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Effects of amisulpride on emotional memory using a dual-process model in healthy male volunteers

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Abstract

Memory dysfunction occurs in a number of neuropsychiatric disorders. Therapeutic psychopharmacological agents may exacerbate such memory impairment. Detailed characterisation of drug-induced memory impairment is therefore important. We recently showed that the D_2/D_3 antagonist amisulpride quantitatively impairs emotional memory in a randomised placebo-controlled study of 33 healthy volunteers. Current evidence suggests that two qualitatively different processes (recollection and familiarity) contribute to recognition memory and can be investigated using a Dual-Process Signal Detection model. Using such a model, we found that amisulpride levels at encoding were significantly inversely correlated with recollection estimates for emotional but not neutral stimuli or familiarity estimates in healthy male volunteers. This suggests that dopamine antagonism at encoding preferentially impairs the recollection component of emotional memory, relative to the familiarity component. This was supported by receiver operating characteristic analysis. We also found a significantly increased false recognition rate, associated with significantly shorter reaction times for emotional but not neutral stimuli in the amisulpride group. These findings have important implications for our understanding of recognition memory processes, as well as the interpretation of neuropsychological findings in medicated patients.

Key words

amisulpride; dopamine; familiarity; memory; recollection

Introduction

Memory is crucial to integrating previous experience to guide future behaviour. Memory dysfunction occurs in a number of neuropsychiatric disorders. However, a number of therapeutic psychopharmacological agents also cause memory impairment and may therefore exacerbate the problem. A full understanding of the nature of drug-induced memory impairment is therefore an important aspect of psychopharmacological research. The term memory encompasses a number of systems including procedural, semantic, working and episodic memory. This article is concerned with the last of these, which refers to the ability to encode and retrieve information related to one's past.

Dopaminergic dysregulation is central to the aetiology of schizophrenia, in which memory dysfunction is a central cognitive feature (Aleman, *et al*., 1999; Pelletier, *et al*., 2005). Dopamine (particularly D_2) antagonism is crucial to the therapeutic effects of antipsychotic agents used to treat schizophrenia. The role of the dopaminergic system in human episodic memory has not been fully investigated. However, there is increasing evidence from animal studies that D_2 antagonists impair episodic memory (Fujishiro, *et al*., 2005; Umegaki, *et al*., 2001). There is evidence to suggest that this may also be the case for certain aspects of memory in humans (Mehta, *et al*., 2005; Gibbs, *et al*., 2007). Further characterisation of the mnemonic effects of dopamine antagonists on humans is therefore warranted.

Recognition memory testing represents a cornerstone of research into episodic memory. Early models of recognition memory were based on Signal Detection Theory (SDT), which posits that recognition memory performance is based on a single process of memory strength or familiarity (Egan, 1958; Green and Swets, 1966). The strongest evidence in support of the use of SDT in recognition memory came from the analysis of receiver operating characteristic (ROC) curves, a function relating the proportion of correct recognitions (hit

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rate) to the proportion of incorrect recognitions (false-alarm rate). However, experimentally observed ROCs differed from those predicted by SDT in that the latter were symmetrical about the diagonal, whereas the former tended to be skewed. This led to the view that recognition memory could not be entirely explained by familiarity alone and consequently the notion that recognition memory performance reflects two distinct processes: recollection and familiarity (Atkinson and Juola, 1974; Jacoby, *et al*., 1993; Mandler, 1980).

Recollection is presumed to be a qualitative threshold process, associated with high levels of contextual detail and high confidence judgements. On the contrary, familiarity is considered to be a quantitative, memory-strength–based process, associated with a 'sense of having previously seen'. This approach to recognition memory constitutes a dual-process model, which can be contrasted with original single-process models. Over the last few decades, considerable evidence has emerged in support of such dual-process models (Yonelinas, 2002). Similarly, a number of approaches to examine the relative contribution of these two processes have evolved: the Remember-Know (R/K) Procedure (Tulving, 1985), the Process Dissociation Procedure (Jacoby, 1991) and the Dual-Process Signal Detection (DPSD) model (Yonelinas, 1994). These methods have been used to quantify relative changes in recollection and familiarity produced by experimental manipulation. Of these, the R/K procedure has been most widely used; however, it suffers from a significant limitation: under this procedure 'remember' and 'know' responses are mutually exclusive and participants are instructed to give a 'know' response only when an item is not recollected. As a result, the proportion of 'know' responses is artificially constrained by the number of 'remember' responses. Thus, the contribution of familiarity to the recognition memory process is likely to be underestimated. On the contrary, the DPSD model suggests that recollection and familiarity judgements both independently contribute to whether an item is recognised or not. As a result, the estimates of familiarity it provides are not limited by the proportion of 'remember' responses. This model, therefore, represents a more useful tool for the further investigation of recognition memory.

We recently reported that the dopamine antagonist amisulpride quantitatively impairs emotional memory in healthy volunteers based on recognition memory testing (Gibbs, *et al*., 2007). However, the relative effects on the recollection and familiarity components of memory remain unclear. In the present study, we used a DPSD model based on ROC analysis to examine emotional memory and its attenuation by amisulpride in more detail. We hypothesised that emotional salience would increase both recollection and familiarity, albeit with a lesser effect on familiarity as suggested by previous studies (Sharot, *et al*., 2007; Ochsner, 2000). We, therefore, further hypothesised that amisulpride would result in a reduction in recollection and to a lesser extent familiarity, for emotionally arousing, but not neutral stimuli.

Methods and materials

Participants

Healthy male volunteers ($n = 33$), aged 18–40 (mean age = 24.2, SD = 5.4) were recruited through an advertisement and were paid for their participation. Potential participants were screened for psychiatric or neurological disorder by means of a checklist questionnaire. Exclusion criteria were: 1) any current or previous history of psychiatric illness; 2) any significant history of substance misuse, including nicotine and 3) taking regular medication. Participants were randomised to receive either drug ($n = 17$) or placebo ($n = 16$). The study was approved by the Institute of Psychiatry Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Following complete description of the study to the participants, written informed consent was obtained.

