Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group

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ABSTRACT

Dysregulation in cognitive control networks may mediate core characteristics of drug addiction. Cocaine dependence has been particularly associated with low activation in the frontoparietal regions during conditions requiring decision making and cognitive control. This functional magnetic resonance imaging (fMRI) study aimed to examine differential brain-related activation to cocaine addiction during an inhibitory control paradigm, the “Counting” Stroop task, given the uncertainties of previous studies using positron emission tomography. Sixteen comparison men and 16 cocaine-dependent men performed a cognitive “Counting” Stroop task in a 1.5 T Siemens Avanto. The cocaine-dependent patient group and the control group were matched for age, level of education and general intellectual functioning. Groups did not differ in terms of the interference measures deriving from the counting Stroop task. Moreover, the cocaine-dependent group showed lower activation in the right inferior frontal gyrus, the right inferior parietal gyrus and the right superior temporal gyrus than the control group. Cocaine patients did not show any brain area with increased activation when compared with controls. In short, Stroop-interference was accompanied by lower activation in the right frontoparietal network in cocaine-dependent patients, even in the absence of inter-group behavioral differences. Our study is the first application of a counting Stroop task using fMRI to study cocaine dependence and yields results that corroborate the involvement of a frontoparietal network in the neural changes associated with attentional interference deficits in cocaine-dependent men.

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1. Introduction

It is generally agreed that drug dependence may be a result of the compromise of the executive processes that control behavior (Moeller et al., 2001; Garavan et al., 2008). Long-term cocaine use produces changes in brain structure and function in the frontal lobe (Fein et al., 2002; Matochik et al., 2003; Lim et al., 2008; Tanabe et al., 2009). Previous studies have shown deficits in the frontal lobe functioning and executive functions related to it in cocaine-dependent patients (Aron and Paulus, 2007). Among the frontal executive functions, the study of interference control in cocaine dependence can reveal the functional and anatomical changes responsible for a cocaine addiction diagnosis criterion in relation to behavioral patterns of diminished control.

Cognitive control has been defined as the processes that allow information processing and behavior to vary adaptively from one time to another in accordance with current goals rather than remaining rigid and inflexible. Cognitive control processes include a broad class of mental operations, including goal or context representation and maintenance, as well as strategic processes such as attention allocation and stimulus–response mapping. Prefrontal networks involving the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) are important for the executive cognitive functions governing cognitive control such as response inhibition and error monitoring (Kerns et al., 2004).

The Stroop effect can serve as a paradigmatic task for studying the interference control-function (Nigg, 2000). The Stroop task demands a number of different cognitive subprocesses like error monitoring, response selection and suppression of inadequate responses. Moreover, the prototypical Stroop interference task is able to provide us much information about attention and cognition mechanisms in normal humans and clinical patients (McLeod, 1991), and also provides information about the frontal lobe’s executive functioning and integrity. In the context of functional magnetic resonance imaging (fMRI), the Stroop paradigm has shown the involvement of a frontoparietal network that includes regions of the frontal lobe (e.g., lateral prefrontal cortex, frontopolar regions, anterior cingulate cortex), as well as the parietal cortex (Pardo et al., 1990; Bush et al., 1998; Leung et al., 2000; Zysset et al., 2001; Laird et al., 2005).

Dysregulation in cognitive control networks may mediate core characteristics of drug addiction (Goldstein and Volkow, 2002) as cocaine abusers have shown dysfunction in decision-making and cognitive control tasks (Bechara and Damasio, 2002). In the specific

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case of the Stroop task, some neuropsychological studies have reported severe effects of cocaine to be related to worsened performance (Roselli et al., 2001; Verdejo-García et al., 2004), which is consistent with the hypothesis that stimulant use alters an individual’s ability to selectively attend stimuli or to inhibit pre-potent responses (Simon et al., 2000; Verdejo-García et al., 2005). However, other studies have not found differences in performance between patients and controls (Hoff et al., 1996; Selhy and Azrin, 1998; Bolla et al., 1999), indicating that neuropsychological results are inconsistent and that those variations in both task and sample characteristics should be taken into account when interpreting results.

