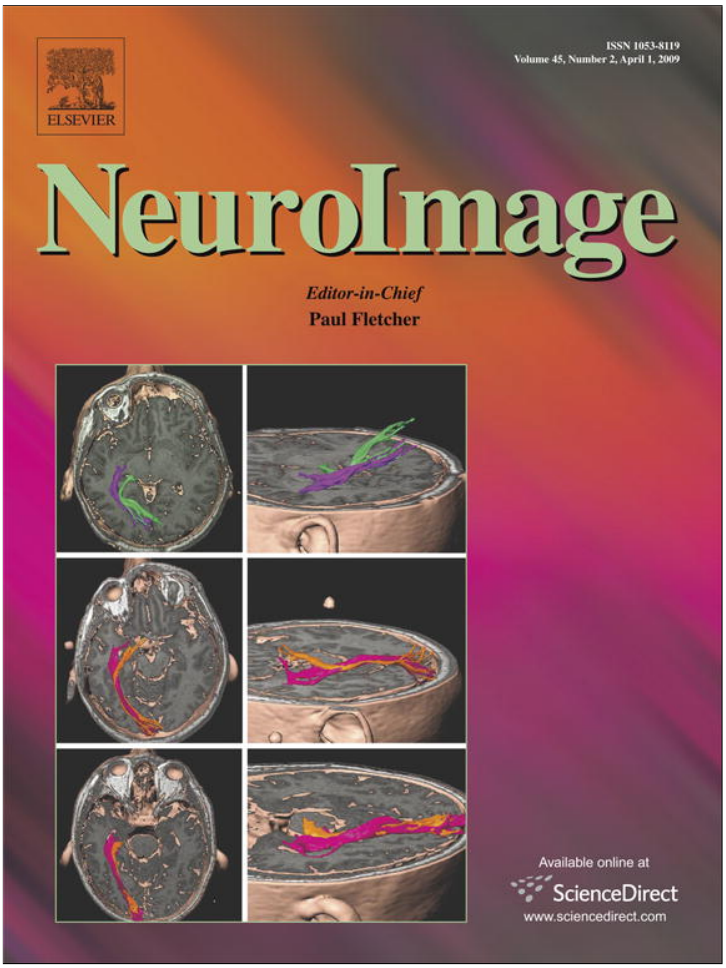

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FMRI evidence of a functional network setting the criteria for withholding a response

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ABSTRACT

That the left prefrontal cortex has a critical role setting response criteria for numerous tasks has been well established, but gaps remain in our understanding of the brain mechanisms of task-setting. We aimed at (i) testing the involvement of this region in setting the criteria for a non-response and (ii) assessing functional connectivity between this and other brain regions involved in task-setting. Fourteen young participants performed a go/nogo task during functional magnetic resonance imaging. The task included two nogo visual stimuli which elicit a high (distractor) or a low (other) tendency to respond, respectively. Two task blocks were examined to assess learning the criteria. First, a multivariate Partial Least Squares (PLS) analysis identified brain regions that co-varied with task conditions, as expressed by two significant Latent Variables (LVs). One LV distinguished go and nogo stimuli. The other LV identified regions involved in the first block when the criteria *not* to respond to distractors were established. The left prefrontal region was prominently involved. Second, a left ventrolateral prefrontal area was selected from this LV as a seed region to perform functional connectivity using a multi-block PLS analysis. Results showed a distributed network functionally connected with the seed, including superior medial prefrontal and left superior parietal regions. These findings extend our understanding of task-setting along the following dimensions: 1) even when a task requires withholding a response, the left prefrontal cortex has a critical role in setting criteria, and 2) this region responds to the task demands within a distinctive functional network.

Introduction

A number of models postulate the existence of an anterior attentional system with a range of top-down cognitive processes, mainly located in the prefrontal cortex (PFC; e.g., Baddeley, 1986; Norman and Shallice, 1986), which receives input from and modulates more specific lower-level functions, centred in other brain areas, such as attention in the parietal lobes (Posner and Petersen, 1990; Shallice, 1982), long-term memory in the temporal lobes (e.g., Moscovitch, 1992), and executive motor functions in the basal ganglia (e.g., Alexander et al., 1986). Fractionation of these top-down functions within PFC has been not only theoretically hypothesized (e.g., Baddeley, 1996; Stuss et al., 1995), but also empirically demonstrated (Burgess and Shallice, 1996; Stuss et al., 2005; Alexander et al., 2007; see Faw, 2003; Shallice, 2004; Stuss and Alexander, 2007; for reviews). However, there is a lack of studies investigating the neural bases of these high-level processes at the network level.

One of these processes is task-setting, the ability to learn new rules especially when those compete with pre-existing and prepotent stimulus–response associations (Stuss et al., 1995). Task-setting can be metaphorically described as a sculpting activity (cf. Fletcher et al., 2000; Frith, 2000), where the surface material to be carved represents a prepotent, habitual response that needs to be overcome, and the emerging shape represents a new strategy or stimulus–response association that one needs to learn to perform the task. Task-setting has been proposed as a key component process in several cognitive tasks: in the color naming version of the Stroop task, the most automatized word reading process should be suppressed in favour of the less habitual color naming; in the first-letter verbal fluency task, word production by semantic relations should be overcome in favour of the less prepotent strategy of searching words by first letter; in the feature integration task, different stimulus features cannot be used alone but need to be integrated in order to set the criteria to respond; in the task-switching paradigm, one has to switch from a recently activated but no longer valid rule to another rule. In all these paradigms, task-setting might require the suppression of prepotent but currently inappropriate rules or strategies, the enhancement of task-relevant ones which may be weaker, or both. An assumption usually made is that task-setting is required as long as the new criteria

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have to be learned in non-routine situations, and its role fades as they become more familiar and practiced (Shallice, 2004; Stuss et al., 1995).

Neuropsychological evidence shows that patients with left lateral prefrontal lesions perform poorly in all these tasks. When tested with Stroop and first-letter verbal fluency tasks, patients with left frontal lesions showed impaired performance (Perret, 1974). In a three-feature integration task left dorsolateral prefrontal patients were impaired in a measure of bias, as they tended to respond more often to a non-target as target (Stuss et al., 2002). Some studies have also investigated learning effects. In a switch task, left lateral prefrontal patients made more errors than both controls and the rest of the prefrontal patients in the first block of a condition with a short cue-to-target interval (200 ms; Shallice et al., 2008). In a continuous rapid 5-choice RT task, left prefrontal patients performed worse than their controls and other prefrontal patients in the first 20% of trials, demonstrating impairment in acquiring the rules (Alexander et al., 2005). All these patterns of performance impairment can be economically interpreted as different manifestations of the same task-setting (Stuss and Alexander, 2007) or strategy production (Shallice, 2004) deficit.

Similar evidence has been accumulated in brain imaging literature. Some studies, for instance, show task-setting related activation of left-lateral PFC in memory encoding (Fletcher et al., 1998, 2000), motor learning (Jueptner et al., 1997) and first-letter verbal fluency (Frith et al., 1991). Paralleling the lesion literature which shows a decrease in errors over time in patients with left lateral damage, practicing a task diminishes activation in this region (e.g., Fletcher et al., 2000; Raichle et al., 1994; Toni et al., 2001; see Bunge, 2004 for a review). These data suggest that this specific region is critical to temporarily assemble novel or weakly associated representations to solve the task at hand and, in addition, to suppress other potential, but context-inappropriate, representations (Buckner, 2003; Duncan and Owen, 2000; Miller, 2000; Nolde et al., 1998; Thompson-Schill et al., 1997). Tasks in which responses are based on a straightforward match between a cue and a specific representation do not seem to engage this region.

The importance of this region in learning has also been highlighted in studies using animal models. Monkeys with lesions to ventrolateral prefrontal cortex (VLPFC) have problems acquiring different kinds of rules (Bussey et al., 2002; Murray et al., 2000; Passingham et al., 2000). Another example comes from a different brain mapping technique and cognitive task. TMS on left (dorsolateral) prefrontal cortex but not on the right homologous area impairs performance of a random number generation task, as this manipulation increased the frequency of the more familiar strategy of counting by ones and decreased the occurrences of the weaker but more appropriate strategy of counting by twos (Jahanshahi et al., 1998; see also Jahanshahi et al., 2000, for PET evidence).