Drugs

A 400 mg dose of amisulpride was chosen as it represents the lower end of the daily dosage range for achieving dopamine blockade and reduction of positive symptoms in schizophrenia (400–1200 mg) and it has been suggested that lower doses (50–300 mg) enhance dopaminergic transmission (Boyer, *et al*., 1995; Schoemaker, *et al*., 1997; Paillere-Martinot, *et al*., 1995). Additionally, a single 400 mg dose of amisulpride has been found to have no effect on general psychomotor or cognitive performance in healthy volunteers (Ramaekers, *et al*., 1999; Rosenzweig, *et al*., 2002). It also has a low propensity for inducing extra-pyramidal side effects (Leucht, *et al*., 2002).

Amisulpride tablets (Solian® 50 mg × 8) were placed in opaque, coloured gelatine capsules. Placebo capsules contained ascorbic acid tablets (100 mg × 2). Both capsules were prepared by the Maudsley Hospital Pharmacy.

Study design

Participants took part in a between-subjects, placebo-controlled study. The study was single-blind in that participants were not informed as to whether they were receiving drug or placebo. However, for safety reasons, the administering doctor was aware of the condition to which they had been assigned. The same doctor was responsible for administering the tasks. However, in this case given that the cognitive task was entirely automated in terms of instructions, stimulus presentation and recording of responses, the role of the doctor in administering the task was limited to initiating the relevant computer programs. We, therefore, considered that the validity of the results would not be compromised by the use of single-blind as opposed to double-blind methodology. A within-subjects design was not possible because of the nature of the task and the limitations of the stimulus set (i.e., participants could not be exposed to the same stimuli on more than one occasion). An age range of 18–40 years was specified to avoid

extremes of age and reduce the likelihood of significant differences between the two groups.

Participants attended two sessions separated by 1 week. They were instructed to abstain from beverages containing alcohol or caffeine for the 24 h before the test sessions. Food intake was not controlled. Sessions were conducted between 9 a.m. and 1 p.m. Upon arrival at the laboratory for the first session, participants received either amisulpride 400 mg or placebo. After 1 h (to allow satisfactory plasma levels to be reached), a peripheral venous blood sample was taken for measurement of amisulpride plasma concentration. To reduce the likelihood of participants anticipating a memory test, they were told that the purpose of the study was to measure their physiological responses to emotional stimuli and they were therefore connected to a Galvanic Skin Response device for the duration of testing. However, skin conductance measures were not recorded. The National Adult Reading Test was used to obtain an estimate of intelligence quotient (IQ). The encoding phase of the emotional memory task was then administered (see below). Participants were told that the second session would be exactly the same as the first but without drug administration. Memory tests were not mentioned. The second session took place 1 week later and consisted of the retrieval phase of the emotional memory task and a debriefing interview to explain the purpose of the study. To assess the effectiveness of blinding, participants were also asked to indicate whether they believed that they had received drug or placebo.

Cognitive task

We used an emotional memory task, which consisted of an encoding phase during which participants viewed scenes, each with a normative rating for arousal and valence, and a delayed recognition memory test in which they viewed all the previously seen pictures along with an equal number of new pictures (foils). All pictures were derived from the International Affective Picture System (IAPS) stimulus set (Lang, *et al*., 1998). During the encoding phase, participants viewed 92 IAPS pictures. Half of the scenes were aversive-arousing (mean valence and arousal ratings of 2.6 and 6.1, respectively) and half were neutral (mean valence and arousal ratings of 5.1 and 3.3, respectively). Stimuli were presented on a laptop computer for 3 s with a 4-s interstimulus interval (ISI), during which a fixation cross was present on the screen. The order of presentation was randomised across participants. Participants were asked to judge whether they felt emotionally aroused (i.e., wide-awake or jittery) or un-aroused (i.e., calm or relaxed) by each scene immediately after its presentation by pressing one of two keys labelled 'aroused' and 'calm' during the ISI. This was to ensure that participants attended to the scenes and that our classification of the pictures as arousing and neutral correlated with that of the participants. One week after the encoding phase, participants returned to the laboratory for an unexpected recognition memory test in which they viewed all the 92 previously seen pictures and 92 foils. The foils were selected to match the previously presented scenes in their content, valence and arousal characteristics. During the recognition test, participants were instructed to press marked keys to indicate whether each picture was 'old' (previously seen) or 'new' (foil). Participants were instructed to respond as soon as they knew the answer but not to compromise accuracy for speed. Reaction times were recorded. After making the old/new judgement, they were asked to rate the confidence of their recognition judgement from 1 (uncertain) to 9 (very certain). They were also asked to rate the arousal and valence of each picture using a 9-point scale.

Statistical analysis

Hit rates (proportion of previously seen items correctly identified as 'old') and false alarm rates (proportion of foils incorrectly identified as 'old') for each stimulus category were calculated for each participant. These were entered as dependent variables in a 2-way analysis of variance (ANOVA) with valence (aversive, neutral) as the within-subject factor and drug (amisulpride, placebo) as the between-subject factor. Mean reaction times were also calculated and entered as the dependent variable in a 3-way ANOVA with valence (aversive, neutral) and recognition state (hit, false alarm) as within-subject factors and drug (amisulpride, placebo) as the between-subject factor.

Estimates of recollection (R) and familiarity (*d'*) for each participant were derived by fitting model dual-process equations to the observed data by reducing the sum of squared errors between the predicted and observed data (Yonelinas, *et al*., 1998). This was carried out using an Excel solver, which utilises hit rate/false alarm rate pairs derived from 6-point confidence scale (*certain old* to *certain new*). In this study, participants were first asked to make an old new judgement followed by a subsequent 9-point confidence judgement, giving rise to a 18-point scale. Hence, the confidence ratings were collapsed by grouping responses over three confidence ratings to give a 6-point scale for each participant from *certain old* (1) to *certain new* (6). The number of items in each response category was examined to establish whether participants had followed the instructions to use the entire response confidence scale. Cumulative hit rate/false alarm rate pairs were derived for each participant for each level of response confidence. The first point was determined by adopting a strict scoring criterion, accepting only the most confidently recognised items (i.e., responses with a score of 6). The next point reflected a slightly less strict criterion, including scores of both 5's and 6's and so on. ROC curves for each participant were generated by plotting the cumulative hit rates versus the false alarm rates as a function of confidence.