Frontoparietal dysfunction has been identified for a wide range of executive functions in cocaine-dependent patients (Kaufman et al., 2003; Aron and Poulus, 2007; Tomasi et al., 2007; Garavan et al., 2008). Previous neuroimaging studies in cognitive functioning have shown a frontal deficit in cocaine addicts in the absence of cognitive deficits (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008) or when concomitant behavioral deficits were present (Kaufman et al., 2003; Hester and Garavan, 2004; Kübler et al., 2005). Moreover, recent studies have shown functional deficits in the parietal lobe in cocaine-dependent patients during working memory (Bustamante et al., 2011) and cognitive control tasks (Garavan et al., 2008). Previous research that compared patients and controls using the Stroop task has found differences in several frontal and cingulate areas. Using a manual version of the Stroop task and positron emission tomography (PET), Bolla et al. (2004) revealed how the anterior cingulate cortex (ACC) and the right lateral prefrontal cortex (rLPFC) were less active in a group of abstinent cocaine-dependent individuals. Goldstein et al. (2001) did not find brain functional differences using PET between cocaine-dependent patients and a group of matched controls during an event-related color-word Stroop task. However, their results revealed increased activation in the orbitofrontal cortex associated with lower and higher conflict in controls and patients, respectively, while groups did not differ in terms of task performance. Otherwise, Brewer et al. (2008) found that activations in the frontal and parietal regions during performance of the Stroop task were related to treatment outcomes. These studies documented the different underlying brain regions associated with the ability to inhibit prepotent response tendencies in cocaine-dependent patients by comparing them to controls. These differences can be attributed to neither disparities in education and general intellectual functioning nor observable behavioral changes in standard neuropsychological measures.

In view of the variability in the PET-obtained results (Goldstein et al., 2001; Bolla et al., 2004) and the relevance of deficits on the Stroop task to the treatment of these patients (Brewer et al., 2008), the objective of the present research work was to study interference-control functioning in cocaine-dependent patients using fMRI, which offers better spatial and temporal resolution than PET. As far as we know, this is the first study to compare cocaine-dependent patients and controls during Stroop performance using fMRI. We selected the counting Stroop task (Bush et al., 1998) as it is better suited for the fMRI environment (Bush et al., 2006). The advantages of this version of the task are the possibility of registering manual on-line response time measurements while obviating speech and increased stimulus–response compatibility. Therefore, the final objective of this study was to identify the brain regions that are differently involved in a counting Stroop task for a cocaine group and a comparison group. We hypothesize that the cocaine-dependent group will show lower activation in the frontoparietal areas that are involved in the Stroop effect and which are affected by cocaine dependence when compared with controls.

2. Methods

2.1. Participants

Eighteen cocaine-dependent men and 20 matched healthy men participated in this study. All the participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). An initial study of their clinical history and a subsequent onsite assessment by a neuropsychologist and a psychiatrist ensured that both groups were physically healthy with no major medical illnesses or DSM-IV Axis-I disorders, had no current use of psychoactive medications, and had no history of head injury with loss of consciousness or neurological illness. All the patients were recruited at the time they came to a clinical service to seek treatment for cocaine addiction. Patients were scanned over a maximum period of 2 months since they were recruited for the study. During this time, they were evaluated and diagnosed, and they could voluntarily attend the counseling group sessions offered by the clinic.

Prior to participation in the study, subjects completed the color-word Stroop test according to the normative Spanish version (1994). We established a minimum performance criterion based on a corrected standard T value of the interference score as described by Golden (1978). We involved those participants who displayed an accuracy performance with a score of over 36 in terms of the standard T value corresponding to their interference score in accordance with the normative Spanish data (see Manual of the Spanish version of the Stroop Color and Word Test, 1994. TEA Ediciones, Madrid). On the basis of these performance criteria, one participant from the control group was not included in the final sample. A urine toxicology test was done to rule out cocaine consumption, which ensured a minimum period of abstinence of over 2/4 days (Vearrier et al., 2010) prior to fMRI data acquisition, as with any urine test done at the clinic before patients participated in the scanning session.

