

Cocaine dependence and attention switching within and between verbal and  
visuospatial working memory

A Kübler<sup>1,2</sup>, K Murphy<sup>1</sup>, H Garavan<sup>1,3</sup>

<sup>1</sup> Department of Psychology and Institute of Neuroscience, Trinity College Dublin,  
Dublin, Ireland

<sup>2</sup> Institute of Medical Psychology and Behavioural Neurobiology, University of  
Tübingen, Tübingen, Germany

<sup>3</sup> Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin,  
Milwaukee, USA

*European Journal of Neuroscience (In Press)*

Correspondence should be addressed to:

Hugh Garavan, PhD

Department of Psychology,

Trinity College Dublin,

Dublin 2, Ireland.

Ph: +353-1-608-3910

Fax: +353-1-671-2006

E-mail: [Hugh.Garavan@tcd.ie](mailto:Hugh.Garavan@tcd.ie)

Keywords: executive function; attention switching; working memory; cocaine;  
addiction; fMRI

## **Abstract**

Many studies have shown the negative effects of cocaine on neuropsychological and cognitive performance in drug dependent individuals but little is known about the underlying neuroanatomy of these dysfunctions. The present study addressed attention switching between items held in working memory (WM) with a task in which subjects were required to store and update two items held in verbal or visuospatial WM. Attention switching frequency varied between trials, thereby allowing us to isolate the switching component of task performance. Behavioural data revealed that cocaine addicts performed worse than healthy controls in all tasks. On the visuospatial task addicts performed at chance levels revealing particular impairment in visuospatial WM. On the verbal task, in which controls and users could be matched for performance, we identified attenuated responses in prefrontal and cingulate cortices and in striatal regions while other areas such as dorsolateral prefrontal cortex did not differ between healthy controls and users. The results reveal that addiction may be accompanied by specific rather than ubiquitous hypoactivation in prefrontal and subcortical areas and suggest a compromised ability in users to control their attention to their thoughts as might be particularly relevant when required to switch away from drug-related thoughts, and thus the dysfunction in attention switching may contribute to the maintenance of addiction.

## **Introduction**

Almost all drugs of abuse, such as cocaine, are known to increase extracellular levels of dopamine (DA), either through binding to monoamine transporters or indirectly by increasing neuronal activity in the ventral tegmental area (Gerdeman *et al.*, 2003).

The behavioural effects of DA are proposed to be mediated by D1 and D2 receptors which are present in the nucleus accumbens (ventral striatum), caudate and putamen (dorsal striatum), amygdala, and prefrontal cortex (Nader *et al.*, 2002). The influence of cocaine on dopamine levels within the mesolimbic system has been demonstrated to be responsible for the powerful reinforcing effects of the drug (Volkow *et al.*, 2002).

Given that the DA-system is not only involved in reward-related processing, but also in working memory (WM) and executive functioning (Bolla *et al.*, 1998; Di Chiara, 2002), and the prefrontal cortex is firmly established to play a crucial role in these functions (Goldman-Rakic, 1996; Owen, 1997), one might expect compromised functioning of dopaminergic and prefrontally-mediated processes in chronic drug abusers. Indeed, altered executive processing is observed in diseases which affect the mesocorticolimbic and nigrostriatal pathways, such as Parkinson's disease or addiction (Volkow *et al.*, 1996; Rinne *et al.*, 2000).

Current models of WM postulate a central executive which allocates attentional resources according to task requirements (Cowan, 1993; Shallice & Burgess, 1996; Cocchini *et al.*, 2002). Central executive functioning has been demonstrated to involve activation in a fronto-parietal network, in which the contribution of the

prefrontal lobes is crucial, albeit not sufficient (Owen *et al.*, 1996; Collette *et al.*, 1999; Kübler *et al.*, 2003). Specifically, dorsolateral prefrontal cortex (DLPFC) appears critical for executive functioning (Owen *et al.*, 1998; Smith & Jonides, 1999), as robust activation has been observed here in many studies that engage a variety of WM and executive functions (see Cabeza & Nyberg, 2000 for a review). One such executive function is attention shifting within WM (Collette & van der Linden, 2002). Attention shifting is thought to include a retrieval mechanism such that switching to an item in WM entails the re-activation of the new item, and switching away from an item in WM may entail the suppression of that old item (Mayr & Kliegl, 2000; Voigt & Hagendorf, 2002). As an executive function, attention switching in WM depends strongly on the prefrontal lobes (e.g., Kondo *et al.*, 2004) and is thus likely to be influenced by the mesocorticolimbic DA-system. It has also been shown that reduced DA-levels in the dorsal striatum are related to increased switch costs (e.g., Cools *et al.*, 2003).

Shifting attention between the contents of WM may be particularly relevant in a number of clinical conditions in which prolonged rumination on certain thoughts may prove debilitating (e.g., sad thoughts in a depressed patient). Bonson and co-workers have suggested that ruminative thoughts activate a WM-like cortical network and this could interfere with WM performance (Bonson *et al.*, 2002). A dysfunction of attention switching within WM could account for the dominance of ruminative and craving thoughts in addicts: the current drug-related content of WM may not be suppressed and the re-activation of other than craving thoughts may be difficult. A dysfunction in attention switching within WM could therefore contribute to continued drug abuse and maintenance of addiction.

To address the neuroanatomical correlates of a possible deficit in attention switching we used a task designed to isolate the allocation of attentional resources within WM while holding constant on-line storage and rehearsal demands (Garavan, 1998). On the basis of Baddeley and Hitch's model of WM (Baddeley & Hitch, 1974) our experiment comprised 3 tasks to address attention switching within the phonological loop (verbal task), within the visuospatial sketchpad (visuospatial task) and between these two WM modalities (combined task). Previously, we have shown that attention switching within and between verbal and visuospatial WM is accomplished by a distributed frontoparietal neuroanatomy rather than a specific and unique locus (Garavan *et al.*, 2000; Kübler *et al.*, 2003). In both studies the attention switching demand was manipulated parametrically and activation increased as a function of switching demand. As WM demands were held constant on all trials (two items were always maintained in WM independent of the number of switches between the items), these results indicate that the task addresses executive functioning rather than WM maintenance.

