Memory Encoding and Dopamine in the Aging Brain: A Psychopharmacological Neuroimaging Study

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Normal aging brings with it changes in dopaminergic and memory functions. However, little is known about how these 2 changes are related. In this study, we identify a link between dopamine, episodic memory networks, and aging, using pharmacological functional magnetic resonance imaging. Young and older adults received a D2-like agonist (Bromocriptine, 1.25 mg), a D2-like antagonist (Sulpiride, 400 mg), and Placebo, in a double-blind crossover procedure. We observed group differences, during memory encoding, in medial temporal, frontal, and striatal regions and moreover, these regions were differentially sensitive across groups to dopaminergic perturbation. These findings suggest that brain systems underlying memory show age-related changes and that dopaminergic function may be key in understanding these changes. That these changes have behavioral consequences was suggested by the observation that drug modulations were most pronounced in older subjects with poorer recognition memory. Our findings provide direct evidence linking ageing, memory, and dopaminergic change.

Keywords: aging, dopamine, encoding, fMRI, memory

Introduction

The cognitive decline that accompanies normal aging is characterized by selectivity as well as generality in the pattern of changes (Light 1991; Salthouse 1996). The marked impairment in episodic memory is thought to arise at least in part from difficulty in encoding new memories (Craik and Rabinowitz 1985; Perfect et al. 1995; Glisky et al. 2001; Friedman et al. 2007). This pattern of functional change may be linked to regional cerebral atrophy, notably in prefrontal cortex (PFC; Raz et al. 1997), and medial temporal lobes (Golomb et al. 1993; see Raz and Rodrigue 2006).

However, a full understanding of age-related changes requires a consideration of the accompanying changes in neurotransmission. There is a substantial age-related decline in dopamine system markers, especially in striatum—of the order of 8% per decade. Postmortem and radioligand binding data have revealed age-related reductions in the number of D1 and D2 receptors, and dopamine (DA) transporters (for reviews see Joseph et al. 1990; Li and Lindenberger 1999; Kaasinen and Rinne 2002; Backman et al. 2006). There is evidence, too, that these changes have perceptuomotor and cognitive correlates (Volkow et al. 1998; Wang et al. 1998; Mozley et al. 2001) that can account for specific age-related variance in measures of

episodic memory, verbal fluency and perceptual speed (Backman et al. 2000; Yang et al. 2003; Erixon-Lindroth et al. 2005). These findings are consistent with those from animal studies which have demonstrated age-related reductions in DA and dopaminergic markers, and associated functional changes, notably in PFC, striatum, and medial temporal lobes (MTL) (Goldman-Rakic and Brown 1981; Lai et al. 1987; Araki et al. 1997; Amenta et al. 2001). Computational models, which can emulate patterns of memory decline, also link DA deficiency to age-related reductions in signal-to-noise characteristics and processing efficiency (Li et al. 2001; Braver and Barch 2002; Li et al. 2005).

In the current study, we sought direct evidence that goes beyond the "correlative triad" observed between adult age, DA, and cognition in humans (Backman et al. 2006), We used functional magnetic resonance imaging (fMRI) to measure specific brain responses to episodic encoding processes in young and old subjects. To determine the relationship between dopaminergic neuromodulation and episodic encoding, we used blinded pharmacological manipulations in the same subjects, with both a DA agonist (Bromocriptine) and an antagonist (Sulpiride). We assessed the differential effects of dopaminergic perturbation on encoding-related activity in young and older adults using "subsequent memory" (SM) measures of the regional brain activity at the time of encoding predictive of success on a later memory test (Sandquist et al. 1980; Wagner et al. 1998). These measures assess the activity elicited by processes specifically associated with successful encoding, independently of other processing engaged during an orienting task. Such studies in the young have shown that DA plays a critical role in episodic encoding in humans (Wittmann et al. 2005; Schott et al. 2006). Our aim was to establish a link between aging and changes in DA transmission, processes involved in episodic encoding, and the regions and networks that support these processes.

