How Cognitive Performance-Induced Stress Can Influence Right VLPFC Activation: An fMRI Study in Healthy Subjects and in Patients With Social Phobia

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Abstract: The neural bases of interactions between anxiety and cognitive control are not fully understood. We conducted an fMRI study in healthy participants and in patients with an anxiety disorder (social phobia) to determine the impact of stress on the brain network involved in cognitive control. Participants performed two working memory tasks that differed in their level of performance-induced stress. In both groups, the cognitive tasks activated a frontoparietal network, involved in working memory tasks. A supplementary activation was observed in the right ventrolateral prefrontal cortex (VLPFC) in patients during the more stressful cognitive task. Region of interest analyses showed that activation in the right VLPFC decreased in the more stressful condition as compared to the less stressful one in healthy subjects and remain at a similar level in the two cognitive tasks in patients. This pattern was specific to the right when compared to the left VLPFC activation. Anxiety was positively correlated with right VLPFC activation across groups. Finally, left dorsolateral prefrontal cortex (DLPFC) activation was higher in healthy subjects than in patients in the more stressful task. These findings demonstrate that in healthy subjects, stress induces an increased activation in left DLPFC, a critical region for cognitive control, and a decreased activation in the right VLPFC, an area associated with anxiety. In patients, the differential modulation between these dorsal and ventral PFC regions disappears. This absence of modulation may limit anxious patients' ability to adapt to demanding cognitive control tasks. *Hum Brain Mapp* 33:1973–1986, 2012. © 2011 Wiley Periodicals, Inc.

Key words: anxiety; cognitive control; emotion; functional imaging; prefrontal cortex; working memory

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INTRODUCTION

Mr. X, a 24-year-old university student, repeatedly fails oral and written exams, whereas, when at ease, he demonstrates an outstanding ability to synthesize acquired knowledge and clearly express complex ideas and concepts. His repeated failure is related to pathological anxiety, presumably leading to the temporary staggering or under-utilization of his intellectual abilities. This observation illustrates a negative and interfering effect of “test” anxiety on cognitive control.

Test or performance anxiety (i.e., anxiety associated with the performance of a given task, in general a cognitive task) is a subtype of pathological anxiety and can be considered as a form of social anxiety disorder [Bögels et al., 2010]. And indeed, fear of negative evaluation is the core of both social and test anxieties [Bögels et al., 2010]. In consequence, social anxiety disorder (or “social phobia”) is typically a pathological condition where anxiety may interfere with the performance of cognitive tasks. Yet, to our knowledge, there is no data showing how social phobia may influence brain networks during the performance of on-line demanding cognitive tasks.

Predictions regarding this pathological influence can, however, be proposed according to the available literature showing the impact of “anxiety” (regardless of its different subtypes) on cognition and on brain activation. First, several experimental studies have shown that anxiety and emotional stress are associated with poorer performance in tasks assessing working memory, executive functions and more generally, cognitive control [Bishop et al., 2004; Davidson et al., 2000; Drevets and Raichle, 1998; Eysenck et al., 2007; Grey et al., 2001]. A plausible general explanation for this negative interaction is the decreased allocation of attention resources toward the performance of cognitive control tasks, due to interferences produced by negative affects and thoughts (either by blocking one’s ability to recruit attention to perform a demanding cognitive task or by the biased orientation of attention resources toward ruminations). This particular orientation of attention toward these task-irrelevant stimuli may decrease the allocation of attention resources normally devoted to executive processes required to perform cognitive control [Ansary et al., 2008; Baddeley et al., 2010; Eysenck et al., 2007].

Second, as regard to the neural basis of the interaction between anxiety and cognitive control, on the one hand, cognitive control relies on a large network in which the dorsolateral prefrontal cortex (DLPFC) plays a major role [Fuster, 1997; Goldman-Rakic, 1996; Miller and Cohen, 2001]. On the other hand, functional imaging studies have shown that pathological anxiety is associated with an increase in the metabolism of the ventrolateral PFC (VLPFC), presumably related to the processing of negative and emotionally colored thoughts [Brody et al., 2001a,b; Drevets and Raichle, 1998; Keedwell et al., 2010; Liotti et al., 2002; Pardo et al., 1993; Rauch et al., 1997]. Moreover, a variety of functional imaging and lesion studies

suggests that the brain network associated with anxiety is asymmetrically organized. It has been shown that negative affects such as stress, fear, and worry are associated with right VLPFC activation [Davidson et al., 2000; Dalton et al., 2004] and compete for attention resources with the dorsolateral fronto-parietal network involved in cognitive processing such as verbal or spatial working memory [Gray et al., 2001, 2002; Shackman et al., 2006].

Accordingly, these data may suggest that healthy subjects, while carrying out tasks requiring cognitive control, are able to inhibit potential interference stemming from stress-induced negative emotions to focus on the ongoing task. In patients presenting with social phobia, the performance of a stressful and effortful cognitive task may be more affected by interfering negative emotions or thoughts. In terms of neural correlates, the above proposal implies that in healthy subjects’ priority is given to the brain regions required to accurately perform executive tasks and that interfering anxious signals are filtered. In patients with social phobia, this functional organization should be altered. When translated to prefrontal activation, according to the knowledge presented above, one may hypothesize that DLPFC and VLPFC activation and the functional interaction between these two areas should be different in patients with social phobia as compared to healthy subjects. Precisely, in normal subjects, one may observe an increased recruitment of DLPFC and possibly a decrease in the activation of right VLPFC. In patients with social phobia, one may observe a greater difficulty in recruiting DLPFC and higher right VLPFC activation, reflecting either its association with the generation of negative thoughts such as anxious ruminations or, inversely, an attempt to filtering out the excess of stress-induced anxiety related to the performance of a demanding executive task.

