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Short communication

Differential dorsolateral prefrontal cortex activation during a verbal *n*-back task according to sensory modality

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ABSTRACT

Functional neuroimaging studies carried out on healthy volunteers while performing different *n*-back tasks have shown a common pattern of bilateral frontoparietal activation, especially of the dorsolateral prefrontal cortex (DLPFC). Our objective was to use functional magnetic resonance imaging (fMRI) to compare the pattern of brain activation while performing two similar *n*-back tasks which differed in their presentation modality. Thirteen healthy volunteers completed a verbal 2-back task presenting auditory stimuli, and a similar 2-back task presenting visual stimuli. A conjunction analysis showed bilateral activation of frontoparietal areas including the DLPFC. The left DLPFC and the superior temporal gyrus showed a greater activation in the auditory than in the visual condition, whereas posterior brain regions and the anterior cingulate showed a greater activation during the visual than during the auditory task. Thus, brain areas involved in the visual and auditory versions of the *n*-back task showed an important overlap between them, reflecting the supramodal characteristics of working memory. However, the differences found between the two modalities should be considered in order to select the most appropriate task for future clinical studies.

Functional neuroimaging studies in psychotic disorders have often focused on the prefrontal cortex, since dysfunctions of this region may play a central role in their pathophysiology [21,26,27]. Working memory, which has been linked to dopaminergic function in the dorsolateral prefrontal cortex (DLPFC), is one of the cognitive domains that has been most often studied in this context [1,10,25]. Working memory impairments have been found in numerous neuropsychiatric disorders involving dopaminergic dysfunction, and especially in psychotic disorders such as schizophrenia [3,8,14,28] and bipolar disorder [11,19].

Working memory has been defined as the process by which a remembered stimulus is held "on-line" to guide behaviour in the absence of external cues or prompts [12]. It has been proposed that working memory may be based on a system that consists of a central executive, a phonological loop, a visuospatial sketchpad and an episodic buffer [2], and the DLPFC [Brodmann area (BA) 9/46] has been identified as being a key region for working memory function [18,20]. However, its neural basis remains poorly specified. The so-called "*n*-back" tasks have been widely used to evaluate working memory. In these tasks, the subject is required to monitor a series of stimuli and to respond whenever a stimulus is presented that is the same, or is located in the same position, as the one presented "*n*" trials previously, where "*n*" is a pre-specified integer, usually 1, 2, or 3. These *n*-back tasks require on-line monitoring, updating, and manipulation of remembered information, and are therefore assumed to place great demands on a number of key processes within working memory. The different *n*-back tasks can be classified according to the type of stimulus presented, and according to the type of monitoring process required during the task. Regarding the type of stimulus, approximately half of all published studies have employed verbal stimuli (e.g. letters and words), whereas the remaining presented nonverbal stimuli (including shapes, faces and pictures). Concerning the type of monitoring required, in some studies it was the identity of the stimulus that had to be monitored, whereas in others it was the location of the stimulus [17].

Functional neuroimaging studies that have been carried out on healthy volunteers during performance of the different *n*-back tasks

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have shown a common pattern of bilateral frontoparietal activation, especially of the DLPFC, which is relatively independent of the type of *n*-back task employed [16]. Thus, in the meta-analysis by Owen et al. [17], the DLPFC was found to be consistently activated both in the global meta-analysis including 24 studies with different *n*-back tasks, and in the three subsidiary meta-analyses which included 12 studies of *n*-back tasks with identity monitoring of verbal stimuli, 6 studies involving *n*-back tasks with identity monitoring of nonverbal stimuli, and 5 studies of *n*-back tasks with location monitoring of nonverbal stimuli.

Few studies have been carried out to investigate the potential differences in DLPFC activation according to the sensory modality (visual or auditory) used to present stimuli, and their results have been contradictory. A PET study comparing the visual and auditory presentation of letters in a 3-back task found an almost complete overlap of activation patterns, which involved the DLPFC [22]. However, a more recent functional magnetic resonance imaging (fMRI) study [6] found differences such as a greater activation of the posterior parietal cortex during the visual *n*-back task, and a greater activation of the left DLPFC during the auditory *n*-back task. We are not aware of any other fMRI studies investigating differences in DLPFC activation during a working memory task according to the sensory modality used.

