and trials in which participants pressed the response button before stimulus onset (0.3%) were excluded from further analyses.

Reaction Times

RT data were first submitted to a mixed ANOVA with FP paradigm (fixed vs. variable) and FP length (1 vs. 3 sec) as the within-subject factors, and task order (FP task performed first vs. last) as the between-groups factor. This ANOVA produced a significant interaction between paradigm and FP length [$F(1, 12) = 11, p < .01$]. This interaction indicated that RT was shorter for the long FP than for the short one in the variable FP task, but this effect was reversed in the fixed FP task (Figure 1). The two tasks were also analyzed separately. A mixed ANOVA with fixed FP (1 vs. 3 sec) and task order as the between-subjects factor yielded a FP main effect only [$F(1, 12) = 7.2, p < .05$]. A subsequent mixed ANOVA was conducted for the variable FP paradigm only, with the current and preceding FP length (1 vs. 3 sec) as the within-subject factors, and the task order as the between-subjects factor. This ANOVA yielded the following significant effects (Figure 1B): a main effect of the current FP [$F(1, 12) = 7.6, p < .05$], indicating that RT was shorter for longer current FPs; preceding FP [$F(1, 12) = 15.4, p < .01$], due to RT being shorter for short preceding FPs; a trend for current by preceding interaction [$F(1, 12) = 3.5, p = .086$], suggesting that the preceding FP effect tended to be stronger for current short FPs than for long ones; a Group by Current FP interaction [$F(1, 12) = 4.7, p < .05$], which was due to the current FP effect being present in the group that performed this task first [$t(6) = 3.5, p < .01$], and absent in the group that performed it last [$t(6) = 0.4, p = .34$]. No other effect was significant.

We also checked whether the RTs of the two groups were significantly different for the short (564 vs. 580 msec) and long (607 vs. 586 msec) variable FP separately by means of two independent-samples t tests. These tests were not significant (for both, $p > .62$). Therefore, task order modulated the overall variable FP effect, but not RTs on the short or long FPs separately. A final repeated measures ANOVA was conducted to check for possible time-related differences within the variable FP paradigm. This analysis included the following factors: run (''1 and 2'' vs. ''3 and 4''), current FP (1 vs. 3 sec), and preceding FP (1 vs. 3 sec). Despite the main effects of the current and preceding FP, which replicate the previous analysis, no main effect or interaction involving the run factor occurred.

fMRI Data

Peak Z-score voxels in each of the clusters revealed by the critical comparisons in the three-factor ANOVA and in a follow-up two-sample t test are reported in Table 1.

Variable vs. Fixed FP Paradigm Contrast

The four runs of the variable FP paradigm were contrasted with the two runs of fixed FP paradigm (see