To verify these predictions, we conducted an fMRI study in healthy subjects and in patients with a social phobia during the performance of cognitive control tasks adapted from the Paced Auditory Serial Addition Test [PASAT; Gronwall, 1977]. PASAT is considered as a demanding verbal executive task that has been constantly found to activate a parietal (left BA7/40)-premotor (BA6)-DLPFC (BA9/46) network, characteristic of that of verbal working memory [Audoin et al., 2003, 2005; Forn et al., 2008]. This paradigm was modified in order to obtain two tasks that differed in the level of elicited anxiety. The modified condition, called the PASAT-random (with pseudorandom time intervals between target items) elicited more anxiety than the standard version of the task, referred to here as the PASAT-3s (with regularly spaced intervals of 3 s between target items). The validation or invalidation of the above working hypotheses was rendered possible by the combination of within- and between-groups (healthy vs. social phobia) comparisons of brain activation under different task conditions (PASAT-random, PASAT-3s and control tasks) as well as the correlations between brain activation and behavioral data observed during this experiment.

MATERIALS AND METHODS

An institutional ethics committee for biomedical research (CCPPRB of the Pitié Salpêtrière Hospital) approved the study and all participants provided informed consent.

General Design

A preliminary psychometric study was conducted in 20 healthy subjects to develop two tasks based on the same elementary cognitive processes and motivational level, but differing from one another in the level of performance-induced anxiety. Two auditory working memory tasks, the PASAT-3s and PASAT-random, adapted from the PASAT paradigm were thus constructed. Following this preliminary study, an fMRI study was undertaken in 15 patients and 15 healthy controls. Subsequent data analysis was performed using within- and between-groups comparisons, for individuals, groups (random effect) and regions of interest (ROIs). Careful attention was paid to the recording of behavioral markers (task performance, markers of stress and anxiety) before, during and after the experimental session. These behavioral markers were also analyzed in correlation with brain activation.

Cognitive Task Design

In the standard PASAT (referred to here as PASAT-3s), a series of auditory stimuli consisting of single digit numbers was delivered at the rate of one every 3 s. After the delivery of each number, subjects were asked to state aloud the sum of the two last numbers heard. Once the subject had provided the sum, a new digit was heard and the subject was required to add this digit to the one heard previously, thus inhibiting the interference produced by the digit (the sum) that he/she had expressed aloud. Instructions regarding the addition were provided on a screen within the MRI apparatus.

To manipulate the level of stress, we designed a second PASAT condition (called the "PASAT-random") in which the interval between stimuli varied randomly (1.5, 2, or 3 s).

A third, control, task was designed to control for sensory and motor aspects of the PASAT. It consisted of repeating aloud each number of a series as it appeared on the screen.

Preliminary Psychometric Study

To verify whether the PASAT-random was more stressful than the PASAT-3s and the control task, a psychometric study was performed in 20 healthy adults (11 females and 9 males; mean age $\pm$ standard deviation [S.D.]: 27 ± 10.64), all with an educational level of 7 (postgraduate). Ten participants were first tested with the PASAT-3s, while the other 10 were first tested with the PASAT-random. Cognitive performance was assessed by the mean

TABLE I. Demographic and clinical characteristics of the patient and control group

	Controls (N = 15)	Patients (N = 15)	P value
Age (years)	34.7 (3)	34.3 (3)	NS
Education level	6.4 (0.25)	6.7 (1.3)	NS
Sex ratio	6M/9F	7M/8F	
MMSE	29.9 (0.06)	29.9 (0.06)	NS
FAB	17.8 (0.1)	17.6 (0.1)	NS
Hamilton anxiety	6.7 (1.28)	27.6 (1.28)	<0.01
HAD anxiety	5.73 (1.1)	10.5 (1.1)	<0.01
Liebowitz anxiety	18.1 (3.13)	39.8 (3.13)	<0.01
Liebowitz avoidance	17.9 (3.66)	32.8 (3.66)	0.04
Spiegel trait	39.1 (2.62)	55 (2.62)	0.04
Spielberger state	35.6 (2.95)	49.7 (2.95)	0.01

Results for the various psychometric tests (from the MMSE to the Spielberger State) are expressed as mean values (S.E.M.). NS: not significant; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; HAD: Hospital Anxiety Depression. Note in bold the statistically significant difference between patients and controls for the values on the Spielberger State Anxiety Inventory, indicating that the state of anxiety of patients was greater than that of controls at the time of the fMRI session.

percentage of correct responses. Stress was evaluated: (i) subjectively by each subject, using the Self-Assessment Manikin (SAM), a 9-point visual analog scale, before and after each group of trials for each condition; and (ii) using the maximum amplitude of the skin conductance response (MA-SCR) as an index of the peripheral vegetative response. Electrodermal activity was averaged for each PASAT condition. The baseline amplitude was normalized to the first two seconds of each event. The MA-SCR is usually observed 4.5 s after the onset of the target event. Average MA-SCR was considered to be significantly different when greater than 2.5 standard deviations (SD) above the baseline amplitude ($+2.5$ SD corresponds to $P = 0.01$).

Statistical analyses were performed using repeated measures ANOVA to compare the cognitive performance, subjective stress and MA-SCR, as well as putative interactions between the variables, between the two PASAT conditions and at different time intervals (1.5, 2, and 3 s).

fMRI Study

Subjects

Fifteen patients presenting with social anxiety disorder as defined by the DSM IV, and 15 healthy control subjects participated in the study (for demographic data see Table I). All patients were recruited from the psychiatry department of the Salpêtrière hospital (Paris, France). Our objective being to explore the brain correlates of stress induced by a challenging task, it was important to include a sample of subjects who would express "performance anxiety". However, performance or test anxiety is not a well-defined

syndrome, e.g. this condition is not included as a diagnosis in the DSM-IV. Thus, our choice was to include a sample of patients with DSM-IV social phobia for the following reasons: (1) to obtain a sufficient clinical homogeneity of the sample, (2) because fear of negative evaluation is the core of both social and test anxieties [Bögels et al., 2010] and, (3) because one can consider that during the tests the subjects were aware of a close presence of non familiar experimenters and of an obvious assessment of their behaviors and performance, even if the tasks were done during an fMRI session and not under the direct gazes of others. Indeed, according to the DSM-IV text [American Psychiatric Association, 1994], “individuals with Social Phobia often fear indirect evaluation by others, such as taking a test” (p. 452). Test anxiety is thus considered as a subtype of social anxiety disorders [Bögels et al., 2010].

