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Amphetamine sensitisation and memory in healthy human volunteers: A functional magnetic resonance imaging study

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Abstract

Amphetamine sensitisation (AS) is an established animal model of the hypersensitivity to psychostimulants seen in patients with schizophrenia. AS also models the dysregulation of mesolimbic dopamine signalling which has been implicated in the development of psychotic symptoms. Recent data suggest that the enhanced excitability of mesolimbic dopamine neurons in AS is driven by a hyperactivity of hippocampal (subiculum) neurons, consistent with a strong association between hippocampal dysfunction and schizophrenia. While AS can be modelled in human volunteers, its functional consequences on dopaminoceptive brain regions (i.e. striatum and hippocampus) remains unclear. Here we describe the effects of a sensitising dosage pattern of dextroamphetamine on the neural correlates of motor sequence learning in healthy volunteers, within a randomised, double-blind, parallel-groups design. Behaviourally, sensitisation was characterised by enhanced subjective responses to amphetamine but did not change performance (i.e. learning rate) during an explicit sequence learning task. In contrast, functional magnetic resonance imaging (fMRI) measurements showed that repeated intermittent amphetamine exposure was associated with increased blood-oxygen-level dependent (BOLD) signal within the medial temporal lobe (MTL) (subiculum/entorhinal cortex) and midbrain, in the vicinity of the substantia nigra/ventral tegmental area (SN/VTA) during sequence encoding. Importantly, MTL hyperactivity correlated with the sensitisation of amphetamine-induced attentiveness. The MTL-midbrain hyperactivity reported here mirrors observations in sensitised rodents and is consistent with contemporary models of schizophrenia and behavioural sensitisation. These findings of meso-hippocampal hyperactivity during AS thus link pathophysiological concepts of dopamine dysregulation to cognitive models of psychosis.

Keywords

Amphetamine, sensitisation, dopamine, motor learning, midbrain, medial temporal lobe

Introduction

Rodents repeatedly administered psychostimulants develop a hypersensitivity to their effects (Kalivas and Stewart, 1991; Piazza et al., 1990), characterised by enhanced hyperlocomotion (Robinson and Becker, 1986) and striatal dopamine-release (Kalivas and Duffy, 1993), termed sensitisation. An analogous hypersensitivity to psychostimulants is evident in patients with schizophrenia who display a significant exacerbation of psychotic symptoms following an acute amphetamine challenge (Laruelle et al., 1996) correlated with the degree of amphetamine-induced dopamine release in the striatum (Laruelle et al., 1999). This dopaminergic sensitisation has been proposed as a 'final common pathway' for the expression of psychosis in patients (Howes and Kapur, 2009) and may be linked to a number of other features of the illness (O'Daly et al., 2005).

Altered hippocampal structure and function are amongst the most robust findings in schizophrenia research (Shenton et al., 2001), characterised by deficits in memory function (Ongur et al., 2006), learning (Eyler et al., 2008) and sensory gating (Adler and Waldo, 1991). Moreover, patients exhibit impairments in explicit and implicit learning of motor and non-motor sequences (Marvel et al., 2005; Pedersen et al., 2008), which critically depend on hippocampal function (Gheysen et al., 2010). This is consistent with hippocampal sensitivity to statistical regularities, the temporal relationship between stimuli, stimulus familiarity and identifying deviations from predictions (Stark and Squire, 2001; Strange et al., 2005). Some models of psychosis place an emphasis on the related role of the hippocampus as an 'associative comparator' and generator of a novelty, mismatch or saliency signal (Gray et al., 1995). The common feature of these,

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and other contemporary models (Kapur, 2003), is the loss of contextual regulation on novelty attribution to a sensory stimulus.

Lesions of medial temporal structures in neonatal rodents (Lipska et al., 1993) and early post-natal primates (Bertolino et al., 1997) lead to dysregulated dopamine signalling once animals reach adolescence, mirroring the onset of schizophrenia and emphasising the hippocampus as a potential source of this disruption of the dopamine system (Pilowsky et al., 1993). This accords with the fact that the ventral portion of the hippocampal complex (i.e. subiculum) indirectly regulates the excitability of dopamine neurons in the ventral tegmental area (VTA) (Lisman and Grace, 2005) and that the behavioural effects of sensitisation are attributable, at least partially, to the increased drive of midbrain dopamine neurons secondary to augmented ventral hippocampal neuronal activity (Lodge and Grace, 2008). Importantly, mesolimbic dopamine also directly modulates hippocampal function (O'Carroll et al., 2006), and co-activation of the midbrain and hippocampus is linked to enhanced memory formation (Schott et al., 2004; Wittmann et al., 2005).

