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TEMPORAL PREPARATION IN AGING: A FUNCTIONAL MRI STUDY

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Abstract

Young and elderly adults performed a choice-RT task while scanned with functional Magnetic Resonance Imaging. A foreperiod separated a warning and a response signal. In the variable condition, the foreperiod varied randomly between 1 and 3 sec. In the fixed conditions, it was kept constant at either 1 or 3 sec. Elderly subjects responded slower than controls in both task conditions. An interaction was observed between age and foreperiod in the variable condition only: in the young group, RT decreased with longer foreperiods, whereas the elderly participants showed the opposite tendency. This was accompanied by difference in brain activation. Right lateral prefrontal regions were more activated in the young than in the elderly group in the variable vs. fixed foreperiod contrast. These findings unveil the neural substrate of age-related preparation deficits, and confirm that the involvement of right lateral prefrontal cortex is essential for strategic preparation under uncertain timing conditions.

Keywords: Foreperiod Effect; Healthy Aging; Motor Preparation; Preparatory Interval; S1-S2 paradigm; Time Processing.

Age-related slowing is commonly observed on speeded tasks (Salthouse, 1996). A decline in the processes involved in response preparation may partially explain this slowing (Kolev, Falkenstein & Yordanova, 2006). However, preparation is a complex cognitive ability that involves many sub-processes supporting the development of an optimal processing state preceding a response. Therefore, the functional locus of age-related slowing may include several cognitive stages preceding motor execution (Sterr & Dean, 2008). We focus here on the processes involved in temporal preparation.

Temporal preparation has been investigated using response time (RT) tasks in which the preparatory interval (foreperiod, FP) between a warning and a response signal is manipulated (Woodrow, 1914). When the FP is constant in each block, responses are usually faster for relatively short FPs than for longer ones (fixed FP effect). This effect is at least partially due to more efficient preparation mechanisms in the motor system for short vs. long time-ranges (Tandonnet, Burle, Vidal, & Hasbroucq, 2003) and to more efficient timing processes for relatively short time intervals (Gibbon, 1977).

However, behavioural effects change radically if the FP varies on a trial-by-trial basis rather than between blocks. In a typical variable FP task, a range of different FPs randomly occurs across trials with the same a priori probability. Responses are usually faster for long FPs than for short ones (variable FP effect). In the variable FP task, the elapsing time contains information about the next response signal onset, since its probability of occurrence increases during the FP, provided that no catch trials are used. A process monitoring this changing conditional probability has been proposed to increase response preparation with relatively longer FPs (see Niemi & Näätänen, 1981, for a review). In the context of explicit temporal cueing studies, Coull and Nobre (1998; see

also Nobre, 2001) provide a clear definition of a similar endogenous process, which is described as the ability to use any information about time intervals to orient attention to a point in time at which a relevant event is expected.

An additional phenomenon observed in variable FP tasks are the sequential effects: RTs are longer after longer previous FPs (e.g., Karlin, 1959). These effects suggest that the preparation level becomes refractory after a relatively long preceding FP, probably due to the fact that keeping preparation for a long FP is a resource-consuming process, and requires time to recover (Vallesi & Shallice, 2007b). Alternatively, sequential effects have been attributed to the conditioning mechanism of extinction, which is induced by the necessity to keep the response system in check in order to prevent an anticipated response during long FPs (Los & van den Heuvel, 2001). Both these views agree on the fact that sequential effects are neither intentional nor strategic in nature. They are indeed resistant to intentional preparation, such as with a temporal cue signalling when the next stimulus will occur (Los & van den Heuvel, 2001). Moreover, they appear at an earlier developmental stage than the variable FP effect (Vallesi & Shallice, 2007b), suggesting a higher degree of automaticity.