Our specific predictions for the 2 groups were as follows. According to the dopamine aging hypothesis, an amelioration of processing inefficiency of older adults under dopaminergic stimulation (Bromocriptine) was expected, and thus an attenuation of the differences from the young. Conversely, the antagonist (Sulpiride) was predicted to render patterns of activity in the young more like those in the old, with evidence of reduced neural efficiency reflected in larger SM effects. This was based on evidence linking optimal levels of DA signaling to optimal neural efficiency, associated with reduced cortical activity alongside

comparable behavioral outcomes (e.g., Rypma and D'Esposito 2000; Gibbs and D'Esposito 2005). Parallel effects on behavior were predicted, although these were expected to be subtle given the relatively low drug doses. The use of such modest doses in pharmacological neuroimaging studies has the important advantage of avoiding confounds of task-specific effects of drugs with secondary influences due to altered arousal or other systemic or general effects (Honey and Bullmore 2004). In this context, we examined the link between neuromodulation and behavior in terms of individual differences in cognition. Given the relationship between aging, dopaminergic markers and individual differences, we investigated whether drug effects would vary according to memory performance. We predicted that drug effects—specifically of the agonist, Bromocriptine—in the older group would be more pronounced in those with poorer memory, that is, those likely to have the greatest underlying age-related cognitive decline. This specific prediction extended the expectation that DA stimulation would ameliorate group differences via predominant effects in the older group. Critically, and more generally, an effect of age on the relationship between performance and dopaminergic neuromodulation in this task would suggest that the changes in DA systems associated with aging are a marker, if not an integral part, of the mechanisms underlying age-related memory decline.

Materials and Methods

Subjects

Sixteen younger (18-35 years) and 16 older (63-79 years) adults underwent functional MRI scanning. Of these, 15 (mean = 24.9, SD = 4.7 years) and 12 (mean = 66.9, SD = 3.3 years) contributed data to the present study. There were the following exclusions: a young participant with too few forgotten items (see fMRI Scanning and Data Analysis), an older participant with an error in fMRI data acquisition in one session, and 3 further older subjects who gave no "Know" responses in one or more sessions (see Behavioral procedures). Recruitment was via locally placed advertisements, with initial telephone screening of volunteers using a standard questionnaire. Exclusion criteria were a history of significant medical or psychiatric condition likely to affect the brain or cerebral vasculature, concurrent vasoactive or neurotropic medication, and any contraindications to the study drugs or to MRI. Prior to taking part in functional MRI scanning, each subject had an electrocardiogram, reviewed by a physician, as well as a structural scan. The 2 groups were matched as far as possible on education and on "crystallized" IQ, as estimated by the National Adult Reading Test (NART; Nelson 1982). For those young and old included in the fMRI analysis, years of formal education were equivalent (mean 4.5 and 4.4 years after age 16 for young and old, respectively), but they differed marginally in NART IQ (mean estimated full scale IQ = 112.0 and 117.3, SDs = 6.2 and 6.9; $t(22.4) = 2.97$, $0.05 < P < 0.1$). Older volunteers also completed the Mini Mental State Examination, and a minimum score of 28 was required for participation (Folstein et al. 1975; Lezak 1995). The study was approved by the Cambridge Local Research Ethics Committee, Cambridge, UK.

Pharmacological Interventions

The study employed a randomized double-blind Placebo-controlled crossover design, each subject attending for 3 main sessions during which oral study medication was given by a physician. This medication contained Sulpiride 400 mg, Bromocriptine 1.25 mg, or a Placebo. To prevent nausea whilst maintaining a double-blind procedure, the study drug on each visit was given with 10 mg of the peripheral DA antagonist Domperidone (Reddymasu et al. 2007). Subjects were also asked to eat before attending. Sulpiride has a mean time to maximal plasma concentration of about 3 h, a plasma half-life of about 12 h, and oral bioavailability of around 35%. Plasma prolactin concentration is