While sensitisation of subjective and dopaminergic responses to amphetamine is seen in healthy volunteers (Boileau et al., 2006) and is associated with fronto-striatal hyperactivity, its regional brain effects on human learning and memory remain unclear. Here we investigate behavioural and functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent (BOLD) responses during an explicit motor sequence learning task in healthy volunteers who underwent a standard amphetamine sensitisation procedure. We hypothesised that repeated amphetamine would lead to a hypersensitivity to the drug's subjective effects, altered sequence learning associated with elevated BOLD signal in the midbrain, hippocampus and striatum.

Materials and methods

Participants and design

The participants recruited, and sensitisation procedure employed, have been described in detail previously (O'Daly et al., 2011): in brief, 22 subjects were divided into two groups receiving placebo or amphetamine. Subjects were scanned approximately 120 min post-administration during sessions 1 (acute exposure) and 4 (following repeated exposure) in an effort to model the effects of sensitisation-related dopaminergic dysregulation on the neural substrates of explicit motor sequence learning. The project was approved by the Institute of Psychiatry Research Ethic Committee (REC ref# 022/03).

Assessment of psychostimulant sensitisation

At each session measures of both subjective drug effects and peripheral physiological processes were obtained. The measurement and analysis of these data have been presented in detail elsewhere and, here, we provide a brief summary of these results for completeness. Subjective drug effects were assessed using the Addiction Research Centre Inventory (ARCI) for amphetamine (Haertzen and Hickey, 1987), the Profile of Mood States (POMS) (McNair et al., 1992), and Visual Analogue Mood scales at baseline and every 60 min for 240 min. Subjects were asked hourly to score each item for 'how they feel at the present moment'. Physiological data (eye-blink rate, pulse and blood pressure (BP)) were also collected (seated, following a resting period of 5 min). Eye-blink rate was taken as the average number of blinks over a three-minute period at rest.

As explained in detail in elsewhere (O'Daly et al., 2011), we expected the expression of behavioural (subjective) sensitisation to mirror previous findings (Boileau et al., 2006; Strakowski et al., 1996), including enhanced amphetamine-like experience, amphetamine-induced euphoria (ARCI-morphine-benzedrine), profile of mood states activity-vigour, alertness and attentiveness and positive affect (happy-sad) as well as sensitisation of resting eye-blink rate. These hypotheses were tested using a group×administration/session repeated measures analysis of variance (ANOVA) for each dependent variable, using a level of significance of $p<0.05$ with Greenhouse-Geisser correction. All calculations were performed using SPSS15 for Windows.

Procedural learning task

The sequence learning task required subjects to watch a rhythmic seven-item sequence of finger movements presented in the form of three flashing circles on a computer screen (encoding) and, following a variable (5–9 s, with a mean of 7 s) storage interval, to replicate this sequence (reproduction) using three fingers of their dominant right hand on three computer keys. This task is analogous to learning to play a specific phrase on a piano as replication of both the sequence and the relative timing (rhythm) were necessary. The encoding and reproduction phases lasted for 7 s with an inter-trial interval of 14 s. Further details are given in the Supplementary Material.

Explicit Sequence Learning Task

The sequence learning task required subjects to watch a rhythmic 7-item sequence of finger movements presented in the form of three flashing circles on a computer screen, and to replicate this sequence using three fingers of their dominant right hand on three computer keys. This task is analogous to learning to play a specific phrase on a piano as replication of both the sequence and the relative timing (rhythm) were necessary. The sequences were adapted from an implicit sequence learning task previously developed by Sakai (Sakai, 2002), known to activate dorsolateral prefrontal cortex, a region known to be disrupted in schizophrenia. Sakai et al proposed that the DLPFC activity reflected an action oriented representation that could only be generate when participants reproduced a sequence with a known ordinal sequence of motor effectors with a known timing. Given that patients displays deficits when attempting to coordinate behaviour in time, and display hypofrontality, we had an additional hypothesis that sensitisation would alter prefrontal function during sequence reproduction. Thus, we modified the task from one previously used to isolate the neural substrates for sequence encoding from the sequence reproduction phase. Each participant experienced a different sequence/rhythm on each session so that task performance was not specific to any one sequence. Each trial began with the presentation of a fixation cross for one second; three discs which flashed 7 time in a given sequence (serial order and rhythm), for example, the first (left) disc may flash, followed by the third, then the second, and then the third again, giving an ordinal sequence of 1, 3, 2, 3. However, in this task the sequences presented involved seven steps. Additionally, the gaps between

each step varied, giving the sequence of flashing discs a temporal rhythm. We used non-metrical intervals between each step in an effort to increase the difficulty of the task .That is, the gaps between step in the sequence were not integer ratios of one another (e.g. in a metric rhythm pattern may be 1 2 4 2 4 2 1, whereas in a non-metric rhythm it would be 1.25 3.5 2.75 3.5 4.25). Such rhythms have previously been shown to make learning more difficult and it was hoped to ensure that participant continued learning throughout the scanning session. The rhythmic sequence of flashes and gaps can be considered like with dots and dashes much like morse code. This sequence presentation lasted for 7 seconds. Following this a fixation cross was presented for a variable duration (5-9 seconds, with a mean of 7 seconds) during which participants had to store "on-line" the sequence for reproduction when cued. When the 3 discs reappeared, subjects were required to reproduce using a button box in their right hand, the sequence as accurately as possible, matching both the order of the flashing discs but also their relationship to one-another in time, their position in the rhythm. This reproduction phase also lasted for 7 seconds after which a fixation-cross was presented for 14 seconds as a null baseline. This cycle was repeated 20 times during the scanning run.