Patients with lesions to right prefrontal cortex (both ventro- and dorso-lateral) do not show the standard variable FP effect, despite a normal fixed FP effect (Stuss et al., 2005; Stuss & Alexander, 2007). On the other hand, this region is not critical for the sequential effects, as revealed by neuropsychological (Vallesi et al., 2007a) and TMS (Vallesi, Shallice, & Walsh, 2007c) evidence. Moreover, a recent fMRI study (Vallesi, McIntosh, Shallice, & Stuss, 2009) showed that not only is right dorsolateral prefrontal cortex (DLPFC) involved in the variable FP task, but its activation also correlates with the

magnitude of the variable FP effect, while such a correlation is not present for the sequential effects. Other neuroimaging and TMS studies have documented that right lateral prefrontal cortex plays a more general role in time processing (e.g., Koch, Oliveri, Torriero, & Caltagirone, 2003; Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Lewis & Miall, 2003) and in attention to time (e.g., Coull, Frith, Buchel, & Nobre, 2000; Coull, 2004), although also left prefrontal areas are involved when attention is explicitly directed to time (Coull & Nobre, 1998; Nobre 2001).

Cognitive impairment with aging often resembles, although to a smaller degree, that observed in patients with frontal lobe lesions (Braver et al., 2001; Craik, Morris, Morris, & Loewen, 1990; Moscovitch & Winocur, 1995; Stuss, Craik, Sayer, Franchi, & Alexander, 1996; West, 1996). Neuroanatomical studies show degeneration in frontal grey and white matter with aging (Buckner, 2004; Coffey et al., 1992; Good et al., 2001; Raz, 2000; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003), although also changes in other brain regions have often been associated with aging (e.g., Jack et al., 1998; Tisserand & Jolles, 2003). These structural changes can be associated with lower performance in older adults (e.g., Colcombe, Kramer, Erickson, & Scalf, 2005; Persson, Lustig, Nelson & Reuter-Lorenz, 2007).

Functional neuroimaging studies show a more mixed pattern of results (see Rajah & D'Esposito, 2005; Grady, 2008, for reviews), with some studies reporting an under-recruitment of frontal regions with aging (e.g., Rypma & D'Esposito, 2000), an over-recruitment of these regions (Morcom, Li, Rugg, 2007; Persson, Sylvester, et al., 2004), or a combination of the two patterns (Logan, Sanders, Snyder, Morris, Buckner, 2002). These age-related functional modifications are likely to be associated to the structural

changes in the brain (e.g., Nordahl, Ranganath, Yonelinas et al., 2006; see Greenwood, 2007, for a discussion).

Given that an age-related decline in frontal functioning has been reported in other domains, and more specifically also in the time domain with more explicit time reproduction tasks (Wild-Wall, Willemssen, Falkenstein, & Beste, 2008), elderly adults are likely to have difficulties also in strategic temporal preparation, as measured with the variable FP effect, which can be considered a marker of right lateral frontal integrity (Stuss et al., 2005; Vallesi et al., 2007a,c).

This prediction has already been tested behaviorally in the literature. In an early study investigating changes in the variable FP effect with aging (Strauss, Wagman, & Quaid, 1983), old adults had difficulties in maintaining preparation for long FPs in the variable paradigm, though a considerably long FP range was used (7-13 sec) and there was no control group. These results were corroborated by a more recent study (Jurkowski, Stepp, & Hackley 2005). Using a shorter FP range (1-6.5 sec), this study showed a reduced variable FP effect in elderly adults with respect to young controls, although this reduction was less dramatic than in patients with Parkinson disease.

