# Functional Magnetic Resonance Imaging Investigation of the Amphetamine Sensitization Model of Schizophrenia in Healthy Male Volunteers

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**Context:** Recent work suggests that the amphetamine sensitization model of schizophrenia can safely be induced in healthy volunteers and is associated both with behavioral and dopaminergic hypersensitivity to amphetamine. However, the effects of a sensitization on brain function remain unclear.

**Objective:** To assess the impact of a sensitizing dosage regimen of dextroamphetamine on human cortical functioning and cognition.

**Design:** Randomized, double-blind, parallel-groups design using pharmacological functional magnetic resonance imaging.

**Setting:** The neuroimaging research unit at the Institute of Psychiatry, King's College London, London, England.

**Participants:** Healthy male volunteers (n=22).

**Interventions:** Dextroamphetamine (20 mg) or placebo administration at 4 testing sessions, using a dosage regimen shown to induce sensitization (ie, 3 doses administered with a 48-hour interdose interval and a final dose after a 2-week washout period).

**Main Outcome Measures:** Sensitization was characterized by enhanced subjective response to the drug, changes in behavioral performance (reaction time and accuracy), and functional magnetic resonance imaging measurements of brain activity during an N-back working memory task.

**Results:** Sensitization was associated with more rapid responding during the performance of an intermediate-load working memory challenge. During a high-load cognitive challenge, sensitization did not produce performance deficits, but functional magnetic resonance imaging showed hyperactivity of the dorsolateral prefrontal cortex and aberrant recruitment of the superior temporal gyrus, caudate nucleus, and thalamus. Furthermore, the change in striatal activity was negatively correlated with the enhanced subjective effects of the drug, whereas prefrontal hyperactivity was positively correlated with sensitized measures of alertness.

**Conclusions:** These transient load-dependent abnormalities of frontal and temporal activity induced by amphetamine sensitization support neuroimaging findings in schizophrenic patients, implying that amphetamine sensitization may help to bridge pathophysiological theories of schizophrenia that focus on pharmacological (dopaminergic) and cognitive mechanisms, respectively.

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PATIENTS WITH SCHIZOPHRENIA, and those with stimulant-induced psychosis, commonly display stress hypersensitivity and a profoundly reduced threshold for the psychotogenic action of stimulant drugs.[1-7] These effects have been linked to enhanced drug-induced striatal dopamine release.[8-10] Rodents receiving repeated intermittent amphetamine exposure display a similar "sensitization" to stress,[11,12] the psychomotor stimulatory effects of the drug,[13-19] and the elevation of striatal dopamine levels.[20] Thus, amphetamine sensitization in rodents is used to model some aspects of schizophrenia.

It is well established that patients with schizophrenia have significant cognitive deficits in various domains, including working memory (WM), executive control, attention, affective processing, and learning.[21-23] This is a challenge for the amphetamine sensitization model in rodents because while sensitization does alter some aspects of rodent function, including prepulse and latent inhibition[24,25] and attentional set-shifting,[26,27]

there is little evidence that sensitized rodents display deficits in, for example, WM where patients are severely impaired.[26,28,29] In contrast, sensitized primates do display profound deficits in spatial delayed response (a test of spatial WM) linked to reduced dopamine turnover in the cortex[30] in addition to a complex set of aberrant behaviors more akin to schizophrenia,[30-32] including hypervigilance and hallucinatory-like activity. In general, the literature shows that the amphetamine model of sensitization replicates a proportion of the cognitive deficits associated with schizophrenia.

In the cortex, dopamine signaling within a narrow "optimal" range enhances cortical efficiency,[33-35] acting to reduce physiological noise and enhancing the signal to noise ratio for salient or sustained prefrontal cortical inputs.[36,37] Notably, both overstimulation and understimulation of cortical $D_1$ receptors are equally detrimental to cognitive performance. It has been suggested that a reduction, rather than an excess, in prefrontal cortical dopamine signaling gives rise to the cognitive dysfunction seen in patients.[38,39] However, the compensatory upregulation of cortical $D_1$ receptors seen in patients[38] would also render patients hypersensitive to drug- or stress-related elevation of cortical dopamine.[40] Following amphetamine administration, healthy controls homozygous for the Val158Met polymorphism of the catechol-O-methyl transferase gene (*COMT*) display a similar pattern of relatively inefficient prefrontal recruitment (ie, hyperactivity to maintain the same performance level) during a high-load WM task.[41] This effect is reminiscent of frontal and striatal hyperactivity seen in patients with schizophrenia during a similar task.[42,43]

Beyond cognitive performance, dorsolateral prefrontal cortex (DLPFC) hyperactivity is also seen in patients with acute psychosis[44,45] and in healthy volunteers following the administration of hallucinogenic agents,[46-49] suggesting that this cortical region plays an important role in the genesis of psychosis.[50] Indeed, while prefrontal lesions block behavioral (locomotor) sensitization in rodents, such ablation in primates impedes only the sensitization of hallucinatory-type behavior and in fact enhances psychomotor sensitization.[51] Such findings suggest important between-species differences in prefrontal function and, implicitly, frontostriatal connectivity, with particular respect to the expression of psychosis-like behaviors.[52]