Three and two subjects were excluded from the control group and the cocaine group, respectively, as they had a positive urine test (one patient), MRI technical issues (one control) and excessive movement during fMRI acquisition (one patient and two controls; more than 2 mm of translation or 2° of rotation). The final sample (16 cocaine-dependent men and 16 comparison men) who took part in the study were matched for age, level of education, and general intellectual functioning (see Table 1). General intellectual functioning was assessed with the Matrix Reasoning test from the Wechsler Adult Intelligence Scale-III (Wechsler, 2001). Some patients reported histories of depressive symptoms (n=3) or anxiety symptoms (n=3), but never of sufficient severity to constitute a DSM-IV Axis-I disorder, and these symptoms were all absent at the time the patients participated in the experiment. The cocaine-dependent participants reported an average (±S.D.) of 19.85 (6.25) and 13.94 (5.85) as first-used cocaine age and years of cocaine use, respectively. Moreover, 10 patients (62.5% of the final sample) compared to nine controls (56.25% of the final sample) were smokers. There were no inter-group distribution sample differences in this variable (p>0.1). On the other hand, eight patients (50%), two patients (12.5%), one patient (6.3%) and one patient (6.3%) reported a sporadic consumption pattern without abuse of alcohol, cannabis, amphetamines and other types of drugs.

<table>
<thead>
<tr>
<th></th>
<th>Comparison group</th>
<th>Cocaine dependent group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.20 (8.86)</td>
<td>38.48 (7.15)</td>
</tr>
<tr>
<td>Years of education</td>
<td>8.53 (1.46)</td>
<td>9.25 (1.69)</td>
</tr>
<tr>
<td>General intellectual functioning</td>
<td>10.87 (2.59)</td>
<td>9.84 (2.41)</td>
</tr>
<tr>
<td>Word test in color-word Stroop version</td>
<td>49.33 (6.32)</td>
<td>48 (7.04)</td>
</tr>
<tr>
<td>Color test in color-word Stroop version</td>
<td>45.27 (6.76)</td>
<td>44.77 (9.12)</td>
</tr>
<tr>
<td>Word/color test in color-word Stroop version</td>
<td>52.40 (8.93)</td>
<td>53.69 (10.68)</td>
</tr>
<tr>
<td>Interference scores in color-word Stroop version</td>
<td>54.27 (6.43)</td>
<td>56.31 (8.95)</td>
</tr>
</tbody>
</table>

Means (and standard deviations) of the main demographic characteristics, and the behavioral results on percentage of correct responses, interference effect and response time (RT) of the cocaine-dependent and the comparison groups (n.s., non-significant).
psychoactive drugs, respectively. These 12 patients did not meet the criteria for either current dependence on or abuse of these substances. Participants were informed of the nature of the research and were provided a written informed consent prior to participation in this study. This research work was approved by the institutional review board of the Universitat Jaume I of Castellón (E. Spain).

2.2. Paradigm

Participants viewed sets of one to four identical words presented on the screen for each trial during the whole paradigm. They were instructed to respond as quickly as possible via button pressing using a keypad with two buttons for each hand (Response Grips, NordicNeuroLab, Norway) to the number of words in each set, regardless of what the words were. During the Stroop or conflict blocks, the words were number words: “one”, “two”, “three” and “four” (“uno”, “dos”, “tres” “cuatro” in Spanish), which were always discordant with the number of words presented. During the control or no-conflict blocks, words were common names from different categories (balanced by frequency and length). Subjects were trained during a 4-min computerized practice version without interference trials, in which they received feedback from the experimenter about their performance. The paradigm within the scanner lasted 4 min corrected for motion artifacts, coregistered with the corresponding anatomical (T1-weighted) image, and normalized (voxels were rescaled to 3 mm³) with the normalization parameters obtained after the anatomical segmentation within a standard stereotactic space (T1–MNI) to 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 Stroop 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. The time series of the hemodynamic responses were high-pass filtered (128 s) to eliminate low-frequency components. To identify the significantly activated brain areas, statistical contrasts to the parameter estimates for each subject were created to the Stroop condition compared to the implicitly modeled control condition. Both the task-related activation in each group and the inter-group differences were studied with a one-sample t-test (p < 0.001, corrected for multiple comparisons at the cluster level p < 0.05; the equivalent to a k-threshold = 37); and a two-sample t-test (p < 0.005, corrected for multiple comparisons at the cluster level (p < 0.05, the equivalent to a k-threshold = 125).