R and *d'* were entered into a 2-way ANOVA with valence (aversive, neutral) as the within-subject factor and drug (amisulpride, placebo) as the between-subject factor. Correlation analyses were carried out to investigate the relationship between amisulpride levels and recollection and familiarity estimates. Average ROC curves were constructed for each group (amisulpride versus placebo) and stimulus category (aversive versus neutral) by plotting hit rate/false alarm rate data pairs

aggregated across subjects. For further detail on the construction of ROC curves, see Macmillan and Creelman (2005).

Results

There was no difference in IQ between the amisulpride (mean = 115.1, SD = 5.6) and placebo (mean = 118.0, SD = 6.8) groups ($t = 1.54$, df = 31, $P = 0.133$). There was no association between what participants believed that they had received (drug or placebo) and what they had actually received ($\chi^2 = 1.67$, df = 1, $P = 0.196$), suggesting that blinding had been effective. The plasma amisulpride concentrations in the drug group ranged from 30 to 1030 μg/L (mean = 354 μg/L, SD = 261 μg/L). The valence and arousal ratings made by the participants during the recognition memory phase were highly correlated with the standardised ratings and there were no differences between the groups in valence or arousal ratings; however, these results are reported in detail elsewhere (Gibbs, *et al.*, 2007). One participant from the amisulpride group had to be excluded from all analyses because a significant delay in his response time on a trial during the recognition phase created an error in the stimulus presentation programme.

The 2-way ANOVA showed a main effect of valence on hit rate [$F(1,30) = 35.9$, $P < 0.001$] and false alarm rate [$F(1,30) = 17.9$, $P < 0.001$]. Post-hoc comparisons showed significant differences between hit rates for aversive compared with neutral stimuli in the placebo group [$t(15) = 4.33$, $P = 0.001$] and the amisulpride group [$t(15) = 4.17$, $P = 0.001$]. There was no main effect of drug but there was a significant drug × valence interaction on false alarm rates [$F(1,30) = 11.09$, $P = 0.002$]. Post-hoc comparisons showed a significant difference between false alarm rates for aversive compared with neutral stimuli in the amisulpride group [$t(15) = 5.23$, $P < 0.001$] but not the placebo group [$t(15) = 0.65$, $P = 0.52$]. The amisulpride group also showed a significantly higher false alarm rate for aversive stimuli than the placebo group [$t(30) = 2.12$, $P = 0.043$]; see Figure 1. The 3-way ANOVA on reaction times showed a significant main effect of recognition state [$F(1,30) = 55.90$, $P < 0.001$] with reaction times being significantly shorter for hits than false alarms for both aversive [$t(31) = 8.25$, $P < 0.001$] and neutral [$t(31) = 5.33$, $P < 0.001$] stimuli. There was also a significant valence × drug interaction [$F(1,30) = 4.45$, $P = 0.043$], with the amisulpride group showing shorter reaction times in response to emotional stimuli compared with neutral stimuli for both hits and false alarms, with the reverse being observed in the placebo group. However, post-hoc *t*-tests were not statistically significant; see Figure 2.

Two participants from the placebo group and one from the amisulpride group had to be excluded from the ROC analysis because they had not followed the instructions to use the entire confidence rating scale, which resulted in abnormal ROC functions. The 2-way ANOVA showed a significant main effect of valence on recollection [$F(1,27) = 6.68$, $P = 0.015$], but not familiarity, with recollection being enhanced for aversive pictures relative to neutral; see Figure 3. There was no main effect of drug on familiarity or recollection or any arousal × drug interaction. However, correlation analyses showed a significant inverse correlation between amisulpride level and recollection estimates for aversive pictures ($r = -0.59$, $P = 0.033$); see Figure 4. There was no significant correlation between recollection estimates and neutral pictures or between familiarity estimates and either group of pictures.

From our examination of ROCs for the individuals in each group, we determined that the average ROCs were representative of the individual participant ROCs. The average ROCs for aversive and neutral conditions for the placebo and amisulpride groups are presented in Figure 5. We conducted a qualitative analysis of the ROC functions in line with Yonelinas (1994) and Yonelinas, *et al.* (1998). All the functions are curvilinear and asymmetrical along the diagonal. This suggests a contribution of both recollection and familiarity to the recognition memory process. The functions of the amisulpride and placebo groups overlap for neutral pictures, indicating no performance benefit for the placebo group over the amisulpride group. The functions of both groups for aversive pictures are skewed relative to those for neutral pictures, indicating a

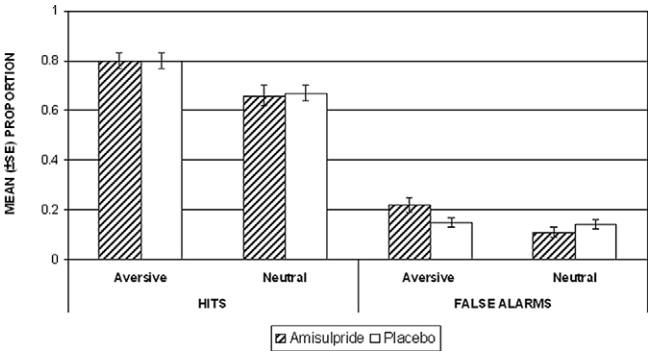

Figure 1 Mean proportion of hits and false alarms in placebo ($n = 16$) and amisulpride ($n = 16$) groups.

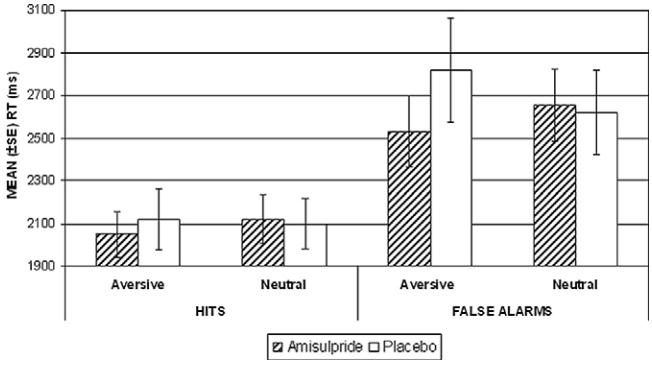

Figure 2 Mean reaction times for hits and false alarms in placebo ($n = 16$) and amisulpride ($n = 16$) groups.