Our objective was to compare the pattern of brain activation in a sample of healthy volunteers while performing an auditory verbal *n*-back task with identity monitoring, and while performing a similar *n*-back task but presenting visual stimuli. Our working hypothesis was that, although both tasks would activate the DLPFC, there would be a greater prefrontal activation in the auditory than in the visual *n*-back task.

Thirteen healthy, right-handed Spanish volunteers (7 male, 6 female), with a mean age of 30.0 (SD = 8.19) years, participated in this study. Before the scan was performed, the *n*-back tasks were explained to and practised by the participants. The general exclusion criterion was a score below 75% in the practice session. In order to exclude possible neuropsychiatric disorders, a semistructured interview based on the M.I.N.I. Screen [23] was used as a screening instrument. Informed consent was obtained from all subjects prior to testing.

The working memory paradigm used was the 2-back task, in which letters are presented sequentially and the subject must indicate when the current letter is identical to the letter that appeared two steps before in the sequence. In our study, participants completed two tasks which differed in their modality of presentation: an auditory verbal *n*-back task and a visual verbal *n*-back task. The order of the tasks was counterbalanced (7 participants performed the visual task first, while the remaining 6 started with the auditory modality). A block design was used, where each of the two modalities (visual and auditory) was composed of 6 blocks: 3 one-minute blocks of a one-letter search task (control condition) alternating with 3 one-minute blocks of a 2-back task (activation condition). Each block began with a two-second instruction: "letter A" (for the control condition) or "2 back" (for the activation condition). Participants were instructed to respond when the current stimulus matched the stimulus 2-back in the activation condition, and when the current stimulus matched the target stimulus ("A") in the control condition, for both the visual and auditory modalities. In the visual task, after the initial instruction a sequence of 29 letters, of which 13.8% were target stimuli, was presented one at a time for 500 ms, with an inter-stimulus interval (ISI) of 1500 ms. All stimuli were black capital letters (Times New Roman, size 80) presented centrally on a white background. In the auditory task, 23 letters presented sequentially conformed each block; 15.9% of the letters were target stimuli. Every trial (stimulus + ISI) lasted 2500 ms. Letter sounds were presented binaurally through VisuaStim (Resonance Technologies) fMRI-compatible headphones, and sound volume was adjusted so that each participant could hear the stimuli properly.

A 1.5 T GE Excite scanner was used for data acquisition in this study. The functional sequences were acquired using a single-shot gradient-echo EPI sequence with the following parameters: TE: 40; TR: 3000; flip angle: 90; bandwidth: 62.5; NEX: 1; matrix: 64×64; slice thickness 3 mm with no gap. The whole brain was covered with 38 axial slices parallel to the AC-PC line. A morphological volumetric axial T1-weighted sequence (3D SPGR, TR: 12,000; TI: 450; TE: 5; thickness: 1.2; matrix: 256×192; 1 NEX) was acquired in order to superimpose statistical maps.

Image processing and analyses of fMRI data were performed using SPM5. After realignment and co-registration using 12-parameter affine transformations, images were spatially normalized ($3\ mm^3$) (MNI coordinates) and smoothed with a Gaussian kernel (FWHM 6 mm). Data for each participant was modelled using a boxcar design convolved with the hemodynamic response function and time derivative. Motion correction parameters from realignment were included as regressors of non-interest at this first level, and a high pass filter with a cut-off period of 128 s was applied. Single-subject contrast images were then used in a second level analysis which included one sample *t*-test ($p < 0.05$) for each task. Differential activation contrasts were obtained using within-subject ANOVA at $p < 0.005$ (uncorrected for multiple comparisons), and activation of common areas was obtained using an ANOVA-based conjunction analysis of both tasks at $p < 0.05$, FDR corrected. MNI coordinates were transformed into Talairach coordinates [24] using the nonlinear transformation described by Matthew Brett (MNI2TAL).

None of the participants encountered any difficulties while performing the two *n*-back task scanning sessions, with all subjects eliciting over 75% correct responses. In the auditory task, accuracy in the control and 2-back conditions was 99.30% (SD = 2.52) and 91.61% (SD = 7.84) respectively; in the visual task, accuracy in the control and activation conditions was 99.36% (SD = 2.31) and 91.67% (SD = 7.61) respectively. No significant differences were found between accuracy in the visual control task and in the auditory control task, or between accuracy in the visual *n*-back and in the auditory *n*-back task.

