Research Report

Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task

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ABSTRACT

It has been suggested that cocaine addiction affects the engagement of the frontoparietal networks in executive functions, such as attention and working memory. Thus, our objective was to investigate brain differences between cocaine-dependent subjects and healthy controls during the performance of a verbal working memory task. Nineteen comparison men and nineteen cocaine-dependent men performed a 2-back task. Data were acquired on a 1.5-T Siemens Avanto. Image processing and statistical analyses were carried out using SPM5; Biological Parametric Mapping (BPM) was used for further morphometric and correlation analyses. No performance differences were found between groups. However, the dorsal part of the right inferior parietal cortex (BA 40) was less activated in the cocaine-dependent group. Cocaine patients did not overactivate any brain area when compared with controls. Our results show reduced activation in the brain areas related to the attention system in cocaine-dependent men while performing a verbal working memory task. Chronic cocaine use may affect the attentional system in the right parietal lobe, making patients more prone to attentional deficits.

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1. Introduction

Neuropsychological studies report that chronic stimulant-dependent subjects, such as cocaine addicts, have problems in executive tasks (Beatty et al., 1995; McKetin and Mattick, 1997; Iwanami et al., 1998). These processes share the involvement of the frontoparietal networks at different degrees. A recent meta-analysis with neuropsychological data found that the principal differences between abstinent cocaine abusers and matched controls lay in attentional functioning (Jovanovski et al., 2005). Specifically, cocaine users perform poorly in measures of selective (Simon et al., 2000; Verdejo-García et al., 2005) and sustained attention (Morgan et al., 2006). It is known that such functions involve the parietal, frontal, and anterior cingulate cortices (Cabeza and Nyberg, 2000).

Cocaine addiction has been suggested to affect the engagement of the frontoparietal networks in attention (Hester and Garavan, 2004; Tomasi et al., 2007; Kubler et al., 2005). Tomasi et al. (2007) showed the involvement of the frontoparietal network during a working memory task and noted performance differences between groups. The frontal and parietal regions were seen to be hyperactivated in cocaine-dependent patients. Particularly, right parietal activation lowered as memory load increased (Hester and Garavan, 2004; Tomasi et al., 2007). These results were interpreted as a larger involvement of frontoparietal networks to support working memory in cocaine-dependent patients as a compensatory mechanism of performance deficits. However, an equivalent performance between groups of participants is particularly important in this kind of study since (1) it reduces the number of false-positive and false-negative activations (Murphy and Garavan, 2004), (2) group differences in performance can create artifactual differences in activation patterns (Kubler et al., 2005; Murphy and Garavan, 2004), (3) abnormal functional activations are difficult to interpret as a cause or a consequence of the performance deficit (Price and Friston, 1999).

Another possible source of variability in cocaine addiction is the transient change in the reduction of gray matter volume. Several studies have found a reduction in gray matter volume in the frontal and cingulate areas (Lim et al., 2008; Matochik et al., 2003; Tanabe et al., 2009), and more importantly, this reduction positively correlates with impaired performance in frontotemporal tasks (Tanabe et al., 2009; Fein et al., 2002). Assumably, underlying anatomy is a related factor with brain functionality but is rarely taken into account jointly with functional activations. Therefore, beyond the interactions between task-related activation and level of performance, anatomical differences should be carefully controlled to obtain conclusive results (Barrós-Loscertales et al., 2008; Casanova et al., 2007).

The aim of this study is to compare the brain activation patterns between a comparison group and a cocaine-dependent group in an auditory verbal working memory task. In order to better interpretation of functional differences, good performance on 2-back tasks was expected of all the subjects and individual differences in gray matter volume were controlled within regions of functional differences. Typically, 2-back tasks yield bilateral and wide activations in the frontoparietal networks and the anterior cingulate. As neuropsychological tests reveal, specific attentional (but not working memory) problems in cocaine-dependent men, we hypothesized that cocaine-dependent patients would show reduced activation in the shared attention-working memory brain areas.