We hypothesized that cocaine users would perform worse than healthy controls in all three subsets of the attention switching task. In one of the few studies investigating the functional neuroanatomy associated with the observed behavioural correlates of cocaine abuse, Kaufman and colleagues, using a GO-NOGO task, found hypoactivity in the anterior cingulate cortex (ACC) and right insula for successful inhibitions and additionally in ACC/pre-supplementary motor area (pre-SMA) and left inferior frontal gyrus for commission errors (Kaufman *et al.*, 2003). No differences in activation

between cocaine users and controls were observed in lateral prefrontal and parietal regions which are commonly activated for WM and executive control tasks. However, during a GO-NOGO task in which WM load was parametrically manipulated, Hester and Garavan found reduced activity in right prefrontal areas and left ACC when WM demands were increased (Hester & Garavan, 2004). In contrast to this study, WM load in the present study was held constant, but executive demands were manipulated by increasing the switching frequency between items in WM. Thus, following Hester and Garavan (2004) we predicted attenuated functional activation in prefrontal cortex (BA 9 / 6) and left ACC (BA 24 / 32).

## **Methods**

### **Participants**

Fourteen right-handed, otherwise healthy, active cocaine users (6 women, mean age  $\pm$  SD:  $37.6 \pm 6.4$ , age range: 23-49) took part in the study and gave informed consent, which was approved by the institutional review board of the Medical College of Wisconsin. The average number of cocaine uses per week was 3.5 (SD:  $\pm 1.5$ , range: 2-7). History of drug consumption varied between 2.5 and 18 years (mean  $\pm$  SD:  $11.0 \pm 5.8$ ). Inclusion criterion was a minimum of 2 years of cocaine use on a weekly basis. Ten of the 12 cocaine users smoked (on average light smokers with 5 cigarettes per day) and drank alcohol while eight also smoked marijuana but no user met the criteria for abuse or dependence on alcohol or marijuana. Consumption of other drugs was strictly excluded.

Urine samples were collected from all participants to test for pregnancy and drug use. Cocaine or its metabolites were found in all participants, indicating that they had used cocaine within the previous 72 hours. All participants were able to estimate their last use, which ranged from the night before to 3 days before the scan session. No user displayed any overt behavioural signs of cocaine intoxication.

Fourteen right-handed healthy, non-cocaine users (11 women, mean age  $\pm$  SD:  $24.3 \pm 3.8$ , age range: 20-33) who took part in a previous study with exactly the same attention switching task (Kübler *et al.*, 2003), served as a control group. In this previous study they received the same amount of practice as the cocaine addicts in the current study. Three were regular and two were occasional nicotine smokers. All, bar one, drank alcohol (but not to abuse levels) and in 8 of the remaining 13 participants their last alcohol intake was more than a week prior to the study. Two smoked marijuana occasionally. Data from this group were published (Kübler *et al.*, 2003) and will only be reported in comparison to cocaine users.

### **Task**

Of the three tasks imaged (Figure 1), two addressed attention switching *within* the verbal or visuospatial modality: The verbal task required participants to keep a count of how many red and how many blue circles were presented and to report the results at the end of each trial. Each circle was presented for 1400 ms and successive circles were separated by a 100 ms fixation cross, the purpose of which was to clearly delineate successive presentations of the circles. The visuospatial task required participants to update the location of one blue and one red dot within an imagined 2 x 2 matrix in accordance with a sequence of red and blue arrows. The locations of

the blue and the red dot at the beginning of each trial were randomly chosen. Red and blue arrows indicating in which direction a dot should mentally be moved were presented for 1400 ms and successive arrows were separated by a 100 ms fixation cross. At the end of each trial, participants had to report the final locations of the dots. The third task addressed attention switching *between* the verbal and visuospatial modalities (combined task): the stimulus stream contained a number of red circles and blue arrows and participants were required to keep a count of how many red circles were presented and to update the location of a blue dot within the imagined 2 x 2 matrix. To report the final location of a dot, participants used a 4-button piano keypad; the keys corresponded to four response options presented on the screen. To report the number of circles, participants were presented with four numbers and had to choose the correct number by pressing the corresponding key of the keypad. Subjects were given 8 s in which to make their responses (Kübler *et al.*, 2003).

All participants took part in one session comprising 6 runs including 9 trials each. There were two runs (18 trials) for each of the three tasks, which were counterbalanced for presentation. To isolate functional activation associated with attention switching, we chose a parametric manipulation of executive demands instead of the more common subtraction method. Thus, trials varied in switching frequency: The 18 trials were comprised of six “High (H)” (5-8 switches), six “Medium (M)” (2-4 switches), and six “Low (L)” (1 switch) switching demand trials. Trial length varied from 11 to 16 circles, arrows or circles and arrows. With regard to the switching demand, the sequence of trials was HLMMLMLM for run 1 and HMMHHLHMH for run 2 in all tasks. Trials were preceded by a 4 s fixation cross. A rest period of 22 s was provided after every third trial. Rest periods of 22 and 26 s

were included at the start and at the end of each run, respectively. At the end of the rest period a change in the fixation cross signalled the start of the next trial. In total the experiment lasted approximately 45 minutes (Kübler *et al.*, 2003). Before scanning participants performed 6 practice trials.

### **Performance analysis**

The number of correct reports of counts or locations, or both, allowing the subjects to score a maximum of two points per trial, determined accuracy (Kübler *et al.*, 2003). All post-hoc t-tests were Bonferroni corrected.

Users performed at chance levels in the visuospatial task and above chance levels in the combined task, but performance on the latter could not be matched with that of healthy controls. Given the inherent ambiguity in comparing functional activation patterns of groups that differ in performance, the functional data of the visuospatial and combined task were not analysed. For example, Murphy and Garavan (2004) have demonstrated that the inclusion of errors in an activation map can lead to a considerable number of false positive and false negative activations and that group differences in performance can create artifactual differences in activation patterns (Murphy & Garavan, 2004). In the case of the present study, we were able to match performance between drug users and healthy controls on the verbal task by excluding the worst performing users and the best performing controls. Failure to match performance by including all participants resulted in an increased number of between-group activation differences (data not reported) thereby justifying the necessity to match for performance.

### **fMRI parameters**

Nineteen contiguous 7 mm sagittal slices covering the entire brain were collected using a blipped gradient-echo, echo-planar pulse sequence (TE = 40 ms; TR = 2000 ms; FOV = 24 cm; 64 x 64 matrix; 3.75 x 3.75 mm in-plane resolution). All scanning was conducted on a 1.5 T GE Signa scanner equipped with a 30.5 cm i.d., three-axis local gradient coil and an endcapped quadrature birdcage radio-frequency head-coil (Wong *et al.*, 1992). Foam padding was used to limit head movements comfortably within the coil. High-resolution (SPGR) anatomic images were acquired prior to functional imaging to allow subsequent anatomical localisation and normalisation of functional activation. Stimuli were back-projected onto a screen at the subject's feet and were viewed with the aid of prism glasses attached to the inside of the radio-frequency head-coil.