In order to study brain activation patterns, three types of analyses were performed (Fig. 1). A conjunction analysis was used to identify supramodal activation areas for both tasks (Table 1a; $p < 0.05$, FDR corrected); our results show a bilateral activation of frontoparietal areas including the DLPFC. The auditory (working memory-control) minus visual (working memory-control) analysis (Table 1b) shows areas with a greater activation during the

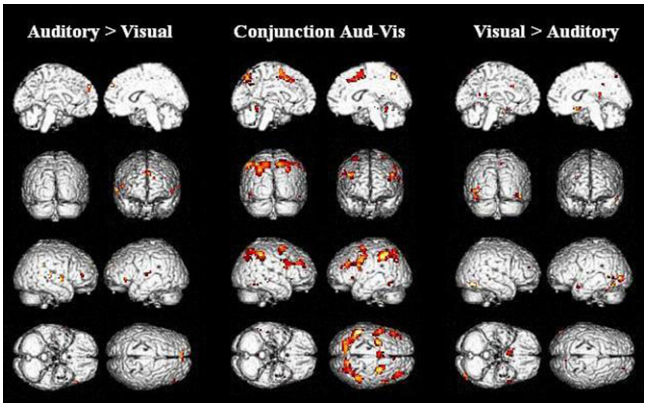

Fig. 1. Working memory domain-specific regions of activation (extent threshold $k = 10$ voxels; $p < 0.005$, uncorrected). The central images show common areas that are activated by both auditory and visual contrasts ($p < 0.05$, FDR-corrected).

Table 1
Brain areas that show (a) conjunction (common activation) during the auditory and visual *n*-back tasks; (b) greater activation during an auditory, compared to a visual, *n*-back task; (c) greater activation during a visual, compared to an auditory, *n*-back task.

	p value	Number of voxels	T score	Peak Talairach coordinates		
				x	y	z
(a) Conjunction [FDR-corrected $p < 0.05$]						
L superior frontal gyrus (BA 6)	0.003	190	5.62	−3	6	54
L medial frontal gyrus (BA 6)	0.004		5.44	−3	0	60
R medial frontal gyrus (BA 6)	0.015		4.08	6	27	42
L inferior frontal gyrus (BA 9)	0.005	305	5.17	−51	3	36
L middle frontal gyrus (BA 9)	0.006		5.03	−45	27	30
L inferior frontal gyrus (BA 9)	0.011		4.33	−42	6	30
L sub-gyral (BA 6)	0.002	128	5.99	−27	−3	57
L middle frontal gyrus (BA 6)	0.003		5.60	−24	−6	48
L inferior parietal lobule (BA 40)	0.001	638	7.73	−42	−45	39
L precuneus (BA 7)	0.002		6.54	−27	−69	39
	0.004		5.47	−27	−54	39
L cerebellum (anterior lobe culmen)	0.016	26	4.01	0	−51	−12
R superior frontal gyrus (BA 9)	0.008	150	4.63	39	36	30
R middle frontal gyrus (BA 9)	0.011		4.39	57	15	33
R middle frontal gyrus (BA 46)	0.011		4.35	45	21	27
R middle frontal gyrus (BA 6)	0.004	164	4.29	33	3	54
R sub-gyral (BA 6)	0.006		4.90	24	0	54
R precuneus (BA 7)	0.002	449	6.09	15	−66	51
R inferior parietal lobule (BA 40)	0.002		6.06	42	−45	51
	0.005		5.18	45	−36	39
(b) Auditory (WM-control) minus visual (WM-control) [uncorrected $p < 0.005$]						
L superior frontal gyrus (BA 9)	<0.001	25	4.07	−3	54	33
R superior frontal gyrus (BA 9)			3.33	9	57	36
L inferior frontal gyrus (BA 47)	0.002	10	3.30	−51	27	−6
L superior temporal gyrus (BA 41)	<0.001	14	4.22	−42	−24	12
R superior temporal gyrus (BA 22)	<0.001	23	4.80	60	−3	0
R superior temporal gyrus (BA 41)	<0.001	17	4.21	51	−27	9
(c) Visual (WM-control) minus auditory (WM-control) [uncorrected $p < 0.005$]						
L inferior temporal gyrus (BA 19)	<0.001	59	4.14	−48	−78	−3
L middle occipital gyrus (BA 18)	<0.001		4.09	−42	−84	−3
L inferior occipital gyrus (BA 19)	<0.001		4.04	−39	−75	−3
L cingulate gyrus (BA 32)	<0.001	12	4.82	−12	15	30
L posterior cingulate (BA 30)	<0.001	11	4.52	−21	−54	15
L fusiform gyrus (BA 37)	<0.001	35	4.79	−42	−63	−18
L cerebellum	<0.001		4.09	−30	−54	−24
L parahippocampal gyrus (BA 19)	0.001	14	3.65	−36	−45	−3
R subcallosal gyrus (BA 25)	<0.001	26	4.95	6	9	−15
R fusiform gyrus (BA 37)	<0.001	40	4.35	48	−60	−15
	<0.001		4.33	39	−63	−15
R fusiform gyrus (BA 19)	<0.001		4.06	45	−69	−15
R cingulate gyrus (BA 31)	<0.001	10	4.10	24	−45	36
R sub-lobar thalamus	<0.001	16	3.91	12	−39	15