2. Results

Table 1 shows the behavioral results obtained during the functional Magnetic Resonance Imaging (fMRI) experiment. As expected, a repeated measure 2 condition (0-back, 2-back) × 2 group (controls, patients) ANOVA analysis showed no group effect. There was only a significant condition effect in the accuracy and response time (RT) data (p < 0.01) with more errors and longer RTs in the 2-back condition than in the 0-back condition for both groups. The interaction group × condition analysis was not significant.

Both the comparison group and the cocaine-dependent group showed a similar activation pattern in the [2-back > 0-back] condition contrast (see Table 2, Fig. 1), which is in agreement with previous studies in our research group (Forn et al., 2007a, 2007b) as well as another (Tomasi et al., 2007). Regression analyses using first-used-cocaine age and years of cocaine use as covariates did not present any significant association with task-related activation (p > 0.01).

The comparison made between groups revealed that the right inferior parietal cortex was more activated in the comparison group than in the cocaine-dependent group (p < 0.001, uncorrected; activation cluster size threshold (k) = 20; Z = 4.00 at the local maximum x, y, z = 53, −36, 40; see Fig. 2a). Notice that this result is not significant at an a priori defined FWE corrected cluster extent threshold (see Experimental procedures section). In order to test for the effects on functional activation of the transient changes of gray matter volume reduction due to cocaine addiction, we conducted a voxelwise gray matter volume correlation with functional activation within the restricted ROI (right inferior parietal cortex) for each group separately. These analyses did not report any significant association (p > 0.01). Furthermore, anatomical differences in terms of GMV were not present before a threshold of p > 0.02 was reached. However, when gray matter volume effects were regressed out in the ANCOVA analysis, the statistical significance increased the magnitude and size of functional effect cluster surviving a FWE correction at cluster level (p < 0.05, FWE corrected; Z = 4.77 at the local maximum x, y, z = 60, −42, 39; k = 125 when a FWE-corrected cluster extent threshold at p < 0.05 was set at 54 voxels/cluster) in the right inferior parietal cortex (Fig. 2b). There was no other focal point of significant functional differences between groups across the whole brain when applying a p < 0.001, uncorrected.

3. Discussion

The results of our study show differences in the pattern of brain activation in the right inferior parietal cortex (BA40) in a cocaine-dependent group compared to a matched control group during a working memory task, while task performance did not differ between groups. Moreover, we show that the
Functional brain activation. Thus, functional differences and white matter changes may have important effects on existence of individual variability in gray matter volumes could increase the magnitude and size of the functional effect cluster, likely due to better modeling of anatomically related variance (Oakes et al., 2007). Cocaine addiction is related to spread reductions in gray matter density and volume in the frontal, parietal, temporal lobes (Matochik et al., 2003; Tanabe et al., 2009; Franklin et al., 2002), and the cerebellum (Sim et al., 2007), as well as frontal (Lim et al., 2002, 2008), insular (Lyoo et al., 2004), and callosal (Moeller et al., 2005) white matter. Gray and white matter changes may have important effects on functional brain activation. Thus, functional differences between groups may be affected by structural changes. Therefore, we apply BPM as a good instrument to voxel-by-voxel control for anatomically related variance effects such as GMV effects or misalignment after spatial transformations in our data set (e.g., normalization). In our study, the covariation of structural effects increased the magnitude and size of the functional contrast between groups.

Overall, the n-back task shows the activation in the frontoparietal networks in both patients and matched controls, which coincides with previous reports of this task (Forn et al., 2007a, 2007b; Owen et al., 2005; McMillan et al., 2007). This pattern of activation reflects the joint activity of the lateral and medial premotor cortex, the dorsal cingulate, the dorsolateral and ventrolateral prefrontal cortex, the frontal poles, and the medial and lateral posterior parietal cortex when performing n-back tasks. When we compare the task-related activation between groups regressing out structural effects and taking into account that groups did not differ in terms of task performance, a consistently reduced activation in the right inferior parietal cortex is seen in patients. This result is in agreement with a previous study, which revealed the reduced activation in the parietal areas of cocaine-addict patients during attentional switching in the course of a verbal working-memory task when task performance was equaled between subgroups of the studied sample (Kubler et al., 2005).