Contemporary cognitive models of schizophrenia emphasize the importance of disrupted cortico-cortical integration (eg, frontotemporal dysconnectivity)[53-57] over dopamine dysregulation in the development of psychotic symptoms.[58] A central challenge for the field is to marry pharmacological and cognitive perspectives of the disorder. For example, dopaminergic medication can partially normalize abnormal frontal activity,[59,60] and recent pathophysiological theories of schizophrenia emphasize the importance of dopamine-dependent regulation of synaptic plasticity.[61-63] Thus, dopamine-sensitive cortical circuits represent attractive targets for translational modeling using amphetamine sensitization. Recently, both behavioral (eyeblink) and neurochemical sensitization of striatal dopamine have been robustly demonstrated in healthy volunteers.[64] However, in contrast to the extensive animal literature, a neurophysiological examination of the effects of amphet-amine sensitization on brain function in humans is still lacking. Herein, we explore the effects of a sensitizing regimen of amphetamine on brain activity during a WM task using language stimuli (letters). Given the extensive literature on schizophrenic abnormalities in frontotemporal areas during language processing[53-57] and in frontostriatal circuitry during executive control processes like WM,[42,65] we put a particular emphasis on the prefrontal cortex, striatum, and temporal cortex, which were used as regions of interest in our functional magnetic resonance imaging (fMRI) analyses. Explicitly, we tested the hypotheses that (1) repeated placebo administration will not be associated with any significant changes in cortical functioning, (2) a sensitizing regimen of amphetamine will lead to reduced efficiency in cortical function, evident as increased prefrontal activity in the high-load condition,[41] and (3) this prefrontal dysfunction will be associated with dysregulation of the temporal ipsilateral lobe

## METHODS

Twenty-two right-handed male volunteers (mean [SD] age, 30.8 [8.5] years) were recruited and assigned to receive either 4 oral doses of dexamphetamine (20 mg) or 4 doses of a placebo, using the same pattern of amphetamine administration, albeit with a fixed dose across all participants, as that used by Boileau et al.[64] Subjects received the first 3 doses with a 48-hour interdose interval (sessions 1-3) and again (fourth dose) after a 2-week washout period (session 4) using a double-blind procedure. Participants were excluded if they had personal history of psychiatric or neurological disorders, were taking any medications, or had a family history of mental illness or substance abuse problems. Furthermore, on each visit, a drug-urine analysis was carried out to exclude the use of recreational drugs. Subjects were scanned approximately 120 minutes postadministration during sessions 1 (short-term exposure) and 4 (repeated/sensitized exposure) in an effort to model the effects of sensitization-related dopaminergic dysregulation on the neural substrates of WM. Participants additionally performed a rewarded decision-making task and an explicit motor sequence learning task. The data from these paradigms are not included herein and will be the subjects of separate articles. The project was approved by the Institute of Psychiatry research ethics committee (REC ref 022/03).

### DATA ACQUISITION

Imaging was performed with a 1.5-T GE scanner (GE Healthcare, Milwaukee, Wisconsin). One hundred eighty volumes (matrix size $64 \times 64$) with whole-brain coverage were acquired during each functional run. Each volume comprised 36 slices, collected in an interleaved manner, with a slice thickness of 3 mm, with an additional 0.3-mm gap between slices. The repetition time was 3 seconds, echo time=40 milliseconds, and flip angle=90°. Total acquisition time was 9 minutes (540 seconds). High-resolution structural scans were also acquired (spoiled gradient recalled and high-resolution gradient echo).

### N-BACK WM TASK

While lying in the scanner, subjects performed a standard blocked N-back WM task using visually presented letters.[66] This task involved 9 alternating 30-second blocks of WM, with 4 levels of difficulty (N=0, 1, 2, or 3). In the control condition (N=0), subjects were asked to press the button whenever they

saw the letter *X*. Subjects were informed at the start of each 30-second block as to the nature of the response required (N=0, 1, 2, or 3). Stimuli were presented with an International Sensitivity Index of 2000 milliseconds.

## ANALYSIS

### Assessment of Sensitization

During each visit, self-reported subjective drug effects were assessed using the Addiction Research Center Inventory (ARCI) Amphetamine Scale,[67-69] the Profile of Mood States,[70] and Visual Analog Mood Scales[71] at baseline and every 60 minutes for 240 minutes. When completing these ratings, subjects were asked to score each item for "how they feel at the present moment" and the questionnaires were administered hourly. Physiological data including eye-blink rate, pulse, and blood pressure were also collected by the same researcher in the same environmental context. Pulse and blood pressure were collected seated following a resting period of 5 minutes using an electronic sphygmomanometer. Eye-blink rate was taken as the average number of blinks counted over a 3-minute period while subjects were at rest; participants were not explicitly informed when this measure was being collected.

We expected the expression of behavioral (subjective) sensitization would mirror previous findings.[64,72-74] While there is some divergence between the findings of Boileau et al[64] and Strakowski et al,[72-74] we expected to see enhanced amphetamine-like experience, amphetamine-induced euphoria (ARCI–Morphine Benzedrine Group Scale), and Profile of Mood States activity-vigor, alertness and attentiveness, and positive affect (happy-sad subscale). Physiologically, we expected that the resting eye-blink rate would show sensitization.