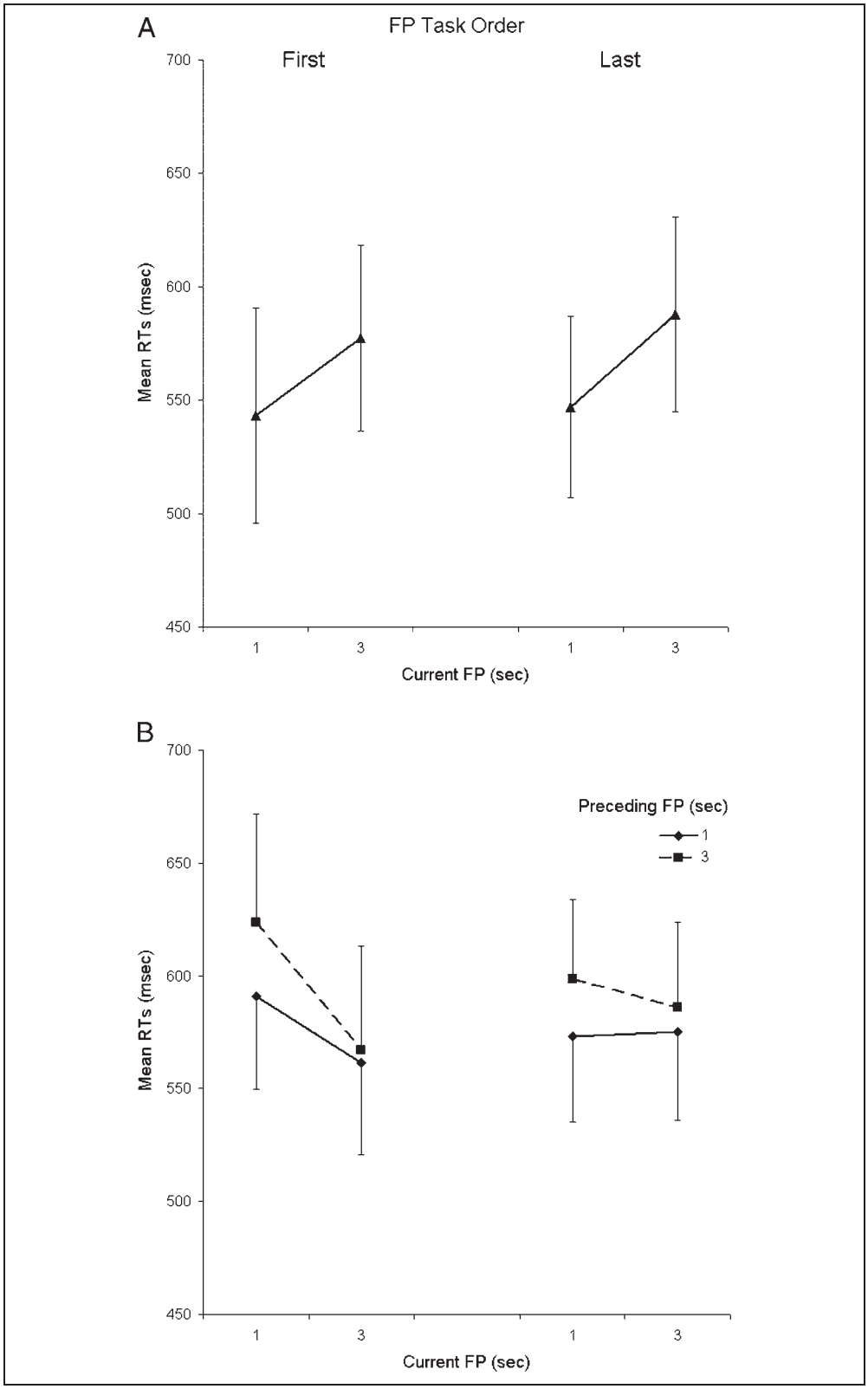

Figure 1. Mean RTs (*y*-axis) as a function of the order of execution of this task and another cognitive task in the scanner. Left and right plots show data obtained from the participants that performed the FP task before and after the other task, respectively. (A) RTs obtained in the fixed paradigm as a function of the foreperiod (FP) length (*x*-axis). (B) RTs obtained in the variable FP paradigm, as a function of the current FP (*x*-axis) and preceding FP (lines). The vertical bars indicate standard errors of the mean.

Table 1 and Figure 2). This contrast revealed activations in the bilateral middle frontal gyri, the left superior frontal gyrus, the left anterior cingulate cortex (ACC), the right posterior cingulate, the right hippocampus, and the left fusiform gyrus and cuneus. In the opposite contrast (i.e., fixed vs. variable FP), no cluster survived correction for multiple comparisons. In order to investigate which areas correlated with the variable FP effect, we extracted the intensity of the peak voxel in each cluster per each subject, and ran a Pearson's correlation analysis between

Table 1. Peak *Z*-Score Voxels Identified from AFNI Analysis of Activation Data

	Talairach						
Voxel No.	*x*	*y*	*z*	*Hemisphere*	*Location*	*BA*	*Z Score*
Variable vs. Fixed FP Paradigm (All Subjects)							
330	−36	−80	−14	L	fusiform/inferior occipital gyrus	19	4.8
61	24	−36	−2	R	hippocampus	–	4.3
35	0	36	54	Both	superior frontal gyrus	8	4.1
120	−16	8	46	L	cingulate gyrus	24	4.0
38	24	−52	10	R	posterior cingulate	30	4.0
22	52	40	26	R	middle frontal gyrus	46	3.8
136	−28	−88	42	L	cuneus	19	3.8
29	−56	24	30	L	middle frontal gyrus	9	3.7
43	−44	48	−2	L	middle frontal gyrus	10	3.6
First vs. Last Two Runs in the Variable FP Paradigm (All Subjects)							
47	16	8	26	R	cingulate gyrus	24	−4
First Two Runs in the Variable FP Paradigm vs. Fixed FP Paradigm (All Subjects)							
86	−36	−76	−10	L	fusiform gyrus	19	−4
29	24	−36	−2	R	hippocampus	–	−4
20	60	40	18	R	middle frontal gyrus	46	−4
Group Performing FP Task before vs. Group Performing FP after the Stroop-like Task, in the Contrast between Variable and Fixed FP Paradigm							
21	−44	−80	2	L	middle occipital gyrus	19	3.5
20	56	32	18	R	middle frontal gyrus	46	3.8

The coordinates refer to the standardized stereotaxic brain atlas of Talairach and Tournoux (1988).