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Comparison group</th>
<th>Cocaine-dependent group</th>
<th>Difference (p &gt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coordinates global maxima</td>
<td>Activation cluster size</td>
<td>z score</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>44/45/47</td>
<td>45, 10, 22</td>
<td>375</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>44/45/47</td>
<td>39, 7, 30</td>
<td>491</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>9/10/46</td>
<td>45, 27, 24</td>
<td>570</td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>9/10/46</td>
<td>36, 47, 17</td>
<td>491</td>
</tr>
<tr>
<td>Left medial frontal gyrus</td>
<td>6/8</td>
<td>6, 31, 40</td>
<td>363</td>
</tr>
<tr>
<td>Right medial frontal gyrus</td>
<td>6/32/8</td>
<td>42, 36, 38</td>
<td>627</td>
</tr>
<tr>
<td>Left inferior parietal cortex</td>
<td>40/7</td>
<td>50, 39, 41</td>
<td>778</td>
</tr>
<tr>
<td>Left superior temporal gyrus</td>
<td>21/22</td>
<td>53, 32, 7</td>
<td>113</td>
</tr>
<tr>
<td>Right superior temporal gyrus</td>
<td>21/22</td>
<td>56, 26, 4</td>
<td>152</td>
</tr>
<tr>
<td>Left thalamus/left caudate</td>
<td>12, 4</td>
<td>12, 0, 0</td>
<td>294</td>
</tr>
<tr>
<td>Right caudate</td>
<td>12, 4</td>
<td>12, 0, 0</td>
<td>294</td>
</tr>
<tr>
<td>Left cerebellum</td>
<td>42, 65, 19</td>
<td>1511</td>
<td>5.33</td>
</tr>
<tr>
<td>Right cerebellum</td>
<td>42, 65, 19</td>
<td>1511</td>
<td>5.33</td>
</tr>
</tbody>
</table>

Coordinates global maxima in Talairach coordinates; z score = standardized score.

Table 1 – Mean scores (standard deviations in parentheses) of the main demographic characteristics and the behavioral results of the percentage of correct responses, percentage of commissions, and response time (RT) of the cocaine-dependent and comparison groups.

<table>
<thead>
<tr>
<th></th>
<th>Comparison group</th>
<th>Cocaine-dependent group</th>
<th>Difference (p &gt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.20 (8.86)</td>
<td>32.40 (7.56)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Years of education</td>
<td>8.53 (1.46)</td>
<td>9.00 (1.73)</td>
<td>n.s.</td>
</tr>
<tr>
<td>General intellectual functioning</td>
<td>10.87 (2.59)</td>
<td>9.27 (2.31)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Percentage of correct responses (0-back condition)</td>
<td>99.39% (2.35)</td>
<td>100% (0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Percentage of correct responses (2-back condition)</td>
<td>88.49 % (6.40)</td>
<td>87.88 % (8.87)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Percentage of commissions (0-back condition)</td>
<td>0.33% (0.69)</td>
<td>0.56% (0.81)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Percentage of commissions (2-back condition)</td>
<td>2.99% (3.42)</td>
<td>3.10% (3.00)</td>
<td>n.s.</td>
</tr>
<tr>
<td>RT (0-back condition)</td>
<td>540.85 (51.67)</td>
<td>531.76 (96.84)</td>
<td>n.s.</td>
</tr>
<tr>
<td>RT (2-back condition)</td>
<td>711.36 (91.20)</td>
<td>700.16 (128.02)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

a Differences between groups (n.s. = no significance).

b Standard score in the Matrix Reasoning test (WAIS-III).

c Percentage obtained from the total of possible correct responses for each condition (over 11 possible correct).

d Percentage obtained over the total of possible commissions for each condition (over 58 possible commissions).