For statistical analyses of each dependent variable, a group × administration/day analysis of variance (ANOVA) with repeated measures on the second factor was used. The group factor had 2 levels (amphetamine vs placebo), and administrations had 4 levels (day 1, 3, 5, and 19). The chosen level of significance was $P < .05$ with Greenhouse-Geisser correction. All calculations were performed using SPSS version 12.1 for Windows (SPSS Inc, Chicago, Illinois).

### Behavioral Analyses

A repeated-measures ANOVA (group × time × load) was used to test for any significant between-group differences in both performance accuracy (false-positives and misses) and reaction time. Additional post hoc paired *t* tests were used to test specific hypotheses in the amphetamine group. To confirm a relationship between behavioral and subjective sensitization, we tested for correlations between both sensitized measures after correcting for individual differences in intersession plasma amphetamine concentration. All calculations were performed using SPSS version 13 for Windows (SPSS Inc).

### fMRI Analysis

After preprocessing, including realignment, image distortion correction,[75,76] and normalization, statistical analysis was carried out using the general linear model[77,78] as implemented in Statistical Parametric Mapping 2 (Wellcome Trust Centre for Neuroimaging, London, England). Each subject's echoplanar imaging data were normalized to a Montreal Neurological Institute (MNI) T1 template. Our model coded separate regressors for each of the 4 conditions (control, 1-back, 2-back, and 3-back). The blood oxygen level–dependent (BOLD) response was convolved with a canonical hemodynamic re-

sponse function.[79] The data were high-pass filtered (cutoff 128 seconds) and corrected for serial correlations using a first-order autoregressive model.

At the group level, we performed a random-effect analysis. Images of parameter estimates for each of the 4 conditions of interest (N=0, 1, 2, and 3) from the first-level analysis were entered into the second level of analysis using 2-sample *t* tests to compare groups (placebo vs amphetamine). Separate 4 × 2 ANOVAs (*F* tests) were used to test for a main effect of time (session) and a time × condition interaction in each group. Finally, because we expected the hypothesized cortical inefficiency to be most apparent during a high-load WM challenge, a paired *t* test (within-group session 1 vs session 2 comparison) was used to probe the effects of sensitization during this primary condition of interest (N=3). In the case of ANOVAs, contrasts were calculated according to the Henson and Penny technical note "ANOVAs and SPM" (http://www.fil.ion.ucl.ac.uk/~wpenny/publications/rik_anova.pdf).

Statistical parametric maps of the *t* statistic were constructed using a generalized Greenhouse-Geisser correction. For both *F* tests and *t* tests, statistical parametric maps were thresholded at $P < .05$ following familywise error correction for multiple testing in predefined volumes of interest. To test our primary hypothesis regarding the reduction in frontal cortical efficiency, a priori regions of interest were defined on the basis of the results of Mattay et al,[41] wherein amphetamine-induced cortical hyperactivity was seen during a high-load cognitive challenge in methionine homozygotes for the Val158Met polymorphism of the *COMT* gene (Met/Met). However, because we had no explicit hypothesis regarding laterality of any sensitization effect, the image used for small-volume correction included 15-mm spheres covering the left middle frontal gyrus[41] and a second sphere in the opposite hemisphere. Additionally, the striatum was defined according to Mawlawi et al.[80] Given the paucity of literature on amphetamine-induced dysregulation of temporal lobe activity in healthy controls, a conservatively defined (ie, large) region of interest including the superior temporal gyrus (STG) bilaterally, drawn from the Automated Anatomical Labeling Toolbox,[81] was used.

To establish that changes in BOLD responses were related to sensitization-related processes, rather than simply a consequence of drug tolerance, we tested for correlation between subjective measures of sensitization and the mean signal in the right prefrontal region of interest and the anatomically defined striatal regions of interest. At the group level, there were no significant differences in mean plasma amphetamine levels across the 2 sessions, suggesting that our group effects did not reflect dosage differences. Because we had used a standard dose for all subjects, we controlled for individual differences in intersession plasma amphetamine concentration in these correlational analyses (using partial correlation).