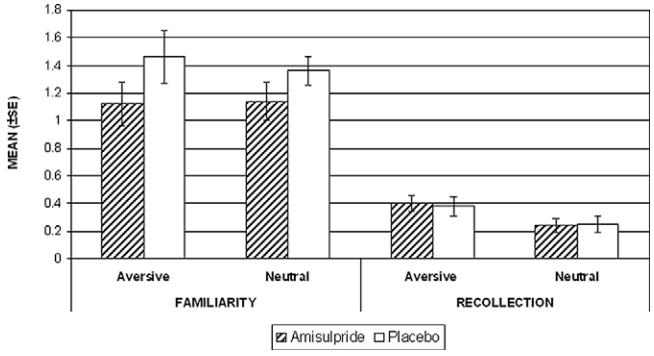

Figure 3 Mean familiarity and recollection estimates in placebo (n = 15) and amisulpride (n = 14) groups.

greater contribution of recollection for the emotionally arousing pictures, compared with neutral pictures in both groups. However, the function of the placebo group for the aversive pictures is skewed relative to that of the amisulpride group, suggesting that recollection made a greater contribution to discrimination in this group, whereas the amisulpride group relied more on familiarity.

Discussion

This study investigated the effects of the dopamine antagonist amisulpride on the recollection and familiarity components of emotional memory using a DPSD model. The main finding was a significant inverse correlation between amisulpride levels at encoding and recollection estimates for emotionally arousing stimuli. Significant correlations were not observed for neutral stimuli or for familiarity estimates. This indicates that amisulpride administered at encoding has a detrimental effect on the recollection, but not familiarity component of emotional memory. This was also supported by qualitative ROC analysis. However, we failed to find main effects or interactions in relation to recollection and familiarity estimates. Possible reasons for this failure are discussed further below. Nevertheless, these results corroborate and extend our previous finding of emotional memory impairment with amisulpride. Recent studies using the R/K procedure have suggested that recollection, but not familiarity, is enhanced by emotional arousal (Dolcos, *et al.*, 2005; Sharot, *et al.*, 2007; Ochsner, 2000; Kensinger and Corkin, 2003). Our results using the more sensitive DPSD model support this. They also suggest that it is the process of recollection, rather than familiarity that is particularly sensitive to the effects of drugs, which impair emotional memory.

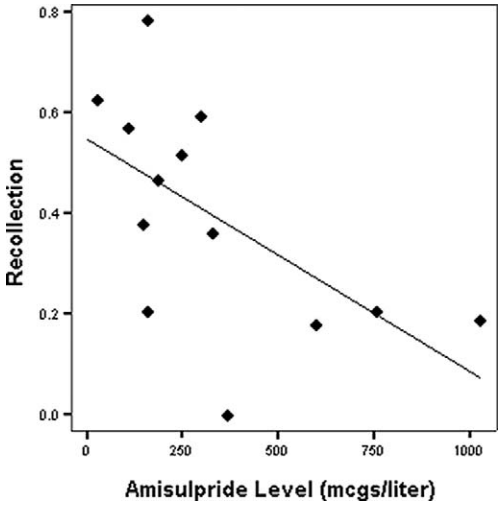

Figure 4 Scatterplot and regression relationship (solid line) between recollection scores and amisulpride plasma levels.

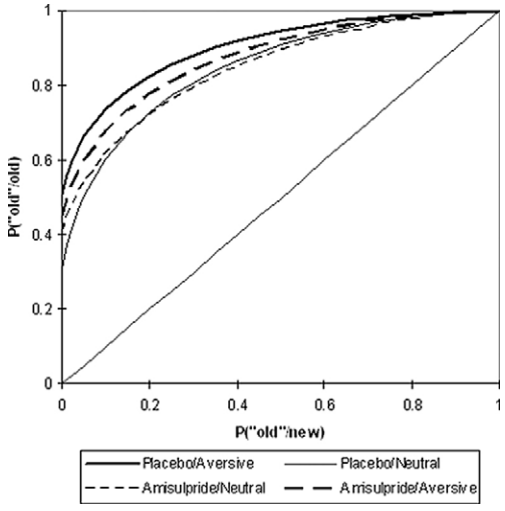

Figure 5 Receiver operating characteristics (ROCs) for the placebo and amisulpride groups for aversive-arousing and neutral conditions plotted in probability space. The x-axis represents the proportion of new pictures incorrectly identified as 'old'. The y-axis represents the proportion of old pictures correctly identified. The diagonal represents chance discrimination.

Recognition rates alone are not considered to provide reliable estimates of recognition memory performance because they are dependent on individual response biases (Macmillan and Creelman, 2005). Recent studies examining recognition memory performance from a single-process perspective have therefore tended to report alternative measures of memory accuracy such as percentage correct, corrected hit rates or measures derived from SDT (d') as the primary outcome measure. Such measures have supported a recognition memory advantage for emotional stimuli (Ochsner, 2000; Kensinger and Corkin, 2003). False alarm rates are often not reported, although there is evidence to suggest that they may also provide a good measure of recognition memory performance (Branconnier, *et al.*, 1982). This is supported by the present study in which