The criterion for inclusion was the presence of social anxiety disorder as diagnosed using the MINI [Mini International Neuropsychiatric Interview; Sheehan et al., 1998], completed by the Hamilton Anxiety Rating Scale [HARS; Hamilton, 1960] and the Hospital Anxiety Depression Scale [HADS; Zigmond and Snaith, 1983] to determine the severity of the anxiety disorder. Only subjects scoring higher than 19 on the HARS and 9 on the HADS were selected. In addition, the Liebowitz scale was used to evaluate the severity of social anxiety and avoidance [Liebowitz et al., 1985]. The Spielberger Trait Anxiety Inventory [STAI; Spielberger et al., 1984] was used to evaluate anxiety symptoms during the screening period while the Spielberger State Anxiety Inventory was administered before the fMRI session, to pinpoint the state of anxiety at the time of the fMRI session. Furthermore, at inclusion, all participants (patients and controls) underwent a brief cognitive evaluation consisting of the Mini Mental State Examination (MMSE) and the Frontal Assessment Battery [FAB; Dubois et al., 2000] (Table I). Exclusion criteria were current depression, any other significant psychiatric disorder, and a history of neurological disease.

A group of healthy participants ($n = 15$) was matched to the group of patients in terms of age, years of education, and sex ratio (Table I). Exclusion criteria were as follows: (i) pathological anxiety (assessed with the MINI) or any current or previous history of psychiatric or neurological disease; (ii) the use of psychoactive substances or medications that could influence cognitive performance or emotional state; and (iii) the presence of a cognitive impairment (MMSE <28 and/or FAB <15).

Functional MRI acquisition

Auditory stimuli were delivered through MRI-compatible headphones. A computer recorded the subject's vocal responses. Instructions (“add” for the two PASAT tasks or “repeat” for the control task) were presented on a screen in the MRI scanner. A foam rubber holder restricted the subject's head movements. Functional images were acquired on a 1.5-T whole body scanner (SIGNA, GE, Milwaukee,

WI), using a T2*-weighted gradient-echo-planar imaging sequence, sensitive to BOLD contrast (repetition time: 2,600 ms, echo time: 40 ms, flip angle: 90°, matrix: 64×64 , field of view: $220 \text{ mm} \times 220 \text{ mm}$). Seventeen contiguous axial slices (in-plane resolution: $3.75 \text{ mm} \times 3.75 \text{ mm}$; thickness: 5 mm) were obtained per volume, at the rate of one volume every 2.6 seconds. High-resolution anatomical T1-weighted images were acquired during the same session (inversion-recovery sequence, inversion time: 400 ms, repetition time: 1,600 ms, echo time: 5 ms, matrix: $256 \times 256 \times 128$, field of view: $220 \text{ mm} \times 220 \text{ mm}$, slice thickness: 1.5 mm).

Practice trials of the PASAT-random were performed outside the MRI. Participants were required to provide five consecutive correct responses in order to start the fMRI session. Then, participants were required to perform three separate runs. During each run, 244 contiguous volumes were acquired, over a total duration of 10 min and 35 s. Each run was composed of six trials (two trials per condition, presented in a pseudorandom order). A trial was defined by 30 consecutive responses under any of the three conditions. The first five volumes of each run were discarded from further analysis to await steady-state tissue magnetization. After each trial, subjects were asked to evaluate the level of stress induced by the previous trial using the modified SAM visual scale.

Data Analysis

Behavioral data acquired during the fMRI session

Cognitive performance was assessed by the mean percentage of correct responses. Stress was evaluated subjectively using SAM, a 9-point visual analog scale, after each group of trials for each condition (see Supp. Info. Fig. 6).

We performed within- and between-groups ANOVAs: (i) for within-group analyses, we studied the effect of the task condition (PASAT-random, PASAT-3s, control task) on the level of cognitive performance, the subjective stress induced by each trial (SAM) and any interaction between these factors; (ii) for between-groups analyses, we studied the effect of group, the effect of task condition and the interaction between these two factors on the level of performance and subjective stress. For significant factors or interactions, post-hoc comparisons were carried out using paired Fisher tests. *P*-values of less than 0.05 were taken to indicate statistically significant differences. Because of a technical problem, the number of correct responses was not recorded for one patient and one healthy subject.

Image analysis

All analyses were carried out with SPM2 software (Wellcome Department of Cognitive Neurology; www.fil.ion.ucl.ac.uk/spm). For each subject, a standard preprocessing protocol was followed: anatomical images were transformed stereotactically using nine rigid linear transformations to the MNI system. Functional imaging data from

each run were postprocessed as follows: image reconstruction, motion correction (six-parameter rigid-body realignment), normalization using the same transformations as the anatomical images, and smoothing with an 8 mm full-width half-maximum Gaussian filter.

Individual and group (random effect) analyses were performed. For both types of analysis, data were processed using the general linear model. For all individuals, each epoch (from the end of the instruction to the end of the trial) was modeled with a delayed hemodynamic response function (convolution of a standard hemodynamic response with a box-car function). Overall signal differences between runs were also modeled. An SPM {F} map was obtained, reflecting the interaction of statistically significant activated voxels and the model used ($P < 0.001$). To test the regionally specific effects of different conditions, the estimates associated with the tasks were compared using linear contrasts. In the design matrix, each condition was modeled with a unique regressor. The resulting set of voxel values for each contrast was used to build an SPM {t} map.