maximal after about 1 h, then declines slowly (Wiesel et al. 1982; von Bahr et al. 1991; Caley and Weber 1995). Bromocriptine's central effects have been shown to be somewhat slower in onset than those of Sulpiride but are also long lasting. Prior data suggest a reliable suppression of plasma levels from as early as 1½ h postdose, that does not reach a maximum until after 3 h postdose and persists for some time after that (Luciana et al. 1998; Muller et al. 1998; Oranje et al. 2004). fMRI data acquisition commenced at approximately 3-h postdrug. The encoding phase was administered first and lasted for 15 min. The first of the 2 retrieval phase (fMRI data not reported here) commenced around 2 min later. This was followed by a 10-min period of an unrelated task (not reported here), then the second retrieval phase. Each of these retrieval phases lasted for just over 17 min. Study visits were separated by a minimum washout period of a week.

Behavioral Procedures

The episodic memory task consisted of a study phase, comprising stimulus attribute decision tasks, and a test phase, comprising 2 recognition memory blocks. The choice of the 2 study phase tasks was motivated primarily by the requirement that with the data collapsed across them there should be sufficient numbers of remembered and forgotten items in the 2 age groups for the fMRI analysis. On the first visit, immediately after the drugs had been given, subjects received task training and practice outside the scanner until they were familiar with the procedure. Instructions for the decision tasks and the memory test were given together, and subjects were informed that both phases were equally important. Standard instructions, with examples, were given for the Remember-Know procedure (Gardiner 1988).

Study Phase

The study phase comprised a series of 16 blocks of 15 trials each, with interspersed periods of fixation. This design was employed to minimize the requirement for subjects to switch between encoding tasks whilst employing an efficient fMRI design. Each block was preceded by a cue, "Living?" or "Syllables?," to indicate whether subjects should perform a living/nonliving or a syllable judgment on the items in that block. On each trial, a noun was presented in the center of the screen. On living/nonliving judgment trials, subjects decided whether the named item was a living or a nonliving thing. On syllable judgment trials, they decided whether the word had an even or an odd number of syllables. The stimulus onset asynchrony (SOA) at study was 3000 ms: each item was presented for 600 ms, followed by a fixation "+" for 2200 ms. The screen was then blanked for 200 ms prior to the next trial.

Test Phase

In the test phase, subjects again saw single words presented in central screen. For each, they were asked to judge whether, and how, they remembered that word being presented in the study phase. If they could remember something specific about seeing the word at study (e.g., what they thought about when they saw the word, the key that was pressed, or what the word looked like on the screen), they were asked to give a "remember" (R) response. If they had no specific recollection of experiencing the item, but thought that the item had been studied, they were asked to give a "know" (K) response. If they thought that the item had not been studied, they were asked to give a "new" response. Each half of the test phase comprised 18 blocks of 10 trials, interspersed with periods of fixation. Each was preceded by a cue, "Remember living" or "Remember syllable," which indicated that any previously seen items in the block that followed would be those from just 1 of the 2 study phase tasks. The SOA at test was 4400 ms: each item was preceded for 600 ms by a warning signal, which was a change in the color of the fixation symbol from white to red. The word was then shown for 600 ms, followed by a fixation "+" for 3000 ms, and a blank screen for 200 ms.

Stimuli

The lists of critical stimuli were constructed from a pool of 1080 nouns between 4 and 9 letters, and between 1 and 3 syllables in length from the CELEX database (http://www.ru.nl/celex/). Three sets of 360 words each were selected at random from this pool, each having the same proportion of items that were living versus nonliving, items that

had even versus odd numbers of syllables, and items with a given number of letters. For each matched pair of one younger and one older subject, 18 lists of 60 words each were formed from this pool, 6 for each study session. Random selection was again constrained to give an even distribution of encoding task-related characteristics (i.e., number of syllables and animacy) across lists. Of the 6 lists, 4 were used as studied items (2 for living/nonliving decisions and 2 for syllable judgments), and the other 2 were used as new items at test. One of the 2 study lists, and 1 of the 2 new item lists, were combined to create the list for each of the 2 test blocks for each session. An additional 90 items formed practice lists for the study and test phases. Except where noted, data in both behavioral and fMRI analyses are collapsed across the 2 encoding tasks. Word stimuli were presented using DMDX (http://www.u.arizona.edu/~kforster/dmdx/dmdx.htm), via a mirror comfortably situated within the subject's field of view. Words were displayed in white uppercase Arial font on a black background. Responses were made using a hand-held response box with counterbalanced response mappings across subjects. In both study and test phases, both speed and accuracy were stressed.