3. Results

3.1. Behavioral results

Table 2 shows the behavioral results obtained during the fMRI scanning session. Two 2 × 2 mixed-model analyses of variance (ANOVAs) were conducted using Condition (Conflict vs. Neutral) as a within-subjects factor and Group (Patients vs. Controls) as a between-subjects factor to analyze RTs and correct responses. The analysis of RTs revealed a main effect of condition (F(1, 30) = 68.96, p < 0.05), showing faster RTs in the Neutral than in the Conflict condition for both groups. Thus, there were significant differences between the conditions in the control group (t(15) = 5.54, p < 0.001) and the patient group (t(15) = 6.35, p < 0.001). There was also an unexpected group effect (F(1,30) = 4.36, p < 0.05), indicating faster responses in controls than in patients in the Neutral condition (t(30) = 2.29, p < 0.05; p = 0.029) and a trend to this effect in the Conflict condition (t(30) = 1.85, p < 0.05; p = 0.074). The same analysis for errors did not yield any significant effect (p > 0.1).

3.2. fMRI results

The comparison group and the cocaine-dependent group showed an activation pattern in the counting Stroop task in a frontoparietal network implicated in this type of manual Stroop task. For both groups, it principally included the right inferior frontal gyrus (BA 9/44/45/47), the left inferior frontal gyrus (BA 9/46), the right middle frontal gyrus (BA 6/9), the left middle frontal gyrus (BA 9), the right inferior parietal lobule (BA 40), the left inferior parietal lobule (BA 39/40) and the left superior parietal lobule (BA 7) (see Table 3, Fig. 1).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Comparison group</th>
<th>Cocaine-dependent group</th>
<th>Statistical difference between conditions/groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral condition</td>
<td>94.79% (2.66)</td>
<td>93.75% (2.73)</td>
<td>n.s./n.s.</td>
</tr>
<tr>
<td>Conflict condition</td>
<td>95.14% (4.15)</td>
<td>94.71% (5.00)</td>
<td>n.s./n.s.</td>
</tr>
<tr>
<td>Interference</td>
<td>55.12 (39.29)</td>
<td>51.43 (32.41)</td>
<td>n.s./n.s.</td>
</tr>
<tr>
<td>RT neutral condition</td>
<td>611.44 (45.40)</td>
<td>678.36 (107.79)</td>
<td>p &lt; 0.05, p = 0.05</td>
</tr>
<tr>
<td>RT conflict condition</td>
<td>666.56 (71.48)</td>
<td>729.79 (116.48)</td>
<td>p &lt; 0.05, p = 0.76</td>
</tr>
</tbody>
</table>
The functional contrast between groups (two-sample t-test; p<0.005, corrected for multiple comparisons at the cluster level, k = 125) showed less activation in the cocaine-dependent group for the right inferior frontal gyrus (BA 47; 45,17,−8; Z = 3.55; k = 329), the right inferior parietal gyrus (BA 40; 53,−39,38; Z = 3.93; k = 261) and the right superior temporal gyrus (BA 22; 53,−41,2; Z = 3.66; k = 189) if compared with the control group (see Fig. 2). As the groups differed in RTs in each condition, inter-group brain activation differences were also studied using two separate analyses of covariance, including the RTs in the conflict and control conditions as covariates separately. The inter-group functional differences remained significant after controlling for the RT in either condition. Likewise, no brain region showed greater activation in the cocaine-dependent group if compared to the control group for any previous inter-group contrast. Lastly, a limited set of exploratory correlations was performed among drug use (years of cocaine use, age of first use), fMRI task behavioral performance (RT difference between conditions) and functional brain activation. These analyses did not report any significant correlation. The coordinates for peak significant activation in each significant cluster of activation were localized using the xjView toolbox (http://www.alivelearn.net/xjview/) based on the MNI Space utility (http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html) and the WFU-Pickatlas (Maldjian et al., 2003).