At first, random effect group analyses for the whole brain were carried out using one-sample *t*-tests for the within-group analysis and two sample *t*-tests for the between-groups analysis. In the within-group analysis, the two PASAT conditions were compared separately with the control task (to detect brain regions activated by each of the two PASAT tasks) and vice versa (to detect brain regions deactivated by each of the two PASAT tasks) and the two PASAT conditions were also compared with each other (to detect differences in activated and deactivated regions between the two PASAT tasks). The threshold of significance applied for those comparisons was $P = 0.05$, after false discovery rate (FDR) correction for multiple comparisons. When there was no significant activation at this corrected threshold, we also applied a threshold set at $P = 0.001$, uncorrected. The main between-groups analysis consisted of comparing the two groups of subjects (patients vs. control/control vs. patients) for differences between the PASAT-random and the PASAT-3s, to detect differences in activation between the two groups, associated with the "emotional stress" factor.

Second, we performed analyses of regions of interest (ROIs), defined prior to fMRI acquisition. According to our working hypotheses and the results of previous imaging studies, ROIs were focused on two prefrontal region: the left DLPFC involved in verbal working memory and the right VLPFC involved in anxious ruminations [Bishop et al., 2004; Brody et al., 2001a,b; Chua et al., 1999; Drevets et al., 1998; Raichle, 1998; Keedwelle et al., 2010; Liotti et al., 2002; Pochon et al., 2002]. In several papers focused on the interaction between cognition and emotion (or stress or anxiety), DLPFC ROIs or activation included parts of the middle frontal gyrus and inferior frontal sulcus (BA 9/46), whereas the VLPFC ROIs or activation included parts of the frontal operculum and anterior insula (BA 47) [Bishop et al., 2004; Chua et al., 1999; Drevets and Raichle, 1998;

Pochon et al., 2002]. We have chosen our ROIs according to Bishop et al. [2004] article, because of a relative closeness in issues raised by our study and Bishop et al.'s one. In consequence, DLPFC and VLPFC ROIs had the following central coordinates: DLPFC ROIs: $-34, 36, 24$; VLPFC ROIs: $38, 20, 0$. We hypothesized, *a priori*, that the DLPFC would be activated to a greater extent in the more stressful condition (PASAT-random vs. PASAT-3s) in healthy controls than in patients, and that the VLPFC would be activated to a greater extent in the more stressful condition (PASAT-random) in patients than in controls. ROIs were 10 mm (diameter) spheres drawn with Pick Atlas GUI Software implemented in SPM2, and centered on the Talairach coordinates of activation maxima reported by previous studies as detailed earlier. Within-ROI statistical analyses were performed for each ROI, using a design for repeated measures (Wald-chi square test) with groups (control/patient), and tasks (PASAT-random/PASAT-3s) as factors. Between-ROI analyses of right-VLPFC and left DLPFC were also carried out with groups (control/patients), task (PASAT-random/PASAT-3s) and ROIs as factors (Wald-chi square test). Given the lines of studies suggesting that negative affect exerts asymmetric effects on the PFC, further analyses were performed to test the degree to which the group differences in task-evoked activation were lateralized. A between-ROI analysis of right and left VLPFC was performed. The Talairach coordinates of left VLPFC were as follows: $-38, 20, 0$ [Bishop et al., 2004]. Wald-chi square test was performed with groups (controls/patients), task (PASAT-random/PASAT-3s) and laterality (right/left) as factors (SPSS 15.0 software for Windows).

Finally, correlation analyses were performed between the Spielberger State and Trait Anxiety Inventory, SAM and accuracy and the level of activation in VLPFC ($33, 21, -6$) and DLPFC ($-39, 33, 27$) clusters identified in the whole brain analysis in all participants gathered in one single group and also studied by separating patients from controls (Statistica 6.0 software; StatSoft, Tulsa, UK).

Correlation analyses were performed on *a priori* determined ROIs and on whole-brain clusters. Both analyses yielded similar results.

RESULTS

Preliminary Psychometric Study

The main results of this preliminary study were as follows: (i) Cognitive performance was lower in the PASAT-random (mean percentage of successful trials $\pm$ standard error of the mean [S.E.M.]: 74.2 ± 7.2) than in the PASAT-3s (87.5 ± 6.1 ; $F [1.19] = 21.6, P = 0.002$); (ii) Performance in trials with a 3-s interval in the PASAT-random (mean score $\pm$ S.E.M.: 76.5 ± 9.9) was lower than performance in the PASAT-3s (87.5 ± 6.1 ; $F [3.57] = 9.6, P = 0.0003$); (iii) Subjective stress (SAM) was rated higher in the PASAT-random (mean score $\pm$ S.E.M.: 4.15 ± 0.59) than in the

PASAT-3s (2.98 ± 0.69 ; $F [2,38] = 19.054$, $P = 0.00001$); (iv) MA-SCR was higher in the PASAT-random (mean value of MA-SCR [μ s] $\pm$ S.E.M.: 0.0028 ± 0.0013) than in the PASAT-3s (0.00085 ± 0.0004 ; $F[1.14] = 4.7$, $P = 0.04$). The differences noted earlier were more marked for the first 30 stimuli. Accordingly, the duration of the trial for each condition was limited to 30 stimuli in the fMRI study. As the PASAT-random was significantly more stressful than the PASAT-3s, these two conditions were used to compare the effects of stress in the fMRI session.

fMRI Study

Behavioral Data (Fig. 2)

Cognitive performance in the PASAT (Fig. 1a). ANOVAs revealed a task effect ($F [2,52] = 69.166$, $P < 10^{-6}$). In both groups, performance (mean percent of correct responses $\pm$ S.E.M.) was lower in the PASAT-random than in the PASAT-3s (control subjects: $P = 0.01$; patients: $P = 0.039$), in the PASAT-random than in the control task (control subjects: $P = 0.0001$; patients: $P = 0.0001$) and in the PASAT-3s than in the control task (control subjects: $P = 10^{-5}$; patients: $P = 0.0001$). Although performance in the two PASAT tasks tended to be lower in the patient group, neither a group effect ($F [1, 26] = 2.16$, $P = 0.15$) nor a group $\times$ task interaction ($F [2, 52] = 1.75$, $P = 0.18$) was detected.