## RESULTS

Group × session interactions identified sensitization-related changes (enhancement confirmed with post hoc *t* tests) in both amphetamine-like experiences (ARCI Amphetamine Scale: $F_{2.5,49.8}=4.15$; $P < .02$) (**Figure 1**). Unlike Boileau et al,[64] but in keeping with findings of Strakowski et al,[72-74] drug-induced euphoria was also sensitized (ARCI–Morphine Benzedrine Group Scale [euphoria]: $F_{2.3,46.3}=5.13$; $P < .009$). Furthermore, subjective vigor (Profile of Mood States activity-vigor subscale: $F_{2.8,55.8}=3.73$; $P < .02$), alertness (Visual Analog Mood Scales alert-drowsy subscale: $F=4.15$; $P < .02$), and attentiveness (Visual Analog Mood Scales attentive-
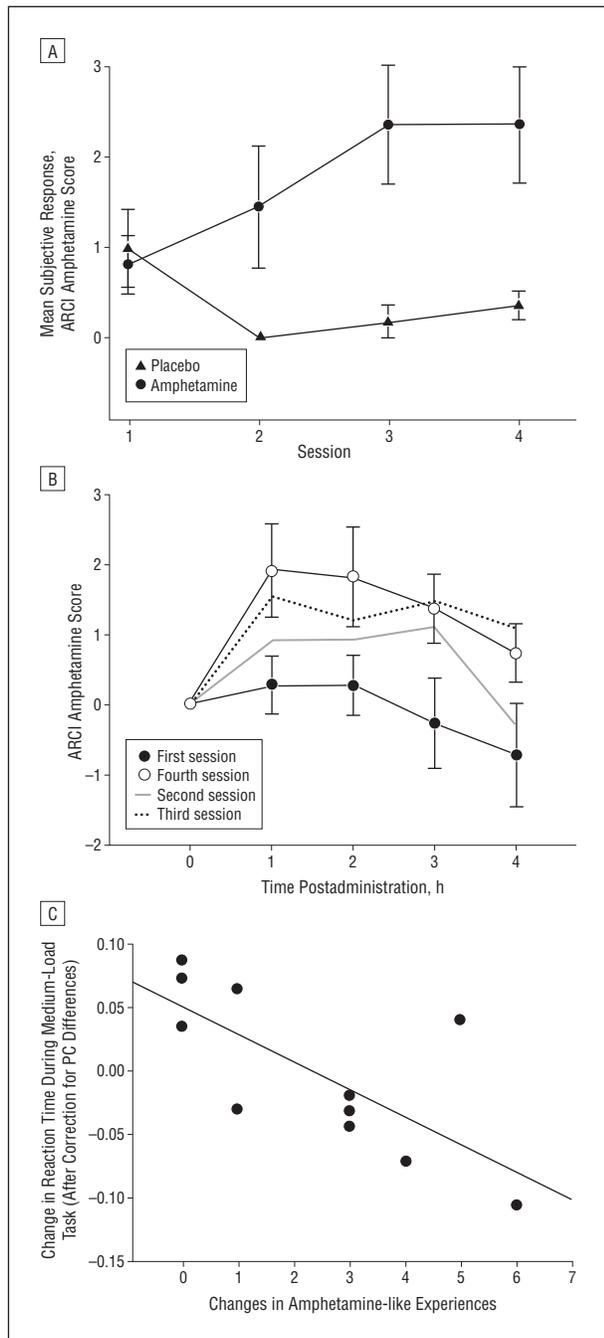
**Figure 1.** Subjective effects of amphetamine sensitization. A, Group × session interaction for the subjective reports of amphetamine-like experience. ARCI indicates Addiction Research Center Inventory. B, Session × hour measures of amphetamine-like effects in the amphetamine group. C, The significant correlation between the sensitization of amphetamine-like experiences (difference between peak amphetamine-like experiences scores at sessions 1 and 4) against the sensitization of reaction time. PC indicates plasma concentration.

dreamy subscale: $F_{3,32.4}=3.99$; $P<.02$) were also significantly enhanced following sensitization. These effects were relatively robust and were evident in at least 7 of 11 participants in each case. Neither eye-blink rate ($F_{2.5,50.9}=1.49$; $P<.63$), a commonly used index of psychomotor activity, nor cardiovascular parameters (pulse: $F_{3,50}=1.49$; $P<.23$; blood pressure: $F_{2.2,44.4}=0.18$; $P<.85$) were sensitized following repeated amphetamine exposure.

We tested whether task performance was sensitive to group (treatment), session (first and last dosing), or WM load using a repeated-measures $4 \times 2 \times 2$ ANOVA for correct responses and reaction time and found evidence for a main effect of WM load on task accuracy ($F_{2,41}=1932.9$; $P<.001$) and response time ($F_{2,38}=32.7$; $P<.001$). No significant interactions were found. However, because we expected sensitization to be linked with psychomotor stimulation only, we tested the corresponding simple main effect and found that the amphetamine group was faster on session 4 (postsensitization) than on session 1 (short-term exposure) ($t_{10}=2.398$; $P<.02$ [1-tailed]). Interestingly, the sensitization of reaction time was most pronounced in the medium-load condition (2-back) ($t_{10}=3.79$; $P<.002$ [1-tailed]) (eFigure 1, http://www.archgenpsychiatry.com). Importantly, this sensitization of reaction time during the medium-load condition was significantly correlated with the sensitization of the subjective "amphetamine-like" experience after correcting for individual differences in plasma amphetamine concentration at the 2 sessions (as measured by the ARCI score for amphetamine; partial correlation coefficient of 0.727; $P<.009$) (Figure 1). Together, these data suggest that there may be a common neural substrate for the behavioral and subjectively perceived aspects of sensitization.