Sequence learning was assessed by the number of errors in the subjects' replication of the observed sequence, while a root-mean-square error metric of rhythm learning was calculated by taking the root of the mean difference between observed button press intervals and target intervals. That way, if subjects are slow to start the sequence or play the rhythm slower or faster they will still score well if the rhythm - or interval ratios- are reproduced accurately. Plotting data indicated that there was very little variance in sequence errors during later trials (i.e. a ceiling effect) and thus a Friedman's test (i.e. a non-parametric repeated-measures test) was employed to demonstrate sequence learning. However, the distribution of the data permitted the use of a repeated measures ANOVA (group×session×trial) to explore rhythm learning (root-mean-square error). Additionally, in order to assess the relationship between sequence learning and BOLD response we calculated the area under the curve (AUC) as a function of trials separately for sequence errors and rhythm errors using the trapezoidal method.

Acquisition of fMRI data

Imaging was performed with a 1.5T GE scanner (GE, USA). A total of 180 volumes (matrix size 64×64) 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 s, echo time (TE)=40 ms, flip angle=90^0. Total acquisition time was 11 min 27 s (687 s). A high resolution structural scan was also acquired (high-resolution gradient echo) with a slice thickness of 3.3 mm, comprising 43 slices and a matrix of 128×128, TE=30 ms and a flip angle of 90^0.

Analysis of fMRI data

After preprocessing, including realignment, image distortion correction (Hutton et al., 2002), and normalisation, statistical analysis was carried out using the general linear model (Friston et al., 1995) as implemented in Statistical Parametric Mapping 2 (SPM2; Wellcome Trust Centre for Neuroimaging, London, UK). Each subject's echo planar imaging (EPI) data were normalised to the Montreal Neurological Institute EPI template. The single subject model included three primary regressors (sequence encoding, storage and reproduction) with the null period serving as an implicit baseline. In all cases, the vectors encoding the onset and duration of trials were convolved with a canonical hemodynamic response function (Friston et al., 1998) to give vector encoding the predicted task-related BOLD signal. Both models also included six regressors encoding volume to volume head movement as nuisance regressors. The data were high-pass filtered (cut-off 128 s) and corrected for serial correlations using a first-order autoregressive model. We also employed a second model which split the three regressors of interest (i.e. encoding, storage and reproduction) into three phases (i.e. early (trials 1–7), middle (trial 8–14) and late (trials 15–20)) with the same nuisance regressors. Including time or learning effects in these (within-subject) linear convolution models enabled us to examine a further factor; namely learning or time (with three levels). In what follows, we will use the simpler general linear model to test for interactions between group and sessions and the augmented model for interactions between group, sessions and time. Since these analyses were at the between-subject level, the estimates from the simple model can be regarded as averages over learning phases from the augmented model.

At the group level, we performed a random effects analysis. Images of parameter estimates for each of the three main task conditions (encode, storage and reproduce) were entered into the second level of analysis using a factorial ANOVA (factors: group (placebo versus amphetamine); session (acute versus repeated); time (early, intermediate and late) which included columns encoding the main effect of subjects (i.e. subject means). Statistical parametric maps (SPMs) of the T-statistics were constructed adjusting the maximum likelihood estimators for non-sphericity using restricted maximum likelihood. For both F-tests and t-tests, SPMs were thresholded at $p<0.05$ following family-wise error (FWE) correction for multiple testing in anatomically predefined volumes of interest. Whole brain correction for multiple comparisons on the basis of cluster extent was carried out for regions not predicted a priori. Clusters surviving whole-brain FWE correction (within a grey matter mask) are indicated in Supplementary Material, Tables 1–4.