amisulpride administration at encoding resulted in an inflated false alarm rate for emotional but not neutral stimuli at recognition memory testing, but had no effect on hit rates. There is evidence that false alarms result primarily from familiarity judgements (Wolk, *et al*., 2006; Rubin, *et al*., 1999). There is also evidence that individuals resort to familiarity-based strategies when recollection is impaired, resulting in increased rates of false recognition (van Erp, *et al*., 2008; Thoma, *et al*., 2006). It has also been suggested that emotionally arousing stimuli are inherently more familiar than neutral stimuli because of enhanced processing fluency (Ochsner, 2000). It, therefore, seems likely that impairment in recollection processes in the amisulpride group led to dependence on a familiarity-based recognition strategy, leading to the observed elevated false alarm rate for the more familiar aversive stimuli. This suggests that recollection may enhance recognition memory performance by superseding familiarity to facilitate rejection of unseen items. This is consistent with previous observations (Hintzman and Curran, 1994). Our study indicates that such a process may be particularly relevant in the case of emotional stimuli and is supported by our reaction time data. In our study, the amisulpride group showed shorter reaction times in response to emotional stimuli compared with neutral stimuli, with the reverse being observed in the placebo group. Previous studies have shown that familiarity-based judgements occur at a faster speed than recollection-based judgements (Yonelinas, 2002). We, therefore, suggest that our reaction time data supports a familiarity- rather than recollection-based recognition strategy for emotional stimuli in the amisulpride group compared with the placebo group. It is, however, possible that the observed differences in reaction times and false alarm rates for aversive stimuli could have occurred because of a speed-accuracy trade-off in the amisulpride group. However, it seems unlikely that this would apply to only one stimulus category. No such differences were observed for neutral stimuli. Additionally, it would also be expected to result in a reduction in the hit rate for aversive stimuli which was not observed. Furthermore, the likelihood of such a trade-off was reduced by explicitly instructing participants not to compromise accuracy for speed.

Amisulpride is a selective D_2/D_3 receptor antagonist with limbic selectivity (Schoemaker, *et al*., 1997; Bressan, *et al*., 2003). Lesion and functional neuroimaging studies in humans have identified limbic structures, particularly the amygdala, as the critical neural substrate for emotional memory (Cahill, *et al*., 1995, 1996; Canli, *et al*., 2000; Hamann, *et al*., 1999; Adolphs, *et al*., 1997). Further studies suggest that this occurs via amygdala-modulation of hippocampus-dependent consolidation processes and is dependent on adrenergic neurotransmission (Cahill and Alkire, 2003; Cahill, *et al*., 1994; van Stegeren, *et al*., 1998, 2005). Others and we have recently reported that dopaminergic transmission is also likely to play a significant role (Mehta, *et al*., 2005; Gibbs, *et al*., 2007) and this is likely to involve the amygdala (Guarraci, *et al*., 1999, 2000; Hariri, *et al*., 2002; LaLumiere, *et al*., 2003, 2004; Takahashi, *et al*., 2005).

The neurobiological underpinnings of the recollection and familiarity components of recognition memory in general, and particularly in relation to emotional memory, have relatively recently begun to be investigated. Lesion studies investigating patients with amnesia suggest that the hippocampus is crucial to recollection-based recognition memory judgements, whereas other temporal lobe regions such as the parahippocampal gyrus subserve familiarity-based discrimination (Yonelinas, *et al*., 2002). More recently, functional imaging studies have also begun to suggest a distinction between brain regions recruited at encoding in subsequent recollection versus familiarity judgements. For example, in an fMRI study using the R/K procedure, Henson, *et al*. reported that left pre-frontal activity at encoding was associated with subsequent 'remember' as opposed to 'know' judgements (Henson, *et al*., 1999). Ranganath, *et al*. found that encoding activity in the rhinal cortex predicted familiarity-based recognition, whereas activity in the hippocampus selectively predicted recollection (Ranganath, *et al*., 2003). However, the relative contribution of different brain regions remains unclear. More recent studies have focused on dissociable neural correlates at retrieval, leaving the issue of encoding unresolved (Skinner and Fernandes, 2007). Similarly, the neural correlates of subsequent recollection and familiarity judgements in relation to emotional memory have not been well investigated. One study investigating emotional stimuli has reported a greater role for the amygdala and hippocampus in recollection judgements at retrieval (Dolcos, *et al*., 2005). However, whether this applies to encoding remains unclear.

Nevertheless, the evidence outlined above suggests that enhanced recollection, as opposed to familiarity for emotional stimuli relative to neutral stimuli, is related to amygdala-modulation of hippocampal-dependent processes. Amygdala activation at encoding may lead to increased binding of affectively related contextual detail, augmenting subsequent recollection. Amisulpride may interfere with this process at encoding by disrupting limbic dopaminergic transmission. Our findings suggest that this may be dose-related. This remains speculative, given that we did not measure limbic dopamine receptor occupancy following amisulpride administration in this study. The complex pharmacokinetic profile of amisulpride should also be taken into account in the interpretation of our findings. There is considerable inter-subject variability in peak plasma levels, which consist with the wide range of values observed in our study (Rosenzweig, *et al*., 2002). This variability may have contributed to our failure to find a main effect of amisulpride on recollection and familiarity estimates. Furthermore, the relationship between amisulpride dose, plasma concentrations and dopamine blockade is unclear. We were unable to find any published studies of dopamine receptor occupancy following a single 400 mg dose in healthy volunteers. However, a number of studies in amisulpride-treated patients with schizophrenia suggest that amisulpride plasma concentrations are highly positively correlated with D_2/D_3 receptor occupancy in both striatal and extra-striatal regions (la Fougere, *et al*., 2005; Martinot, *et al*., 1996). Xiberas, *et al*.

(2001) found that relatively low plasma concentrations (28–92 μg/L) induced marked extrastriatal occupancy. The amisulpride levels achieved in our study are consistent with extrastriatal receptor occupancies ranging from 48% to 93% (Bressan, *et al*., 2003; Xiberas, *et al*., 2001). However, it is difficult to extrapolate these data, based on repeated dosing steady-state concentrations to the present study where a single dose was given. There is evidence indicating that permeation of amisulpride across the blood–brain barrier is poor and it has been suggested that it therefore reaches its target brain structures via the blood–cerebrospinal fluid barrier (Hartter, *et al*., 2003). This much slower route may result in delayed brain availability following a single dose. Combined with the considerable variation in plasma levels, this may have contributed to our failure to find a main effect of amisulpride on recollection and familiarity estimates. Further studies using amisulpride should consider a repeated dosing regime.