### **fMRI analysis**

All data processing was conducted with the software package AFNI (Cox, 1996). Time shifting, using Fourier interpolation to adjust for differences in slice acquisition times, 3D motion correction and edge detection algorithms were first applied to the functional data. For each subject the 2 runs of each task were concatenated to produce one continuous dataset. The average percentage change in signal for all trials of each switching demand was calculated relative to the average signal during the rest periods. The average signal produced during the performance of each trial was based on only those images acquired during the updating portion of each trial (images acquired while the subject reported the final results or during the brief pre-trial periods were modelled with separate nuisance covariates). These percent-change

scores served as the basic unit of analysis and are subsequently referred to as ‘activation.’

Activation maps were converted to a standard stereotaxic coordinate system (Talairach & Tournoux, 1988) and spatially blurred using a 4.2 mm full-width-at-half-maximum isotropic Gaussian filter. Monte Carlo simulations revealed that a voxelwise threshold ( $p \leq 0.001$ ) combined with a minimum cluster size criterion (170  $\mu$ l) resulted in a 0.01 false positive level for a cluster of activation and a final voxelwise threshold of  $p \leq 10^{-6}$ . This thresholding was used for all subsequent t-tests and ANOVAs.

Basic task activation maps for each level of switching demand were identified with one-sample t-tests against the null hypotheses of no change in activation. To compare activation in users and controls and to identify areas that differed as a function of switching demand, a 3 (SWITCHING DEMAND)  $\times$  2 (GROUP) voxelwise ANOVA with subjects as a random factor was calculated for the verbal task only. A voxel was regarded as showing switching effects if it was significant in both the ANOVA and any one of the task t-test maps. Cortical areas that changed in activation with switching demand were interpreted as subserving the attention switching executive function.

As voxelwise analyses tend not to be as statistically powerful as region-of-interest (ROI) analyses, we functionally defined ROIs for the low, medium, and high conditions of the verbal task for the entire sample. For each condition of the task and separately for users (N=13) and controls (N=14), one-sample t-tests against the null

hypothesis of zero activation change were calculated. The t-test maps of users and controls were then combined for each condition (voxels were included if significant in either the user or control map). This process resulted in very large ROIs which were separated into smaller regions by only including significant voxels if 80% of their contiguous neighbour voxels were also significant (this procedure has the effect of separating functionally distinct activations that might be connected by a “finger” of activation). For each of these ROIs, activation was averaged over the voxels and a separate 3 (SWITCHING DEMAND)  $\times$  2 (GROUP) repeated measures ANOVA was calculated. All post-hoc t-tests were Bonferroni corrected.

## **Results**

One participant was discarded because she fell asleep during scanning and was not able to comply with the task requirements leading to a final sample size of 13 drug users. Differences in age ( $t_{25} = 18.66$ ,  $p < .001$ ) and sex ( $\chi^2_1 = 4.49$ ,  $p < .05$ ) between the users and healthy controls were significant.

## **Performance**

A 3 (TASK)  $\times$  3 (SWITCHING DEMAND) repeated measures ANOVA performed on the performance data of the users revealed main effects of task ( $F_{2/24} = 13.43$ ,  $p < .001$ ) and switching demand ( $F_{2/24} = 10.50$ ,  $p < .001$ ); the interaction was not significant (Figure 2). Differences in performance, dependent upon switching demands, were in the expected direction, but not all pairwise contrasts were significant. Users performed significantly better in the low compared to the high

switching condition ( $p < .01$ ); no differences were found between the low and medium and the medium and high switching demands. Performance in the visuospatial task was significantly worse compared to both the verbal and combined task ( $p < .01$ ); no differences were found between the verbal and combined task. A minimum number of 6 correct responses per run was considered above chance level (binomial distribution).

On the verbal task, performance could be matched between users and controls if the 8 worst controls and 8 best users were included. With this restricted sample, there were no significant group differences ( $F_{2/13} = .64$ ,  $p = .546$ , age as covariate) but the main effect of switching remained ( $F_{2/28} = 8.48$ ,  $p < .01$ ). There were no differences in age and sex between included and excluded participants, i.e. exclusion of participants did not skew the samples. However, age ( $t_{14} = 4.74$ ,  $p < .001$ ) and sex ( $\chi^2_1 = 6.35$ ,  $p < .05$ ) remained significantly different between users and healthy controls. All functional activation results are based on this restricted sample of 8 users and 8 healthy controls matched for performance on the verbal task.

In the visuospatial task only 4 users performed above chance in all switching conditions, 5 performed at chance level in all conditions and the average performance of all users was also at chance level. In the combined task, users performed above chance, but performance could not be matched with that of healthy controls.

Functional data of both tasks were excluded from analysis (see methods).

Performance in the visuospatial task correlated with years of drug consumption ( $r = -.63$ ,  $p < .05$ , uncorrected for multiple correlations; partial correlation coefficient when

controlling for age  $r = -.57$ ,  $p = .07$ ). Performance in the verbal and combined task did not depend on years of drug consumption.

## **Functional activation**

### Voxelwise Analysis

We found a main effect of switching demand but no main effect of group and no interaction. Attention switching was associated with bilateral activation changes in a broadly distributed WM network that included DLPFC, cingulate gyrus, basal ganglia, premotor areas, thalamus, parietal lobules, precuneus, temporal and occipital lobes and cerebellum.

### Functionally defined ROIs

Twenty-five ROIs were identified and, similar to the previous voxelwise analysis, these regions were broadly distributed and included prefrontal, cingulate, parietal, temporal, cerebellar and subcortical areas (see Table 1). Except for two deactivated clusters in medial frontal gyrus and posterior cingulate cortex and one activated cluster in left middle temporal gyrus, all clusters showed a significant main effect of demand (all  $p < .05$ ). A main effect of group with less activation in users was found in clusters in the left cingulate gyrus including medial frontal gyrus (BA6), left cingulate gyrus (BA32), right middle frontal gyrus (BA6), cingulate gyrus (BA24), in left thalamus, lentiform nucleus (globus pallidus / putamen); and in right precuneus (see Table 1 and Figure 3).

Significant demand  $\times$  group interactions were observed in left cingulate gyrus, right precuneus and the culmen of the left cerebellum (see Table 1 and Figure 3).