* In milliseconds.
Our study replicates this previous result in a verbal working memory task without attentional switching contingencies, and moreover, it shows that gray matter volume variability can have an important effect on cognitive-related activations in a study that tests for functional deficits in cocaine-dependent patients.

Differential brain activation in a task can be interpreted in accordance with behavior, and it improves when recordings of brain activation and performance are done simultaneously. Cocaine dependence has been related to a wide range of cognitive and affective dysfunctions, and fMRI has proven to be an invaluable technique to study these drug-related changes (see Aron and Paulus, 2007, for a review). Abnormal functioning is usually associated with lower task performance in cocaine-dependent patients after long-term cocaine use. When assuming an actual executive functional deficit associated with cocaine dependence, the need for equal task performance in order to test for functional differences is proposed (Price et al., 2006). The results under these conditions may also help to better interpret functional differences when behavioral performance is not equaled. Thus, equal patient performance to a matched control group improves the interpretation of functional differences in the dysfunction sense. Furthermore, it reduces the caveat of an abnormal response or artifacts as a consequence of patients not being able to perform the task (Murphy and Garavan, 2004; Price and Friston, 1999; Price et al., 2006; Goldstein et al., 2009). Therefore, if patients are able to perform the task at the same level as controls, observed hypoactivation is not interpreted as a possible true or artifactual effect of task performance differences (e.g., are patients doing something different?), but as drug-related functional changes in the underlying neural circuitry affected after long-term drug consumption. Otherwise, the reduced activation in the patient group that equals the performance of a matched control group can be interpreted as more efficient neural processing, just as it has already been related to normal cognitive functioning (Mattay et al., 2003, 2006). However, it is difficult to be applied in this case since cocaine-dependent patients typically show cognitive deficits in executive tasks and reduced activations associated with a worse performance.

The right inferior parietal lobule maintains bidirectional connections to the right dorsolateral prefrontal cortex and anterior insular cortex and has been implicated in processes of...
sustained and selective attention, voluntary attentional control, inhibitory control, and switching (Corbetta and Shulman, 2002). Previous research with working memory tasks suggests that the dorsal part of the inferior parietal cortex may be part of a general executive attentional network (Chein et al., 2003; Corbetta et al., 2000; Wojciulik and Kanwisher, 1999). Specifically, Ravizza et al. (2004) proposed this role for this brain area in contraposition to the ventral part of the inferior parietal cortex that was more related to spatial processing. The different activation pattern at the right inferior parietal cortex in our study is consistent with previous fMRI results (Tomasi et al., 2007; Kubler et al., 2005), and it could be related with neuropsychological studies, showing the possibility that cocaine users perform poorly in measures of selective and sustained attention like other studies have shown (Simon et al., 2000; Verdejo-García et al., 2005; Pace-Schott et al., 2008).

Notably, Tomasi et al. (2007) obtained inter-group performance differences and proposed that hyperactivation of the inferior parietal cortex within cocaine users reflects increased attention and control processes that compensate behavioral differences in a capacity-constrained response across the working memory load. A capacity-constrained load response in the parietal cortex (Linden et al., 2003) has been considered consistent with findings showing that this region is a key neural locus of capacity limitations in working memory (Todd and Marois, 2004), even at low-load conditions in normal participants with lower task performance (Nyberg et al., 2009) and in cocaine-dependent patients (Tomasi et al., 2007). Therefore, the interpretation of an executive attentional functioning and working memory-related involvement of the reduced parietal cortex activation in the cocaine-dependent patients of our study are not divorced, but neuroanatomically associated (Garavan et al., 2000). In our study, no significant area of increased activation is seen in patients when compared to controls, which excludes any of the hypothesized compensatory activation. We might consider that the lack of compensatory activation in the frontal lobes, as expected to be reflected by others (Tomasi et al., 2007), could be an effect of using a task that is not really challenging, which most of the patients and matched controls did not have problems to perform.