The fMRI data showed a similar load-dependent network during memory performance in both the placebo and amphetamine groups (eFigure 2, eTable 1, and eTable 2). No significant differences were seen between the placebo and amphetamine groups on day 1 (presensitization). Similarly, no main effect of session, or session × WM load interaction, was seen in the placebo group. However, in the amphetamine group, activity in the right STG showed a significant main effect of time (MNI coordinates 60, –9, and 6; $P<.05$ corrected), with activity in this region elevated following sensitization, compared with the first session (short-term exposure) (**Table 1** and **Table 2**). A significant interaction between session and WM load was also evident in the STG in this group, although the cluster extended into the operculum and putamen (MNI coordinates 60, –9, and 6; $P<.007$) (**Figure 2** and Table 1). In particular, in the STG BOLD signal decreased with greater WM load following short-term exposure (day 1), whereas it increased at the highest load following sensitization (Figure 2A).

We scrutinized this interaction further by testing for a simple main effect of time under a high-load WM task, contrasting the effects of amphetamine exposure following sensitization with those after short-term exposure. This contrast confirmed a significant increase of BOLD activity within the right STG (MNI coordinates 57, –12, and 12; $P<.04$). The same increase was found in the right DLPFC (MNI coordinates 33, 48, and 30; $P<.02$), and there was a trend toward significance within the striatum (MNI coordinates 15, 15, and 9; $P<.06$). As explained in the "Methods" section, these results were based on height-level correction for multiple comparisons within predefined volumes of interest. Notably, however, all 3 regions (and an additional 2 regions within the right hemisphere, thalamus, and precuneus) survived a whole-brain correction for multiple comparisons at the cluster level (**Figure 3** and Table 2). This amphetamine-

**Table 1. Amphetamine Effect of Time and Load × Time Interaction[a]**

| Region Label | Side | Size, No. of Voxels | z Score | mm x | mm y | mm z |
|---|---|---|---|---|---|---|
| Amphetamine main effect of time | | | | | | |
| STG | R | 338 | 4.35 | 60 | −12 | 3 |
| Rolandic operculum | R | | 4.21 | 60 | 0 | 9 |
| Insula | R | | 3.81 | 39 | 3 | 9 |
| Precuneus | R | 31 | 3.87 | 12 | −54 | 69 |
| Putamen | L | 30 | 3.83 | −36 | −9 | 3 |
| Fusiform | R | 53 | 3.63 | 36 | −54 | −21 |
| Cerebellum | R | | 3.39 | 30 | −54 | −30 |
| Inferior temporal | R | | 3.31 | 48 | −51 | −18 |
| Amphetamine load × time interaction | | | | | | |
| Heschl gyrus | R | 158 | 4.22 | 60 | −9 | 6 |
| Rolandic operculum | R | | 4.17 | 63 | 3 | 15 |
| Precuneus | R | 39 | 3.97 | 9 | −54 | 69 |

Abbreviation: STG, superior temporal gyrus.

[a] Coordinates, statistics, and labels for brain areas identified with a main effect of time and time × working memory load interaction in a 4 × 2 analysis of variance ($P < .001$ uncorrected; 30-voxel cluster extent minimum for visualization). Blood oxygen level–dependent signal changes, indicative of a main effect of time and a time × load interaction, within the superior temporal gyrus survived correction for multiple comparisons ($P < .05$ familywise error corrected) within an anatomically defined region of interest.

**Table 2. Amphetamine Paired *t* Test Session 4 Greater Than Session 1 (High-Load Working Memory Task Greater Than Control)[a]**

| Region Label | Side | Size, No. of Voxels | z Score | mm x | mm y | mm z |
|---|---|---|---|---|---|---|
| Precuneus | L | 226 | 4.26 | −3 | −75 | 42 |
| Precuneus | R | | 3.79 | 3 | −63 | 39 |
| STG/operculum | R | 174 | 3.97 | 57 | −12 | 12 |
| Putamen | R | | 3.51 | 33 | 0 | 9 |
| Thalamus | R | 55 | 3.91 | 15 | −6 | 15 |
| Caudate | R | | 3.64 | 15 | 15 | 9 |
| Middle frontal | L | 54 | 3.86 | −33 | 0 | 51 |
| Superior frontal | L | | 3.65 | −21 | 6 | 60 |
| Middle frontal | R | 43 | 3.78 | 33 | 48 | 30 |

Abbreviations: BOLD, blood oxygen level–dependent; STG, superior temporal gyrus.

[a] Coordinates, statistics, and labels for brain areas where BOLD signal during the high-load cognitive challenge, compared with the control condition, was significantly elevated following sensitization compared with short-term amphetamine administration (maps presented are corrected for multiple comparisons on the basis of cluster extent at an uncorrected voxel threshold of $P < .001$). The BOLD signal increases in the dorsolateral prefrontal cortex survived correction for multiple comparisons within an independently defined region of interest.

induced hyperactivity in the prefrontal cortex, striatum, and thalamus during a high-load WM challenge shows striking parallels to previous findings of abnormally high activity in these regions in schizophrenic patients performing a similar WM task.[42]

Finally, the increase in prefrontal activity following sensitization was evident in 10 of 11 individual participants. Furthermore, the change in prefrontal BOLD signal was positively correlated with the sensitization of subjective alertness (after controlling for between-session differences in amphetamine plasma concentration; partial correlation coefficient of 0.657; $P < .02$ [1-tailed]) (Figure 3B and C). The right striatum showed correlation with the sensitization of subjective happiness (Visual Analog Mood Scales happy-sad subscale), although surprisingly it reflected a negative relationship ($r = −6.08$; $P < .04$ [2-tailed]), but was at trend significance following correction for individual differences in drug concentration (partial correlation coefficient of −6.08; $P < .06$ [2-tailed]).