Activation in the cingulate gyrus was higher in healthy participants in all switching demands (all  $p < .01$ ). Activation increased as a function of switching frequency (L<M<H all  $p < .01$  in healthy participants and L<H, M<H both  $p < .05$  in users). In users, no difference was found between the low and medium switching conditions. Activation in the right precuneus was higher for controls in the medium and high switching conditions ( $p < .05$ ). Activation as a function of switching frequency showed the same pattern as in the cingulate gyrus. In the left culmen, activation was higher in controls than in users for the high switching condition ( $p \leq .05$ ). The increase in activation from the low to the high switching demand reached significance in controls ( $p < .01$ ). In users, this area was deactivated during the low condition; the difference in activation between the low and medium switching conditions was significant ( $p < .05$ ).

## **Discussion**

### **Working memory abilities**

Active cocaine users performed significantly worse than healthy controls in all tasks corroborating the frequently reported performance differences between addicts and non-addicted controls (Beatty *et al.*, 1995; Bolla *et al.*, 2000; Goldstein *et al.*, 2004). However, the level of impairment was task specific. Users' performance was best in the verbal task and could be matched with that of healthy participants. Performance in the combined task was above chance but was too poor to be matched while performance on the visuospatial task was particularly poor. In contrast, healthy participants did not differ in performance between tasks (Kübler *et al.*, 2003). Thus,

any differences between the tasks in task difficulty (as reflected in the performance of the controls) is unlikely to be the cause of the disproportionate impairment of the users in the visuospatial task. Furthermore, the relatively good performance in the verbal task showed that users were not uniformly impaired in all aspects of attention switching while the performance differences across tasks underline the separateness of the two WM modalities (Baddeley & Hitch, 1974; Cocchini *et al.*, 2002).

Performance in the visuospatial task tended to depend ( $r = -.57$ ,  $p = .07$ ) on years of drug consumption with the longer the history of drug use the poorer the performance. Attention switching in the verbal and combined tasks, however, did not show this relationship. Visuospatial WM has previously been shown to be negatively affected by reduced DA or D2-receptor levels in mice (Glickstein *et al.*, 2002; Miyoshi *et al.*, 2002), and in patients with Parkinson's disease (Costa *et al.*, 2003) and in healthy volunteers when treated with a D2-receptor antagonist (Mehta *et al.*, 2004). These results support the view of specific rather than general cognitive deficits in cocaine users mediated by DA modulation and D2-receptor density (Hoff *et al.*, 1996; Volkow *et al.*, 1997).

### **Neuroanatomy of attention switching in cocaine users**

Attention switching when applied to the phonological loop within WM activated similar and broadly distributed areas of the brain (Kübler *et al.*, 2003) that have repeatedly been found to subserve WM (D'Esposito *et al.*, 1998; Haxby *et al.*, 2000). Reduced activation was observed in users in prefrontal (bilateral middle and medial frontal gyrus) and parietal (right precuneus) areas and in the cingulate cortex, an area which has previously been shown to be hypoactive in drug addicts during tasks

requiring executive control (Kaufman *et al.*, 2003; Forman *et al.*, 2004; Hester & Garavan, 2004). Bolla and colleagues tested abstinent cocaine users on a modified version of the Stroop task (Bolla *et al.*, 2004). Compared to healthy participants, the authors found hypoactivation in right lateral prefrontal cortex and left caudal ACC and hyperactivation in right rostral ACC for the conflict condition, that is, on trials in which the word and colour were incongruent. Both groups performed equally well on the task leading the authors to speculate that the higher activation in the right ACC might reflect a compensatory mechanism. The hypoactivated cluster in the left caudal ACC ( $x = -6, y = 18, z = 41$ ) is in the same location to the one found in the present study. Other evidence of a compensatory mechanism was found by Hester and Garavan (2004) who observed the reduced activity in the ACC to be accompanied by increased cerebellar activity in users. Such a reciprocal cortico-cerebellar relationship has also been reported for alcoholics (Desmond *et al.*, 2003). It is important to note that the majority of the functionally defined ROIs of our study did *not* show a group effect. This finding renders it unlikely that the specific hypoactivation in prefrontal and cingulate areas in users was due to global group differences in vascular reactivity.

Prefrontal and cingulate cortex are thought to interact in top-down cognitive control or action monitoring such that the ACC detects variations in the need for cognitive control which is then implemented by the prefrontal cortices (Gehring & Knight, 2000). Such action monitoring is also necessary for attention switching in WM (MacDonald *et al.*, 2000). Prefrontal areas including DLPFC and ACC have repeatedly been shown to be involved in task switching (Dove *et al.*, 2000; Kimberg *et al.*, 2000; Sohn *et al.*, 2000; Kondo *et al.*, 2004). The diminished responsiveness of prefrontal and cingulate areas in users could account for their difficulties in task

performance such that an under-responsive monitoring mechanism fails to signal to the lateral prefrontal lobes the necessity to implement an attentionally more demanding action.

Accompanying hypoactivation in cortical areas was subcortical hypoactivation in the thalamus and in the lentiform nucleus (globus pallidus / putamen). From the results of their study on task switching in patients with left or right frontal lesions or Parkinson's disease, Rogers and colleagues (1998) proposed an interaction between frontal and striatal regions such that left and right frontal cortices are necessary to organize global behaviour when confronted with a new task. After practice the left frontal cortex together with other brain regions maintains endogenous control over the task set and activates appropriate behaviour according to the exogenously imposed task demands. Flexible reactions to changing task demands such as in a switching task are suggested to depend on the balance of excitation of appropriate and inhibition of inappropriate stimulus-response associations in the frontal lobes. The striatum is suggested to contribute to flexible behaviour such that cortically initiated operations are communicated via the striatum to other parts of the corticostriatal circuitry, which control their implementation (Rogers *et al.*, 1998). It has been shown that Parkinson patients, in whom the striatum is depleted of DA, have difficulties maintaining representations of a cue active in WM for a long period of time and have therefore higher switch costs or make more errors when task switching is required (Rogers *et al.*, 1998; Cools *et al.*, 2003; Pollux, 2004). Kelly and co-workers have reported striatal involvement for executive functioning on a response inhibition task (Kelly *et al.*, 2004) and recently Lewis and colleagues demonstrated striatal contributions to WM such that the nucleus caudate was specifically involved in manipulating

information in WM (Lewis *et al.*, 2004). Taken together, these results underline the importance of striatal regions to cognitive functioning and a disruption of the nigrostriatal pathways through chronic cocaine abuse is likely to contribute to impaired performance when attention switching within WM is required.