4. Discussion

The comparison made between cocaine-dependent patients and matched controls showed lower cerebral activation in the right inferior frontal cortex for the cocaine-dependent group during the counting Stroop task. We also noted lower activation in the patient group for the right inferior parietal and the superior temporal cortex. These inter-group differences in brain activation were obtained in the absence of other differences like RT interference effects or response accuracy during task performance. Moreover, patients showed no significant area of increased activation when compared to controls, which excluded any compensatory activation.

Both the cocaine and control groups displayed a prototypical pattern of brain activation during the counting Stroop task, which is in agreement with previous studies (Pardo et al., 1990; Bush et al., 1998; Leung et al., 2000; Laird et al., 2005) and supports the validity of applying the counting Stroop fMRI paradigm to our samples. This activation pattern reflects the joint activity of the bilateral frontoparietal networks during Stroop task performance, principally in the manual versions of the task. These results are consistent with those reported in the study of Bush et al. (1998) where the bilateral DLPFC and the anterior cingulate were activated (including areas of the SMA as reported in the manual versions of the Stroop paradigm; see Laird et al., 2005).

The current findings also indicate that the interference score overlaps significantly between cocaine-dependent patients and controls. This interference score in the Stroop task can be influenced by multiple sensory and motor conditions, and by other mental processes (such as effort) which are not directly related to the measure of interest. Moreover, we cannot rule out that the selection criteria in the word-color Stroop test may equate performance. Thus the interference score, as a behavioral measure within the adaption of the counting Stroop to fMRI environment, may not capture the inter-group differences in the cognitive control processes. However, this study reveals that neuroimaging is an additional tool to explore the neural processes associated with impaired cognitive control in cocaine-dependent patients. In fact, the differences observed in regional brain activation, despite similar behavioral performance, are reminiscent of other imaging studies into drug addiction (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008; Hester et al., 2009; Bustamante et al., 2011). Previous authors have highlighted that this scenario has the advantage of restricting the number of interpretations of results since inter-group performance differences or engagement may not explain neural differences (Price et al., 2006; Goldstein et al., 2009). The fact that our results indicate lower activation in brain areas similarly to those of previous research works, which studied executive dysfunctions as an effect of cocaine dependence, validates our interpretation of the neural results in the absence of behavioral differences.

How do we interpret these differences between groups? The joint effects of reduced brain activation in the cocaine group when compared with the control group, plus the absence of differences in the interference effect between these same groups, may be interpreted in several ways. One way is to consider that cocaine patients recruit less neural resources to perform the task than controls do, as usually interpreted in studies with healthy participants (Mattay et al., 2003, 2006). Likewise, another consideration may be that the areas of lower activation, although typically active during task completion, are not essential to perform the task since patients’ performance is not worse than that of controls (Price and Friston, 1999). However, these two interpretations are difficult to apply in cocaine dependence since cocaine-dependent patients typically show lower accuracy in executive tasks and lower activations associated with worse performance in these regions. Having said that, the cocaine group may have a higher baseline metabolism, which would give rise to a lower contrast effect of the conflict condition vs. the control condition in those regions of functional differences between groups. However, previous studies have not