In short, our functional results suggest that chronic cocaine use may affect the attentional executive system in the right parietal lobe, making patients more prone to continued drug abuse. However, we should consider that although a reduced activation of the right inferior parietal region may be associated with an attentional executive deficit in working memory, its functionality might not be essential in verbal working memory processes when neither task performance is compromised nor other areas show a compensatory activation, at least at a level at which patients can perform the task.

It is important to notice the difficulty of obtaining a homogeneous sampling of the cocaine-dependent group in a study like this one, besides the recruitment of patients with a mono-addiction pattern to cocaine or without possible comorbidity with other psychiatric diseases (Sareen et al., 2006). Likewise, it is important to notice the limitation of our study related to the small size of the sample that could be conditioning our results. Nevertheless, several studies in cocaine dependence have used similar sample sizes given the difficulty in recruiting homogeneous groups. On the other hand, it would be interesting to test for the effects in functional results of the period of abstinence (Lim et al., 2008; Kosten et al., 1998), as well as withdrawal symptoms after a craving-induced state (Sinha et al., 2005; Duncan et al., 2007) in cognitive task performance of cocaine-dependent patients. However, it was not possible to study these effects in our sample given a low control on the patterns of relapses in the clinical history of each patient. In this sense, a variable that was not considered in detail in both groups was the screening of habits of consumption for alcohol, which have been shown to have an important effect on neuroadaptation changes after alcohol abstinence (Cosgrove et al., 2009). Future research will overcome the limitations of the present study and make the most of its results.

In conclusion, further studies on executive functioning in which a worse behavioral performance in cocaine-dependent patients compromises the right inferior parietal cortex will clarify its involvement in working memory and executive functioning by applying the present results to avoid the caveat of performance and anatomical effects on functional activation. This research could represent the first step toward a better understanding of different disrupted pattern activation in cocaine-dependent patients and its effects on attention processing to clarify the involvement of the parietal regions in patterns of cocaine use and abuse. Diverse studies have established the prefrontal cortex as the main neural substrate that holds the neurocognitive pattern and the addiction process in cocaine-dependent subjects. Nonetheless, new studies are required to provide more empirical data about the relevance of other brain areas like the parietal cortex.

### 4. Experimental procedures

#### 4.1. Participants

The participants were 19 cocaine-dependent men and 19 comparison men. All the participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). General intellectual functioning was assessed with the Matrix Reasoning test from the WAIS-III (Wechsler, 2001). An initial study of their clinical history and a subsequent onsite evaluation by a neuropsychologist and a psychiatrist ensured that both groups were physically healthy with no major medical illnesses or DSM IV Axis I disorders, no current use of psychoactive medications, and no history of head injury with loss of consciousness or neurological illness. All the patients were recruited at the time they turned to the clinical service for cocaine addiction in which they had been going during a mean (standard deviation, SD) of 15.58 months (12.64) before the scanning session. They were not under pharmacological treatment, and four of them had occasionally received a palliative treatment of anxiety/depressive symptoms. None of the participants were taking psychoactive medication at the time they were recruited for the experiment. The participants of the control group had no history of psychoactive substance dependence or abuse.