these values and the magnitude of the variable FP effect. The latter was calculated as the RT difference between the short and the long FP conditions on trial *n*. Only two areas were found to positively correlate with this behavioral measure, namely, the left cuneus ($r = .55$, two-tailed $p < .05$) and the right middle frontal gyrus ($r = .53$, two-tailed $p < .05$; see Figure 2B). A trend was also found in the right superior frontal gyrus ($r = .44$, two-tailed $p = .11$). All the other clusters showed no correlation with the variable FP effect (for all, $p > .27$). It has been proposed that the FP effect is a side effect of the trace conditioning mechanisms occurring in the preceding trial that give rise to the sequential effects (e.g., Los & van den Heuvel, 2001; but see Vallesi & Shallice, 2007). To control for this possibility, we carried out the same correlation analysis using the magnitude of the preceding FP effect (ΔRT between a long and a short FP in the preceding trial). However, there was no significant correlation between the preceding FP effect and activation in any of the clusters extracted (for all, $p > .23$).

Moreover, the contrast between the first and the last two runs of the variable FP paradigm showed that the ACC was more activated in the last runs than in the first ones. Finally, the contrast between the first two runs of the variable FP paradigm and the two fixed FP runs (which was carried out to balance the number of trials between the two kind of paradigms) confirmed activation in the right middle frontal gyrus and the hippocampus, and in the left fusiform gyrus (see Table 1). Critically, even in this contrast, no areas were more activated for the fixed than for the variable FP paradigm.

Variable vs. Fixed FP According to the Task Order

The overall ANOVA showed an interaction between group and FP paradigm in the right middle frontal gyrus (*x*, *y*, *z* Talairach coordinates of the peak voxel: 52 44 22; peak *Z*-score: 3.9). In order to investigate more directly the neural differences between the two task-order groups, we compared them through a subsequent two-sample

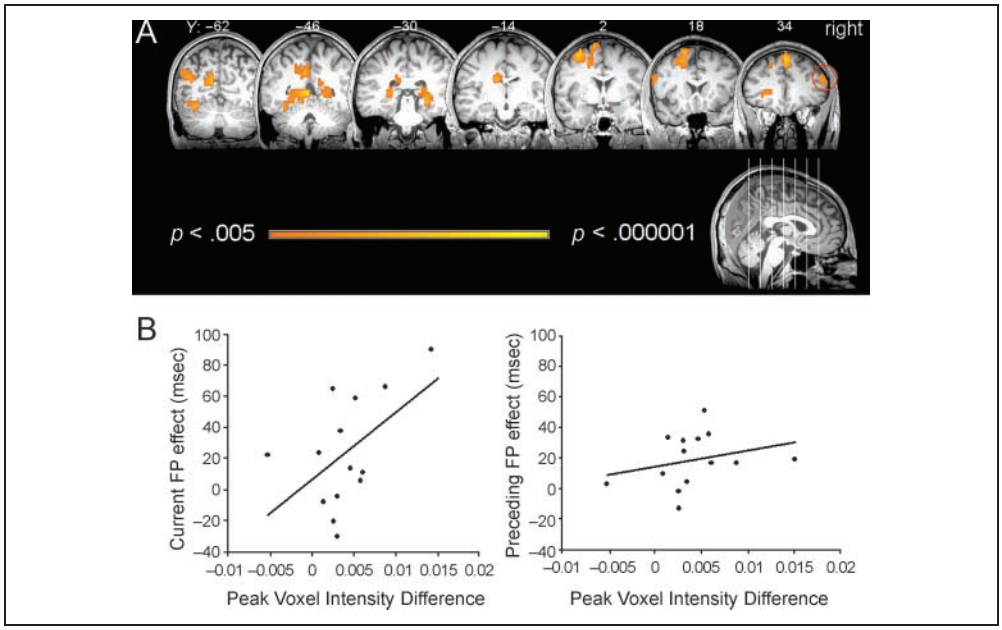

Figure 2. (A) The figure shows group-averaged activation map for the contrast between variable and fixed FP paradigm, superimposed on the brain of an individual subject. Hot colors denote regions more activated for the variable FP paradigm than for the fixed FP paradigm. Voxels were defined at $p < .005$, corrected using family-wise error correction (Monte Carlo simulation), which takes into account both alpha level and cluster size (20 voxels). The red circle surrounds a cluster in the right middle frontal gyrus (BA 46; Talairach x, y, z for the peak voxel = 52, 40, 26). (B) Percent signal change difference between variable and fixed FP paradigm in the peak voxel of the right middle frontal gyrus, plotted as a function of the current FP effect (left) and preceding FP effect (right) in the variable FP paradigm. Pearson coefficient was significant only for the correlation between the current FP effect and ($r = .53$, $p < .05$). FP = foreperiod.

t test (AFNI program 3dttest), using the beta values extracted from the variable versus fixed FP contrast as the dependent variable (see Table 1, bottom). This analysis revealed that the group performing the FP task before the Stroop-like task had a higher activation than the group performing the tasks in the reverse order in the right middle frontal gyrus and the left cuneus, which are approximately the same areas that showed a positive correlation with the variable FP effect.