In regions where we had a priori hypotheses regarding the effects of repeated amphetamine exposure we corrected for multiple comparisons with a small volume correction (SVC). All three region of interests (ROIs) (i.e. medial temporal, striatal and midbrain) were independently-derived to avoid statistical bias (Kriegeskorte et al., 2009). For the medial temporal lobe (MTL), we generated an anatomical mask combining the entorhinal cortex and subiculum bilaterally as these regions were shown to regulate dopaminergic neuron activity in the ventral tegmental area (Todd and Grace, 1999). This anatomical mask was defined using the SPM anatomy toolbox (Eickhoff et al., 2005) based on work by (Amunts et al., 2005). For subsequence correlational analysis, we created a second more focused mask (10 mm radius sphere, centred on the coordinates (42, –27, –11)) in the right MTL (Wittmann et al., 2005). The midbrain ROI was defined based on coordinates from the same paper using a sphere (10 mm radius) around a peak coordinate in the SN/VTA (9, –21, –14) . Finally, the limbic and associative functional subdivisions of the striatum were defined

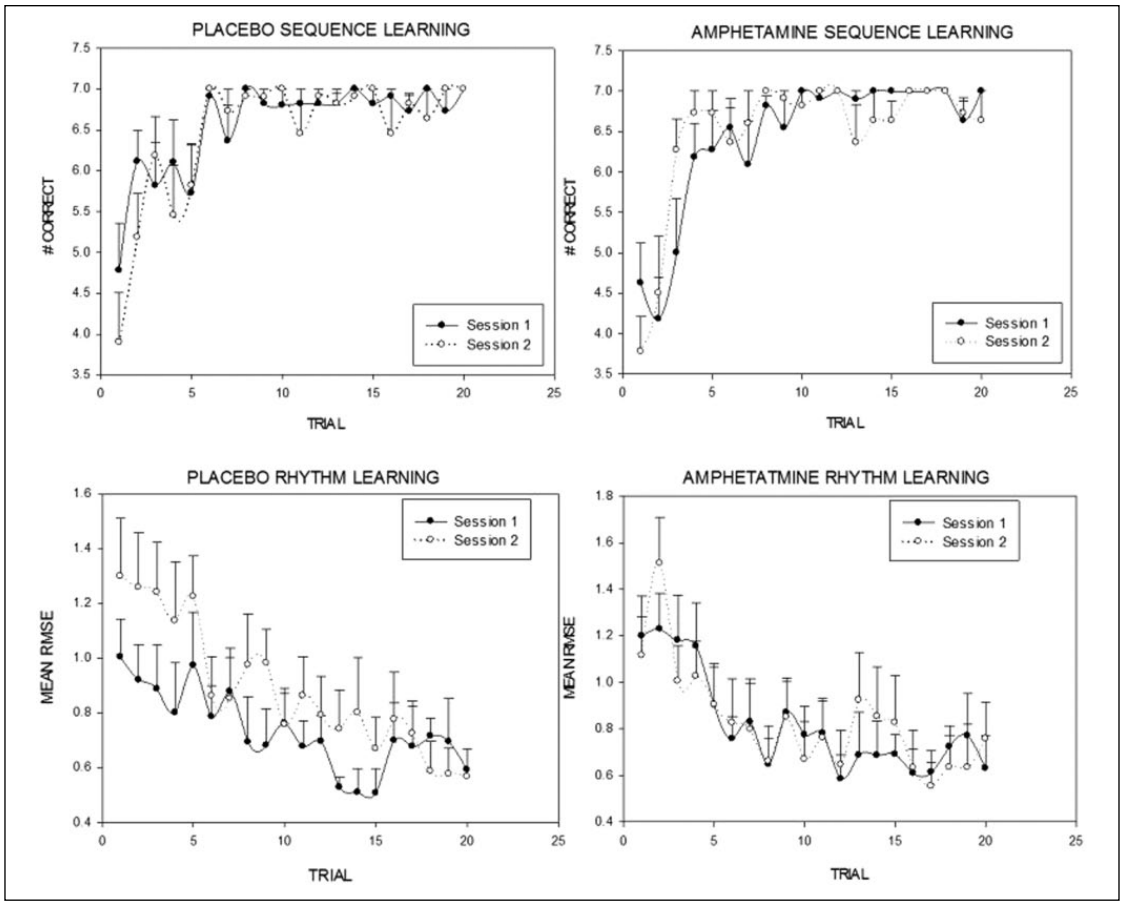

Figure 1. Learning curves for the sequence (top) and rhythm learning (bottom) in both the placebo (left) and amphetamine (right) groups. Sequence performance is plotted as the number of correct steps in each trial whereas the rhythm learning values reflect the root mean error of the interval ratio (subtraction of target interval vector from that produced). All errors are standard errors of the mean.

anatomically by an were combined for both the left and right hemisphere to create a single mask (Mawlawi et al., 2001).

Results

Subjective and behavioural sensitisation to the effects of amphetamine

The analysis of subjective and behavioural sensitisation effects found evidence for sensitisation of subjective effects as demonstrated by significant group×session interactions for amphetamine-like experience (p=0.015), drug-induced euphoria (p<0.009), Activity-Vigour scale (p=0.018) and Dreamy-Attentive scale (p=0.019) (O'Daly et al., 2011). In contrast, physiological measurements (pulse, eye-blinks and blood pressure) did not show evidence of sensitisation.