In another study using two different FP ranges (1-5 and 5-7 sec) with variable FP paradigms, Bherer and Belleville (2004) found somewhat opposite effects, since elderly adults showed an exaggerated variable FP effect with respect to young controls. Specifically, older adults showed longer RTs for the shortest FP when its a priori probability of occurrence was low (33%), while increasing this probability removed the RT cost for the short FPs but still did not reverse the effect as in Strauss et al. (1983). Bherer and Belleville (2004) adopted a dual task-like procedure in which participants had

to lift their finger from a button (initiation time, which was what showed the reported effect) and then move it to press another button. Dual-task interference increases with aging, especially with increasing motor demands (Riby, Perfect, & Stollery, 2004). Elderly subjects in Bherer and Belleville's study (2004) may have suffered from this interference, particularly with relatively short FPs that had a low probability of occurrence. To avoid dual-task type of interference, we adopted a simpler procedure with a single button-press. Moreover, we used 2 FPs only, to increase the probability of stimulus occurrence for the shortest FP. This manipulation seems critical to prevent spurious age-differences, since elderly adults tend not to prepare in advance a response for a low probability short FP (Bherer & Belleville, 2004; but see Jurkowski et al., 2005).

We predicted that elderly participants will have a similar fixed FP effect as young ones, since more basic motor mechanisms are expected to be involved with fixed FP presentations (Tandonnet et al., 2003). Based on the hypothesis that prefrontal function declines with aging (West, 1996) we expected, at the neural level, age-related changes in the engagement of right prefrontal regions used by young adults to monitor elapsing time in the variable FP task (Vallesi et al., 2009), accompanied by a reduction of the variable FP effect at the behavioural level. The latter prediction is partially supported by the limited literature reviewed above (e.g., Jurkowski et al., 2005; Strauss et al., 1983; but see Bherer & Belleville, 2004). To assess these predictions, young and elderly healthy individuals were tested using a task with a 2 FP (1 vs. 3 sec) by 2 paradigm (fixed vs. variable) factorial design, while their brain activity was measured with functional MRI. A blocked fMRI design was adopted to study the sustained brain activity underlying temporal preparation under the fixed and variable FP paradigms.

Method

Participants

Fourteen young [8 females; mean age: 27 years (20-34)] and 14 elderly [9 females; mean age: 70 years (60-80)] volunteers participated to the study. All participants were right-handed, with normal or corrected-to-normal vision and no history of psychiatric/neurological disorders. No older participant had dementia (Mini Mental State Examination score range: 28-30/30; Folstein, Folstein, & McHugh, 1975). Participants signed an informed consent form and received 50 dollars for participating. The study was previously approved by the local ethical committee. The young subjects' data have been reported elsewhere (Vallesi et al., 2009).

Experimental material and design

A warning stimulus (WS, an asterisk lasting 200 ms) appeared before the response signal (RS) onset. The RS was a square or a triangle (height: 4 cm) lasting 300 ms. In the fixed FP conditions, the FP between the WS and the RS onset lasted either 1 or 3 sec, for the short and long fixed FP runs, respectively. In the variable condition (4 consecutive runs), the FP varied trial-by-trial between 1 and 3 sec, with each combination of 2 current (1, 3 sec) by 2 preceding (1, 3 sec) FPs occurring pseudo-randomly and equiprobably. There were 40 trials in each run. The response deadline was 2 sec post-RS onset, after which the inter-trial interval was jittered between 0.5 and 2.5 sec. The task was to get prepared when the WS appeared and to respond with either the right index or middle finger according to the RS shape (shape-response correspondence and order of the 3 FP

conditions counterbalanced across participants). Participants received instructions before each run about which kind of FP paradigm was going to be administered (i.e., short fixed, long fixed, or variable).

Image acquisition and data analysis

MRI data were collected on a 3T Siemens Trio scanner. T1-weighted anatomical MP-RAGE sequences (echo time, TE: 2.63 s; repetition time, TR: 2 s; 160 oblique axial slices, with a 1 mm^3 voxel size; field of view, FOV: 25.6 cm; acquisition matrix, AM: 256x256) were acquired either before or after the functional images (order counterbalanced). Functional data were acquired using a whole head T2*-weighted echo-planar image (EPI) sequence (TE: 30 ms; TR: 2 s; flip angle: 70º; 28 oblique axial slices with interleaved acquisition, 3x3x5 mm voxel resolution; FOV: 20 cm; AM: 64x64). The first 10 scans were discarded to allow the magnetization to reach steady state. Physiological data (pulse and respiration rate) were also acquired. Stimuli were projected on a mirror above the coil. A response pad was used to collect responses.