DISCUSSION

Time is an important determinant of behavior even when people are not directly required to attend to it. The present experiment evaluated the neural substrate underlying the use of temporal information during a choice RT task, when the temporal interval (i.e., the FP) either varied randomly or was kept fixed within a block. Behaviorally, participants showed opposite effects of the FP length according to the paradigm type. Specifically, there was an RT benefit for long as compared to short FPs in the case of the variable FP paradigm (variable FP effect), and an RT benefit for short as compared to long FPs in the case of the fixed FP paradigm (fixed FP effect), confirming extensive previous literature (e.g., Stuss et al., 2005; Simon & Slaviero, 1975; Elliott, 1970; Requin & Granjon, 1969; see Niemi & Näätänen, 1981, for a review). This suggests that, in the variable FP paradigm, participants used the probabilistic information conveyed by the passage of time to predict the likelihood of stimulus presentation and increase the preparation level at long FPs (e.g., Näätänen, 1970; Baumeister & Joubert, 1969; Elithorn & Lawrence, 1955). In the fixed FP paradigm, instead, it is possible that automatic preparation engaging the motor circuitry underlies the relatively fast responses in the short FP condition (cf., Lewis & Miall, 2003). By contrast, increasing time uncertainty as the FP gets longer (e.g., Gottsdanker, 1970), not compensated by a monitoring process unlike in the variable FP task, would explain the RT costs observed for long fixed FPs. Thus, the divergence in the RT results between the two FP paradigms legitimizes our choice of the fixed FP conditions as a ''cognitive'' baseline for the variable FP paradigm.

As reviewed in the Introduction, previous neuropsychological studies (Vallesi, Mussoni, et al., 2007; Stuss et al., 2005) suggested a role of the right DLPFC in modulating preparation as a function of elapsing time in the variable FP paradigm, as measured through the FP effect. This finding was confirmed here by multiple complementary results. First, the right DLPFC was more activated when the FP was variable than when it was constant. Second, this activation positively correlates with the magnitude of the variable FP effect. We also controlled for a possible role of more automatic processes, as measured through the sequential FP effects that occur during the variable FP effect (e.g., Vallesi & Shallice,

2007; Los & van den Heuvel, 2001). However, none of the areas activated in the variable versus fixed FP contrast correlated with the sequential effects. These results confirm those of another recent study (Vallesi, Shallice, et al., 2007), which showed a selective reduction in the current FP effect when the right DLPFC was temporarily inhibited by TMS. That result was not only location-specific, because analogous TMS on the contralateral site and on the right angular gyrus did not affect the magnitude of the current FP effect, but also effect-specific, because sequential effects did not change after TMS.

Together, these data suggest a neural dissociation between the two effects. It is possible to speculate that the cognitive processes and neural mechanisms responsible for the sequential effects might be common to the variable and fixed FP tasks. That could be a reason why no areas correlated with the sequential effects in the contrast between variable and fixed FP paradigms. Areas involved in sequential effects, indeed, might have been cancelled out in this contrast. Future research should assess this hypothesis. Importantly, the dissociation found here is compatible with the hypothesis that different neural mechanisms underlie the two effects (Vallesi, Mussoni, et al., 2007; Vallesi & Shallice, 2007; Vallesi, Shallice, et al., 2007).

Finally, activation of the right DLPFC and of a visual area was higher in a subgroup of participants that performed the FP task before a Stroop-like task in the scanner than in another subgroup that performed the two tasks in the reverse order. Importantly, only the former subgroup showed a reliable variable FP effect. Once more this pattern, especially when considered together with the positive correlation between the FP effect and activation of the right DLPFC, supports the role of this region in generating this RT effect. These task-order effects in both behavioral and fMRI measures were not expected a priori and their meaning is somewhat puzzling. The higher activation of the right DLPFC in the group showing the variable FP effect than in the group that lacked this effect cannot be accounted for by the time within the scanner per se because usually the task-independent effect of time inside the scanner shows an increase of activation in the right DLPFC instead (e.g., Rajah, Hussey, Houle, Kapur, & McIntosh, 1998), which is somewhat opposite to what is found here. This possibility is also minimized by the fact that the contrast between the first and the last two runs of the variable FP effect did not yield differential activation in this area. General arousal or tiredness cannot account for the differences between the two groups because their absolute RTs were comparable. More basic regulation of preparation level was also comparable between the two groups, as suggested by similar sequential FP effects, in the variable paradigm, and a similar fixed FP effect, in the fixed paradigm. A possibility is that the group performing the Stroop-like task first developed a strategy of preparing for that demanding task at the beginning of each trial and maintaining that high level of preparation continually during the trial. They then maintained that high preparation level when they move to the FP task without further increasing it as time elapses during long FPs. At present, this can, at most, be a plausible hypothesis. Nevertheless, whatever the reason for these task-order effects is, they further suggest that the right DLPFC is responsible of the variable FP effect because this area is more activated in the subgroup that showed the variable FP effect at the behavioral level than in the group that did not.