Non-parametric Friedman's test for repeated measures was used to confirm learning of the sequence (ordinal structure) in both groups on both sessions. We found that the sequence was successfully encoded by the placebo group on session one ($\chi^2_{(19)}$=46.172, p<0.001) and session two ($\chi^2_{(19)}$=76.778, p<0.001), and the amphetamine group on the first ($\chi^2_{(19)}$=63.64, p<0.001) and second visit ($\chi^2_{(19)}$=81.356, p<0.001). The rhythm learning was tested with a group×session×trial ANOVA, showing a significant main effect of trial ($F_{(19,152)}$=6.912, p<0.001). No other significant main effects or interactions were observed, suggesting that rhythmic sequence learning was similar for both groups on both visits (see Figure 1).

fMRI results

Encoding. In the placebo group encoding of the visuospatial sequence was associated with activation in a distributed network which included the precuneus, extending to the inferior parietal and occipital lobe. Unsurprisingly, significant activation was observed in the striate and extrastriate visual cortex during visuospatial encoding. Additionally, the temporal lobe and fronto-striatal system (i.e. dorsolateral prefrontal cortex and caudate nucleus) were also recruited during the sequence encoding phase of the task (see Supplementary Material, Figure 2(a) and Table 1). The amphetamine group displayed a similar pattern of sequence encoding-related increases; with no significant between group differences in encoding-related BOLD signal.

Reproduction. During sequence reproduction, the placebo group displayed increases in parietal, frontal and temporal BOLD signal on session 1. Additionally, the encoding-related BOLD signal was elevated in the orbitofrontal and cingulate