## COMMENT

The sensitization of subjective measures seen herein is in keeping with earlier observations of enhanced amphetamine-like experiences, euphoria, happiness, activity-vigor, and attentiveness.[64,72-74] We suggest that the dosage pattern used herein produces a robust sensitization. This is supported by the first demonstration, to our knowledge, of a functional consequence of experimentally induced sensitization in humans, ie, faster cognitive performance. Within the context of the study design, it is not possible to determine whether this reaction time effect reflects simple psychomotor sensitization, enhanced motor readiness, attentional processing, or increased motivation to perform. However, the lack of faster responding during control and low-load conditions would argue against a simple psychomotor speeding. Furthermore, the lack of significant enhancement during the high-load con-
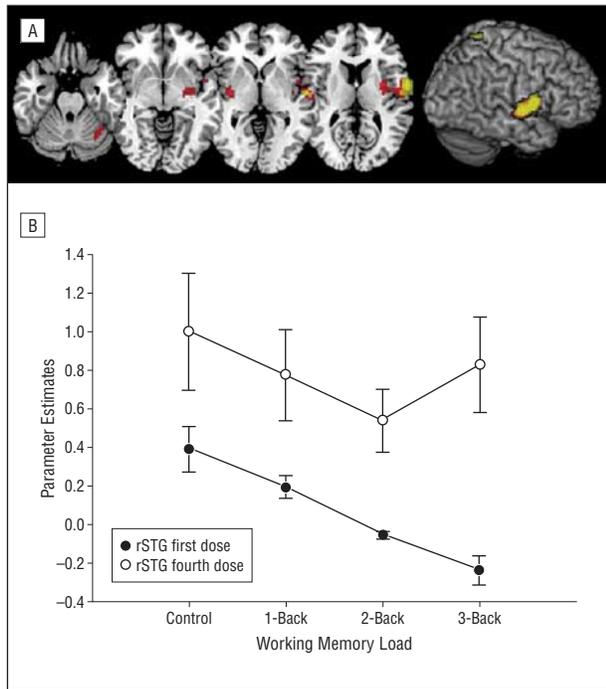
**Figure 2.** Effects of sensitization on N-back–related blood oxygen level–dependent responses. A, The red brain regions' activity shows a main effect of session (time) in the amphetamine group whereas the yellow regions show a significant load × session interaction (for display purposes, results are shown at $P < .001$ uncorrected, with a cluster threshold of 30 contiguous voxels). B, For visualization of the nature of the interaction, the parameter estimates extracted from the peak voxel in the right superior temporal gyrus (rSTG) are plotted (Montreal Neurological Institute coordinates 60, −9, and 6). This demonstrates a load-dependent failure of the normal suppression of the STG, with increasing demands on the working memory system.

dition suggests that this performance benefit is dependent on efficient prefrontal cortical recruitment.

When exploring the fMRI data in the amphetamine group, a simple main effect of time contrast, across all loads, was associated with increased BOLD signal in the right STG, precuneus, rolandic operculum and insula, putamen, cerebellum, and a number of areas on the ventral visual pathway. We will discuss the STG and precuneus in greater detail later. However, because these other regions were not predicted a priori, it is hard to be definitive about these effects. Nonetheless, the evidence for changes in motor networks (ie, putamen and cerebellum) is consistent with the speeding of reaction times following sensitization and the role of dopamine in motor function. Furthermore, the enhancement of the ventral visual pathway (ie, fusiform and inferior temporal gyri) could be indicative of enhanced attentional processing following sensitization.

We also observed a significant load × time interaction in the right STG and precuneus activity during our verbal WM paradigm (N-back). The left-lateralized homologues of these 2 regions, in addition to the middle frontal gyrus (DLPFC) and anterior cingulate cortex,[83] subserve verbal fluency performance.[84] Numerous neuroimaging studies of schizophrenia have demonstrated disruption of this network across a number of different paradigms,[55,85-88] often in a load- or state-dependent manner.[54,87,89] Importantly, some evidence suggests that disruption of this network, and associated failure to
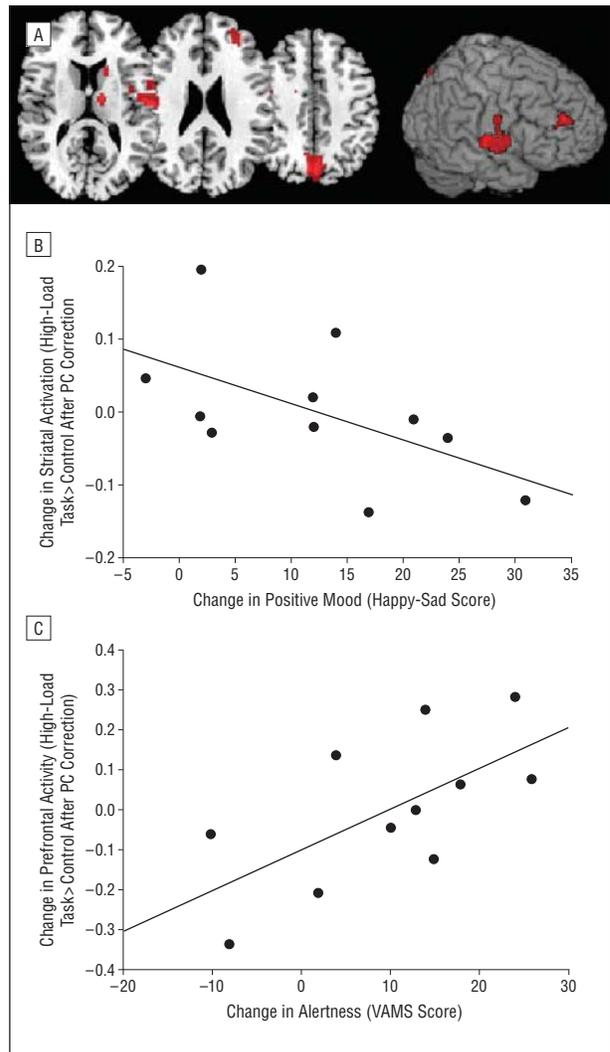