Markers of anxiety (Fig. 1b). ANOVAs also revealed a task effect ($F [2, 52] = 71.6$, $P < 10^{-6}$) on the subjective evaluation of stress. The PASAT-random was given a higher stress rating, using the SAM visual scale, than the PASAT-3s or the control task, in both healthy subjects (PASAT-random vs. PASAT-3s: $P = 0.04$; PASAT-random vs. control task: $P = 10^{-6}$) and patients (PASAT-random vs. PASAT-3s: $P = 0.016$; PASAT-random vs. control task, $P = 10^{-4}$) (Fig. 2b). SAM was rated higher in the PASAT-3s than in the control task in healthy subjects ($P = 10^{-6}$) and in patients ($P = 0.0004$). No difference was observed between the two groups of subjects for each cognitive condition ($F [1, 26] = 0.01$, $P = 0.15$) while group $\times$ task interaction was close to statistical significance without reaching it ($F [2, 52] = 3.9$, $P = 0.06$).

Nevertheless, the state of anxiety when starting the fMRI session was more marked in patients than in healthy subjects, as detected by significant differences in the Spielberger State Anxiety Inventory (Table I).

fMRI data (Figs. 2–4; Table II)

Whole-brain analysis. In whole-brain analyses of both patients and healthy controls, within-group contrasts between the PASAT-3s and the control task and between the PASAT-random and the control task revealed a common network involving the parietal (BA 7/40), the lateral premotor (BA 6) and the DLPFC (BA 9/46) cortices bilaterally,

Figure 1.

Cognitive performance and subjective stress of patients and healthy participants in each cognitive task. (a) Cognitive performance, expressed as mean percentage of correct responses ($\pm$ S.E.M.); (b) Subjective stress during the tasks, expressed by mean values ($\pm$ S.E.M.) in the modified SAM, a visual scale from 0 to 9; * $P < 0.05$, ** $P < 0.001$ (ANOVA). Vertical bars represent standard errors of the mean.

ally, known to be involved in working memory and cognitive control (Fig. 2a,b; Table IIa). A comparison between the PASAT-3s and the control task also showed signal changes in the VLPFC (BA47) in both groups (Table II).

Within the patient group, the contrast between the PASAT-random and the control task revealed the additional activation of a large cluster in the right VLPFC (BA47) and anterior insula (BA48) (Fig. 2b, Table IIa). This activation was not observed in healthy subjects with the same contrast

Figure 2.

Statistical maps of activation showing the contrast between two PASAT conditions and the control task for within-group comparisons, and the contrast between the PASAT-random and PASAT-3s for between-groups comparisons.

(Fig. 2a, Table IIa). Moreover, within the group of healthy subjects, right VLPFC activation was lower in PASAT random than in PASAT-3s (Fig. 2a, Table IIa).

Finally, the most significant results of whole brain analyses were obtained in the between-group comparison for the PASAT-random versus PASAT-3s. Right VLPFC (BA 47) was lower in the healthy controls as compared to patients (Fig. 2c, Table IIb).

In both within-group and between-groups analyses, no difference above threshold values was seen using the reverse contrast (PASAT-3s vs. PASAT-random) (Table IIa,b).

ROI analysis. A within-ROI analysis centered on right VLPFC showed no significant group effect (Wald-chi-square = 2.46, $df = 1$, $P = 0.117$), but did show a significant task effect (Wald-chi-square = 7.55, $df = 1$, $P = 0.006$) and a significant task $\times$ group interaction (Wald-chi-

square = 3.92, $df = 1$, $P = 0.048$). Post-hoc analysis revealed that in healthy participants, activation was lower with the PASAT-random than with the PASAT-3s ($P = 0.006$; Fig. 3b). Such a difference was not observed in the patient group ($P = 0.238$).

A between-ROI analysis of right and left VLPFC showed a significant group $\times$ task $\times$ laterality interaction (Wald-chi-square = 4.39, $df = 1$, $P = 0.036$). The group difference between right and left VLPFC activation was found in the PASAT-random. In the PASAT random, right VLPFC activation was higher in patients than in healthy subjects ($P = 0.051$). Such a difference was not observed for left VLPFC activation. Further, in healthy subjects, right VLPFC activation was significantly lower than left VLPFC activation in the PASAT-random ($P = 0.01$; Supp. Info. Fig. 5).

A within-ROI analysis centered on left DLPFC showed a significant group effect (Wald-chi-square = 4.57, $df = 1$, P

TABLE IIA. Within-group comparisons: maxima of activation associated with each of the two PASAT conditions contrasted to the control task and to each other in the two groups of subjects