Following classical explanations of the variable FP effect (e.g., Näätänen, 1970; Elithorn & Lawrence, 1955), this set of results is interpreted here as a confirmation of the monitoring role of this area, which checks the nonoccurrence of a stimulus for short FPs, and its increasing conditional probability of occurrence with long FPs (Stuss et al., 2005). The function of the right DLPFC in the variable FP paradigm may also be related to, and perhaps overlapping with, its role in estimating temporal intervals, especially in the suprasecond range, as shown by imaging (e.g., Lewis & Miall, 2003; see also Coull, Frith, Buchel, & Nobre, 2000) and TMS results (Koch et al., 2007; Koch, Oliveri, Torriero, & Caltagirone, 2003). However, general and more basic processes such as temporal perception or estimation of suprasecond intervals cannot entirely explain the fMRI effects found here because these would apply just as much in the fixed as the variable FP conditions.

In order to avoid the risk of overspecification of function, however, the monitoring explanation proposed here has to be broadened to comprehend a role of this area in monitoring overall (e.g., Fleck, Daselaar, Dobbins, & Cabeza, 2006). A general monitoring role fits well with a number of other studies showing an involvement of the right DLPFC in domains different from temporal preparation. For instance, patients with lesions in the right lateral prefrontal cortex show a monitoring deficit in episodic memory retrieval (Schacter, Curran, Galluccio, Milberg, & Bates, 1996; Stuss et al., 1994), feature integration (Stuss, Binns, Murphy, & Alexander, 2002), cognitive estimation (Smith & Milner, 1984), and problem solving (Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005). Monitoring accounts have also been proposed to explain activation of this region in several imaging studies using different tasks, such as episodic memory retrieval (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Rugg et al., 1998; see Vallesi & Shallice, 2006, for ERP evidence), visual perception (Fleck et al., 2006), working memory (Cabeza, Dolcos, Graham, & Nyberg, 2002; D'Esposito et al., 1998), and decision making (Yarkoni, Braver, Gray, & Green, 2005). However, the present experiment was not designed to check the generality of the monitoring account. Future studies should address this issue more directly by using, in the same fMRI session, tasks involving the same monitoring process in different domains, and investigating whether activations in the right DLPFC overlap or dissociate according to the task domain

(see Fleck et al., 2006; Cabeza et al., 2002 for a similar approach).

Involvement of the DLPFC was bilateral in the current experiment, as activation in the left middle frontal gyrus was also found in the variable versus fixed FP contrast. Because this area did not correlate with the FP effect here, its role in this context could be complementary, but not the same as that played by its right homologous area. In the light of previous literature (Shallice, Stuss, Picton, Alexander, & Gillingham, 2008; Alexander et al., 2007; Aron, Monsell, Sahakian, & Robbins, 2004; Brass & von Cramon, 2004; Derfuss, Brass, & Von Cramon, 2004; Stuss et al., 2002), it is possible to infer that the left DLPFC may be responsible for setting task-relevant mechanisms, especially when the onset of the task-relevant stimulus is unpredictable and task-relevant processes need to be continuously re-established with the changing conditional probability of stimulus occurrence.

Other prefrontal areas showing differential activation in the variable versus fixed FP contrast were the ACC and the superior medial frontal cortex. Activation of the superior medial frontal cortex increases with uncertainty, independently of the (internal or external) source of uncertainty (Volz, Schubotz, & von Cramon, 2005). In the current study, uncertainty concerns timing of stimulus onset and involvement of these regions may support preparation in this condition. A function attributed to superior medial frontal regions is *energization* (Stuss et al., 2005; see also Paus, 2001), defined as the process of sustaining task-relevant processes. Patients with damage in this region show slower responses than controls in a variety of RT tasks (Alexander, Stuss, Shallice, Picton, & Gillingham, 2005; Stuss et al., 1998, 2002, 2005), and systematic correlation between speed and activation in the ACC has been found with PET (Naito et al., 2000) and fMRI (Fleck et al., 2006).