**Figure 3.** Effect of sensitization on blood oxygen level–dependent response to a high-load cognitive challenge. A, The red brain regions' activity is elevated during the high-load condition following amphetamine sensitization ($P < .05$ whole-brain corrected at the cluster level, with a voxel-level threshold of $P < .001$). B, The negative correlation between sensitization of positive affect (Visual Analogue Mood Scales [VAMS] happy-sad subscale) and the change in striatal activation during the high-load working memory challenge. C, The positive correlation between sensitized alertness and the change in prefrontal activity during the high-load working memory challenge.[82] PC indicates plasma concentration.

suppress temporal lobe activity in the face of frontal hyperactivity, may be linked to elevated cortical dopamine transmission, rather than hypodopaminergia.[59,60] Further examination has demonstrated a dynamic pattern of effective connectivity within this network during task performance, with the prefrontal cortex modulating cingulate function and frontotemporal connectivity, possibly via the precuneus.[84] Our findings could reflect a similar process in the right hemisphere, where increased cognitive demand might lead to failure in recruiting the cingulate and thus an inability to maintain prefrontal cortical suppression of the STG.

We failed to identify a significant load × session interaction in the DLPFC. This may be because of the complex nonlinear relationship known to exist between prefrontal neuronal recruitment, baseline cortical dopamine levels,

task difficulty, and performance.[22,41,90] When the high-load condition was examined in isolation, we found that sensitization was associated with prefrontal hyperactivity, in the absence of any performance deficits. Ten of the 11 participants in each group in this study were heterozygous for the Val/Met polymorphism of *COMT*, and thus, variation in baseline dopamine level due to this polymorphism was theoretically minimized. In accordance with this intermittent (Val/Met) phenotype, we found that amphetamine and placebo groups showed very little difference in prefrontal activation during session 1 (short-term amphetamine exposure), with both groups demonstrating a linear recruitment of the prefrontal cortex up to the high-load condition, but importantly, neuronal recruitment diminished as WM capacity was exceeded (consistent with the inverted-U load-activity curve). The shifting of this curve to the left in patients with schizophrenia is thought to lead to the same hyperrecruitment, followed by hypoactivity, at far lower-load cognitive challenges (ie, hypofrontality). Our findings are suggestive of a similar frontal "inefficiency" as that seen in patients, albeit with a far smaller magnitude more akin to the effects of short-term amphetamine use in Met-Met homozygotes. Thus, the cortical effects of sensitization in humans are to some degree equivalent to those associated with gaining a *COMT* methionine allele (Val/Met to Met/Met).

Comparisons of amphetamine sensitization effects across species are complicated by several confounding factors, including differences in the source of prefrontal dopaminergic innervation[91,92] or cortical dopamine kinetics.[93] Primates display reduced cortical dopamine turnover following chronic exposure to amphetamine,[30] although it has been suggested that a transient period of hyperresponsivity of the ascending dopamine system precedes the decline seen with chronic use.[52] The cortical hyperactivity evident in our volunteers following brief exposure to amphetamine aligns with these suggestions.

Unlike the cortical inefficiency observed by Mattay et al,[41] in addition to disrupting frontal and temporal activity, the hyperactivity seen during the high-load condition following sensitization was evident throughout the associative frontostriatal loop,[94,95] similar to that seen in schizophrenia.[42] Given the role of striatal dopamine signaling in modulating cortico-striato-thalamic activity, the hyperactivity of the caudate nucleus may be relevant for clarifying the origin of the concomitant observed frontal hyperactivity. In transgenic mice, Kellendonk et al[96] have shown that selective upregulation of striatal $D_2$ dopamine receptors produced a prolonged prefrontal dysfunction in rodents that was maintained even after the transgene had been switched off and striatal $D_2$ receptors had normalized. This suggests that dysregulation of striatal $D_2$ signaling can have a long-lasting deleterious effect on prefrontal development and functioning and that the prefrontal dysfunction evident in patients with schizophrenia, as well as sensitized animals, could arise from the dysregulation of striatal dopamine signaling. Such striatal dependency is also seen for the recruitment of the frontal lobes in patients with Parkinson disease. In this case, frontal hypoactivity, linked to reduced striatal dopamine, is only evident when task performance necessitates the recruitment of the caudate nucleus.[83,97,98] In our

study, the higher-load cognitive task demands greater manipulation of information and consequent caudate activation.[99] Thus, the striatal recruitment, combined presumably with elevated striatal dopamine, would be expected to elicit the observed hyperactivation of the prefrontal cortex. This would accord with the recent observations in patients with schizophrenia that dopamine depletion unmasks significantly more $D_2$ receptors, indicating higher basal dopamine function, in the associative rather than limbic portion of the striatum.[100]