<p>| Table 3 | Coordinates of the main brain activations during the “Counting” Stroop task for each group (p&lt;0.001, corrected for multiple comparisons at cluster level p&lt;0.05). Coordinates of global maxima in MNI coordinates. |
|---------|-------------------------------------------------------------------------------------------------|--------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th>Brain region</th>
<th>Brodmann area</th>
<th>Coordinates</th>
<th>Activation cluster size</th>
<th>Z score</th>
<th>Coordinates</th>
<th>Activation cluster size</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right superior frontal gyrus</td>
<td>6</td>
<td>15,14,52</td>
<td>304</td>
<td>5.38</td>
<td>Right superior frontal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right medial frontal gyrus/SMA</td>
<td>6</td>
<td>15,9,55</td>
<td>347</td>
<td>5.47</td>
<td>Right medial frontal gyrus/SMA</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>9</td>
<td>−45,22,32</td>
<td>686</td>
<td>4.98</td>
<td>Left middle frontal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>6,9</td>
<td>42,−1,36</td>
<td>772</td>
<td>5.01</td>
<td>Right middle frontal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>9,44,45,47</td>
<td>59,21,7</td>
<td>605</td>
<td>4.51</td>
<td>Right inferior frontal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>9,46</td>
<td>−45,22,29</td>
<td>555</td>
<td>4.76</td>
<td>Left inferior frontal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right superior temporal gyrus</td>
<td>21,22</td>
<td>53,−26,1</td>
<td>170</td>
<td>4.78</td>
<td>Right superior temporal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right inferior temporal gyrus</td>
<td>37</td>
<td>45,−64,−2</td>
<td>215</td>
<td>5.17</td>
<td>Right inferior temporal gyrus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right superior parietal lobule</td>
<td>7</td>
<td>53,52</td>
<td>172</td>
<td>4.56</td>
<td>Right superior parietal lobule</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Left superior parietal lobule</td>
<td>7</td>
<td>−30,−64,53</td>
<td>310</td>
<td>5.15</td>
<td>Left superior parietal lobule</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right inferior parietal lobule</td>
<td>40</td>
<td>50,−42,38</td>
<td>317</td>
<td>4.85</td>
<td>Right inferior parietal lobule</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Left inferior parietal lobule</td>
<td>39,40</td>
<td>−36,−45,38</td>
<td>576</td>
<td>4.83</td>
<td>Left inferior parietal lobule</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>−15,−11,6</td>
<td>15,5,11</td>
<td>566</td>
<td>4.41</td>
<td>Right thalamus</td>
<td>Coordinates</td>
<td>Activation cluster size</td>
</tr>
</tbody>
</table>
reported a homogeneous brain pattern of basal metabolism in relation to cocaine dependence (Goldstein et al., 2001; Tomasi et al., 2007); moreover, the lack of a resting condition to test the baseline effects in our design makes it difficult to conclude a basal metabolic effect from our results. On the other hand, cognitive-behavioral impairments in cocaine addiction have been suggested to be associated with compromised habituation or practice effects (Goldstein et al., 2007). As an effect of cocaine addiction, a signal change activation and deactivation toward the baseline has been shown to be an effect of neural habituation in an incentive-sustained attention task associated with more severe cocaine use (Goldstein et al., 2007). However, talking about the habituation or basal metabolism effect in our results may be rather speculative given that these effects are subject to a wide range of factors (Petersen et al., 1998; Garavan et al., 2000; Kelly and Garavan, 2005). In summary, a plausible interpretation of these results would be to relate patients’ neural lower activation as a vulnerability index toward the cognitive dysfunction underlying the neuronal changes associated with lengthy drug use. This interpretation is the most frequent one in drug addiction research to refine neuropsychological investigations (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008; Hester et al., 2009), and would probably imply a more cognitively demanding Stroop task to be able to translate neural differences into behavioral deficits. Further research will be necessary to clarify the conditions under which a behavioral deficit is sensitive to a cognitive change in order to reflect a concomitant reduced functional activation, or vice versa.