Aim of the current study is to further understand the neural correlates of task-setting. To answer this question we scanned participants with fMRI while they were performing an adapted version of a task that has already demonstrated to be sensitive to left prefrontal lesions (Alexander et al., 2007). In the original study (Alexander et al., 2007) target stimuli were obtained by combining two letters and colors ("blue O" and "red X"). The same letters but with a different color ("red O" and "blue X") required instead a different response (*distractors*). That alternative response was also associated with different colored letters (*others*). This task shares features with the Stroop task and with the feature integration task. In the case of a *distractor* condition, participants cannot rely on the information concerning letter identity, which is quickly available due to an automatized reading capacity, because that would prompt to a wrong target response. Instead, they have to set new criteria to respond, that is to combine letter identity with color identity and associate the result with the less prepotent but correct response. Left lateral prefrontal patients showed a selective increase of commission errors in the *distractor* condition.

It has been proposed that the role of left PFC is sculpting the response space by combining suppression of the inappropriate response criteria, on the one side, and selection of the appropriate ones, on the other (Fletcher et al., 2000; Frith, 2000). A critical question is, then, whether setting the criteria for suppressing the inappropriate responses, without the complementary request to set the criteria to respond, is a sufficient condition to observe activation in the left PFC. To explore that possibility, we adapted the original design (Alexander et al., 2007) to a go/nogo task. In that case, task-setting will be required independently of the selection and preparation of an alternative motor response. In this new task, participants were instructed not to respond to non-target trials. Moreover, we used a different category of stimuli for the *other* condition (i.e., numbers instead of letters), in order to make it more distinguishable from targets and minimize task-setting requirements with respect to *distractors*, while matching *others* and *distractors* for frequency of occurrence and absence of an overt response. The *other* condition is therefore intended as a high-level cognitive baseline in this task (i.e., less or no task-setting at all is required).

If the left lateral PFC is involved in task-setting, which is conceivably more required in the initial phase of a novel task (e.g., Fletcher et al., 2000), a decrease in the level of activation should be observed in this region, and in the functional network connected to it, when the task becomes well-learned. After a certain amount of practice, indeed, participants may learn to associate the *distractors* to a nogo response in an automatized fashion, possibly bypassing the task-setting process. We investigated the neural bases of this learning process by splitting the task in two consecutive runs.

Finally, if left PFC plays a critical role in task-setting, as can be inferred from brain lesion studies (e.g., Stuss and Alexander, 2007), an open question is how this area implements this function in the brain. We wanted to address this question by investigating which other brain regions are not only activated together with left lateral PFC, but also functionally connected with this area when task-setting is required. To assess functional connectivity, a Partial Least Square (PLS) multivariate approach was used here to analyze the fMRI data (McIntosh et al., 1996). Our rationale for using this multivariate approach is that brain works as distributed inter-correlated regions rather than as independent voxels.

In summary, we predict that left PFC is selectively involved in setting the criteria for not to respond to distractors associated with a prepotent response tendency in the first phase of the task. We also predict that this region is part of a diffuse functional network including other areas involved in learning task-relevant processes. Among those processes, feature integration between color and letter identity would be necessary to resolve response conflict between distractors and targets. Therefore, we expected superior parietal lobule and superior medial prefrontal cortex to be nodes of this network, given their role in feature integration (Corbetta et al., 1995) and response conflict resolution (Mostofsky and Simmonds, 2008; Rushworth et al., 2007), respectively. Finally, this network is expected not to be required for the other nogo condition (numbers), since those stimuli are easy to distinguish from the targets based on salient semantic differences (numbers vs. letters) and no task-setting is required.

Method

Participants

Fourteen healthy volunteers (8 females; mean age: 27 years, range: 20–34) took part in the study. All the participants reported to have normal or corrected-to-normal vision, normal color vision, and right handedness. The average score on the Edinburgh Handedness Inventory (Oldfield, 1971) was 87 (range: 69–100). For all, English was the native language or a proficient second language for at least 10 years. All of them signed an informed consent that was previously approved by the Ethics Research Board of Baycrest. None reported any

history of psychiatric or neurological disorders. Participants received 50 Canadian dollars in compensation for their time.

Experimental material and design

Visual stimuli were presented foveally against a constantly grey background. Go–nogo stimuli were letters and numbers written in Times New Roman font, and were colored in blue or red (50% each). Go stimuli were "red O" and "blue X" (*targets*), and nogo stimuli were "blue O" and "red X" (*distractors*), on the one side, and red and blue numbers 2 and 3 (*others*), on the other side. Association between color and go–nogo letters were reversed for the other half of the subjects.

Each trial began with a go/nogo stimulus lasting for 300 ms. Deadline for the go response was 2 s after the onset of the go stimulus. A blank screen followed the stimulus presentation. Inter-Stimulus-Interval varied randomly and continuously between 2.2 and 4.2 s. This manipulation was important for the jittering of repetition time with respect to the experimental conditions. Participants performed 2 runs for this task. Each run had 64 *targets* (50%), 32 *distractors* (25%) and 32 *others* (25%). The total number of test trials was 256. Participants were instructed to press a button with the index finger of their dominant hand as soon as they saw a go stimulus (target), and refrain from responding when a nogo stimulus appeared. Thus, the experiment consisted of a 2 run (first vs. second) by 3 task condition (*target*, *distractor*, *other*) factorial design. Six familiarization trials preceded each run. During the presentation of these initial trials, participants received visual feedback about their performance.

Participants additionally performed two other tasks in the scanner (temporal preparation and another Stroop-like task), which are not reported here. The order of presentation of the 3 tasks was counterbalanced across participants.

Image acquisition and data pre-processing

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 s, echo time, TE: 30 ms, 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 a MP-RAGE sequence (TR: 2 s, TE: 2.63 s, 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 acquired for the three tasks in the session (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 a MRI-compatible response pad.

Part of the pre-processing was performed with 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) and for difference in the timing of slice acquisition (program 3dTshift). Six-parameter rigid body inter- and intra-run motion correction was then performed by co-registering volumes to a reference EPI volume (AFNI program 3dvolreg). Co-registration to a functional MNI template (EPI.nii) and spatial smoothing (8-mm Gaussian kernel) was performed in SPM5 (Friston et al., 1995). Group analyses were carried out using PLS, a multivariate analysis software for imaging data (McIntosh et al., 1996). The anatomical scan was first co-registered to the closer of the two functional runs of this experiment in AFNI during reconstruction (program siemenstoafni-beta2), and then co-registered to a structural MNI template (T1.nii) in SPM5.

PLS

PLS is a set of multivariate statistical analyses for neuroimaging data that assess the relations between any set of independent measures, such as the experimental design or activity in a seed region, and a set of dependent measures, in our case the rest of the brain (see McIntosh et al., 1996). PLS carries out the computation of the optimal least squares fit to cross-block correlation between the independent and dependent measures. With respect to principal component analysis (PCA), PLS has the advantage that solutions are constrained to relevant experimental manipulations, behavior or activity of a seed region (McIntosh and Lobaugh, 2004). With respect to more traditional general linear model (GLM) univariate analyses, PLS is more sensitive in detecting distributed patterns of brain activity (McIntosh et al., 2004).

Task-PLS analysis

Task-PLS identifies patterns of brain voxels whose signal change co-varies with the experimental conditions. All the six task conditions (2 runs×3 go/nogo conditions) were included in this analysis. For each condition, the hemodynamic response function (HRF) of each voxel was defined as the intensity difference from trial onset during 7 consecutive post-stimulus temporal lags (lag=2 s TR) averaged across trials. No assumption was made about the shape of HRF, allowing investigation of changes in task-related activity at different lags along the whole temporal segment. The data matrix containing all voxels and associated temporal segments (columns) for all conditions and subjects (rows) was mean-centered column-wise with respect to overall grand average. The matrix was decomposed using singular-value decomposition (SVD) to produce a set of mutually orthogonal latent variables (LVs) with decreasing order of magnitude, analogous to principal component analysis (PCA). Each latent variable consisted of: (i) a singular value, (ii) a pattern of design scores, which identifies the contrasts between task conditions, and (iii) a singular image, which shows how the spatio-temporal distribution across the brain relates to the identified contrasts. Although we had specific a priori hypotheses relating our task conditions and some brain areas, design scores in each LV were determined in a data-driven fashion.