Healthy participants							Patients						
Brain area	BA	Stereotaxic coordinates			Z score	Brain area	BA	Stereotaxic coordinates			Z score		
		x	y	z				x	y	z			
PASAT-3s vs. control task													
Middle frontal gyrus	L	9	−48	6	36	4.7	Superior frontal gyrus	L	6	−9	6	54	4.26
Middle frontal gyrus	L	46	−39	33	27	3.72	Middle frontal gyrus	L	6	−36	−3	48	3.78
Superior frontal gyrus	L	6	−6	9	54	4.45	Inferior frontal gyrus	R	44	57	9	18	3.46
Superior frontal gyrus	R	6	3	9	54	4.45	Inferior frontal gyrus	R	47	45	21	−3	3.29
Middle frontal gyrus	R	9	51	6	33	3.66	ACC	R	24	6	21	24	3.72
Middle frontal gyrus	R	46	42	39	33	3.2	ACC	L	32	−6	24	27	3.41
Insula	R	48	39	−9	−9	2.38	Inferior parietal gyrus	L	40	−48	−42	36	4.29
Inferior frontal gyrus	R	47	39	24	0	2.39	Inferior parietal gyrus	R	40	42	−42	51	3.32
PCC	R	23	6	−30	27	4.46	Superior tempor. gyrus	R	42	66	−33	15	3.33
Inferior parietal gyrus	L	40	−39	−54	42	4.7	Mesial lenticular	L		−15	−3	3	4.36
Inferior parietal gyrus	R	40	42	−51	54	3.7	Thalamus	R		9	−9	3	3.95
Superior tempor. gyrus	L	42	−42	−36	9	3							
Thalamus	L		−12	−3	15	3.38							
PASAT-random vs. control task													
Middle frontal gyrus	R	6	39	3	51	4.39	Inferior frontal gyrus, anterior insula	R	47/48	33	21	−6	4.45
Middle frontal gyrus	R	9	45	9	42	4.32	Middle frontal gyrus	R	46	45	51	15	4.06
Middle frontal gyrus	L	9	−48	9	39	4.22	Middle frontal gyrus	R	10	33	51	18	3.98
Superior frontal gyrus	R	6	3	3	54	3.72	Middle frontal gyrus	R	8	33	24	48	3.43
Superior frontal gyrus	L	6	−9	0	60	3.65	Superior frontal gyrus	R	6	36	0	60	2.83
Superior parietal gyrus	R	7	36	−51	51	3.63	Middle frontal gyrus	L	6	−27	6	51	4.43
Inferior parietal gyrus	R	40	36	−30	39	2.98	Superior frontal gyrus	L	6	−9	6	54	4.37
Inferior parietal gyrus	L	40	−51	−45	51	3.66	Middle frontal gyrus	L	46	−33	24	21	3.98
Precuneus	L	7	−15	−78	48	3.65	Inferior frontal gyrus	L	45	−48	21	20	3.65
Hippocampus	R	27	33	−42	0	3.21	Inferior frontal gyrus	L	47	−24	24	−3	3.70
Caudate nucleus	R		9	−6	21	2.75	Insula	L	48	−39	9	6	3.35
Thalamus	L		−12	−27	18	3.98	ACC	R	32	9	21	27	4
							ACC	L	32	−12	24	27	3.75
							Inferior parietal gyrus	L	40	−30	−57	42	3.76
							Précuneus	L	7	−6	−75	45	3.82
							Inferior parietal gyrus	R	40	36	−42	33	3.29
							Caudate nucleus	R		9	−6	0	3.88
							Thalamus, dorso-median	L		−3	−21	12	3.84
								R		6	−31	9	3.75
PASAT-random vs. PASAT 3s													
No significant activation													
PASAT 3s vs. PASAT-random													
Inferior frontal gyrus	R		36	9	−15	3.9	No significant activation						

$P = 0.05$ corrected

ACC, anterior cingulate cortex; BA = Brodmann Area

TABLE IIB. Between-group comparisons: maxima of activation associated with PASAT-random condition in contrast to the PASAT-3s

Patients vs. healthy participants							Healthy participants vs. patients						
Brain area	BA	Stereotaxic coordinates			Z score		Brain area	BA	Stereotaxic coordinates			Z score	
		<i>x</i>	<i>y</i>	<i>z</i>					<i>x</i>	<i>y</i>	<i>z</i>		
PASAT-random vs. PASAT-3s													
Inferior frontal gyrus	R	47	36	21	−18	3.64	No significant activation						
Superior frontal gyrus	R	6/8	12	21	57	3.36							

$P = 0.001$ non-corrected.

Figure 3.

Mean signal changes in the two PASAT tasks using within-ROI analyses. Mean activation in “cognitive” DLPFC (a). Mean activation in “emotional” VLPFC (b). *P* values correspond to results of post-hoc analyses and analyses of main interactions (Wald-chi-square). Vertical bars represent standard errors of the mean.

= 0.033), no significant task effect (Wald-chi-square = 1.87, $df = 1$, $P = 0.172$) and no group $\times$ task interaction (Wald-chi-square = 1.01, $df = 1$, $P = 0.314$). Post-hoc analyses demonstrated that left DLPFC activation in the PASAT-random was higher in the group of healthy participants than in patients ($P = 0.033$; Fig. 3a). This difference was not significant for the PASAT-3s task ($P = 0.167$).

A between ROIs analysis of right VLPFC and left DLPFC showed a near significant group $\times$ task $\times$ ROI interaction (Wald-chi-square = 5.128, $df = 2$, $P = 0.07$). However, group $\times$ ROI and task $\times$ ROI interactions were both significant (group $\times$ ROIs: Wald-chi-square = 4.65, $df = 1$, $P = 0.031$; Task $\times$ ROIs: Wald-chi-square = 10.8, $df = 1$, $P = 0.001$). In healthy participants, a difference between DLPFC and VLPFC signals was observed with PASAT-random ($P = 0.004$) but not with PASAT-3s ($P = 0.9$) whereas in patients, there was no significant variation in mean signal change between DLPFC and VLPFC with either PASAT task (p PASAT-random = 0.5, P PASAT-3s = 0.4).

Correlation Between Hemodynamic Signal and Anxiety Markers (Fig. 4)

Correlation analyses including all participants (healthy controls and patients) showed that the mean signal in

right VLPFC in the more stressful condition (PASAT-random) was positively correlated with the state of anxiety at the time of the fMRI session, as measured by the Spielberger State Anxiety Inventory ($r = 0.41$, $P = 0.002$). Since it could be hypothesized that the significance of this correlation depended on one outlier, we performed an additional correlation analysis without this outlier. The correlation remained statistically significant ($r = 0.39$, $P = 0.048$; Fig. 4). Correlations between left-DLPFC and STAI collapsed across groups for random and 3-s conditions.

Correlation analyses between dorsal and ventral prefrontal areas and other clinical parameters (accuracy, SAM) failed to demonstrate significant relationships (see Supp. Info. Table III).

DISCUSSION

The main results of this study can be summarized as follows: (1) behavioral data obtained in the preliminary study and during the fMRI session showed that in all participants the PASAT-random was more difficult (decreased accuracy) and more stressful (higher SAM scoring and higher MA-SCR) than the PASAT-3s and the control task; (2) While performing the two cognitive control tasks (PASAT-random and -3s), both groups of subjects activated a classical parieto-premotor-dorsolateral prefrontal

Figure 4.

Correlation analysis between anxiety and activation in the ventrolateral prefrontal cortex during the PASAT-random. Correlation analysis between the level of anxiety measured by the Spielberger State Anxiety Inventory (STAI) and activation in the right VLPFC in all subjects. STAI and VLPFC scores are reported in rank transformed values.