There were other differences between users and controls in their drug usage, such as amount of consumed alcohol and marijuana, so further studies will be needed to determine that the reported results are specific to cocaine and not polydrug use. There were also significant age and sex difference between users and healthy volunteers with the user group being older and comprising more men. However, when including age as a covariate in the repeated measures ANOVAs on the functionally defined ROIs the drug effect remained in almost all areas including middle and medial prefrontal gyrus, ACC, and lentiform nucleus. Although we have not tested sufficient numbers of subjects on this attention switching task to make any conclusions about the effects of sex on activation patterns, we have previously reported no sex-related activation differences (N = 44) for commission errors (failed inhibition during NOGO trials) in similar regions to those observed in the present study including the ACC and the thalamus (Hester *et al.*, 2004).

## **Conclusions**

With the results of the present study we provide behavioural and neuroanatomical evidence for impaired attention switching in cocaine users. Results revealed hypoactivity in cingulate and prefrontal areas, and the lentiform nucleus (globus

pallidus / putamen), whereas many other task related cortical areas, such as DLPFC and anterior frontal cortex (Kübler *et al.*, 2003) were unaffected. By demonstrating that differences in cortical processing between users and controls are anatomically specific and not ubiquitous, our results confirm those of Kaufman and colleagues (2003), Hester and Garavan (2004), and Bolla and colleagues (2004), all of which found hypoactivation restricted to the ACC and prefrontal areas in tasks requiring inhibitory control. The intent of the current task was to identify brain regions involved in switching from one thought to another, that is, switching between items held in WM. Impairment in this function may compromise the ability of users to switch away from drug-related thoughts and, thus, may contribute to the maintenance of addiction.

## **References**

- Baddeley, A. & Hitch, G.J. (1974) Working memory. In Bower, G.H. (ed.) *The Psychology of Learning and Motivation*. Academic Press, New York, pp. 47-89.
- Beatty, W.W., Katzung, V.M., Moreland, V.J. & Nixon, S.J. (1995) Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend.*, **37**, 247-253.
- Bolla, K.I., Cadet, J.L. & London, E.D. (1998) The neuropsychiatry of chronic cocaine abuse. *J. Neuropsychiatry Clin. Neurosci.*, **10**, 280-289.
- Bolla, K.I., Ernst, M., Kiehl, K.A., Mouratidis, M., Eldreth, D.A., Contoreggi, C.S., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A., Funderburk, F.R. & London, E.D. (2004) Prefrontal cortical dysfunction in abstinent cocaine abusers. *J. Neuropsychiatry Clin. Neurosci.*, **16**, 1-9.
- Bolla, K.I., Funderburk, F.R. & Cadet, J.L. (2000) Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology*, **54**, 2285-2292.
- Bonson, K.R., Grant, S.J., Contoreggi, C.S., Links, J.M., Metcalfe, J., Weyl, H.L., Kurian, V., Ernst, M. & London, E.D. (2002) Neural systems and cue-induced cocaine craving. *Neuropsychopharmacology*, **26**, 376-386.
- Cabeza, R. & Nyberg, L. (2000) Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.*, **12**, 1-47.
- Cocchini, G., Logie, R.H., Della Sala, S., MacPherson, S.E. & Baddeley, A.D. (2002) Concurrent performance of two memory tasks: evidence for domain-specific working memory systems. *Mem. Cognit.*, **30**, 1086-1095.
- Collette, F., Salmon, E., van der Linden, M., Chicherio, C., Belleville, S., Degueldre, C., Delfiore, G. & Franck, G. (1999) Regional brain activity during tasks

- devoted to the central executive of working memory. *Cogn. Brain Res.*, **7**, 411-417.
- Collette, F. & van der Linden, M. (2002) Brain imaging of the central executive component of working memory. *Neurosci. Biobehav. Rev.*, **26**, 105-125.
- Cools, R., Barker, R.A., Sahakian, B.J. & Robbins, T.W. (2003) L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, **41**, 1431-1441.
- Costa, A., Peppe, A., Dell'Agnello, G., Carlesimo, G.A., Murri, L., Bonuccelli, U. & Caltagirone, C. (2003) Dopaminergic modulation of visual-spatial working memory in Parkinson's disease. *Dement. Geriatr. Cogn. Disord.*, **15**, 55-66.
- Cowan, N. (1993) Activation, attention, and short-term memory. *Mem. Cognit.*, **21**, 162-167.
- Cox, R.W. (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.*, **29**, 162-173.
- Desmond, J.E., Chen, S.H., DeRosa, E., Pryor, M.R., Pfefferbaum, A. & Sullivan, E.V. (2003) Increased frontocerebellar activation in alcoholics during verbal working memory: an fMRI study. *Neuroimage*, **19**, 1510-1520.
- D'Esposito, M., Aguirre, G.K., Zarahn, E., Ballard, D., Shin, R.K. & Lease, J. (1998) Functional MRI studies of spatial and nonspatial working memory. *Cogn. Brain Res.*, **7**, 1-13.
- Di Chiara, G. (2002) Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav. Brain Res.*, **137**, 75-114.
- Dove, A., Pollman, S., Schubert, T., Wiggins, C.J. & von Cramon, D.Y. (2000) Prefrontal cortex activation in task switching: an event-related fMRI study. *Cogn. Brain Res.*, **9**, 103-109.

- Forman, S.D., Dougherty, G.G., Casey, B.J., Siegle, G.J., Braver, T.S., Barch, D.M., Stenger, V.A., Wick-Hull, C., Pisarov, L.A. & Lorensen, E. (2004) Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol. Psychiatry*, **55**, 531-537.
- Garavan, H. (1998) Serial attention within working memory. *Mem. Cognit.*, **26**, 263-276.
- Garavan, H., Ross, T.J., Li, S.J. & Stein, E.A. (2000) A parametric manipulation of central executive functioning. *Cereb. Cortex*, **10**, 585-592.
- Gehring, W.J. & Knight, R.T. (2000) Prefrontal-cingulate interactions in action monitoring. *Nat. Neurosci.*, **3**, 516-520.
- Gerdeman, G.L., Partridge, J.G., Lupica, C.R. & Lovinger, D.M. (2003) It could be habit forming: drugs of abuse and striatal synaptic plasticity. *Trends Neurosci.*, **26**, 184-192.
- Glickstein, S.B., Hof, P.R. & Schmauss, C. (2002) Mice lacking dopamine D2 and D3 receptors have spatial working memory deficits. *J. Neurosci.*, **22**, 5619-5629.
- Goldman-Rakic (1996) The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **351**, 1445-1453.
- Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G.J., Fowler, J.S. & Volkow, N.D. (2004) Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia*, **42**, 1447-1458.
- Haxby, J.V., Petit, L., Ungerleider, L.G. & Courtney, S.M. (2000) Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage*, **11**, 380-391.