Cocaine consumption is principally related to orbitofrontal cognitive deficits (Winstanley, 2007) and subtle dorsolateral prefrontal deficits, whose standard neuropsychological test might not be sensitive enough for detection (Goldstein et al., 2001), or can be detected at different degrees (Fernandez-Serrano et al., 2010). As our results suggest, fMRI can detect these deficits in the absence of executive deficits in neuropsychological tasks (Goldstein et al., 2001). Thus, the results of our study are consistent with previous reports showing lower frontoparietal activations during executive tasks in cocaine-addicted patients in the absence of behavioral deficits (Goldstein et al., 2001; Bolla et al., 2004; Li et al., 2008) or are concomitant with behavioral...
inhibitory control paradigms were applied (Garavan et al., 1999; Kübler et al., 2004). The lower activation observed while patients performed the counting Stroop task may be considered an indicator of their proneness toward executive deficits. Specifically, the differences in activation of the right inferior frontal gyrus are relevant to and coincident with the previous literature. This brain area has been repeatedly associated with inhibitory processing and stimulus reconfiguration after using different paradigms such as the stop-signal task, switching tasks, go/no go tasks, the Wisconsin Card Sorting Test (WCST) or Stroop tasks (Aron et al., 2007; Robbins, 2007). With Stroop tasks, a series of recent neuroimaging studies has detected activity in the dorsal cingulate and the dorsomedial prefrontal cortex, which is associated with conflict monitoring, whereas activity in the lateral inferior prefrontal cortices is associated with conflict resolution (Botvinick et al., 1999; Kerns et al., 2004; Egner and Hirsch, 2005). In studies conducted with cocaine-addicted patients, this area has repeatedly yielded reduced activation during the Stroop task in patients when compared with controls (Bolla et al., 2004), and when performing other inhibitory control tasks (Kaufman et al., 2003; Hester and Garavan, 2004). Furthermore, a recent report has shown that the lower activation observed in the right lateral prefrontal cortex during inhibitory tasks was reversed with an intravenous administration of cocaine (Garavan et al., 2008). Therefore, this study corroborates previous results of dysfunction in the right inferior frontal cortex associated with cognitive control in cocaine-dependent patients.

The inferior parietal cortex has been seen to be implicated in tasks involving resolution interference processes such as the Stroop task (Derrfuss et al., 2004; Nee et al., 2007). Several studies have implicated the parietal lobes in supporting a notation-independent semantic representation of quantities (see Dehaene and Cohen, 1995, for a review). More specifically in a numeric Stroop task, the intraparietal sulcus and the precuneus have been found to be implicated in the comparison process of numbers, and the activity of these regions is modulated by the numerical distance effect: smaller numerical distances associated with high activation levels (Pinel et al., 2001). This area has been proposed to be altered in cocaine addiction as an effect of an attentional deficit (Tomasi et al., 2007; Bustamante et al., 2011). The right inferior parietal cortex maintains bidirectional connections with the right dorsolateral prefrontal cortex and the 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). The altered activation pattern of the right inferior parietal cortex is consistent with not only previous fMRI results (Kübler et al., 2005; Tomasi et al., 2007), but also with neuropsychological studies showing how cocaine users perform poorly in the measures of selective (Simon et al., 2000; Verdejo-García et al., 2005) and sustained attention (Pace-Schott et al., 2008), these being the brain functions related to this brain area. Thus, the attentional control processes affected in cocaine-dependent patients may explain this lower activation in the right inferior parietal cortex during cognitive control.

The superior temporal gyrus displayed lower activation in cocaine-dependent patients compared to matched controls while performing the counting Stroop task. Task-related activation indicates that this area is involved in the execution of the counting Stroop task in both groups (see Table 3). This activation has also been shown when other inhibitory control paradigms were applied (Garavan et al., 1999; Braver et al., 2001; Kiehl and Liddle, 2001; Menon et al., 2001; Garavan et al., 2002). Furthermore, this region reveals a lower gray matter density in cocaine-dependent patients in early studies applying voxel-based morphometry (Franklin et al., 2002; Sim et al., 2007). Thus, its decreased activation in the patient’s group might be associated with inhibitory control dysfunction as an effect of the neuropathology underlying cocaine dependence. However, its role in inhibitory control processes has not been defined in functional studies and further research will be necessary to clarify this result.

One of the unexpected results of this research is that both groups differed in terms of the overall response speed in the absence of both differences in speed of reading and the magnitude of the interference in both the paper and fMRI versions of the task. These differences, however, may not be responsible for the observed functional results since covarying out these effects did not change the functional differences between groups. Otherwise, it may be unclear whether reaction time differences might be captured by individual differences in the temporal characteristics of the hemodynamic response. Future event-related designs could better test the possible effect of variability in the reaction time on cocaine-dependent patients’ hemodynamic response. The fact that patients displayed slower reaction times than comparison subjects for general task performance could be related to the fact that cocaine use has been shown to lead to general psychomotor slowing in cognitive processing, principally in the Stroop task (Vassileva et al., 2007), as others have shown during working memory tasks (Tomasi et al., 2007). This slowing in cognitive processing could be associated with the disrupted integrity of white matter and fiber tracts in cocaine dependence (Lim et al., 2002; Schlaepfer et al., 2006; Liu et al., 2008), which has an effect on ongoing task performance.