The significance for each LV as a whole is determined using a permutation test (Edgington, 1980). At each permutation, the data matrix rows are randomly reordered and a new set of LVs is calculated each time. The singular value of each new LV is compared to the singular value of the original LV. A probability is assigned to the initial value based on the number of times a statistic from the permuted data exceeds this original value (McIntosh et al., 1996). For the current experiment, 500 permutations were used. If the probability was less than 0.05 then the LV was considered significant. Since the brain scores are derived in a single analytical step, correction for multiple comparisons is not required here.

Voxel saliences are weights that indicate how strongly a given voxel contributes to a LV. To determine the reliability of the saliences for the voxels characterizing each pattern identified by the LVs, all data were submitted to a bootstrap estimation of the standard errors, by randomly re-sampling subjects with replacement 100 times. PLS is recalculated for each bootstrap sample to identify those saliences whose value remains stable regardless of the sample chosen (Sampson et al., 1989). The ratio of the salience to the bootstrap standard error (bootstrap ratio, BSR) is approximately equivalent to a *z* score given a normal bootstrap distribution (Efron and Tibshirani, 1986). For each lag, clusters with at least 15 contiguous voxels with a BSR≥4 (approximately equivalent to a *z*-score corresponding to $p<.0001$) were considered as reliable. Coordinates of the voxel with the peak BSR within each cluster were obtained in MNI space and converted into Talairach space to find the likely gyral locations using Matthew Brett's transformation (http://www.mrccbu.cam.ac.uk/

Umaging/mnispace.html). Approximate Brodmann areas were then identified using the Talairach Daemon tool (Lancaster et al., 2000).

To understand the relation between the polarity of the saliences in the singular image and the direction of HRF change in the areas reliably activated in each LV, it is useful to relate the saliences to the design scores. For instance, positive saliences would indicate areas that are relatively more active in conditions with positive weights in the design scores. Conversely, negative saliences would indicate areas that are relatively more active in conditions with negative weights in the design scores (see Fig. 2 below, for an example).

Multi-block PLS analysis: functional connectivity analysis

The second LV of the task-PLS identified, among others, a region in the left VLPFC (peak voxel Talairach $x=-44$, $y=12$, $z=24$) which showed reliable learning effects selectively for the distractors. These effects were reliable at lags 2 and 3. The HRF values for this voxel and the 26 neighbor voxels in each subject and condition were therefore averaged across lags 2 and 3. Given our a priori hypothesis on the role of this region in task-setting, these values were used as a seed for a functional connectivity PLS analysis to detect the neural network co-varying with the seed and with the experimental conditions. This analysis, known as multi-block PLS, computes the covariance not only between the two blocks of information used in the task-PLS (brain voxels activity and experimental conditions), but also between these blocks and a third one, represented by the activity of the seed in this case, in a single analytical step (e.g., McIntosh et al., 1998). Results from the multi-block PLS were also submitted to permutation and bootstrap testing, as described above. In order to concentrate our discussion on the more reliable clusters, only the saliences that

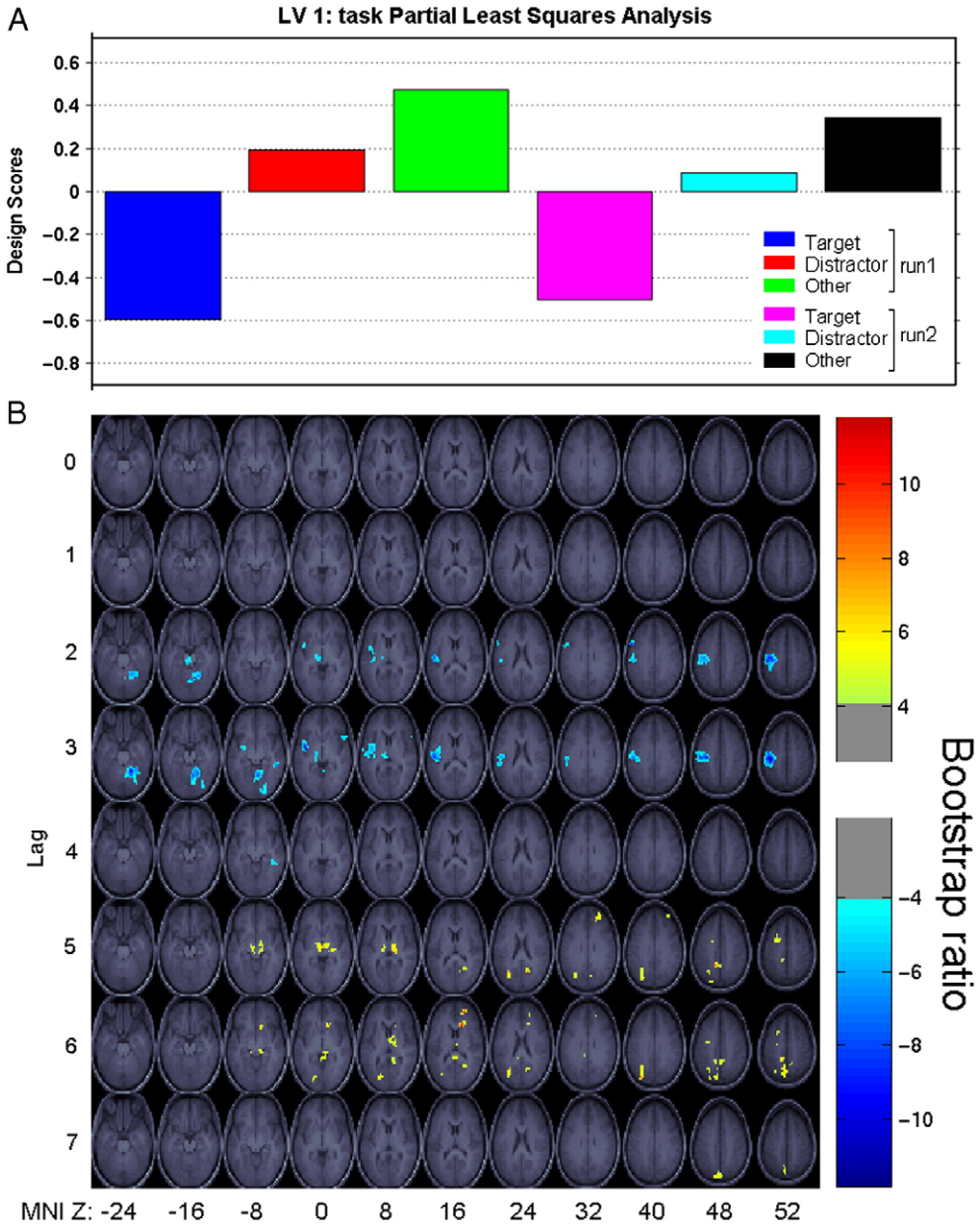

Fig. 1. (A) Design scores for the significant latent variable 1 (LV1) from the task-PLS analysis. (B) Clusters (number of voxels ≥ 15, bootstrap ratio ≥ 4) in which activation was associated to LV1 (singular image). Time from stimulus onset is indicated on the *Y* axis of the singular image and is expressed in lags (1 lag = 2 s repetition time). The *X* axis shows the location of the axial slice in reference to the MNI atlas space. Warm colors indicate clusters with positive bootstrap ratios, which were differentially more activated for task conditions with positive design scores in A, whereas cold colors indicate clusters with negative bootstrap ratios, which were differentially more activated for task conditions with negative design scores. The bootstrap ratio map is superimposed on the average anatomical scans from all 14 participants.

survived a more conservative BSR threshold ≥6 are reported for this analysis.