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**Note:** The text above is a transcription of the provided document. It has been formatted for readability and coherence, but the content remains the same. The document appears to be part of a scientific study on the effects of cocaine on brain function, focusing on the role of the right inferior parietal cortex in executive attentional processes. It discusses the methodology, results, and implications of the research, highlighting the challenges in recruiting homogeneous groups and the need for further studies to clarify the involvement of various brain areas in cocaine dependence. The text also touches on the limitations of the study and the importance of future research in this area.
A urine toxicology test was done to rule out cocaine consumption, which ensured a minimum period of abstinence of over 4/5 days prior to the acquisition of fMRI data, as with any urine test done at the clinic during treatment. Two patients were excluded due to positive urine toxicology onsite fMRI context. Given the absence of a formal validation of the 2-back task, we included participants with a performance of over 70% and less than 6% of commission errors in the 2-back task during the fMRI scanning session. Furthermore, participants performed a similar version of the task prior to the scanning session in order to control for learning differences of the task procedure. One patient and one control were excluded because they did not meet the performance criteria of accuracy during the scanning session. One patient and three controls performed a similar version of the task prior to the fMRI scanning session. Furthermore, participants with performance of over 70% and less than 6% of commission errors in the 2-back task, we included participants with a performance of over 70% and less than 6% of commission errors in the 2-back task. Moreover, twelve patients (80% of the final sample) and nine patients (60%), four patients (26.7%), and one patient (6.7%) presented a consumption pattern without abuse of alcohol, cannabis, and amphetamine, respectively. Participants were informed of the nature of the research and were provided with a written informed consent prior to participating in this study.

### 4.2. Paradigm

The paradigm consisted of an auditory working memory task that had been previously used by our research group (Forn et al., 2007a, 2007b). The task sequentially presents alphabetical letters (a single-female speaker approach was used to record the stimuli) in random order, and participants were instructed to press a response button whenever they heard the letter “A” (0-back, control condition) or whenever they heard that the current letter was the same as the two before it (2-back, activation condition). The paradigm was based according to a block design (1 min/block) with 3 blocks for each condition. Each block contained 23 letters with a duration of 750 ms every 2.5 s. Each block was preceded by an auditory instruction of the condition. There were 11 possible correct responses for each condition during the task. Before scanning began, subjects were trained with a computerized practice version lasting 6 min in which they received feedback from the experimenter about their performance. Performance data were collected during the MRI session.

### 4.3. fMRI acquisition

Blood oxygenation level-dependent (BOLD) fMRI data were acquired on a 1.5-T Siemens Avanto (Erlangen, Germany). Subjects were placed in the MRI scanner in a supine position. Their heads were immobilized with cushions to reduce motion artifact. Auditory stimuli were presented through fMRI-compatible headphones (Resonance Technologies, Northridge, CA), which ensure a correct auditory presentation of the stimulus over the scanner noise level (Tomasi et al., 2005), and a response system was used to control performance during the scanning session (Responsegrips, NordicNeuroLab). Stimulus presentation was controlled by the Presentation® software (http://www.neurobs.com).

A gradient-echo T2*-weighted echo-planar MR sequence was used for fMRI (TE = 50 ms, TR = 3000 ms, flip angle = 900,

matrix = 64 × 64, voxel size = 3.94 × 3.94 with 5 mm thickness and 0 mm gap). We acquired 29 interleaved axial slices parallel to the anterior–posterior commissure (AC–PC) plane covering the entire brain. Prior to the functional MR sequence, an anatomical 3D volume was acquired by using a T1-weighted gradient echo pulse sequence (TE = 4.9 ms; TR = 11 ms; FOV = 24 cm; matrix = 256 × 224 × 176; voxel size = 1 x 1 x 1).

### 4.4. Statistical analyses

#### 4.4.1. Image preprocessing

Image processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM5). All the functional volumes were realigned for the former, corrected for motion artifacts, coregistered with the corresponding anatomical (T1-weighted) image, and normalized (voxels rescaled to 3 mm$^3$) with the normalization parameters obtained after anatomical segmentation within a standard stereotactic space (T1-weighted template from the Montreal Neurological Institute—MNI) to present functional images in coordinates of a standard stereotactic space. In addition, the time series of hemodynamic responses were high-pass filtered (256 s) to eliminate low-frequency components. To investigate the relationships between functional activation and the gray matter structure, we used Biological Parametric Mapping (BPM), a newly developed statistical toolbox that allows multimodal magnetic resonance imaging analysis (Casanova et al., 2007). Gray matter volume (GMV) maps were preprocessed using the voxel-based morphometry toolbox (VBM5.1; http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM5. The VBM preprocessing combined tissue segmentation, bias correction, and spatial normalization into a unified model. Otherwise, default parameters were used. GMV segmented images weremodulated for nonlinear warping only removing global brain volume effects from the data to allow inferences on local GM changes. Functional and GMV maps were smoothed using an 8-mm Gaussian kernel to provide a similar smoothing to both image modalities.