The fMRI data were processed using Analysis of Functional NeuroImages software (AFNI; Cox, 1996). EPI time-series were corrected for cardiac and respiratory parameters. Six-parameter rigid body inter- and intra-run motion correction was performed by co-registering volumes in the EPI scans to a reference EPI volume. Time series in each run were normalized based on the mean intensity, concatenated and de-trended with a cubic polynomial.

A block-design approach was used to maximize power and estimate the sustained brain activity associated to each FP condition. The short and long fixed FP conditions

were collapsed and used as the high-level baseline condition. The rationale for this choice was that the critical process, namely monitoring of the changing conditional probability of stimulus occurrence at each given FP, cannot take place in these conditions since the FP is kept constant in a block. Single-subject analysis was performed by generating the hemodynamic response function model for each FP condition based on the convolution of a gamma function and the TRs with the WS onset. Brain activity maps were produced by fitting a general linear model to the measured fMRI time-series at each voxel (AFNI program 3dDeconvolve). The model contained 6 parameters, one for each run. The brain activity in the critical variable vs. fixed FP contrast was calculated using a paired t-test within the 3dDeconvolve program. The activation map for this contrast in each participant was spatially normalized to an average volume of 152 skull-stripped brains (www.bic.mni.mcgill.ca) matching a Talairach template (Talairach & Tournoux, 1988), re-sampled (4x4x4-mm voxel size) and spatially smoothed (8-mm FWHM).

A two-sample t-test was used for the whole-brain group analysis (AFNI program 3dttest) with age as the between-groups factor, and activation maps of the variable vs. fixed FP contrast as the dependent variable. A single-voxel $p < .001$ and a cluster-size $\geq$ 10 voxels were used for multiple comparison correction. This combination of p-value and cluster-size was obtained running a Monte Carlo simulation (program AlphaSim with whole-brain mask).

Given the prior fMRI evidence of a right DLPFC activation (BA 46) for the variable vs. fixed FP contrast in the young group (Vallesi et al., 2009; see also Vallesi et al., 2007c), a region of interest (ROI) analysis on this area (Talairach coordinates of the peak voxel: x = 52, y = 40, z = 26) was also carried out. The mean intensity of the voxels

belonging to this cluster was extracted for each subject (in Talairach space) and a two-sample t-test was run on these values with age as the between-groups factor.

Finally, to check which areas correlated with the variable FP effect in the two age groups, Pearson correlation analyses were carried out between the critical brain activations and the variable FP effect (RT difference between the short and long FP), separately for the young and elderly subjects.

Results

Excluded trials. RTs from the first trial of each run (3%), RTs outside the 100-1500 ms range (2.2%), error trials (2.6%), and trials with responses preceding RS onset (0.18%) were not analyzed.

Response Times. Figure 1 shows RT data. RTs from the fixed and variable FP conditions were submitted to mixed ANOVAs with FP length (1, 3 sec) as the within-subject factor, and age (young, elderly) as the between-groups factor. In the fixed FP paradigm, elderly participants responded more slowly than young participants [age main effect, $F(1,26)=7.2$, $p < 05$]. Responses were slower for the long than for the short fixed FP [FP main effect, $F(1,26)=11.1$, $p < 01$]. This effect was significant in both groups, as demonstrated by two separate dependent samples t-tests with FP length (1, 3 sec) as the independent variable [$t(13)=2.79$, $p < .05$, and $t(13)=2.24$, $p < .05$ for the young and elderly groups, respectively]. The fixed FP x age interaction was not significant ($p = .58$).