Results

Behavioral results

The first trial was discarded from analyses. Moreover, since performance on the *other* condition was at ceiling with 99.94% of correct nogo responses, this condition was discarded from subsequent behavioral analyses.

Accuracy

Misses to go-targets and false alarms to nogo *distractors* contrasting first and second runs were analyzed separately with non-parametric Wilcoxon matched pairs tests. These analyses did not show any significant difference between the two runs in the percentage of either false alarms to *distractors* (3.4 vs 3.6%; p=.76)

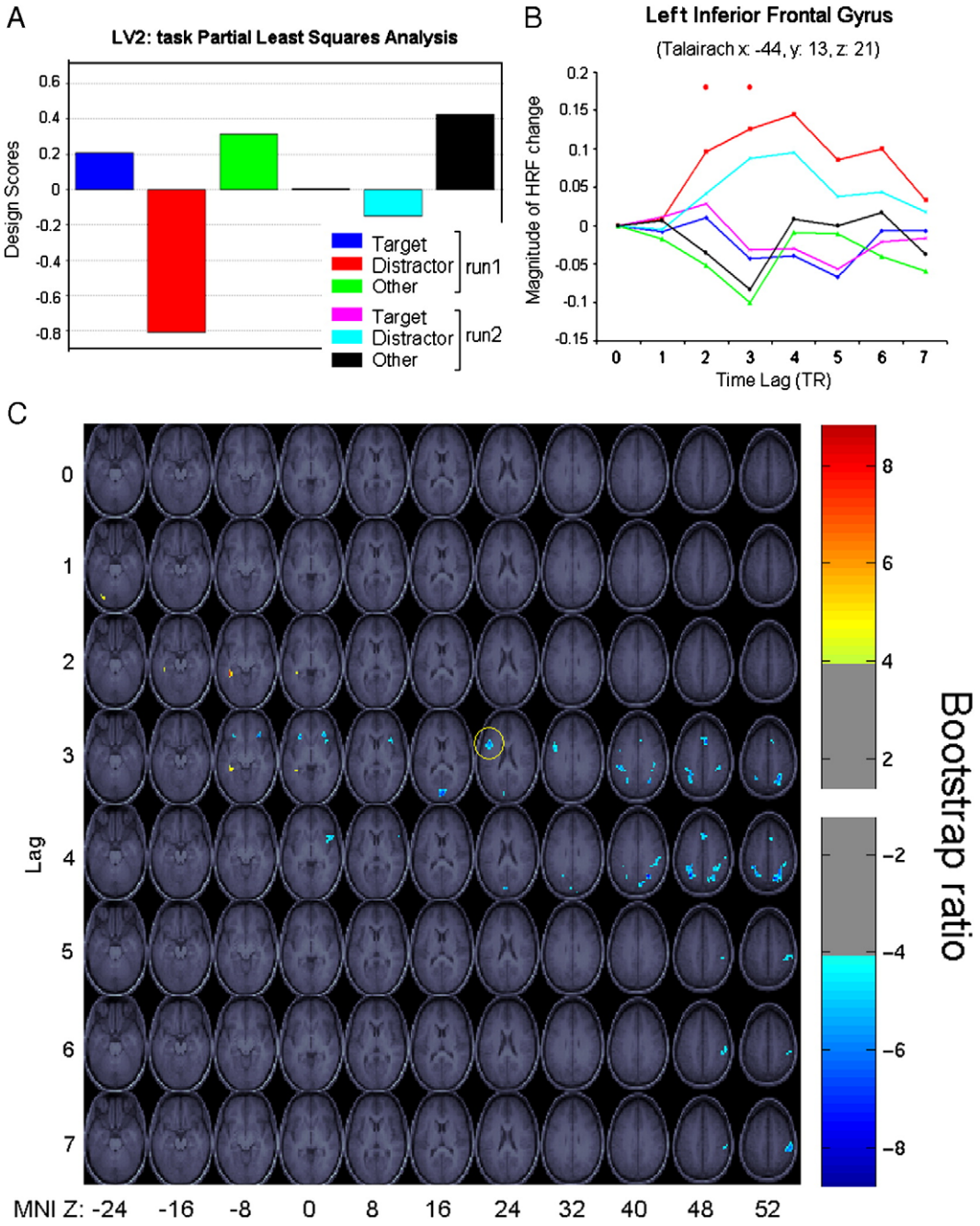

Fig. 2. (A) Design scores for the significant latent variable 2 (LV2) from the task-PLS analysis. (B) Magnitude of average Hemodynamic Response Function (HRF) change in a cluster of 26 voxels adjacent to a voxel with peak bootstrap ratio in the left inferior frontal gyrus. This cluster was used as a seed for the subsequent multi-block PLS analysis. The red dots indicate that LV2 was significant in the time lags 2 and 3 for this particular voxel. (C) Clusters (number of voxels ≥15, bootstrap ratio ≥4) in which activation was associated to LV2. Time from stimulus onset is indicated on the *Y* axis of the singular image and is expressed in lags (1 lag=2 s repetition time). The *X* axis shows the location of the axial slice in reference to the MNI atlas space. Warm colors indicate clusters with positive bootstrap ratios, which were differentially more activated for task conditions with positive design scores in A, whereas cold colors indicate clusters with negative bootstrap ratios, which were more activated for task conditions with negative design scores. The yellow circle in the Lag 3 shows a region in the left inferior frontal gyrus (see B panel), chosen as seed in the following multi-block PLS analysis.

Table 1
Reliable clusters identified for LV1 in the task-PLS analysis (bootstrap ratios≥±4)

Lag	Cluster region	BA	Talairach			Size	Bootstrap
			x	*y*	*z*		
Negative saliences/bootstrap ratios							
2	L postcentral gyrus	2	−48	−25	53	19	−11
2	L middle frontal gyrus	9	−55	10	36	–	−8.2
2	R culmen	–	4	−63	−10	–	−8
2	L postcentral gyrus	43	−51	−18	19	8	−7.9
2	L thalamus	–	−4	−23	1.2	24	−6.7
2	L culmen	–	−4	−32	−15	30	−6.5
2	L superior temporal gyrus	22	−48	0	4	24	−5.5
3	L precentral gyrus	4	−36	−24	56	30	−12
3	R declive	–	20	−55	−14	46	−9.8
3	R inferior semi-lunar lobule	–	16	−64	−41	19	−8.7
3	R middle temporal gyrus	22	48	−39	−1	8	−7.5
3	L thalamus: ventral posterior medial nucleus	–	−16	−19	1	24	−5.6
3	L uvula	–	−24	−75	−23	30	−5.6
3	R lingual gyrus	17	12	−89	−2	24	−5.5
4	R parahippocampal gyrus	19	40	−43	−1	30	−6.1
Positive saliences/bootstrap ratios							
5	L precuneus	7	−12	−48	47	17	8.1
5	R thalamus: ventral lateral nucleus	–	12	−11	4	127	7.9
5	R medial frontal gyrus	9	20	40	27	23	7.0
5	R precuneus	31	16	−61	25	27	6.9
5	L superior frontal gyrus	6	−24	7	62	42	6.9
5	L middle temporal gyrus	39	−32	−61	25	61	6.9
5	R pyramis	–	12	−79	−26	35	6.8
5	L tuber	–	−44	−64	−27	25	5.8
6	R caudate body	–	16	20	14	25	11.8
6	R medial frontal gyrus	10	20	47	12	20	9.9
6	L pyramis	–	−16	−83	−33	16	9.1
6	L precuneus	19	−32	−76	41	117	7.1
6	R caudate head	–	12	15	−4	17	6.7
6	R thalamus: ventral lateral nucleus	–	16	−15	8	31	6.6
6	L middle occipital gyrus	18	−24	−81	8	20	6.1
6	L paracentral lobule	5	−12	−40	54	18	5.9
6	L cerebellar tonsil	–	−44	−49	−38	20	5.9
6	R thalamus	–	8	−27	−2	51	5.6
6	L superior occipital gyrus	19	−32	−73	22	19	5.5
6	R precuneus	31	20	−57	21	18	5.5
6	R uvula	–	12	−83	−26	21	5.2
6	L posterior cingulate	29	0	−42	17	19	5.0
7	L postcentral gyrus	7	−8	−59	69	79	7.8

Lag refers to the time period, in TRs of 2 s each, after stimulus onset during which the peak bootstrap ratio occurred. Cluster region and BA indicate the locations and Brodmann areas as determined by reference to Talairach and Tournoux (1988). *x*, *y*, and *z* indicate voxel coordinates in Talairach space. Size denotes the number of contiguous voxels included in the cluster. Bootstrap refers to the bootstrap ratio, which is an index of reliability across participants.

or misses to targets (1.9 vs. .9%; $p=.75$). An additional Wilcoxon test was carried out to directly compare misses and false alarms (run factor collapsed). This test was significant ($z=2.2$, $p<.05$), demonstrating that participants made more false alarms to *distractors* than misses to targets (3.5 vs. 1.4%).