“cognitive control/working memory” network; (3) An important distinction between the two groups in the whole brain analysis was the significant difference in right VLPFC activation in the PASAT-random vs. PASAT-3s contrast. Unlike the patients, healthy controls demonstrated decreased activation in PASAT-random compared with PASAT-3s; (4) Right VLPFC ROIs analyses showed that in healthy participants, activation was lower in the PASAT-random than in the PASAT-3s. Such a difference was not observed in the patient group; (5) A decrease in VLPFC activation in healthy subjects was found in right as compared to left VLPFC. The group difference during the more stressful cognitive task appears in right but not in left VLPFC; (6) Although there was no significant difference in performance and task-induced stress (SAM evaluation during fMRI) between patients and healthy subjects, there was a positive correlation between right VLPFC activation and anxiety before fMRI (STAI evaluation); (7) Although in the within-ROIs analyses centered on DLPFC, there was no significant group $\times$ task interaction, post-hoc analyses showed that in healthy participants, DLPFC activation was higher in the PASAT-random than in the PASAT-3s. Such a difference was not observed in the patient group.

This set of results suggests that in healthy participants, the more stressful cognitive control task has an opposite impact on the left dorsal and right ventral prefrontal areas: It is associated with a decrease of BOLD signal in right VLPFC and an increase in left DLPFC. These findings suggest that under normal conditions, stress promotes (or does not prevent) an increase in the activation of the prefrontal areas involved in cognitive control and a decrease

in the prefrontal areas associated with negative thoughts. In patients with pathological anxiety, the difference in activation between stressful and less stressful cognitive task disappears in the dorsal and the ventral prefrontal cortices. This may suggest that increased anxiety leads to a less efficient modulation of prefrontal activation while performing stressful cognitive tasks.

Our results were obtained in a sample of patients with social anxiety disorder, and this inclusion criterion can obviously limit their generalization to other conditions. However, we think that our findings can be, at least, partially transposed to other forms of anxiety because social anxiety disorder shares many cognitive and cerebral attributes with other anxiety disorders. For example, personality profiles of patients with social anxiety disorder is marked by high levels of “harm avoidance,” a temperament trait including fear of uncertainty and anticipatory worry tendencies and known to be also elevated in almost all anxiety disorders [Ball et al., 2002; Pelissolo et al., 2002]. Moreover, we chose to include only patients with significant anxiety scores (HARS and HAD-anxiety scales), to ensure that they had not only very specific and focused forms of social anxiety.

Significant behavioral differences were demonstrated between PASAT-random and PASAT-3s (accuracy, SAM, and SCR) in both groups of subjects. One important feature of the task design was that the two cognitive conditions rely on the very same elementary cognitive processes (the use of identical stimuli, similar type of answer and above all, the same cognitive operations were required to resolve the tasks). Neither perceptual nor affective supplementary information (affective pictures, use of electrical shocks...) has been added to modulate the level of stress. Here, the unpredictability in the temporal occurrence of the stimuli to be processed seems to be the parameter that modifies the performance. Therefore, a plausible interpretation of the differences between the PASAT-random and the PASAT-3s is that the unexpectedness of the stimulus to be cognitively processed was sufficient to generate stress-induced emotional signals, which may have interfered with cognitive control, as already demonstrated [Fischer et al., 2003; Hasler et al., 2007; Wright et al., 2001]. In this line of ideas, in the PASAT-random, when isolating trials where the stimuli occur at 3 s and comparing the performance for these trials to that of the PASAT-3s, the behavioral differences remain significant. Finally, although the precise nature of what SCR assesses has been debated [Lavric et al., 2003], a recent work suggests that electrodermal activity has a high discriminative power in distinguishing stress from cognitive load [Setz et al., 2010]. Altogether, these behavioral data indicate that the PASAT-random is more stressful than the PASAT-3s. Therefore, difference in brain activation in the comparison between the two tasks could be interpreted according to differences in the level of stress.

According to the hypothesis that anxiety interferes with cognitive control, one would also expect a decrease in

accuracy in the PASAT-random with an increase of self-report stress as measured by the SAM. Contrary to this expectation, no significant difference was found between the two groups of subjects in terms of accuracy and SAM, although they tended to be lower in the patient group. However, in terms of brain activation, the similar level of cognitive performance between the two groups does not imply that the achievement of this level of executive control relies on the same brain mechanisms, a divergence that has been shown in other pathological states such as depression [Harvey et al., 2005]. In addition, SAM evaluation reflects one's ability to assess stress from a personal or subjective perspective only, and may depend on each individual's stress scale. For instance, a stress rating of "5" by a group of anxious patients may not be equivalent, in terms of the absolute level of stress, to the same rating in healthy subjects. As suggested by several authors, self-report instruments may not objectively measure the affect experienced during cognitive task as they inquire only about the stress induced by the current experience [Ray and Ochsner et al., 2005; Shackman et al., 2006]. In addition, self-report measures may be the output of many processes and for that reason may be "noisier" than the imaging measures of activation in brain structures related to affective information processing [Canly et al., 2001; Rey et al., 2005]. The patient group only differed from the control one by the existence of a pathological anxiety (i.e. their anxiety interfered with daily living activities and need specific psychiatric follow-up). And indeed, when compared to the control group, the anxious patients obtained higher severity scores at all of anxiety scales (see Table I). Therefore, difference in brain activation between the two groups could be interpreted as difference related to pathological anxiety.

Was this difference in brain activation due to a pathological performance-induced stress or to a non task-specific, general excessive state of anxiety? STAI results indicated that patients were anxious prior to the fMRI session. It is thus plausible that a general (and task-independent) state of anxiety has contaminated the task performance. However, this hypothesis could only partially explain the results as one should expect such a "contamination effect" to affect all tasks (or at least to the two cognitive tasks). This was not the case as a positive correlation between right VLPFC signal and STAI was only found for the PASAT-random. On the whole, it seems reasonable to assume that the degree of stress experienced by the patients during the PASAT-random was sufficient to modify brain activation without significantly affecting their cognitive performance. It is also likely that the difference in right VLPFC and left DLPFC activation between patients and control in the more stressful task was due to the combination of a "general anxiety factor" and a "task performance induced-stress."