- Hester, R., Fassbender, C. & Garavan, H. (2004) Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the GO/NOGO task. *Cereb. Cortex*, **14**, 986-994.
- Hester, R. & Garavan, H. (2004) Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate and cerebellar activity. *J. Neurosci.*, **24**, 11017-11022
- Hoff, A.L., Riordan, H., Morris, L., Cestaro, V., Wieneke, M., Alpert, R., Wang, G.J. & Volkow, N. (1996) Effects of crack cocaine on neurocognitive function. *Psychiatry Res.*, **60**, 167-176.
- Kaufman, J.N., Ross, T.J., Stein, E.A. & Garavan, H. (2003) Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J. Neurosci.*, **23**, 7839-7843.
- Kelly, A.M., Hester, R., Murphy, K., Javitt, D.C., Foxe, J.J. & Garavan, H. (2004) Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI. *Eur. J. Neurosci.*, **19**, 3105-3112.
- Kimberg, D.Y., Aguirre, G.K. & D'Esposito, M. (2000) Modulation of task-related neural activity in task-switching: an fMRI study. *Cogn. Brain Res.*, **10**, 189-196.
- Kondo, H., Osaka, N. & Osaka, M. (2004) Cooperation of the anterior cingulate cortex and dorsolateral prefrontal cortex for attention shifting. *Neuroimage*, **23**, 670-679.
- Kübler, A., Murphy, K., Kaufman, J., Stein, E.A. & Garavan, H. (2003) Co-ordination within and between verbal and visuospatial working memory: network modulation and anterior frontal recruitment. *Neuroimage*, **20**, 1298-1308.

- Lewis, S.J., Dove, A., Robbins, T.W., Barker, R.A. & Owen, A.M. (2004) Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. *Eur. J. Neurosci.*, **19**, 755-760.
- MacDonald, A.W., Cohen, J.D., Stenger, V.A. & Carter, C.S. (2000) Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, **288**, 1835-1838.
- Mayr, U. & Kliegl, R. (2000) Task-set switching and long-term memory retrieval. *J. Exp. Psychol. Learn. Mem. Cogn.*, **26**, 1124-1140.
- Mehta, M.A., Manes, F.F., Magnolfi, G., Sahakian, B.J. & Robbins, T.W. (2004) Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D(2) receptor antagonist sulpiride in human volunteers. *Psychopharmacology (Berl)*.
- Miyoshi, E., Wietzikoski, S., Camplessei, M., Silveira, R., Takahashi, R.N. & Da Cunha, C. (2002) Impaired learning in a spatial working memory version and in a cued version of the water maze in rats with MPTP-induced mesencephalic dopaminergic lesions. *Brain Res. Bull.*, **58**, 41-47.
- Murphy, K. & Garavan, H. (2004) Artfactual fMRI group and condition differences driven by performance confounds. *Neuroimage*, **21**, 219-228.
- Nader, M.A., Daunais, J.B., Moore, T., Nader, S.H., Moore, R.J., Smith, H.R., Friedman, D.P. & Porrino, L.J. (2002) Effects of cocaine self-administration on striatal dopamine systems in rhesus monkeys: initial and chronic exposure. *Neuropsychopharmacology*, **27**, 35-46.
- Owen, A.M. (1997) The functional organisation of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *Eur. J. Neurosci.*, **9**, 1329-1339.

- Owen, A.M., Evans, A.C. & Petrides, M. (1996) Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cereb. Cortex*, **6**, 31-38.
- Owen, A.M., Stern, C.E., Look, R.B., Tracey, I., Rosen, B.R. & Petrides, M. (1998) Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proc. Natl. Acad. Sci. U. S. A.*, **95**, 7721-7726.
- Pollux, P.M.J. (2004) Advance preparation of set-switches in Parkinson's disease. *Neuropsychologia*, **42**, 912-919.
- Rinne, J.O., Portin, R., Ruottinen, H., Nurmi, E., Bergman, J., Haaparanta, M. & Solin, O. (2000) Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. *Arch. Neurol.*, **57**, 470-475.
- Rogers, R.D., Sahakian, B.J., Hodges, J.R., Polkey, C.E., Kennard, C. & Robbins, T.W. (1998) Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain*, **121**, 815-842.
- Shallice, T. & Burgess, P. (1996) The domain of supervisory processes and temporal organization of behaviour. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **351**, 1405-1411; discussion 1411-1412.
- Smith, E.E. & Jonides, J. (1999) Storage and executive processes in the frontal lobes. *Science*, **283**, 1657-1661.
- Sohn, M.-H., Ursu, S., Anderson, J.R., Stenger, V.A. & Carter, C.S. (2000) The role of prefrontal cortex and posterior parietal cortex in task switching. *Proc. Natl. Acad. Sci. U. S. A.*, **97**, 13448-13453.

- Talairach, J. & Tourneaux, P. (1988) *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme Medical, New York.
- Voigt, S. & Hagendorf, H. (2002) The role of task context for component processes in focus switching. *Psychologische Beiträge*, **44**, 248-274.
- Volkow, N.D., Ding, Y.S., Fowler, J.S. & Wang, G.J. (1996) Cocaine addiction: hypothesis derived from imaging studies with PET. *J. Addict. Dis.*, **15**, 55-71.
- Volkow, N.D., Fowler, J.S., Wang, G.J. & Goldstein, R.Z. (2002) Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiol. Learn. Mem.*, **78**, 610-624.
- Volkow, N.D., Wang, G.J., Fischman, M.W., Foltin, R.W., Fowler, J.S., Abumrad, N.N., Vitkun, S., Logan, J., Gatley, S.J., Pappas, N., Hitzemann, R. & Shea, C.E. (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature*, **386**, 827-830.
- Wong, E.C., Boskamp, E. & Hyde, J.S. (1992) A volume optimized quadratureelliptical endcap birdcage brain coil *Eleventh Annual Scientific Meeting, Society for Magnetic Resonance Medicine*, Berlin, pp. 4015.