Reaction times (RTs)

A sufficient number of RT data was obtained for targets only. Therefore, RTs were analyzed for this condition only. A 2 sample *t*-test demonstrated that go responses to targets became significantly faster from run 1 to run 2 (696 vs. 673 ms; $t(13)=2.16$, $p<.05$).

fMRI data

Task-PLS results

This analysis identified two significant LVs (LV1, explained cross-block variance=35.3%, $p<.004$; LV2, explained cross-block variance=25.8%, $p<.044$). The design scores for these two LVs are shown in Figs. 1A and 2A, respectively.

The first LV differentiated between go *targets* and nogo conditions, especially *others*. The clusters with negative and positive saliences are listed in Table 1 and are shown in Fig. 1B. The negative saliences in LV1 correspond to greater activity for *targets* (whose design scores are negative) in both runs. Reliable negative saliences spanned the first portion of the examined time-window (lags 2–4). The positive saliences in LV1 correspond to greater activity for *others* (whose design scores are also positive), and to a minor extent for *distractors*, than for *targets* in both runs. Reliable positive saliences spanned the late portion of the examined time-window (lags 5–7).

The second LV was more relevant for the aim of the present study. This LV differentiates the *distractors* from the *target* and *other* conditions but mostly in the first run, with the design score for this condition reduced by almost a factor of 5 in the second run (Fig. 2A). This indicates that brain regions identified by this LV are likely to be involved in setting the criteria to learn the task, especially for the most difficult *distractor* condition. The clusters with positive and negative saliences are listed in Table 2 and are shown in Fig. 2B according to the time-lag. The negative saliences identified clusters whose pattern of activation mainly differentiated *distractors* (negative design scores) from the other two conditions (positive design scores) in the first run. The brain regions showing negative saliences were located in the left inferior frontal gyrus and claustrum, fusiform gyrus, visual areas and cerebellum, right inferior and medial frontal gyrus, superior temporal gyrus, and post-central gyrus, and bilateral superior and inferior parietal lobules. The positive saliences indicate areas mainly involved in *other* or *target* conditions and only included left cerebellum, parahippocampal and fusiform gyri.

Multi-block PLS results

This analysis was run to assess functional connectivity between a region in the left inferior frontal gyrus (VLPFC), identified in the second LV of the previous analysis and the rest of the brain, and how the connectivity pattern co-varies with the different task conditions. This analysis also yielded two significant LVs (LV1, explained cross-block variance=23.4%, $p<.002$; LV2, explained variance=17.4%, $p<.016$). The design scores (saliences) for these two LVs are shown in Figs. 3A and 4A, respectively.

Table 2
Reliable clusters identified for LV2 in the task-PLS analysis (bootstrap ratios≥±4)

Lag	Cluster region	BA	Talairach			Size	Bootstrap
			x	*y*	*z*		
Negative saliences/bootstrap ratios							
3	R inferior frontal gyrus	47	32	27	−5	38	−7.9
3	L claustrum	–	−28	23	−1	16	−7.1
3	L cuneus	18	0	−88	19	28	−6.9
3	L inferior parietal lobule	40	−48	−33	38	74	−6.8
3	R superior parietal lobule	7	28	−52	54	22	−6.8
3	R medial frontal gyrus	6	8	14	47	30	−6.8
3	L inferior frontal gyrus[a]	9	−44	13	21	54	−6.2
3	R inferior parietal lobule	40	40	−29	42	42	−6.2
4	R precuneus	7	16	−63	51	179	−8.8
4	L superior parietal lobule	7	−32	−60	47	102	−8.0
4	L cuneus	19	−4	−84	30	18	−7.3
4	R superior temporal gyrus	22	48	11	−4	30	−6.6
4	R medial frontal gyrus	8	4	22	43	24	−6.3
5	R postcentral gyrus	40	59	−29	49	25	−5.9
6	R postcentral gyrus	2	59	−21	49	22	−5.9
7	R postcentral gyrus	40	51	−32	50	40	−6.8
Positive saliences/bootstrap ratios							
1	L declive	–	−32	−75	−20	16	6.1
2	L parahippocampal gyrus	36	−40	−35	−8	20	8.7
3	L fusiform gyrus	37	−36	−39	−8	18	6.2

See Table 1 for an explanation of the meaning of each column.
[a] This voxel and the 26 surrounding neighbor voxels were chosen as a seed for the subsequent functional connectivity analysis (see text for details).