A role of the ACC in energization is further corroborated here by the results of the contrast between the first and the last two runs of the variable FP paradigm, which showed that, despite no behavioral difference in terms of RTs, this region is more activated in the last two runs, probably to contrast fatigue with energization of the task-relevant processes in order to maintain an optimal level of performance. The latter finding has some potential implications for other current theories of the ACC function, such as conflict monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001), outcome evaluation (Gehring & Willoughby, 2002), or their integration in the recently proposed avoidance learning account (Botvinick, 2007). In the contrast between the first and last two runs of the variable FP paradigm, there is no conflict to monitor, feedback to evaluate, or conditions to avoid. What remains is a simple need to continue optimal preparation despite the fatigue possibly derived by performing the same task for a relatively long period of time. It is possible that all the theories concerning ACC function may be integrated under the umbrella of the energization account (Paus, 2001; Stuss, Shallice, Alexander, & Picton, 1995). On this account, the ACC could be involved in any condition in which energization is required. Even in its initial formulation, the conflict monitoring theory also conceded that the ACC may respond to a variety of events, all signaling that attentional adjustments are needed to optimize performance (Botvinick et al., 2001). These adjustments may concern a reactivation of the relevant processes. Future research should address this hypothesis more directly.

No area showed more activation during the fixed FP paradigm than during the variable paradigm (see Van Oostende, Van Hecke, Sunaert, Nuttin, & Marchal, 1997, for analogous findings). A possible explanation for this asymmetrical involvement of brain regions could be that, in this contrast, we used a double number of runs for the variable than for the fixed FP conditions, therefore yielding a lack of power for the latter. We controlled for this possibility by analyzing fMRI data including only the first two runs of the variable FP paradigm, in order to have a balanced number of runs per condition (i.e., fixed and variable FP). Results concerning an involvement of the right DLPFC did not change from those of the analysis with all four runs included and, critically, no area showed greater activation for the fixed than for the variable FP paradigm even in that analysis. Therefore, it is possible to suppose that the advance information provided by the warning stimulus does not involve, when the FP is kept constant, any extra brain area not already required to perform the variable FP task.

Other areas outside the frontal lobes showed differential activation in the variable versus fixed FP contrast, which may be related to the need to optimize, perhaps through top–down influences, task-relevant processes during strategic preparation. Activation in the visual cortex and its correlation with the variable FP effect suggests top–down modulation of perceptual processes required to perform the visual discrimination task. Visual stimuli that are attended in time have been shown to evoke an enhanced P1, an early visual evoked potential, when visual discrimination is required (Correa, Lupianez, Madrid, & Tudela, 2006). Activation in the fusiform gyrus could also be related to top–down optimization of the process of shape discrimination required here (e.g., Haxby et al., 1991). Hippocampal involvement may be interpreted on the light of the role of this structure in rule retrieval (Dolan & Fletcher, 1999). The role of the posterior cingulate may be related to anticipatory allocation of attention, as it has already been shown in the spatial attention domain (Small et al., 2003).

In conclusion, the present findings confirm that the right DLPFC plays an important role in modulating preparation during irregular timing, and extend previous literature by showing that other brain regions, ranging from primary sensory areas to other higher-level prefrontal regions, may also be involved in the task. Future research should further investigate issues left open by

the present study, such as the neural bases of the probably less strategic, but not less important, processes underlying the sequential effects and the fixed FP effect.

Acknowledgments

This research was supported by postdoctoral fellowship funding from Heart and Stroke Foundation Centre for Stroke Recovery and Canadian Institute of Health Research (CIHR, MFE-87658) to A. V., by CIHR grants to D. T. S. (MT-12853, GR-14974), and by grants from the J.S. McDonnell foundation to A. R. M. (220020082) and D. T. S. (21002032).

Reprint requests should be sent to Antonino Vallesi, Rotman Research Institute at Baycrest, 3560 Bathurst St., Toronto, ON, Canada, M6A 2E1, or via e-mail: avallesi@rotman-baycrest.on.ca or antoniovallesi@yahoo.it.

REFERENCES

Alegria, J. (1975). Sequential effects of foreperiod duration as a function of the frequency of foreperiod repetitions. *Journal of Motor Behaviour, 7,* 243–250.

Alexander, M. P., Stuss, D. T., Picton, T., Shallice, T., & Gillingham, S. (2007). Regional frontal injuries cause distinct impairments in cognitive control. *Neurology, 68,* 1515–1523.

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.

Aron, A. R., Monsell, S., Sahakian, B. J., & Robbins, T. W. (2004). A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain, 127,* 1561–1573.

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.