Concerning the relation between neurophysiological consequences of amphetamine sensitization and subjectively perceived state, we found that subjective measures of sensitization-induced happiness were negatively correlated with striatal activity, while the DLPFC showed a positive correlation with subjective measures of alertness. The finding that subjective experience of sensitization does not correlate with DLPFC activity, but sensitized alertness does, accords with the role of the prefrontal cortex in mediating sensitization-induced hypervigilance in primates and suggests negative striatal correlation and two separate neural substrates of sensitized behavior.

Our present findings on the effects of amphetamine sensitization are of interest with regard to current pathophysiological theories of schizophrenia. Amphetamine has previously been shown to blunt striatal BOLD activity during the performance of a monetarily rewarded task,[101] which sits well with the absence of striatal activity change in the current study. A mechanism underlying this could be an enhancement of well-established regulatory glutamatergic projections from the prefrontal cortex to the ventral tegmental area,[102,103] a critical pathway for sensitization in rodents.[104] This enhanced prefrontal influence on the ventral tegmental area would result in an augmentation of activity in GABAergic interneurons in the ventral tegmental area, suppressing dopaminergic mesostriatal transmission. *N*-methyl-D-aspartic acid–dependent synaptic plasticity plays a central role in regulating the strength of the glutamatergic projections from the DLPFC to the ventral tegmental area.[105,106] Critically, this *N*-methyl-D-aspartic acid–dependent plasticity is modulated by dopamine itself, and this modulation has been proposed as a critical pathophysiological component in schizophrenia.[63] Furthermore, the interaction between $D_1$ dopamine and *N*-methyl-D-aspartic acid receptor signaling may play a vital role in determining the synaptic consequences of repeated stimulant exposure.[52,107]

Finally, the observed change in prefrontal activity during a high-load WM challenge after only 4 intermittent low-dose exposures to amphetamine suggests that the recent rapid growth in the use of psychostimulants to boost alertness[108] or to enhance cognitive performance[109] may necessitate caution, especially given that sensitization is still evident 1 year after cessation of amphetamine use[64] and preliminary evidence demonstrates cross-sensitization with stress following this dosage regimen.[110] While our data might be expected to speak to the long-term use of stimulants to treat attention-deficit/hyperactivity disorder, the evidence for elevated risk of psychosis in these patients is scant,[111] especially considering the number of individuals using these drugs. It is likely that brain maturational processes in adolescents and the pattern of ad-

ministration are not conducive to this form of neuroadaptation. In clinical practice, sensitization could offer one explanation for the relapsing nature of schizophrenia: while symptoms can be controlled by dopamine-blocking antipsychotic medication, they are still sensitive to any stress-induced perturbations. This may be because sensitized responses remain in place over a much longer period than the short-term effects of the stimulant drugs.

The primary limitation of this study is the relatively small sample size. Despite the small group size, we found that sensitization was associated with a significant change in frontostriatal and temporal BOLD signal in accord with our hypotheses and consistent with the observed role of dopamine modulation of cognitive function. The addition of placebo scans either presensitization or postsensitization would have permitted a more powerful within-subjects test for the main effect of amphetamine use (short-term) and could permit us to assess whether sensitization-related changes were evident without drug administration, indicating altered cortical sensitivity at baseline. However, the primary aim of this study was to assess whether the effects of amphetamine in a "sensitized brain" were different from short-term exposure, and the repeated-measures design ensured that we could test this directly. The degree to which sensitization alters baseline (ie, drug-free) brain function remains to be explored, although data suggest that sensitized volunteers also display an elevated placebo-induced dopamine release, consistent with a role for conditioning in the effects of sensitization.[112] Finally, because of the small sample size, we limited ourselves to testing our primary (core) hypotheses. With a larger sample size, we could have carried out additional secondary examination of other interesting correlations with appropriate multiple-comparisons correction.

To conclude, we present herein the first demonstration, to our knowledge, of amphetamine sensitization-related changes in task performance and cortical functioning in healthy humans. As in nonhuman primates, striatal and cortical systems displayed separate, opposed, sensitization profiles. We found similarities between the neural substrates of sensitization-related changes in cognition in humans (eg, hyperactivity of DLPFC, striatum, and thalamus during a high-load WM challenge) and previous neuroimaging findings in patients with schizophrenia performing similar tasks. This implies that amphetamine sensitization may be a useful model for investigating pathophysiological processes in schizophrenia and may help to bridge theories that emphasize pharmacological (dopaminergic) and cognitive mechanisms, respectively.

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