Table 1: Functionally defined ROIs (25) in the verbal task. Clusters are sorted first by lobe then by region.

Structure	Brodmann Area	Hemisphere	Volume (μl)	Centre of mass (T-T atlas)		
				x	y	z
<i>Frontal lobe</i>						
Cingulate gyrus and medial frontal gyrus <sup>*††</sup>	6/24/32	L	1509	-21	-2	45
Cingulate gyrus <sup>*‡</sup>	32	L	286	-3	12	42
Cingulate gyrus <sup>*‡</sup>	24	L	111	-6	1	24
Cingulate gyrus <sup>‡</sup>		R	102	15	10	40
Middle frontal gyrus (posterior margin: incl cingulate gyrus) <sup>*‡</sup>	6	R	282	22	-3	51
Medial frontal gyrus (anterior margin: superior frontal gyrus) !	9	R	215	13	43	28
Inferior frontal gyrus <sup>‡</sup>	44/9	L	107	-51	6	20
Precentral gyrus <sup>‡</sup>		L	648	-30	2	26
Precentral gyrus (anterior margin: middle frontal gyrus) <sup>‡</sup>	13	R	242	43	-3	5
<i>Parietal lobe</i>						
Posterior cingulate (anterior margin: incl. cingulate gyrus) <sup>‡ !</sup>	23/31/30	L,R	1995	-2	-52	22
Cingulate gyrus (anterior margin: caudate) <sup>‡</sup>	31	R	444	19	-36	23
Inferior parietal lobule <sup>‡</sup>	40	L	646	-44	-40	42
Precuneus <sup>*††</sup>	7	R	485	12	-61	45
Supramarginal gyrus <sup>‡</sup>	40	R	357	40	-39	35
<i>Temporal lobe</i>						
Middle temporal gyrus	37	L	104	-43	-56	5
<i>Cerebellum</i>						
Culmen <sup>*††</sup>		L	144	-7	-40	-26
Cerebellar lingual <sup>‡</sup>		L	136	-5	-44	-11
<i>Subcortical</i>						
Thalamus and ventral lateral nucleus (anterior margin: lentiform nucleus (globus pallidus / putamen)) <sup>*‡</sup>		L	958	-16	-12	10
Thalamus and ventral lateral nucleus <sup>‡</sup>		R	499	11	-11	3
Caudate and caudate body (anterior margin: putamen and insula) <sup>‡</sup>		R	389	22	-10	24
Clastrum (anterior margin: insula, posterior: lentiform nucleus and putamen) <sup>‡</sup>		R	246	31	9	3
Lentiform nucleus (globus pallidus / putamen) <sup>*‡</sup>		L	174	-19	-1	1
Putamen (anterior margin: claustrum, posterior: incl. lentiform nucleus) <sup>‡</sup>		R	165	24	4	18
Putamen (anterior margin: claustrum, posterior: caudate body) <sup>‡</sup>		L	100	-21	12	16
<i>Brain stem</i>						
Red nucleus <sup>‡</sup>		L	296	-1	-20	-10

Positive center-of-mass coordinates for x, y, and z refer to locations right (x), posterior (y), and superior (z) to the anterior commissure. Brain areas which showed main effects of switching demand or group or switching demand by group interaction are denoted as follows: \* significant group effect ( $p < .05$ ), ‡ significant effect of switching demand ( $p < .05$ ), † significant group  $\times$  switching demand interaction ( $p < .05$ ), ! deactivation.

## Figure captions

### Figure 1

Schematic of the three tasks (dark grey corresponds to blue and light grey to red in the actual task). A: in the verbal task, blue and red circles had to be counted, B: in the visuospatial task, the locations of a blue and red dot had to be updated, C: in the combined task circles had to be counted and the location of a dot had to be updated. Storage and rehearsal demands were equal in all tasks and the manipulation of interest was the switch between the count or location presentations.

### Figure 2

Performance of users (top panel) and controls (bottom panel\*) measured as correct trial reports (final counts or final locations). Bars indicate the mean percentage of correct reports per task and switching demand. Error bars are SEM. Healthy controls performed equally in all tasks.

\*From Kübler et al. (2003), *Neuroimage* 20 (2), 1298-308 with permission.

### Figure 3

Functionally defined ROIs (overlaid on one participant's anatomical structure) in which a main effect of group or a group  $\times$  switching demand interaction was observed. 1 Cingulate gyrus and medial frontal gyrus (BA6 / 24 / 32); 2 Thalamus and ventral lateral nucleus (anterior margin: lentiform nucleus); 3 Cingulate gyrus (BA32); 4 Culmen; 5 Precuneus (BA7); 6 Middle frontal gyrus (BA6); 7 Lentiform nucleus (globus pallidus and putamen). \* significant group effect ( $p < .05$ ), ‡ significant switching demand effect ( $p < .05$ ), † significant group  $\times$  switching demand

interaction ( $p < .05$ ). Graphs depict interactions: mean activation is plotted as a function of switching demand for controls and addicts. Grey bars represent controls, black bars users. Error bars are standard error of the mean.