Botvinick, M. M. (2007). Conflict monitoring and decision making: Reconciling two perspectives on anterior cingulate function. *Cognitive, Affective & Behavioral Neuroscience, 7,* 356–366.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108,* 624–652.

Brass, M., & von Cramon, D. Y. (2004). Selection for cognitive control: A functional magnetic resonance imaging study on the selection of task-relevant information. *Journal of Neuroscience, 24,* 8847–8852.

Brunia, C. H., & van Boxtel, G. J. (2001). Wait and see. *International Journal of Psychophysiology, 43,* 59–75.

Cabeza, R., Dolcos, F., Graham, R., & Nyberg, L. (2002). Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage, 16,* 317–330.

Correa, A., Lupianez, J., Madrid, E., & Tudela, P. (2006). Temporal attention enhances early visual processing: A review and new evidence from event-related potentials. *Brain Research, 1076,* 116–128.

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.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers in Biomedical Research, 29,* 162–173.

Derfuss, J., Brass, M., & Von Cramon, D. Y. (2004). Cognitive control in the posterior frontolateral cortex: Evidence from common activations in task coordination, interference control, and working memory. *Neuroimage, 23,* 604–612.

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 Research, Cognitive Brain Research, 7,* 1–13.

Dolan, R. J., & Fletcher, P. F. (1999). Encoding and retrieval in human medial temporal lobes: An empirical investigation using functional magnetic resonance imaging (fMRI). *Hippocampus, 9,* 25–34.

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. *Journal of Experimental Child Psychology, 9,* 86–107.

Fleck, M. S., Daselaar, S. M., Dobbins, I. G., & Cabeza, R. (2006). Role of prefrontal and anterior cingulate regions in decision-making processes shared by memory and nonmemory tasks. *Cerebral Cortex, 16,* 1623–1630.

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,* 1249–1256.

Gehring, W. J., & Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science, 295,* 2279–2282.

Gibbon, J., Church, R. M., & Meck, W. H. (1984). Scalar timing in memory. *Annals of the New York Academy of Sciences, 423,* 52–77.

Gottsdanker, R. (1970). Uncertainty, time keeping and simple reaction time. *Journal of Motor Behavior, 2,* 245–260.

Haxby, J. V., Grady, C. L., Horwitz, B., Ungerleider, L. G., Mishkin, M., Carson, R. E., et al. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proceedings of the National Academy of Sciences, U.S.A., 88,* 1621–1625.

Karlin, L. (1959). Reaction time as a function of foreperiod duration and variability. *Journal of Experimental Psychology, 58,* 185–191.

Klemmer, E. T. (1957). Simple reaction time as a function of time uncertainty. *Journal of Experimental Psychology, 54,* 195–200.

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

Koch, G., Oliveri, M., Torriero, S., Salerno, S., Lo, G. E., & Caltagirone, C. (2007). Repetitive TMS of cerebellum interferes with millisecond time processing. *Experimental Brain Research, 179,* 291–299.

Lewis, P. A., & Miall, R. C. (2003). Brain activation patterns during measurement of sub- and supra-second intervals. *Neuropsychologia, 41,* 1583–1592.

Los, S. A., & van den Heuvel, C. E. (2001). Intentional and unintentional contributions to nonspecific preparation during reaction time foreperiods. *Journal of Experimental Psychology: Human Perception and Performance, 27,* 370–386.

Madison, G. (2001). Variability in isochronous tapping: Higher order dependencies as a function of intertap