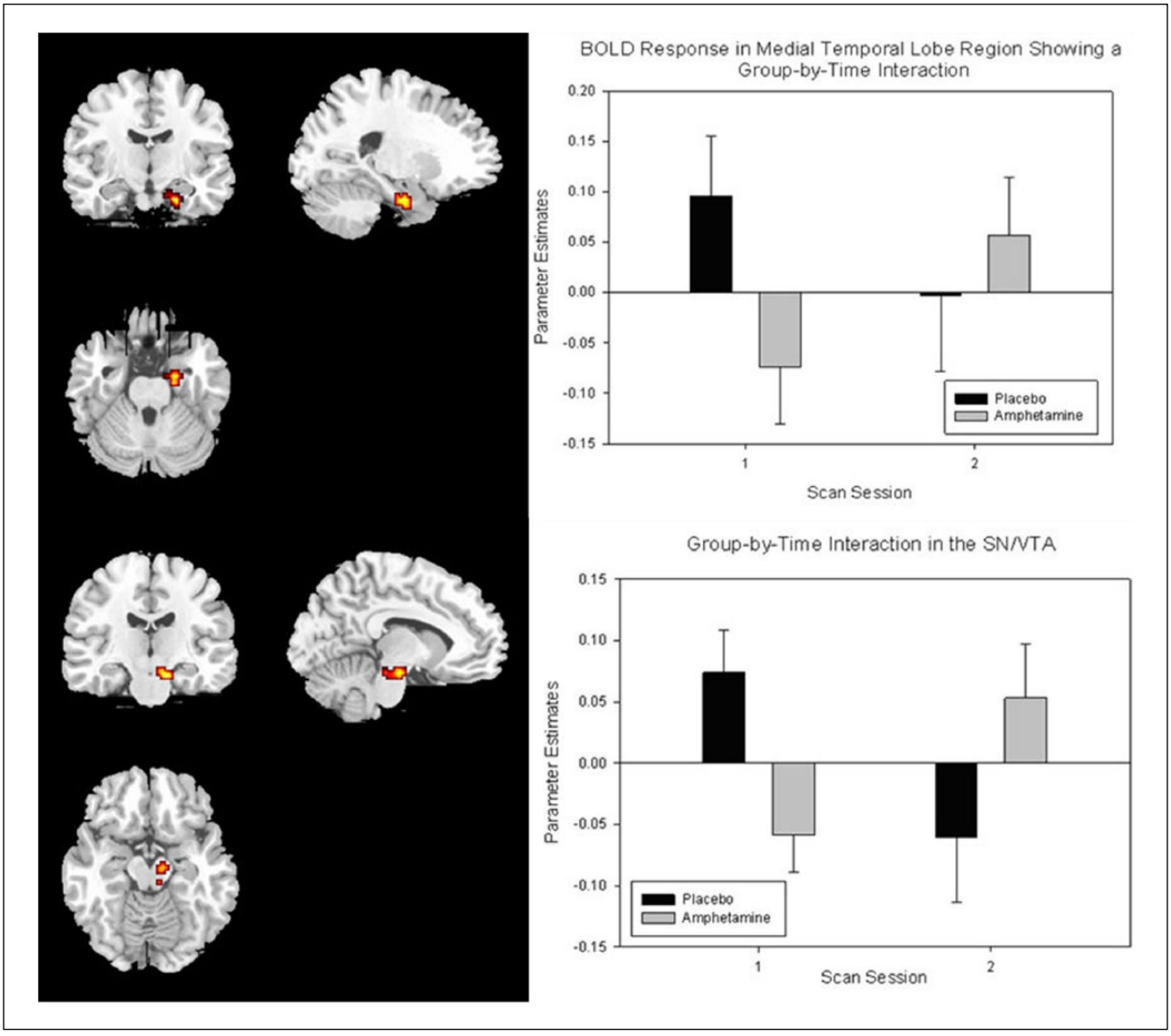

Figure 2. Significant regions of activation are shown where we detected a group-by-time interaction in encoding related blood-oxygen-level dependent (BOLD) signal (left) and parameter estimates (right) including the right medial temporal lobe (upper) and the midbrain (substantia nigra/ventral tegmental area (SN/VTA) (lower). For display purposes, significant regions of activation are shown at an uncorrected *p*-value of 0.01.

cortex following the first placebo administration (Supplementary Material, Figure 2(c) and Table 2). Acute amphetamine exposure revealed no statistically significant changes.

Correlates of learning performance. We next tested for evidence of learning-related changes in encoding-related BOLD responses over the 20 trials. We found that in the placebo group BOLD signal throughout the sequence, the encoding network decreased linearly across the trials. These regions included the occipital, temporal, parietal and superior frontal lobes, supplementary motor area caudate nucleus, putamen and the cerebellum (see Supplementary Material, Figure 3(a) and Table 3), similar linear reductions were evident in the basal ganglia and precentral gyrus in the amphetamine group (see Supplementary Material, Figure 3(b) and Table 3). Following placebo, sequence reproduction-related linear-reduction of BOLD responses was observed in the temporal, occipital, frontal lobes, caudate and hippocampus (Supplementary Material, Figure 3(c) and Table 4). The amphetamine group did not show any statistically significant differences.

Effects of repeated amphetamine exposure

We used a group-by-session second level ANOVA to test for evidence for sensitisation of BOLD response, within anatomically constrained regions on interest (i.e. SVC), during the three phases of the task (i.e. sequence encoding, storage and reproduction). Repeated amphetamine exposure was associated with a significant group-by-session interaction in the right SN/VTA ($p<0.023$) and the right MTL (i.e. subiculum and entorhinal cortex; $p<0.048$) during the encoding of the visuospatial sequence (see Figure 2). Additionally, a significant group-by-session-by-learning interaction was identified during sequence encoding in the left MTL ($p<0.025$; see Figure 3).