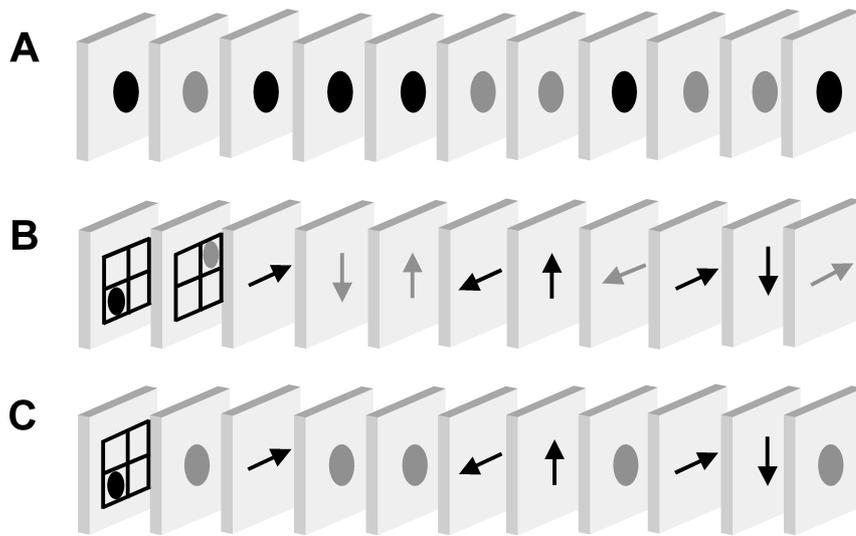


Figure 1

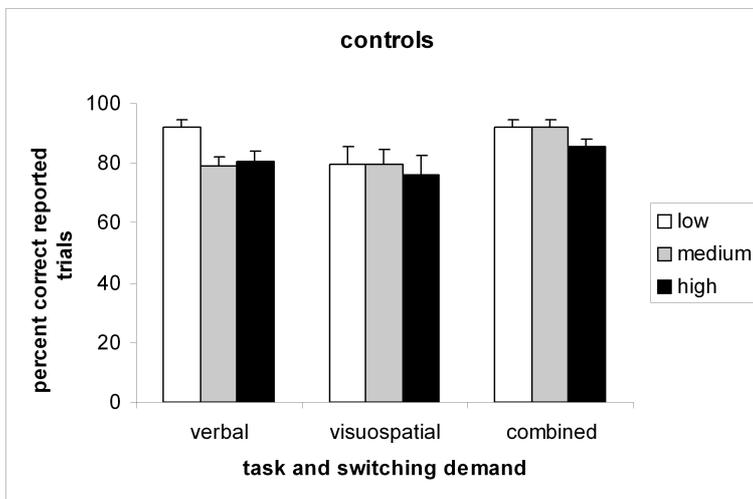
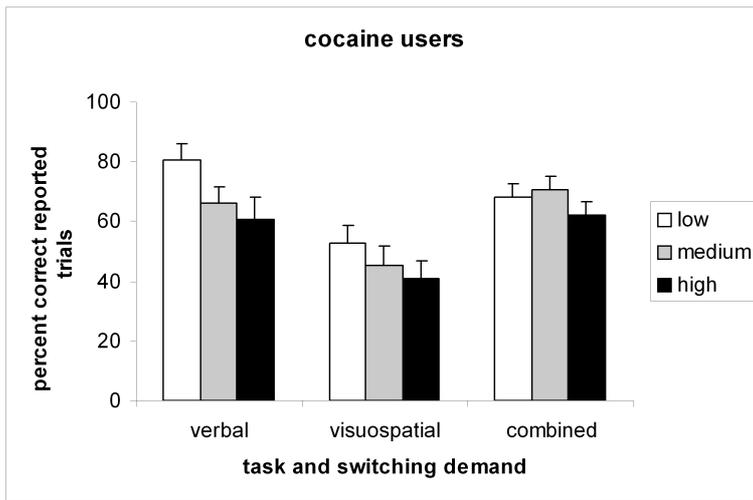


Figure 2

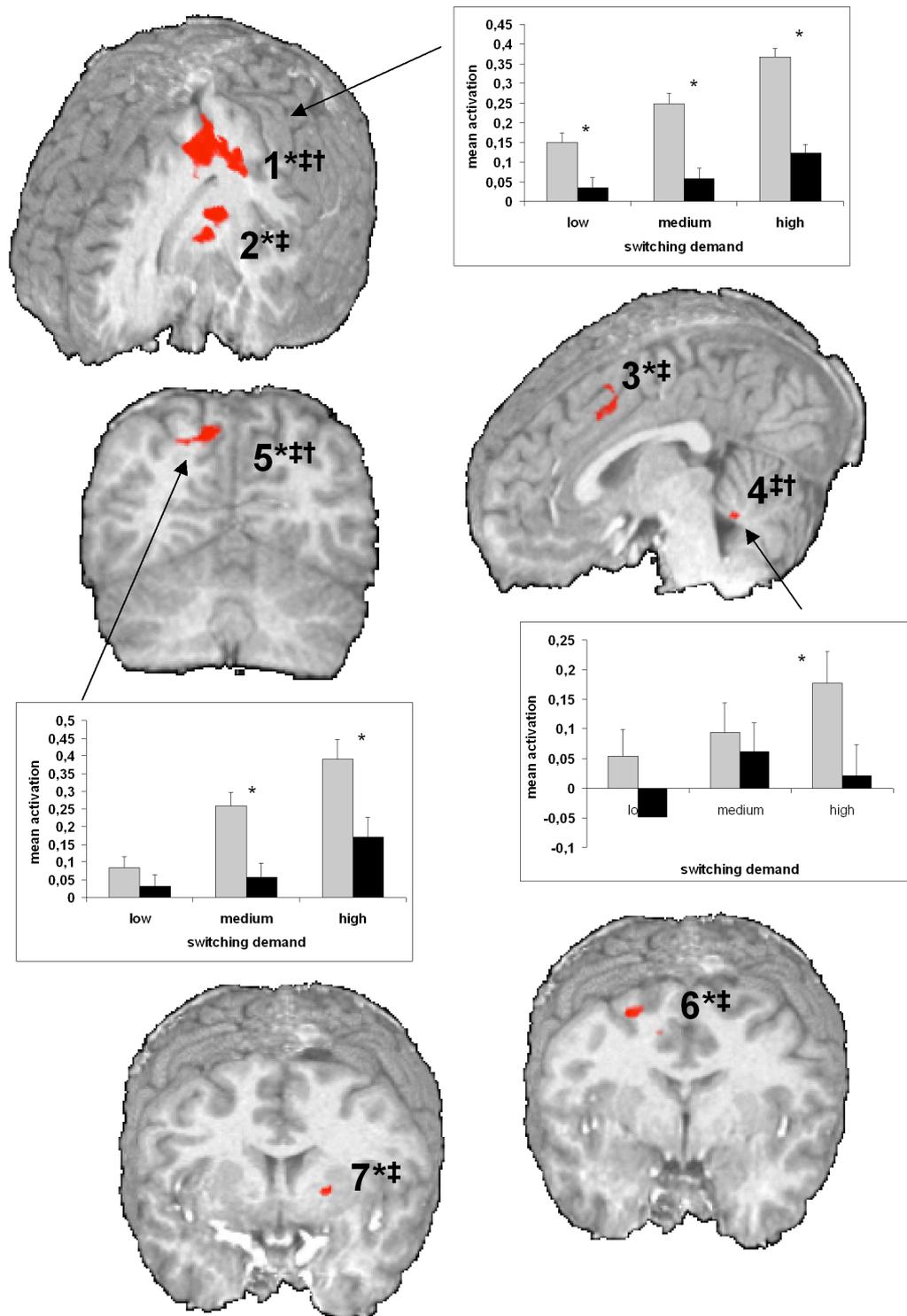


Figure 3