interval. *Journal of Experimental Psychology: Human Perception and Performance, 27,* 411–422.
Mattes, S., & Ulrich, R. (1997). Response force is sensitive to the temporal uncertainty of response stimuli. *Perception & Psychophysics, 59,* 1089–1097.
Michon, J. A., & van der Valk, N. J. (1967). A dynamic model of timing behavior. *Acta Psychologica (Amsterdam), 27,* 204–212.
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.
Naito, E., Kinomura, S., Geyer, S., Kawashima, R., Roland, P. E., & Zilles, K. (2000). Fast reaction to different sensory modalities activates common fields in the motor areas, but the anterior cingulate cortex is involved in the speed of reaction. *Journal of Neurophysiology, 83,* 1701–1709.
Nickerson, R. S. (1967). Expectancy, waiting time and the psychological refractory period. *Acta Psychologica (Amsterdam), 27,* 23–34.
Niemi, P., & Näätänen, R. (1981). Foreperiod and simple reaction time. *Psychological Bulletin, 89,* 133–162.
Nobre, A., Correa, A., & Coull, J. (2007). The hazards of time. *Current Opinion in Neurobiology, 17,* 465–470.
Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9,* 97–113.
Paus, T. (2001). Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nature Reviews Neuroscience, 2,* 417–424.
Rajah, M., Hussey, D., Houle, S., Kapur, S., & McIntosh, A. R. (1998). Task-independent effect of time on rCBF. *Neuroimage, 7,* 314–325.
Requin, J., & Granjon, M. (1969). The effect of conditional probability of the response signal on the simple reaction time. *Acta Psychologica (Amsterdam), 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.
Rugg, M. D., Fletcher, P. C., Allan, K., Frith, C. D., Frackowiak, R. S., & Dolan, R. J. (1998). Neural correlates of memory retrieval during recognition memory and cued recall. *Neuroimage, 8,* 262–273.
Sanders, A. F. (1966). Expectancy: Application and measurement. *Acta Psychologica (Amsterdam), 25,* 293–313.
Schacter, D. L., Curran, T., Galluccio, L., Milberg, W. P., & Bates, J. F. (1996). False recognition and the right frontal lobe: A case study. *Neuropsychologia, 34,* 793–808.
Shallice, T., Stuss, D. T., Picton, T. W., Alexander, M. F., & Gillingham, S. (2008). Multiple effects of prefrontal lesions on task-switching. *Frontiers in Human Neuroscience, 1,* 1–12.
Simon, R. J., & Slaviero, D. P. (1975). Differential effects of a foreperiod countdown procedure on simple and choice reaction time. *Journal of Motor Behavior, 7,* 9–14.
Small, D. M., Gitelman, D. R., Gregory, M. D., Nobre, A. C., Parrish, T. B., & Mesulam, M. M. (2003). The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. *Neuroimage, 18,* 633–641.
Smith, M. L., & Milner, B. (1984). Differential effects of frontal-lobe lesions on cognitive estimation and spatial memory. *Neuropsychologia, 22,* 697–705.
Stilitz, I. (1972). Conditional probability and components of RT in the variable foreperiod experiment. *Quarterly Journal of Experimental Psychology, 24,* 159–168.
Stuss, D. T., Alexander, M. P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., et al. (1998). The effects of focal anterior and posterior brain lesions on verbal fluency. *Journal of the International Neuropsychological Society, 4,* 265–278.
Stuss, D. T., Alexander, M. P., Palumbo, C. L., Buckle, L., Sayer, L., & Pogue, J. (1994). Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list 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., 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., Shallice, T., Alexander, M. P., & Picton, T. W. (1995). A multidisciplinary approach to anterior attentional functions. *Annals of the New York Academy of Sciences, 769,* 191–211.
Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain: 3-Dimensional proportional system: An approach to cerebral imaging*. New York: Thieme Medical Publishers.
Teichner, W. H. (1954). Recent studies of simple reaction time. *Psychological Bulletin, 51,* 128–149.
Thomas, E. A. (1967). Reaction-time studies: The anticipation and interaction of responses. *British Journal of Mathematical & Statistical Psychology, 20,* 1–29.
Vallesi, A., McIntosh, A. R., Alexander, M., & Stuss, D. T. (submitted). A neural network responsible for setting the criteria for not to respond: Evidence from functional connectivity analysis.
Vallesi, A., Mussoni, A., Mondani, M., Budai, R., Skrap, M., & Shallice, T. (2007). The neural basis of temporal preparation: Insights from brain tumor patients. *Neuropsychologia, 45,* 2755–2763.
Vallesi, A., & Shallice, T. (2006). Prefrontal involvement in source memory: An electrophysiological investigation of accounts concerning confidence and accuracy. *Brain Research, 1124,* 111–125.
Vallesi, A., & Shallice, T. (2007). Developmental dissociations of preparation over time: Deconstructing the variable foreperiod phenomena. *Journal of Experimental Psychology: Human Perception and Performance, 33,* 1377–1388.
Vallesi, A., Shallice, T., & Walsh, V. (2007). Role of the prefrontal cortex in the foreperiod effect: TMS evidence for dual mechanisms in temporal preparation. *Cerebral Cortex, 17,* 466–474.
Van Oostende, S., Van Hecke, P., Sunaert, S., Nuttin, B., & Marchal, G. (1997). FMRI studies of the supplementary motor area and the premotor cortex. *Neuroimage, 6,* 181–190.
Volz, K. G., Schubotz, R. I., & von Cramon, D. Y. (2005). Variants of uncertainty in decision-making and their neural correlates. *Brain Research Bulletin, 67,* 403–412.
Woodrow, H. (1914). The measurement of attention. *Psychological Monographs, 5,* 1–158.
Yarkoni, T., Braver, T. S., Gray, J. R., & Green, L. (2005). Prefrontal brain activity predicts temporally extended decision-making behavior. *Journal for the Experimental Analysis of Behavior, 84,* 537–554.