On the basis of our previous findings, we hypothesised that the anti-psychotic effect of dopamine antagonists may derive, in part, from their ability to 'dampen down' emotional memory. It is the recollection component of emotional memory that is likely to be associated with the binding of affective contextual detail at or around encoding. There is evidence to suggest that memory for such detail may be important in the genesis and maintenance of delusional beliefs (Bentall, 1994; Bentall, *et al*., 1995). The present study, therefore, suggests that the antipsychotic effect of amisulpride may relate in part, to its attenuation of the recollection component of emotional memory, with relative sparing of the familiarity component. However, the observed increase in false recognition of emotional stimuli following amisulpride administration warrants further consideration. If the consequence of attenuation of recollection is an increase in false memory because of over-reliance on familiarity processes, this could also contribute to delusion formation in psychosis. In considering this effect, it is important to note that in this study we only considered the effect of a single dose of amisulpride at encoding. It has been suggested that dopaminergic transmission (Windmann and Kutas, 2001) and amygdala activity (Sharot, *et al*., 2004) may underlie the tendency to falsely recognise emotional stimuli at retrieval. Although speculative, it is possible that dopamine antagonism at retrieval (as would be the case in the therapeutic administration of dopamine antagonists) may also contribute to a reduction in 'false' emotional memory. However, this requires further investigation.

The present study also has further implications for recognition memory testing in medicated patients. A number of studies using different methods to investigate recognition memory have concluded that recollection is impaired in schizophrenia relative to healthy controls, whereas familiarity is preserved (Huron and Danion, 2002; Danion, *et al*., 1999; Weiss, *et al*., 2008). Other recent studies have either failed to find such an effect (Ragland, *et al*., 2006), found the reverse (Weiss, *et al*., 2008), or found impairment in both recollection and familiarity (Danion, *et al*., 2003). This last study also compared the effect of emotional salience on recollection and familiarity estimates in patients with schizophrenia and healthy controls, but failed to find any significant interaction. Our study suggests that the inconsistency in findings may be due not only to differences in paradigms and the emotional salience of the stimuli used but also to differences in medication. For example, in a group of medicated patients with schizophrenia, Thoma, *et al*. (2006) showed an association between negative symptoms and impairment of recollection using an R/K procedure and a standard recognition memory test for lists of words. However, it is of note that the mean dose of anti-psychotic medication was higher in the group with higher negative symptom scores. The extent to which medication may interact with disease processes to produce observed neuropsychological effects therefore remains unclear.

Further limitations to this study include the relatively small sample size, which may have contributed to our failure to find a main effect of amisulpride on recollection and familiarity estimates. Additionally, while the between-subjects design was necessary, it allows for possible confounding of the results by individual differences. Given the increasing evidence for differences in emotional memory and emotional processing between men and women, we chose to limit our sample to a single gender to minimise between-group differences and avoid the potential loss of power associated with a mixed-gender group of the same size. Hence, the extent to which the present findings are applicable to women is unclear. We also chose to use a single class of emotional stimuli. There is substantial evidence that emotional memory is mediated by the arousal characteristics of stimuli as opposed to valence *per se* (Anderson, 2005; Keil and Ihssen, 2004; Bradley, *et al*., 1992). There is also evidence to suggest that aversive stimuli are associated with greater arousal properties than their positive counterparts (Bradley, *et al*., 2001). We, therefore, chose to use aversive stimuli to maximise emotional enhancement of memory and increase the likelihood of detecting drug effects. However, we would predict that our findings are also applicable to positively valenced stimuli, but this requires further investigation. Finally, it is possible that amisulpride may have had an effect on other cognitive processes (e.g., attention) that may have contributed to the observed effects as opposed to a specific effect on memory *per se*. However, in our previous study, we also reported that amisulpride had no effect on the affective modulation of attention (Gibbs, *et al*., 2007). This suggests that the effect of amisulpride in this study is unlikely to be mediated by effects on attention.

This study further contributes to our understanding of how dopamine antagonists may exert their therapeutic effects at a cognitive level. It also contributes not only to our understanding of the cognitive effects of dopamine antagonism on the recollection and familiarity components of emotional memory but also to our understanding of the nature of recognition memory processes in general. Our results suggest that the effects of dopamine antagonists on these components of emotional memory warrant further investigation. In the meantime, caution should be applied in attributing neuropsychological findings to disease processes in medicated patients.

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References

Adolphs, R, Cahill, L, Shul, R, Babinsky, R (1997) Impaired declarative memory for emotional material following bilateral amygdala damage. Learn Mem *4*: 291–300.

Aleman, A, Hijman, R, de Haan, EHF, Kahn, RS (1999) Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry *156*: 1358–1366.

Anderson, AK (2005) Affective influences on the attentional dynamics supporting awareness. J Exp Psychol Gen *134*: 258–281.

Atkinson, R, Juola, J (1974) Search and decision processes in recognition memory. In: Krantz, D, Atkinson, R, Luce, R, Suppes, P (eds), Contemporary Developments in Mathematical Psychology: Learning, Memory and Thinking. Freeman: San Francisco, pp. 242–293.

Bentall, R (1994) Cognitive biases and abnormal beliefs: towards a model of persecutory delusions. In: David, A, Cutting, J (eds), The Neuropsychology of Schizophrenia. Lawrence Erlbaum: London, pp. 337–360.

Bentall, R, Kaney, S, Bowen-Jones, K (1995) Persecutory delusions and recall of threat-related, depression-related and neutral words. Cognit Ther Res *19*: 331–343.

Boyer, P, Lecrubier, Y, Puech, AJ, Dewailly, J, Aubin, F (1995) Treatment of negative symptoms in schizophrenia with amisulpride. Br J Psychiatry *166*: 68–72.

Bradley, MM, Codispoti, M, Cuthbert, BN, Lang, PJ (2001) Emotion and motivation I: defensive and appetitive reactions in picture processing. Emotion *1*: 276–298.

Bradley, MM, Greenwald, MK, Petry, MC, Lang, PJ (1992) Remembering pictures: pleasure and arousal in memory. J Exp Psychol Learn Mem Cogn *18*: 379–390.