Elderly participants were slower than young ones also in the variable FP paradigm [age main effect, $F(1,26)=4.3$, $p < 05$]. Moreover, the age by variable FP interaction was

significant in the variable FP paradigm [F(1,26)=9.7, $p < 01$]: while the young subjects showed the usual RT shortening from the short to the long current FP (FP effect: 25 ms), elderly participants showed the opposite pattern, since their RTs increased by 29 ms from the short to the long FP. To further assess the statistical significance of these effects, dependent sample t-tests were carried out separately for each group with FP length (1, 3 sec) as the independent variable. The standard variable FP effect (i.e., longer RTs for short vs. long FPs) was significant in the young subjects [t(13)=2.49, $p < .05$]. On the other hand, older adults showed a strong trend towards the opposite pattern, namely longer RTs for longer FPs [t(13)=2.07, $p = .059$].

To assess possible age differences in the sequential effects, another ANOVA was run introducing the FP on the preceding trial (1, 3 sec) as a within-subject factor, in addition to the current FP length and age. Besides age main effect and current FP by age interaction, this analysis yielded only a significant preceding FP main effect [F(1,26)=6.7, $p < 05$], showing that RTs were longer after a long preceding FP, but no preceding FP by age interaction ($p = .24$).

---*Figure 1 here*---

fMRI Data.

Only one cluster located in the ventro-lateral prefrontal cortex (VLPFC, BA 47) survived correction for multiple comparisons in the t-test comparing young vs. elderly subjects in the variable vs. fixed FP contrast (Figure 2a). The ROI analysis using the activation of the right DLPFC in the young subjects (Vallesi et al., 2009) was significant

[t(26)=1.84, $p < .05$], indicating that young subjects activated this region more than elderly in the variable vs. fixed FP contrast (Figure 2b).

Activation in right VLPFC, as obtained in the variable vs. fixed FP contrast, did not correlate significantly with the variable FP effect in either group (for both groups, $p > .1$). On the other hand, activation in the right DLPFC correlated positively with the variable FP effect in the young group ($r = .53$, $p < .05$), while this correlation was negative in older adults ($r = -.66$, $p < .05$).

---Figure 2 here---

Discussion

We tested the hypothesis that a possible source of impairment in motor preparation with aging is a problematic frontally-based process monitoring the conditional probability of RS occurrence in time. This process is more critical when the FP varies between trials rather than between blocks, since the conditional probability that a RS occurs at a given FP changes on a trial-by-trial basis only in the former case. As a result, if subjects monitor this changing conditional probability in a variable FP paradigm, and increase preparation accordingly, response speed increases with longer FPs (variable FP effect).

Behavioral results of the present study showed that the fixed FP effect (slower responses for longer FPs) and the automatic sequential effects in the variable FP task (slower responses for preceding long FPs) were comparable in the two age-groups tested. Importantly, a standard variable FP effect (faster responses for longer FPs) was only present in the young group, while the elderly showed an opposite pattern. These results

confirm and extend previous ones (Jurkowski et al., 2005; Strauss et al., 1983), although they seem in contrast with those reported in Bherer and Belleville (2004, experiment 1), which showed a larger variable FP effect in the elderly. Differences in the experimental design, such as a simpler response procedure adopted in the present study and the fact that the probability of stimulus occurrence on the short FP was higher here (50% vs. 33%; also see Bherer & Belleville, 2004, experiment 2), may explain the discrepancy between the two studies.

The whole-brain fMRI analysis showed that elderly individuals engage right VLPFC to a smaller extent than young adults when they perform the variable FP task. The involvement of right VLPFC in the variable FP task was not reported in the companion paper focusing on the young group only (Vallesi et al., 2009). In that dataset, this area was also activated in the young group, but fell below the threshold for multiple comparison correction by 2 voxels. A role of the right VLPFC in the variable FP effect was shown by Stuss and colleagues' hot-spot method of analysis of performance of patients with brain lesion (Stuss et al., 2005; Stuss & Alexander, 2007). It has been proposed that the VLPFC is a key area in the interaction between attention and time processing (Coull, 2004). This region is also part of a ventral fronto-parietal network involved in the selection of behaviourally relevant stimuli (Corbetta, Patel, & Shulman, 2008). While elderly seem to over-process task-irrelevant information (Vallesi, Stuss, McIntosh & Picton, 2009), they may have a selective deficit when attending to relevant information whose onset time is not predictable unless online time monitoring occurs, such as in the variable FP task. The under-engagement of right VLPFC in older adults is likely to be a neural correlate of this deficit.