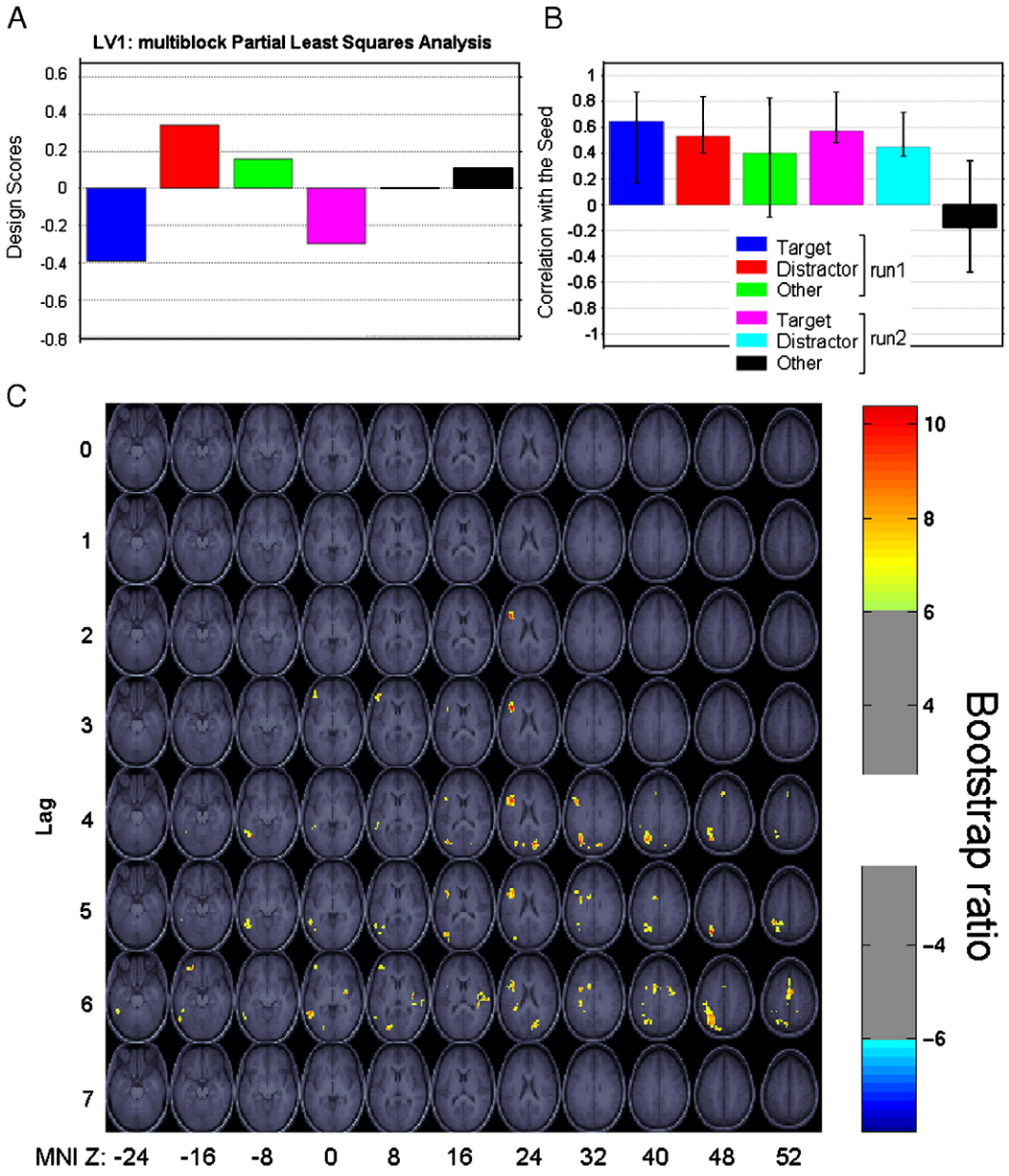

Fig. 3. (A) Design scores for the significant latent variable 1 (LV1) from the multi-block PLS analysis. (B) Pattern of correlation between the seed and the other clusters expressed in the LV1 as a function of the task condition. (C) Clusters (number of voxels ≥ 15, bootstrap ratio ≥ 6) in which activation was associated to LV1 from the multi-block PLS analysis. Time from stimulus onset is indicated on the *Y* axis of the singular image and is expressed in lags (1 lag = 2 s repetition time). The *X* axis shows the location of the axial slice in reference to the MNI atlas space. Warm colors indicate clusters differentially more activated for task conditions with positive design scores in A, which have a positive bootstrap ratio, whereas cold colors indicate clusters more activated for task conditions with negative design scores, which have a negative bootstrap ratio.

The first LV distinguished nogo *distractors* and, to a minor extent, *others* (positive design scores) from go *targets* (negative design scores) in the first run only. The design scores for *targets* and *others* do not change substantially from the first to the second run, whereas the design score for *distractors* was high in the first run and close to 0 in the second run (note the similarity with saliences of LV2 in the task-PLS analysis). Therefore, this LV shows which brain regions functionally connected with the seed are involved in learning to distinguish *distractors* from *targets*. The clusters extracted by this LV are listed in Table 3 and are shown in Fig. 3C. Fig. 3B shows the correlations between the identified networks and the seed. No clusters with negative saliences (corresponding to greater activity for *targets* in both runs) survived the threshold (BSR ≥ 6) in this LV.

The greater activity for *distractors* in the first run than in the second one (positive saliences) included, on the left hemisphere, inferior, middle and superior frontal gyri, superior parietal lobule, premotor areas, anterior cingulate, middle temporal gyrus and fusiform gyrus; on the right hemisphere, medial frontal gyrus, claustrum, cerebellum, and cuneus; and bilaterally, pre- and post-central gyri. Apart from left inferior and middle frontal gyri, the role of the other areas started to emerge from lag 4 on. Correlation with the seed is positive for *distractors* in both runs. This indicates that the identified brain areas constitute a functionally connected network that shares the same pattern of activations/deactivations with the seed, even when activation of this network is low for *distractors* in the second run.

A modest contribution to the activation of this network is also played by the *other* condition in both runs (see design scores in Fig. 3A). However, for this condition, the positive correlation between the identified areas and the seed in the first run shows large confidence intervals that include the 0 value, and is almost null in the second run

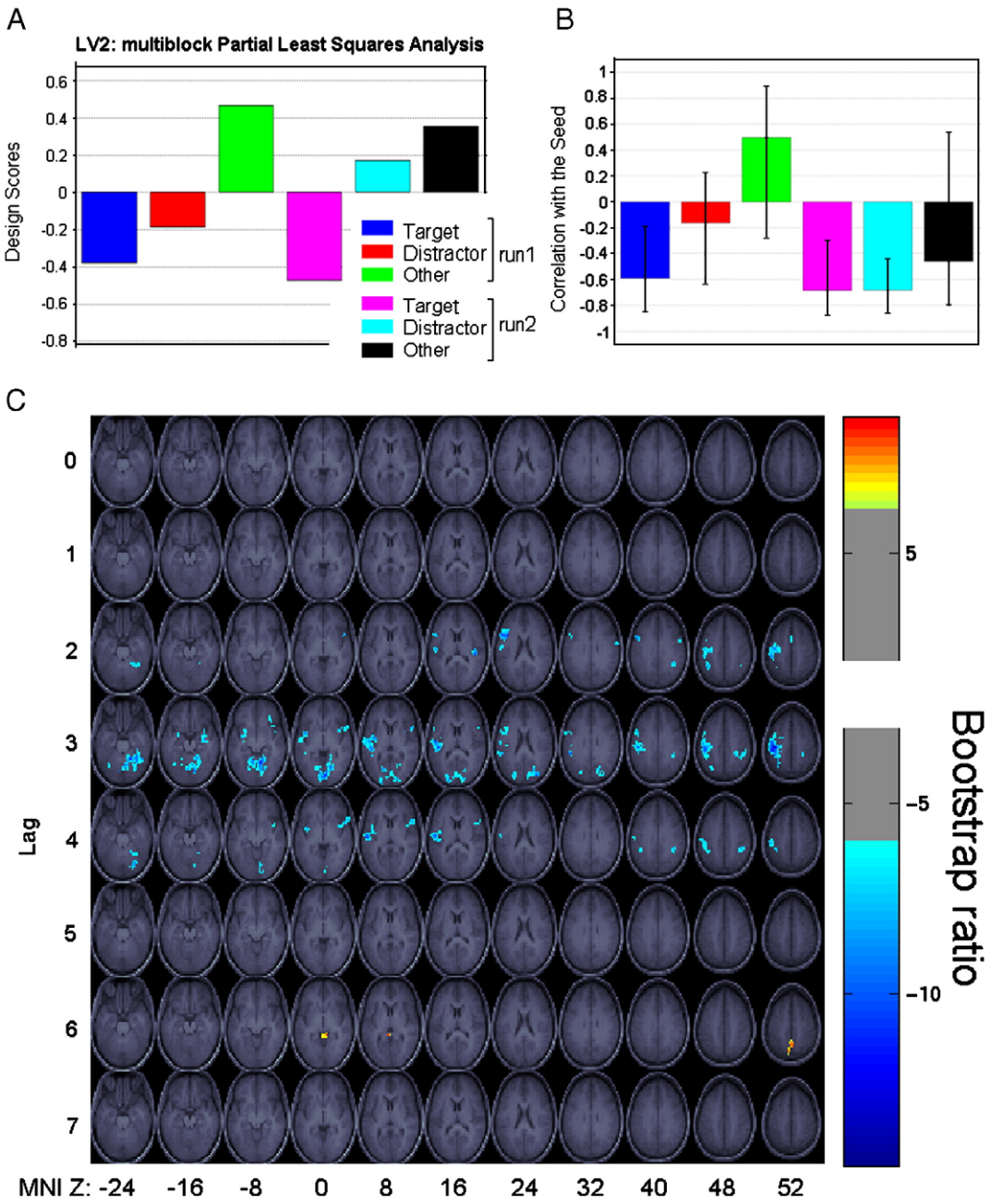

Fig. 4. (A) Design scores for the significant latent variable 2 (LV2) from the multi-block PLS analysis. (B) Pattern of correlation between the seed and the other clusters expressed in the LV2 as a function of the task condition. (C) Clusters (number of voxels ≥15, bootstrap ratio ≥6) in which activation was associated to LV2 from the multi-block PLS analysis. Time from stimulus onset is indicated on the *Y* axis of the singular image and is expressed in lags (1 lag=2 s repetition time). The *X* axis shows the location of the axial slice in reference to the MNI atlas space. Warm colors indicate clusters differentially more activated for task conditions with positive design scores in A (and positive bootstrap ratio), whereas cold colors indicate clusters more activated for task conditions with negative design scores (and negative bootstrap ratio).