Branconnier, R, Cole, J SPera, K, De Vitt, D (1982) Recall and recognition as diagnostic indices of malignant memory loss in senile dementia: a Bayesian analysis. Exp Aging Res *8*: 189–193.

Bressan, RA, Erlandsson, K, Jones, HM, Mulligan, R, Flanagan, RJ, Ell, PJ, *et al.* (2003) Is regionally selective D2/D3 dopamine occupancy sufficient for atypical antipsychotic effect? An in vivo quantitative [123I]epidepride SPET study of amisulpride-treated patients. Am J Psychiatry *160*: 1413–1420.

Cahill, L, Alkire, MT (2003) Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. Neurobiol Learn Mem *79*: 194–198.

Cahill, L, Babinsky, R, Markowitsch, H, McGaugh, JL (1995) The amygdala and emotional memory. Nature *377*: 295–296.

Cahill, L, Haier, RJ, Fallon, J, Alkire, T, Tang, C, Keator, D, *et al.* (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci U S A *93*: 8016–8021.

Cahill, L, Prins, B, Weber, M, McGaugh, JL (1994) Beta-adrenergic activation and memory for emotional events. Nature *371*: 702–704.

Canli, T, Zhao, Z, Brewer, J, Gabrieli, JDE, Cahill, L (2000) Event-related activation in the human amygdala associates with later memory for individual emotional experience. J Neurosci *20*: 1–5.

Danion, JM, Kazes, M, Huron, C, Karchouni, N (2003) Do patients with schizophrenia consciously recollect emotional events better than neutral events. Am J Psychiatry *160*: 1879–1881.

Danion, JM, Rizzo, L, Bruant, A (1999) Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. Arch Gen Psychiatry *56*: 639–644.

Dolcos, F, LaBar, KS, Cabeza, R (2005) Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. Proc Natl Acad Sci U S A *102*: 2626–2631.

Egan, J (1958) Recognition Memory and the Operating Characteristic. Bloomington: Indiana University, Hearing and Communication Laboratory.

Fujishiro, H, Umegaki, H, Suzuki, Y, Oohara-Kurotani, S, Yamaguchi, Y, Iguchi, A (2005) Dopamine D2 receptor plays a role in memory function: implications of dopamine-acetylcholine interaction in the ventral hippocampus. Psychopharmacology *182*: 253–261.

Gibbs, A, Naudts, K, Spencer, E, David, A (2007) The role of dopamine in attentional and memory biases for emotional information. Am J Psychiatry *164*: 1603–1609.

Green, D, Swets, J (1966) Signal Detection Theory and Psychophysics. New York: Wiley.

Guarraci, FA, Frohardt, RJ, Falls, WA, Kapp, BS (2000) The effects of intra-amygdaloid infusions of a D2 dopamine receptor antagonist on Pavlovian fear conditioning. Behav Neurosci *114*: 647–651.

Guarraci, FA, Frohardt, RJ, Young, SL, Kapp, BS (1999) A functional role for dopamine transmission in the amygdala during conditioned fear. Ann N Y Acad Sci *877*: 732–736.

Hamann, SB, Ely, TD, Grafton, ST, Kilts, CD (1999) Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat Neurosci *2*: 289–293.

Hariri, AR, Mattay, VS, Tessitore, A, Fera, F, Smith, WG, Weinberger, DR (2002) Dextroamphetamine modulates the response of the human amygdala. Neuropsychopharmacology *27*: 1036–1040.

Hartter, S, Huwel, S, Lohmann, T Abou el ela, A, Langguth, P, Hiemke, C, *et al.* (2003) How does the benzamide antipsychotic amisulpride get into the brain?—An in vitro approach comparing amisulpride with clozapine. Neuropsychopharmacology *28*: 1916–1922.

Henson, RN, Rugg, MD, Shallice, T, Josephs, O, Dolan, RJ (1999) Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. J Neurosci *19*: 3962–3972.

Hintzman, DL, Curran, T (1994) Retrieval dynamics of recognition and frequency judgments: evidence for separate processes of familiarity and recall. J Mem Lang *33*: 1–18.

Huron, C, Danion, JM (2002) Impairment of constructive memory in schizophrenia. Int Clin Psychopharmacol *17*: 127–133.

Jacoby, L (1991) A process dissociation framework: separating automatic from intentional uses of memory. J Mem Lang *30*: 513–541.

Jacoby, L, Toth, J, Yonelinas, AP (1993) Separating conscious and unconscious influences of memory: measuring recollection. J Exp Psychol Gen *2*: 1–16.

Keil, A, Ihssen, N (2004) Identification facilitation for emotionally arousing verbs during the attentional blink. Emotion *4*: 23–35.

Kensinger, E, Corkin, S (2003) Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words. Mem Cogn *31*: 1169–1180.

La Fougere, C, Meisenzahl, E, Schmitt, G, Strauss, J, Fordl, T, Tatsch, K, *et al.* (2005) D2 receptor occupancy during high- and low-dose therapy with the atypical antipsychotic amisulpride: a 123I-iodobenzamide SPECT study. J Nucl Med *46*: 1028–1032.

LaLumiere, RT, Buen, T, McGaugh, JL (2003) Post-training intrabasolateral amygdala infusions of norepinephrine enhance consolidation of memory for contextual fear conditioning. J Neurosci *23*: 6754–6758.

LaLumiere, RT, Nguyen, LT, McGaugh, JL (2004) Post-training intrabasolateral amygdala infusions of dopamine modulate consolidation of inhibitory avoidance memory: involvement of noradrenergic and cholinergic systems. Eur J Neurosci *20*: 2804–2810.

Lang, PJ, Bradley, MM, Cuthbert, BN (1998) International Affective Picture System (IAPS): Technical Manual and Affective Ratings. Gainesville: University of Florida, Center for Research in Psychophysiology.

Leucht, S, Pitschel-Walz, G, Engel, RR, Kissling, W (2002) Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. Am J Psychiatry *159*: 180–190.

Macmillan, NA, Creelman, DC (2005) Detection Theory: A User's Guide. Cambridge: Cambridge University Press.