The ROI analysis showed age differences also in the involvement of right DLPFC, with elderly under-recruiting this region with respect to young controls in the variable vs. fixed FP contrast. Since lower activation in right VLPFC and DLPFC accompanied a tendency towards an inverted variable FP effect, the present data overall confirm their role in temporal preparation. Previous studies mainly focused on DLPFC, showing that its damage yields to a significant reduction in the variable FP effect (Stuss et al., 2005; Vallesi et al., 2007a; see also Vallesi et al., 2007c for TMS evidence), although VLPFC was also damaged in some of the right lateral prefrontal patients tested in those studies.

However, the brain-behavior correlation analysis underscores the possibility that the functional meaning of brain activation may change with age. While the right VLPFC did not show a reliable pattern of correlation with the FP effect in either group, the right DLPFC activation correlates with the FP effect in opposite ways for the two age groups: this correlation is positive in the young group (see also Vallesi et al., 2009), while it becomes negative with aging. In other words, those elderly individuals who show the least FP effect activate this area most, a pattern that suggests that the use of the right DLPFC, which is typically involved in sustained activity underlying temporal preparation in normal adulthood, may become inefficient and even detrimental with aging.

In a recent behavioral study, elderly adults showed lower performance than young controls on a more explicit time reproduction task, similarly to patients with Parkinson and Huntington disease (Wild-Wall et al., 2008). The authors of that study hypothesized that these time processing deficits were due to a deterioration in the dopaminergic function of fronto-striatal circuits, conceivably common to the three categories of patients tested, although to a different degree. The current results provide partial support for this

hypothesis, since they show that at least some nodes of this circuit (i.e., in the right lateral prefrontal cortex) are under-recruited in elderly adults.

While the present study and others show under-recruitment of frontal regions with aging (e.g., Grady et al., 1995; Gutchess et al., 2007; Mitchell, Raye, Johnson & Greene, 2006; Rypma & D'Esposito, 2000), there is an extensive literature showing neural over-recruitment of these and other regions with aging (e.g., Cabeza, Anderson, Locantore, McIntosh, 2002; Nielson, Langenecker, & Garavan, 2002; Park & Reuter-Lorenz, 2009; Vallesi, McIntosh & Stuss, in preparation). The nature of age-related differences in brain activation is difficult to characterize, and it may change according to the task difficulty, the strategy used and the cognitive functions required in the task (Logan et al., 2002; see Grady, 2008 for a review).

Another important determinant of these neuro-functional differences is probably the kind of neural activity (sustained vs. transient) under investigation, with elderly adults engaging the right frontally-based circuit, also responsible for sustained attention, to a lesser extent than their young controls (e.g., Dennis, Daselaar, & Cabeza, 2007; but see Grady et al., 2008). The latter pattern may reflect a functional shift in older adults from a sustained/proactive cognitive control strategy to a transient/reactive one (Paxton, Barch, Racine, & Braver, 2008; also see Velanova, Lustig, Jacoby, & Buckner, 2007). Further mixed-design fMRI studies should focus on this possibility.

A possible limitation of this study is the fact that it cannot disentangle whether elderly adults engaged the right prefrontal regions more in the fixed FP task or less in the variable FP task with respect to young controls. The behavioral data seem to support the latter possibility, since elderly individuals showed a normal fixed FP effect and a trend

for an inverted variable FP effect. However, a study including a lower level baseline, to which one could compare each FP paradigm, would be more appropriate to assess these two alternatives.