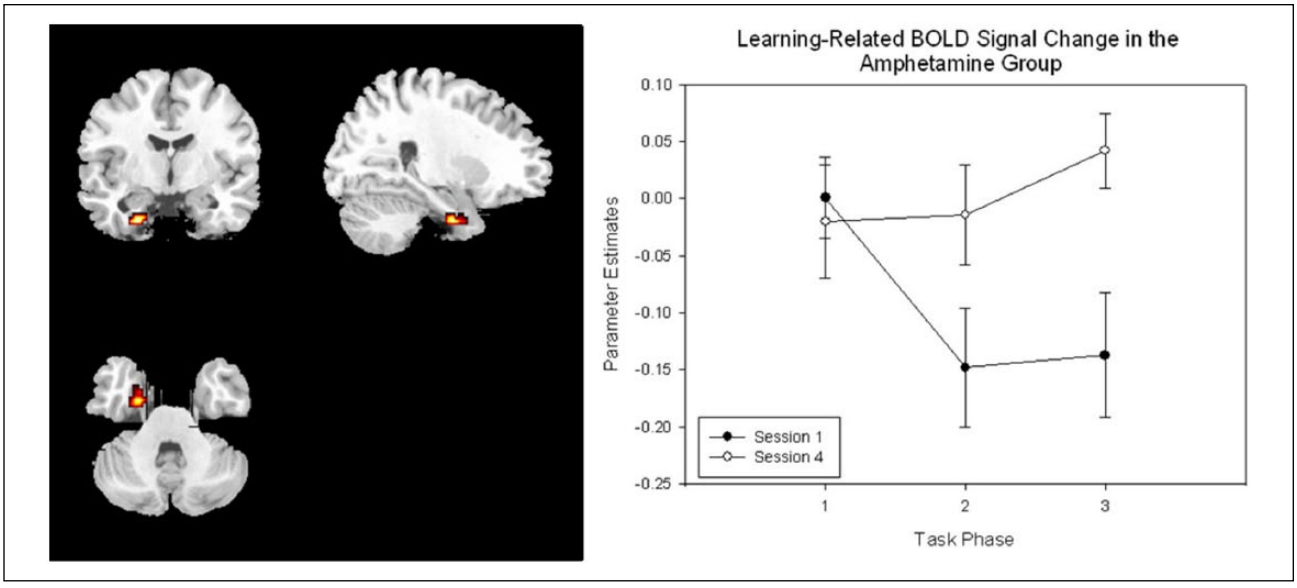

Figure 3. Region of the left medial temporal lobe displaying (left) a significant group-by-time-by-session interaction and (right) encoding-related parameter estimates for the three phases of the task (trials 1–7, trials 7–14, and trials 15–20) following the first dose of amphetamine (session 1, acute, filled circles) and the same participants on session 4 (sensitised, empty circles). For display purposes, significant regions of activation are shown at an uncorrected *p*-value of 0.01. BOLD: blood-oxygen-level dependent.

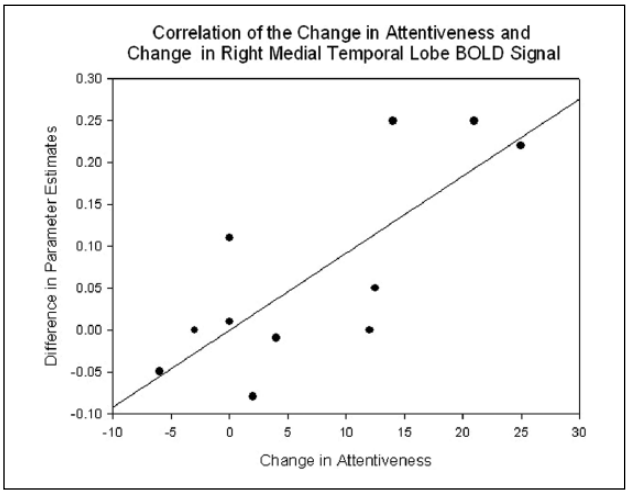

Figure 4. Correlation of the change in right medial temporal lobe blood-oxygen-level dependent (BOLD) signal with sensitisation of the subjective attentiveness.

Finally, we employed a regression model to identify the degree to which the mean activation during the third phase (i.e. last seven trials) of sequence encoding in the right MTL BOLD signal, a region which showed a sustained elevation rather than learning-related decrements, following repeated amphetamine exposure, was explained by the sensitisation of subjective responses to amphetamine. We found that a model including ARCI: amphetamine (ARCI): euphoria, alertness (visual analog scale (VAS): alert-drowsy) and attentiveness (VAS: attentive-dreamy) explained a significant amount of the variance (adj. R^2=0.775, $F(4,10)$=9.629, p<0.009). However, sensitisation of attentiveness (i.e. attentive-dreamy) was the largest contributor (std. beta=0.794, t-score=4.376, p<0.005; see Figure 4) to this effect, with ARCI euphoria also contributing significantly (std. beta=0.872, t-score=2.59, p<0.041).

Discussion

In this present work we explored the effect of a sensitising regimen of amphetamine on explicit motor skill learning and its neural correlates and found evidence for augmented medial temporal and midbrain BOLD responses following repeated intermittent amphetamine exposure. These effects were expressed in terms of group differences – which were further validated by orthogonal within-group effects. Crucially, the magnitude of the BOLD signal change in the subiculum/entorhinal cortex was significantly correlated with the sensitisation of amphetamine-induced attentiveness.

As reported previously (O'Daly et al., 2011), this study found enhanced subjective responsiveness to amphetamine reported consistent with earlier work on dopaminergic sensitisation in humans (Boileau et al., 2006; Sax and Strakowski, 2001; Strakowski et al., 1996). In contrast, physiological sensitisation effects (changes in blink rate or BP) were not observed.

In accordance with a large body of data exploring sequence learning (Sakai et al., 1999; Trumbo et al., 1968) both groups successfully learned to reproduce the rhythmic and ordinal aspects of the sequence and the set of brain areas recruited was generally consistent with the literature (Hikosaka et al., 1998; Sakai et al., 1999). Interestingly, there were no significant differences between the placebo and the amphetamine groups on session 1. These findings suggest that while dopamine plays an important modulatory role in brain regions linked to processing temporal intervals (Meck et al., 2008), a brief intermittent regimen of amphetamine exposure does not significantly disrupt the representation of the ratio of short temporal intervals in a sequence.

In contrast, repeated amphetamine exposure was associated with a sustained elevation in right MTL (including the subiculum)

activation (at a lower threshold the effect was bilateral) and right SN/VTA throughout the task. The hippocampus has been suggested to represent the major neural substrate of relational memory, the 'associative processes that bind multiple perceptual, cognitive, and motor aspects of events into a flexible memory trace' (Bunsey and Eichenbaum, 1993; Dusek and Eichenbaum, 1997; Schnedan et al., 2003). Sensitive to ordinal and temporal information, this region is recruited during sequence learning tasks, particularly when they are temporally challenging (Dolan and Fletcher, 1997), or dependent on the predictability of the sequence (Ergorul and Eichenbaum, 2006). It is strongly recruited during the formation of higher-order association between successive sequence elements in humans (Schendan et al., 2003) and rodents (Ergorul and Eichenbaum, 2006). Importantly, midbrain and hippocampus are linked to reward-related boosting of memory formation (Adcock et al., 2006; Wittmann et al., 2005). Thus, the observed hyperactivity may reflect an aberrantly strong reward signal following excessive stimulus-independent mesocorticolimbic dopamine release in sensitised individuals.