Mandler, G (1980) Recognizing: the judgment of previous occurrence. Psychol Rev *87*: 252–271.

Martinot, JL, Paillere-Martinot, ML, Poirier, M, Dao-Castellana, M, Loc'h, C, Maziere, B (1996) In vivo characteristics of dopamine D2 receptor occupancy by amisulpride in schizophrenia. Psychopharmacology *124*: 154–158.

Mehta, MA, Hinton, EC, Montgomery, AJ, Bantick, RA, Grasby, PM (2005) Sulpiride and mnemonic function: effects of a dopamine D2 receptor antagonist on working memory, emotional memory and long-term memory in healthy volunteers. J Psychopharmacol *19*: 29–38.

Ochsner, KN (2000) Are affective events richly recollected or simply familiar. J Exp Psychol Gen *129*: 242–261.

Paillere-Martinot, ML, Lecrubier, Y, Martinot, JL, Aubin, F (1995) Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. Am J Psychiatry *152*: 130–134.

Pelletier, M, Achim, AM, Montoya, A, Lal, S, Lepage, M (2005) Cognitive and clinical moderators of recognition memory in schizophrenia: a meta-analysis. Schizophr Res *74*: 233–252.

Ragland, JD, Valdez, JN, Loughead, J, Gur, RC, Gur, RE (2006) Functional magnetic resonance imaging of internal source monitoring in schizophrenia: recognition with and without recollection. Schizophr Res *87*: 160–171.

Ramaekers, JG, Louwerens, JW, Muntjewerff, ND, Milius, H, de Bie, A, Rosenzweig, P, *et al.* (1999) Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. J Clin Psychopharmacol *19*: 209–221.

Ranganath, C, Yonelinas, AP, Cohen, MX, Dy, CJ, Tom, SM, DEsposito, M (2003) Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia *42*: 2–13.

Rosenzweig, P, Canal, M, Patat, A, Bergougnan, L, Zieleniuk, I, Bianchetti, G (2002) A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. Hum Psychopharmacol *17*: 1–13.

Rubin, SR, Van Petten, C, Glisky, EL, Newberg, WM (1999) Memory conjunction errors in younger and older adults: event-related potential and neuropsychological data. Cogn Neuropsychol *16*: 459–488.

Schoemaker, H, Claustre, Y, Fage, D, Rouquier, L, Chergui, K, Curet, O, *et al.* (1997) Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. J Pharmacol Exp Ther *280*: 83–97.

Sharot, T, Delgado, M, Phelps, E (2004) How emotion enhances the feeling of remembering. Nat Neurosci *7*: 1376–1380.

Sharot, T, Verfaellie, M, Yonelinas, AP (2007) How emotion strengthens the recollective experience: a time-dependent hippocampal process. PLoS ONE *2*: e1068.

Skinner, EI, Fernandes, MA (2007) Neural correlates of recollection and familiarity: a review of neuroimaging and patient data. Neuropsychologia *45*: 2163–2179.

Takahashi, H, Yahata, N, Koeda, M, Takano, A, Asai, K, Suhara, T, *et al.* (2005) Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological study. Neuroimage *27*: 991–1001.

Thoma, P, Zoppelt, D, Wiebel, B, Daum, I (2006) Recollection and familiarity in negative schizophrenia. Neuropsychologia *44*: 430–435.

Tulving, E (1985) Memory and consciousness. Can Psychol *26*: 1–12.

Umegaki, H, Munoz, J, Meyer, RC, Spangler, EL, Yoshimura, J, Ikari, H, *et al.* (2001) Involvement of dopamine D2 receptors in complex maze learning and acetylcholine release in ventral hippocampus of rats. Neuroscience *103*: 27–33.

Van Erp, TGM, Lesh, TA, Knowlton, BJ, Bearden, CE, Hardt, M, Karlsgodt, KH, *et al.* (2008) Remember and know judgments during recognition in chronic schizophrenia. Schizophr Res *100*: 181–190.

Van Stegeren, AH, Everaerd, W, Cahill, L, McGaugh, JL, Gooren, LJG (1998) Memory for emotional events: differential effects of centrally versus peripherally acting beta-blocking agents. Psychopharmacology *138*: 305–310.

Van Stegeren, AH, Goekoop, R, Everaerd, W, Scheltens, P, Barkhof, F, Kuijer, JPA, *et al.* (2005) Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. NeuroImage *24*: 898–909.

Weiss, AP, Goff, DC, Duff, M, Roffman, JL, Schacter, DL (2008) Distinguishing familiarity-based from source-based memory performance in patients with schizophrenia. Schizophr Res *99*: 208–217.

Windmann, S, Kutas, M (2001) Electrophysiological correlates of emotion-induced recognition bias. J Cogn Neurosci *13*: 577–592.

Wolk, DA, Schacter, DL, Lygizos, M, Sen, NM, Holcomb, PJ, Daffner, KR, *et al.* (2006) ERP correlates of recognition memory: effects of retention interval and false alarms. Brain Res *1096*: 148–162.

Xiberas, X, Martinot, JL, Mallet, L, Artiges, E, Canal, M, Loc'h, C, *et al.* (2001) In vivo extrastriatal and striatal D2 receptor blockade by amisulpride in schizophrenia. J Clin Psychopharmacol *21*: 207–214.

Yonelinas, AP (1994) Receiver-operating characteristics in recognition memory: evidence for a dual-process model. J Exp Psychol Learn Mem Cogn *20*: 1341–1354.

Yonelinas, AP (2002) The nature of recollection and familiarity: a review of 30 years of research. J Mem Lang *46*: 441–517.

Yonelinas, AP, Kroll, NEA, Dobbins, IG, Lazzara, M, Knight, RT (1998) Recollection and familiarity deficits in amnesia: convergence of remember-know, process dissociation and receiver operating characteristic data. Neuropsychology *12*: 323–339.

Yonelinas, AP, Kroll, NEA, Quamme, JR, Lazzara, MM, Sauve, MJ, Widaman, KF, *et al.* (2002) Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. Nat Neurosci *5*: 1236–1241.