The variable FP effect starts to emerge not earlier than at 5-6 years of age, when these regions are likely to undergo developmental maturation (Vallesi et al., 2007b). The present data complete this picture from a life-span perspective, by showing that temporal preparation during the variable FP paradigm is not as efficient in older adults as it is in young adults. Behavioral impairment under uncertain time conditions in aging may be due to deficits in functional activation of critical brain regions. FMRI allowed investigation of the role of right lateral prefrontal regions in temporal preparation, demonstrating that, at least when sustained block-related activity is measured, these regions are less activated in the elderly than in the young adults when response preparation and execution occur in a variable FP regime.

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Figure Captions

Figure 1. Mean response times (y-axis) as a function of age, foreperiod (FP) paradigm and FP length. Vertical bars: standard errors of the mean. For each group and FP paradigm, black asterisks above the histograms indicate significant differences between the short and long FPs (1 and 3 sec, respectively), as assessed with dependent samples t-tests ($p < .05$), while the grey asterisk indicates a trend towards significance ($p = .059$).

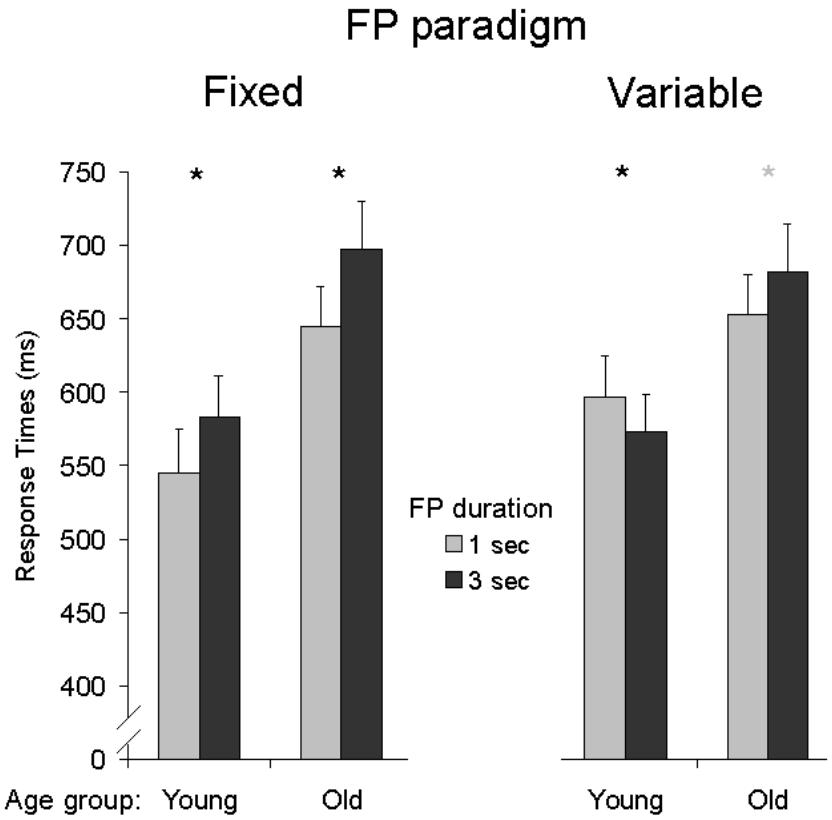

Figure 2. (a) Ventrolateral prefrontal area (Brodmann area 47; Talairach coordinates of the peak voxel: x = 32, y = 32, z = -10; cluster-size: 10 voxels; z-score: 4.06) more activated in the young subjects than in the elderly, in the variable vs. fixed FP contrast. (b) Right dorsolateral prefrontal ROI (Brodmann area 46; Talairach coordinates: x = 52, y = 40, z = 26; cluster-size: 22 voxels) used to test age differences in the engagement of this region for the variable vs. fixed FP contrast (coordinates from Vallesi et al., 2009).