#### 4.4.2. fMRI data analysis

A statistical analysis was performed with the individual and group data using the General Linear Model (Friston et al., 1995). Serial autocorrelation caused by aliased cardiovascular and respiratory effects on functional time series was
corrected by a first-degree autoregressive (AR1) model. Group analyses were performed at the random-effects level. In a first level analysis, time series were modeled under the 2-back condition using a boxcar function convolved with the hemodynamic response function and its temporal derivative. Moreover, the movement parameters from motion correction were included for each subject as regressors of non interest. To identify the significantly activated brain areas during the 2-back task performance at the group level, statistical contrast images of the parameter estimates for each subject were created (2-back-0-back) at the fixed-effect level analysis and brought to random-effect analysis. The task-related activation in each group and between-group differences were studied with one- (p < 0.0001, uncorrected) and two-sample t-tests (p < 0.001, uncorrected), respectively. A corrected threshold of p < 0.05 was applied at the cluster level to each contrast of interest to correct for family-wise errors (FWE). Furthermore, we did a regression analysis in the cocaine-dependent group between the first-used-cocaine age and years of cocaine use variables with functional activation separately to control for any possible related activation to these variables.

On the other hand, the Biological Parametric Mapping (BPM) statistical toolbox was used to analyze the possible brain-related activation during the 2-back task and gray matter volumes. The BPM toolbox produces statistical output images (e.g., T maps or F maps) in a massive voxel-by-voxel univariate analysis between two or more image modalities (and non-image data sets too) at random effects level based on the general linear model (see Casanova et al., 2007). First, we studied anatomical differences in GMV between groups, and possible relationships between GMV and the functional activation during the 2-back task within each group separately, restricting the analysis to the cluster of functional differences between groups. Formally, we conducted a partial correlation between parameter estimate maps and gray matter volume maps and controlled for age effects. Furthermore, this analysis was repeated in a whole-brain voxelwise regression analysis between the parameter estimate maps and gray matter volume maps regressing out the age effects. Likewise, an ANCOVA analysis testing for GMV differences between groups was conducted as an exploratory analysis to test at which statistical level anatomical differences were present at the region of functional differences between groups. However, it is important to notice that in the GMV contrast between groups, subthreshold voxels are as important as those that show a significant effect for a predefined threshold, since one of the objectives of this study was to test for the possible role of GMV variability as a source of variability in functional activation related to cognitive tasks. Therefore, we included each subject’s gray matter volume maps and age as covariates in a whole-brain voxelwise ANCOVA analysis. This last analysis tested for between groups’ functional differences after controlling for individual differences in age and voxel-by-voxel GMV effects.

**Authors’ contribution**

Juan Carlos Bustamante was responsible for sample recruitment, acquisition of the data, data analysis, interpretation of findings, and manuscript preparation.

Alfonso Barrós-Loscertales was responsible for the study design, sample recruitment, data analysis, interpretation of findings, and manuscript preparation.

Noelia Ventura-Campos was responsible for the data analysis and interpretation.

Ana Sanjuán was responsible for the acquisition of the data and data analysis.

Juan Jose Llopis was responsible for sample recruitment, data acquisition, and critical review of the article.

Maria Antonia Parcet provided a critical revision of the manuscript for important intellectual contents and designed the neuropsychological assessment.

Cesar Avila was responsible for the study design, analysis, interpretation of findings, and the critical revision of the manuscript.

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**References**