(Fig. 3B). These results suggest that the network identified does not show reliable connectivity for the *other* condition.

The second LV mainly distinguished a network more activated for *targets* (negative design scores) from another network more activated for *others* (positive design scores) but also shows, to a minor extent, learning effects concerning *distractors* (negative design scores in the first run turning into positive in the second run, see Fig. 4A). Negative saliences spanned lags 2–4 and included areas such as claustrum, middle frontal gyrus, cerebellum, and post-central gyrus, on the left hemisphere; medial frontal gyrus and parahippocampal gyrus, on the right hemisphere; and inferior frontal gyrus, insula, pre-central gyrus, inferior parietal lobule, and cerebellum, bilaterally. The correlation with the seed in the clusters identified by LV2 is shown in Fig. 4B. For the *target* condition in both runs, there is negative correlation with the seed. This means that the more the seed was activated (less deactivated, in this case) in a subject for the *target* conditions, the more this network was activated (i.e., more negative brain scores).

Positive saliences only included left precuneus and right parahippocampal gyrus at the sixth lag (see Table 4 and Fig. 4C). The basically null correlation for *distractors* in the first run turns into negative in the second run. This indicates that these two regions were more activated for *distractors* in the subjects that activated the seed less in the second run (possibly suggesting an automatized performance in this condition, relying on more posterior regions). Finally, *others* show even stronger opposite effects from the first to the second run, with the correlation with the seed changing from negative

Table 3
Reliable clusters identified for LV1 in the multiblock PLS analysis (bootstrap ratios≥±6)

Lag	Cluster region	BA	Talairach			Size	Bootstrap
			x	*y*	*z*		
Positive saliences/bootstrap ratios							
2	L middle frontal gyrus	46	−44	17	21	29	9.5
3	L middle frontal gyrus	46	−44	17	21	38	10.3
3	L inferior frontal gyrus	46	−48	39	5	29	7.6
4	L middle frontal gyrus	9	−40	9	25	88	10.3
4	L inferior temporal gyrus	37	−40	−62	−4	19	9.7
4	R cuneus	18	16	−76	26	52	9.6
4	L superior parietal lobule	7	−32	−68	44	188	9.2
4	L middle temporal gyrus	22	−48	−42	6	21	8.4
4	L medial frontal gyrus	8	−8	29	39	17	7.9
5	L superior parietal lobule	7	−32	−68	48	80	10.4
5	L inferior frontal gyrus	45	−44	13	18	68	9.9
5	L superior parietal lobule	7	−20	−48	58	40	9.0
5	L middle temporal gyrus	37	−40	−62	7	39	8.9
5	L middle temporal gyrus	19	−40	−77	22	31	8.8
5	L postcentral gyrus	3	−40	−28	60	17	8.2
5	L cingulate gyrus	24	−8	−2	37	19	8.1
5	L middle temporal gyrus	37	−44	−62	−4	23	7.4
5	R medial frontal gyrus	6	8	−1	59	18	7.3
6	L superior parietal lobule	7	−36	−68	44	186	10.2
6	L middle occipital gyrus	18	−24	−81	8	18	9.1
6	L cingulate gyrus	31	−24	−41	28	27	9.0
6	R medial frontal gyrus	6	8	−1	55	72	8.9
6	R vermis	–	4	−33	−32	16	8.8
6	L cingulate gyrus	24	−12	6	37	59	8.6
6	L middle temporal gyrus	37	−59	−51	−1	46	8.6
6	R postcentral gyrus	7	20	−47	65	17	8.5
6	L precentral gyrus	6	−32	2	33	53	8.5
6	R precentral gyrus	6	36	−6	33	20	8.4
6	R claustrum	–	36	−15	8	44	8.3
6	R cuneus	18	12	−76	26	19	8.1
6	R postcentral gyrus	43	51	−19	16	30	8.0
6	L superior frontal gyrus	6	−20	7	62	18	8.0
6	L fusiform gyrus	37	−51	−44	−18	19	7.5

See Table 1 for an explanation of the meaning of each column.

to positive. However, similar to LV1, the confidence intervals appear to be large and to include 0 value for the *other* condition in both runs. This pattern demonstrates no functional connectivity with the seed for the *other* condition.

Discussion

Task-setting, the capacity to initially set up task-relevant criteria, has been attributed to left lateral PFC (Alexander et al., 2005; 2007; Fletcher et al., 2000; Stuss and Alexander, 2007). The aim of the present study was to identify the brain network that is functionally connected with this region to support task-setting in a task that requires learning the criteria for not to respond to some stimuli (*distractors*) despite a prepotent tendency to respond. Accuracy data show that participants make most errors for the *distractor* condition in both a first and a second run. Analysis of responses to go stimuli (*targets*) shows that participants get faster from the first to the second run. This pattern suggests that participants learn how to perform the task more efficiently, at least in terms of speed of execution, although RT data are not available for correct nogo responses, for obvious reasons.

A task-PLS analysis of the fMRI data was used here as a first step to identify which brain regions changed their activity as a function of practice (first vs. second run) and task condition (*targets*, *distractors*, *others*). Particularly, we aimed at detecting a distributed pattern of brain regions involved in learning to set the criteria for not to respond, in the condition where a prepotent response should be overcome (*distractors*). This analysis allowed us to identify two sets of brain regions underlying different effects of the experimental conditions, which were comprehensively captured by two significant latent variables (LVs). A first LV distinguished between go and nogo stimuli. More relevant for the present study, the second LV identified regions involved in learning the criteria not to respond to *distractors*, since the contribution of the regions faded from the first to the second run selectively for this condition.

Left lateral (particularly ventrolateral) PFC was one of the activated regions (BA 9, Talairach coordinates of the most stable voxel: *x*: −44, *y*: 13, *z*: 21). This result corroborates previous neuropsychological evidence showing a critical role of this area in the *distractor* condition of a similar task (Alexander et al., 2007). However, in the neuropsychological study, *distractors* were associated to a different response from *targets*, rather than to a no response, as required by the go/nogo structure of the task used here. Therefore, the current results extend previous ones to a condition in which the criteria to be set in order to overcome a prepotent response tendency concerned a non-response, without the need to produce an alternative motor response. These results confirm those of a recent fMRI study, where left lateral prefrontal cortex showed a reduced activation after an extensive amount of practice with a task requiring rule retrieval (Fincham and Anderson, 2006). Moreover, previous imaging literature has generally shown learning-related changes in left lateral prefrontal cortex (Bunge 2004; Fletcher et al., 2000; Raichle et al., 1994). There is also neuropsychological evidence that this region is critical in acquiring the criteria in the initial phase of the task in several domains (e.g., Alexander et al., 2005; Shallice et al., 2008).

Based on this previous evidence, we selected this region as a seed for a subsequent multi-block PLS analysis. This analysis showed that the seed was functionally connected to a range of other regions, with which it correlated in terms of activation/deactivation patterns in a manner closely related to some task conditions. The first LV showed a network of regions that positively correlated with the left VLPFC seed, and was mainly activated for *distractors* in the first run and deactivated for *targets* in both runs. This LV, therefore, shows a

Table 4
Reliable clusters identified for LV2 in the multiblock PLS analysis (bootstrap ratios≥±6)