BA: Brodmann area; WM: working memory.

auditory than during the visual modality ($p < 0.005$, uncorrected). These regions are primarily located in auditory processing areas of the temporal lobe and in (predominantly left) frontal areas. On the other hand, the visual (working memory-control) minus auditory (working memory-control) analysis shows areas with a greater visual than auditory activation (Table 1c). These regions are mainly located in posterior occipital, temporal and parietal areas, as well as in the anterior cingulate. However, no other frontal areas appear to be more activated during the visual task than during the auditory task. Other differences in regional activation are shown in Table 1.

The *n*-back task is probably the most widely used task in neuroimaging studies of working memory [17]. However, different studies have used the auditory and visual versions of this task, without taking into account the possible differences between these two modalities. The present study performs a within-subject comparison of the two sensory modalities, showing that they involve more common than different brain areas, in line with results of a previous fMRI study of similar characteristics [6].

The conjunction analysis for the two types of *n*-back task showed a frontoparietal activation pattern that was common to both sensory modalities and includes the DLPFC. Thus, it may be inferred that working memory depends on a number of supramodal brain areas that are not specific to the sensory input mode, and thus the sensory modalities may be interchanged without expecting important differences in brain activation patterns.

However, our results do show some differences in regional activation depending on the sensory modality used, and these variations should be considered when designing working memory studies. Some of the differential activation is located in regions that are specific to each type of input. Thus, the visual *n*-back task elicits greater activation in occipital areas, while the auditory task does the same in the superior temporal lobe. These differences arise as a result of the increased encoding demands required for the activation (2-back) task as compared to the control task (0-back).

In addition, our results show differences in areas that are involved in working memory processes. The most relevant difference found was the greater bilateral activation of the DLPFC in the auditory when compared to the visual *n*-back task. This suggests that the auditory version elicits a greater implication of the central executive than the visual task [7], perhaps due to the more intrusive nature of auditory stimuli, or to the fact that scanner noise may interfere with stimulus delivery. Thus, the auditory task would be

more sensitive when studying differences in the central executive.

Exploring the inverse condition (greater visual than auditory activation), we only found differences in anterior cingulate activation, but not in frontal regions. The anterior cingulate cortex is thought to play a central role in the neural mechanisms that underlie conflict monitoring and adjustments in cognitive control [4], and its activity is interpreted as reflecting a need for increased effort, complexity, or attention [17]. In short, the auditory version of the *n*-back task seems to require more of the central executive, while the visual version requires more selective attention.

Different pharmacological approaches are currently being developed which aim to improve cognitive function in psychotic disorders, and especially in schizophrenia. Several strategies have been proposed to improve working memory [13], such as D1 agonists [15] and COMT inhibitors [9], as well as other non-dopaminergic drugs [5]. Given the fact that one of the strategies for evaluating treatment efficacy is to measure changes in the activation of the DLPFC when performing different *n*-back tasks, a better knowledge and understanding of the different activation patterns elicited by different modalities of the task will help improve study designs, and will contribute to the development of better therapeutic approaches for cognitive deficits in psychotic disorders.

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