To our knowledge, this is the first study to report lower activation in the right frontoparietal network of treatment-seeking cocaine-dependent patients while performing a Stroop task in an fMRI block design. The Stroop test, when compared to others (e.g., Five Digit test, Go/no Go task), has proved to be a good discriminating interference task between the controls and polysubstance abusers enrolled in therapeutic communities (Fernandez-Serrano et al., 2010), and as a tool to identify cocaine-dependent patients at risk for treatment dropout (Streeter et al., 2008). In a similar sample, a previous event-related fMRI study (Brewer et al., 2008) analyzed the relationship between brain activation during the color-word Stroop task and treatment outcomes for a sample of 20 treatment-seeking cocaine-dependent subjects, without involving healthy control subjects. Their study (Brewer et al., 2008) strictly controlled the variables related to treatment outcomes which, although related to brain activation, questioned possible inter-group functional differences during Stroop performance since no group of controls was involved. Although we could not strictly control the treatment outcome-related variables in this study, we involved a group of cocaine-dependent patients and a matched control group to allow for group comparisons in terms of task performance and brain activation. Furthermore, and as reported before, the Stroop-related activations we obtained were studied under blocked-performance conditions. Therefore, brain functional differences should be interpreted by considering the possible effect of sustained rather than transient activations in the observed functional differences if compared to more common event-related paradigms which do a detailed analysis of brain transient activation to cognitive and response interference to a stimulus (Laird et al., 2005).

Study limitations include a relatively small sample size within which there is a pattern of concurrent substance use in the patient group other than cocaine. A limited assessment ignored the effect of the variables that have already shown their association with brain activation in cocaine dependence such as craving (Li et al., 2010), drug compulsivity abuse (Ersche et al., 2010) or treatment outcome (Brewer et al., 2008). Likewise, a variable that was not considered in detail in both groups was the screening of consumption habits for alcohol, which have been shown to have an important effect on neuroadaptation changes (Cosgrove et al., 2009). Otherwise, the sample is restricted to male participants and involves limitation and strength at the same time. Although restricting the present study to males offers the advantage of maximizing the patient group’s homogeneity, this selection limits the scope of the present results. Furthermore, it would be useful to know the structural correlates of these functional differences in the patients. In a previous report by our research group (Bustamante et al., 2011), individual structural variability was seen to
affect inter-group functional differences. However, the individual variability in structural changes did not have a significant effect on the inter-group functional differences during the counting Stroop task analyzed in this study (data not shown; see Bustamante et al., 2011, for a description of the procedure). Finally, the present study does not include another psychometric psychological assessment to test whether lower functional activations are plausibly related to the known behavioral deficits in cocaine addicts, such as impulsivity or compulsivity. Future investigations will overcome the limitations of the present study by considering the difficulties of controlling the wide range of variables involved in cocaine dependence.

In conclusion, our study is the first application of a counting Stroop task in the study of cocaine dependence, and provides more empirical data on the involvement of a frontoparietal network in the neural changes associated with attentional-interference deficits in cocaine-dependent men. All these results indicate the existence of a network of the prefrontal, parietal and temporal regions mediating attentional-cognitive control in tasks of cognitive coordination, inhibitory processes and interference control, such as the Stroop task (Egner and Hirsch, 2005). These processes may be associated with the cocaine-related cognitive deficits that have been linked to the relationship between drug cues and compulsive drug self-administration in drug dependence (Goldstein et al., 2001; Carpenter et al., 2006).

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Authors’ contribution

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

Juan Carlos Bustamante was responsible for data acquisition, data analysis, interpreting the results and preparing the manuscript.

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

Juan José Llopis was responsible for sample recruitment, data acquisition and critically reviewing the article.

María Antonia Parcet critically revised the manuscript for important intellectual content and designed the neuropsychological assessment.

Cesar Ávila was responsible for the study design, analysis, interpreting the findings and for critically revising the manuscript.

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