Lag	Cluster region	BA	Talairach			Size	Bootstrap
			x	*y*	*z*		
Negative saliences/bootstrap ratios							
2	L precentral gyrus	6	−28	−13	60	149	−11.8
2	L inferior frontal gyrus	9	−44	9	22	93	−10.9
2	R insula	13	44	−26	16	17	−10.4
2	L inferior parietal lobule	40	−40	−48	50	17	−9.4
2	R culmen	–	28	−52	−21	29	−8.7
2	L postcentral gyrus	43	−51	−18	19	23	−8.6
2	R medial frontal gyrus	6	8	3	59	17	−8.4
2	R precentral gyrus	6	63	−2	33	19	−7.7
3	L postcentral gyrus	3	−44	−21	53	418	−14.5
3	R culmen	–	8	−58	−4	732	−12.4
3	L insula	13	−44	−15	19	206	−11.1
3	L inferior parietal lobule	40	−51	−37	28	22	−10.1
3	R inferior semi-lunar lobule	–	16	−64	−37	24	−9.8
3	L middle occipital gyrus	18	−20	−92	19	62	−9.0
3	L declive	–	−32	−63	−20	21	−8.7
3	L middle frontal gyrus	9	−51	6	37	61	−8.7
3	R supramarginal gyrus	40	40	−41	35	47	−8.6
3	R hippocampus	–	36	−12	−13	19	−8.6
3	L claustrum	–	−36	−8	−6	33	−8.5
3	R precentral gyrus	44	51	8	11	49	−8.4
4	L transverse temporal gyrus	41	−51	−19	12	130	−12.7
4	R inferior frontal gyrus	44	55	16	10	66	−9.7
4	R culmen	–	32	−55	−21	32	−8.8
4	R declive	–	28	−75	−16	24	−8.6
4	R inferior parietal lobule	40	40	−41	39	31	−8.3
4	L inferior parietal lobule	40	−44	−44	43	83	−8.2
4	R lingual gyrus	18	8	−74	−3	25	−7.2
Positive saliences/bootstrap ratios							
6	L precuneus	7	−4	−63	58	20	8.1
6	R parahippocampal gyrus	30	8	−39	2	50	7.9

See Table 1 for an explanation of the meaning of each column.

learning effect at the level of a neural network specific for the *distractor* nogo condition.

After showing local functional connectivity within left lateral PFC (BA 46) at lag 3 (i.e., 6 s post-stimulus onset), the seed becomes functionally connected with a more widely distributed network. A node of this network, starting to emerge at lag 4 (8 s post-stimulus onset), was located in the posterior portion of the superior medial frontal gyrus, especially on the right (BA 6, Talairach coordinates: *x*: 8, *y*: −1, *z*: 55), probably corresponding to the supplementary motor area (SMA). Previous evidence has suggested that the SMA, and especially the pre-SMA portion, plays an important role in resolving cognitive conflict selectively at the response level (Milham et al., 2001; Rushworth et al., 2007). This region is in fact involved in response suppression, by sending the immediate inhibitory input to the motor areas involved in the response (Goldberg, 1985; Tanji and Kurata, 1985; Vidal et al., 1995). Lesions to this region cause an increase of false alarms to nogo stimuli (e.g., Picton et al., 2007). Micro-stimulations of the SMAs can suppress ongoing movements (e.g., Fried et al., 1991; Fried, 1996). A role of this region in suppressing a response has also been found with the stop-signal paradigm, both in neuropsychological (Floden and Stuss, 2006) and in imaging studies (Aron et al., 2007). Therefore it is possible that this region contributes to the suppression of an inappropriate but prepotent response in the presence of *distractors*, especially in the initial phase of the task.

Previous neuropsychological work has also shown that the superior medial prefrontal region is important to activate ('energize') task-relevant processes, since patients with lesions in this region show increased RTs especially, but not only, in demanding task conditions (e.g., Alexander et al., 2005, 2007; Stuss et al., 2002, 2005). Moreover, lesions to this region cause maximal impairment in both accuracy and speed in the incongruent condition of a classical Stroop task (i.e., reading a color word written with an incongruent color; Stuss et al., 2001). Since in that study the incongruent condition was administered in a block, the authors interpreted the result as failure of maintenance of consistent activation ('energization') of the intended response in the incongruent condition.

It is not clear whether the same or different areas within superior medial prefrontal cortex play a role in selection and suppression of a response. It is possible that the two processes are different aspects of the same energization mechanism, that is of paramount importance not only when a response is required, but also when the circuitry responsible for suppressing a prepotent tendency to respond needs to be activated. Based on evidence from different imaging methodologies, Mostofsky and Simmonds (2008) propose that some of the neural circuits involved in response selection overlap with neural substrates of response suppression. In line with the present findings, the authors focused on the pre-SMA as a critical area for both response selection and suppression. To confirm this view, or to possibly find dissociations between sub-areas within the same SMA region, future studies are clearly needed that directly compare conditions requiring activation of a non-prepotent response and suppression of a prepotent response in the same sample of subjects.

Left superior parietal lobule (BA 7, Talairach coordinates: *x*: −32, *y*: −68, *z*: 48) was also part of this network. The present task requires feature integration between color and letter identity. Activation in this area has been previously found during feature integration tasks (Corbetta et al., 1995) and visual attention in general (Wojciulik and Kanwisher, 1999). This area may also play an inhibitory role in selective attention, suppressing task-irrelevant *distractors* (Wojciulik and Kanwisher, 1999), probably by implementing task-related selection biases established by the prefrontal areas (Corbetta and Shulman, 2002; Wager and Smith, 2003). Previous imaging studies have shown learning-related decreases in the activation of fronto-parietal regions as arbitrary rules (both verbal and non-verbal) became more familiar (Chein and Schneider, 2005; Deiber et al., 1997). In line with these studies, the current findings show functional connectivity between frontal and parietal regions as a function of learning.

Moreover, cross-talk between the prefrontal seed and temporal regions (e.g., left inferior and middle temporal gyrus) may be important for building up a neural representation of task rules during the learning phase (Bussey et al., 2002; Messinger et al., 2001) and for retrieval of these rules later on (Bunge, 2004). Finally, primary and associative visual areas (e.g., fusiform gyrus) have already been shown to functionally interact with the left prefrontal cortex, when top-down attention has to distinguish relevant and irrelevant visual material (Gazzaley et al., 2007).

The requirement to withhold a response in the presence of a nogo stimulus is not sufficient to activate this learning network, as shown by the unreliable pattern of functional connectivity for the *others* condition. Moreover, the learning effects reflected by this LV cannot be simply attributed to unspecific adaptation or habituation as a function of time spent on the task, because LV1 of the task-PLS analysis does not show any decrease in activation in another network related to a different combination of task conditions (i.e., mainly contrasting *targets* and *others*). Additionally, LV2 of the multi-block PLS analysis does not show learning effects for *targets* and *others* either (see next paragraph).

The second LV of the multi-block PLS analysis showed a complementary network which was more activated for the go stimuli than for the nogo ones. This network is likely to be involved in response preparation and execution as required by go *targets*. The involvement of sensorimotor areas, cerebellum, inferior parietal lobule, among other areas, in the early portion of the BOLD response corroborates this interpretation. This network also showed functional connectivity with the seed in the left prefrontal cortex in some task conditions, such as *targets* in both runs and, importantly, *distractors* in the second run. Assuming that this network is involved in response preparation and execution, it is conceivable that it has to be deactivated in the presence of nogo *distractors* in order to perform the task well. The degree to which this deactivation occurs is inversely proportional to the degree to which the seed is still activated in the second run. This suggests that participants who still activate the seed in the second run do not suppress this motor network adequately in the distractor nogo condition. Finally, for the *other* nogo stimuli, this network is mainly deactivated in both runs. Moreover, connectivity with the seed is unreliable for this condition (as indicated by confidence intervals crossing the 0 value).

In conclusion, the present multivariate analysis approach identified two distinct functional networks underlying the performance in a go/nogo task. On the one side, go stimuli require a network involved in response preparation and execution. On the other side, nogo stimuli, especially those in which a suppression of a prepotent response is required (*distractors*), involve a different network. This network is modulated by learning, since it is more important in the first part of the task, when the task criteria to not to respond need to be still acquired, than in the second part, when task performance becomes more efficient. A critical node of this task-setting network was the left VLPFC, which was chosen as the initial seed to perform functional connectivity analysis. The importance of this area in setting the criteria to perform the task, which has already been shown in previous literature (e.g., Alexander et al., 2005, 2007), is confirmed here and extended to a task in which the rules to be established concern a non response. Functional connectivity analysis unveiled the "neural team" which sculpted the task space in the first phase of the experiment. Left ventrolateral prefrontal cortex is, indeed, a node of a more distributed network, spanning frontal, parietal and temporal regions, which underlies learning task criteria.

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