In both groups, the two PASAT tasks activated a network involving parietal, premotor and dorsolateral prefrontal regions, in accordance with previously observations

in executive control paradigms [D'Esposito et al., 2000], including the PASAT [Audoin et al., 2003, 2005]. In healthy participants, DLPFC activation was higher with the PASAT-random. As performance accuracy in this task was significantly lower than in the PASAT-3s, it is possible that the PASAT-random, due to the unexpectedness of the occurrence of stimuli, required more cognitive control, and in particular, more attention resources. It is unlikely that this additional activation was related to other elementary cognitive processes involved in the PASAT, such as working memory maintenance or manipulation, as these processes were equivalent for the two PASAT tasks. An alternative hypothesis is that the network involved in cognitive control and working memory also intervenes in predicting temporal intervals [Beudel et al., 2009; Brunia et al., 2000; Harrington, 1998]. However, a recent study suggests that in most cases, this timing network has been significantly overestimated and confounded with activation related to task demand in working memory and decision-making [Livesey et al., 2007]. Finally, it is also possible that the increased activation in left DLPFC reflects the need to compensate for the potential interfering effect of stress on cognitive performance. This hypothesis is supported by the fact that a positive correlation was found between level of anxiety at the time of the fMRI session and DLPFC activation, in healthy participants.

By contrast, in patients, DLPFC activation was not higher during the PASAT-random than during PASAT-3s. In other words, the increased difficulty and stress induced by PASAT-random was not associated with an increase in DLPFC signal.

In parallel, in patients as compared to healthy participants, we observed in both whole-brain and ROI analyses, an important activation (both in terms of magnitude and of statistical significance) of the right VLPFC. This increase was explained by the fact that in healthy subjects, VLPFC activation was decreased in the case of the PASAT-random (as compared to the PASAT-3s), while in patients, VLPFC activation was similar for the two PASAT tasks. As for the DLPFC, this set of results argues for the absence of modulation of VLPFC activation in patients. Interestingly, for the more stressful cognitive task, our results showed a clear effect of laterality between the two groups. Different modulation of VLPFC activation between patients and healthy subjects during PASAT-random was observed in the right and but not in the left VLPFC. This result further supports the association between anxiety and right VLPFC, in accordance with previous literature showing dominant right prefrontal activation in association with the presence of negative affects [Davidson et al., 2000, 2002; Shackman et al., 2009; Tomarken et al. 1992], and anxious states [Baas et al., 2004; Dalton et al., 2005; Rauch et al., 1997], in particular social anxiety disorders [Etkin and Wagner, 2007]. This result extends previous knowledge by showing that right VLPFC activation is also associated with the performance of a stressful cognitive task as compared to less stressful ones.

How can one interpret the decrease in right VLPFC activation in healthy subjects in the stressful cognitive task with the absence of such modulation in patients with excessive anxiety? Two opposite ideas can be discussed: One may hypothesize that right VLPFC activation is a compensatory mechanism aimed at filtering negative thoughts in an attempt to prevent them from interfering with cognitive control [Blair et al., 2007; Dolcos and McCarthy, 2006; Dolcos et al., 2006]. It might help patients to more effectively regulate initial responses to anxiety provoking stimuli, thereby reducing severity of symptoms and maintaining the same level of performance as the healthy subjects [Monk et al., 2006]. Against this proposal, one may argue that, if true, one would expect to observe an increase rather than a decrease in the activation of this region with stress in subjects with an effective mechanism of anxiety regulation. However, this is based on the idea that normal subjects and patients share similar mechanisms of stress regulation with pathological anxiety. It is also plausible that anxious patients require more brain resources than healthy subjects to regulate their anxiety. In this line of ideas, it has been shown that VLPFC activation is associated with changes in the affective relevance of stimuli and greater necessity to regulate it [Bechara et al., 2000; Ochsner et al., 2004].

Another plausible explanation is that right VLPFC activation in cognitive control is a pathological pattern related to the expression of negative emotions or thoughts associated with anxiety. The evidence for this comes from the findings that the level of VLPFC activation was positively correlated with anxiety, and that VLPFC activation was significantly higher in patients than in healthy subjects in the more stressful situation. Several studies have shown that VLPFC activation is associated with the processing of negative and emotionally colored thoughts, particularly those related to “the experience of being preoccupied” [Drevets and Raichle, 1998] or negative ruminations [Brody et al., 2001a,b; Ray et al., 2005]. We speculate that ruminations (in the form of subvocal rehearsal of negative preoccupations) could be associated with the recruitment of brain systems associated with representing and updating the contextual value of anxiety and therefore could compete for attention resources necessary for cognitive control. Our findings and previous data may support the concept of “emotional gating” [Harvey et al., 2005; Pochon et al., 2002] in healthy individuals: more stressful and cognitively demanding conditions require additional activation of the areas involved in cognitive processing (DLPFC) and, at the same time, decreased activation in areas associated with the occurrence of interfering thoughts or emotions (VLPFC). In anxious patients, this gating effect could be less effective.

In conclusion, in healthy subjects, stress induces a modulation of activation in the dorsal and ventral PFC, with an increased activation in left DLPFC, a critical region for cognitive control, and a decreased activation in right VLPFC, an area associated with the occurrence of negative

thoughts. Inversely, in patients with pathological anxiety, this modulation disappears. To date, it is, however, not possible to indicate whether in anxious patients, right VLPFC activation is a physiological mechanism aimed at filtering out negative thoughts or on the contrary, a pathological state associated with an excess of persistent negative ruminations or preoccupations. In both situations, it is expected that in more severe conditions, a possible consequence of this absence of modulation could be to limit one’s ability to adapt cognitive control to the most demanding cognitive tasks.

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