Notably, patients with schizophrenia display a similar hyperactivity of the MTL during memory encoding and retrieval (Ragland et al., 2004; Zierhut et al., 2010). Hippocampal hyperactivity has also been linked to the emergence of psychotic symptoms (Friston et al., 1992), a proposal supported by imaging data (Shergill et al., 2000) and evidence that antipsychotics blunt this over-activity. Importantly, sensitised rodents also display greater hippocampal activity (Lodge and Grace, 2008) and an increase in spontaneously active midbrain dopamine neurons, albeit using more direct electrophysiological measures, akin to that seen in patients and our sensitised participants.

Our data also speaks to a common neural substrate underlying the sensitisation of amphetamine-induced alertness and encoding-related hippocampal BOLD activity. One putative substrate arises from evidence of sensitisation-related changes in the MTL preceding the disinhibition of midbrain neurons via excitation of the accumbens-pallidum-VTA pathway (Lisman and Grace, 2005). This disinhibition leads to greater spontaneous firing of the dopamine neurons, and it is only in this excitable state that dopamine neurons can produce burst firing in response to external stimuli (Lisman and Grace, 2005). Despite evidence for sensitisation-related prefrontal inefficiency during high-load working memory challenge in these subjects we found no evidence for prefrontal cortex changes during sequence reproduction. A likely explanation for this failure to observe a significant effect may be that the motor sequence task did not place sufficient load on prefrontal cortical resources.

A number of contemporary models of psychosis suggest that loss of contextual control on dopaminergic activity results. The aberrant salience attribution proposes that dopamine signalling imbues environmental stimuli and internal representations with motivational significance. A dysregulated and hypersensitive mesolimbic pathway may lead to the inappropriate attribution of salient of innocuous or irrelevant cues (Kapur, 2003; Roiser et al., 2009) with delusions resulting from attempts to understand, and rationally explain, the resultant phenomenology. An alternative framework, based on Bayesian and predictive coding models of brain function (Fletcher and Frith, 2009; Friston, 2005), suggest that dopaminergic activity, via modulation of post-synaptic gain, confers precision-weighting on cortical prediction errors. Here, psychotic symptoms emerge from perturbations of perceptual inference and learning-related neuroplasticity (Stephan et al., 2006, 2009). Specifically, excessive dopamine signalling may lead to an imbalance between top-down prior expectations and bottom-up sensory evidence yielding both abnormal percepts and considerable confidence in one's aberrant beliefs about the world (Adams et al., 2013). It is clear that the dysregulation of the SN/VTA-MTL circuit seen here is consistent with both models and speaks more to the neuroplastic mechanisms at play in the dysregulation of dopamine which is central to both models. However, under the hierarchical temporal memory framework (George and Hawkins, 2009) the observed failure of the medial temporal responses to adapt during learning may be consistent with aberrant prediction errors signalling in the hippocampus (Krishnan et al., 2009).

The primary limitations of this study are the relatively small sample size and the lack of placebo scans in the amphetamine group. Despite the small group size we found that sensitisation was associated with a significant change in MTL and midbrain in accord with our hypotheses. The addition of placebo scans would have permitted a more powerful within-subjects test for the main effect of amphetamine (acute) and for sensitisation-related changes in hippocampal function at baseline, although at the within-subject level it would be impossible to disentangle order and drug sensitisation effects. However, the primary aims of this study was to assess whether the effects of amphetamine following a 'sensitising' dosage regimen were different from the effects following an acute exposure and the repeated measures design ensured that we could test this directly.

There is a dearth of direct evidence linking contemporary cognitive theories of psychosis with observed dopaminergic perturbations. This missing link is highly problematic for drug development. Thus, translation of this animal model of psychosis into humans and altered responses in neural circuits disrupted in schizophrenia is an important step. We have shown elsewhere that AS alters frontostriatal and frontotemporal systems during working memory function (O'Daly et al., 2011) in a manner akin to that seen in patients with psychotic symptoms. These context-dependent effects suggest that the core neuroplastic mechanism underlying AS, dysregulation of mesolimbic dopamine release, offers a potential link between the cognitive models of schizophrenia and the large body of evidence implicating dopaminergic abnormalities in the pathogenesis of psychosis.

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Conflict of interest

The authors declare that there are no conflict of interest.

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