Other Measures

In order to assess nonspecific drug effects, subjects were required to complete 2 further tests at the start of each session, just before scanning commenced, and at the end of the session. The first was an analog Apathy Scale consisting of 5 100-mm lines ranging from "not at all" to "very" for the following items: motivated, excited, energetic, interested and full of initiative (McLean et al. 2004). Subjects were required to indicate a point on each line that was consistent with their current subjective feeling. The second was a 10-item version of the Benton judgment of line orientation test (Benton et al. 1983). In the final session, they were also asked to report in which sessions they thought they had received drugs versus Placebo.

Analysis of Behavioral Data

All analysis of behavioral data were conducted using full-factorial ANOVA with the principal factors of age group (young, old) and drug (Sulpiride, Placebo, Bromocriptine). The analysis of study phase mean response times (RTs), and proportions of correct responses, also included the factor SM (whether items attracted R or K responses, or were forgotten, F, i.e., classified as new). Test phase RT analysis had the factors of age group, drug, and old/new (hits/correct rejections). In the test phase, discrimination of old from new items across both R and K responses was indexed by $Pr = (P_{hit} - P_{false\ alarm})$ (Snodgrass and Corwin 1988). The response bias index Br was also computed ($P_{false\ alarm}/1 - (P_{hit} - P_{false\ alarm})$) (Snodgrass and Corwin 1988): values less than 0.5 suggest a conservative tendency to classify both old and new items as "new." As "remembered" items defined the SM measures (see fMRI scanning and data analysis), age group and drug effects on the proportions of items judgments recollected versus familiar, and on RTs for these response categories, were also assessed. Separate ANOVAs were conducted on the level of recollection (using the corrected R proportions index: proportion of R hits—proportion of R false alarms (Gardiner and Java 1991), the level of familiarity under the assumption of independence (Yonelinas and Jacoby 1995), and comparing the 2 (with the additional factor of recollection vs. familiarity). The latter analysis was also conducted for RTs.

fMRI Scanning and Data Analysis

Subjects performed the stimulus attribute decision tasks while T_2^*-weighted gradient-echo echo planar (EPI) images with blood oxygen level-dependent contrast were acquired, using a 3.0T Medspec S300 system (Bruker Medical, Ettlingen, Germany) in the Wolfson Brain Imaging Centre (Cambridge, UK). Each EPI volume consisted of 23 interleaved 4 mm thick axial slices with 64 × 64 pixels, separated by a 1-mm interslice gap, angled to the intercommisural line. Seven hundred and fifty-five volumes were acquired, with a flip angle of 90°, a repetition time (TR) of 1200 ms, an echo time of 27.5 ms, and an in-plane resolution of 3.125 mm. The first 7 volumes were discarded to allow for T_1 saturation effects.

Preprocessing

Preprocessing and data analysis were carried out using Statistical Parametric Mapping (SPM5, Wellcome Department of Cognitive Neurology, London, UK; Friston et al. 1995, http://www.fil.ion.ucl.ac.uk/spm/spm5). Data quality control employed outlier detection (slices of variance >5 standard deviations) to identify problem scans. Where present, these were replaced with the mean of the 2 neighboring scans to avoid the generation of temporal interpolation artifacts during slice timing correction. They were then modeled as confounds in the design matrix by placing a "1" at the appropriate time-point in a column of zeros (see below). All volumes in each time series were realigned spatially to the first volume, using B-spline interpolation. Inspection of movement parameters generated during spatial realignment indicated that no participant moved more than 3 mm or 3° in any direction during task performance. Each volume was normalized using nonlinear basis functions and then resampled into 3 × 3 x 3 mm voxels, using a standard EPI template volume based on the Montreal Neurological Institute (MNI) reference brain (Cocosco et al. 1997) in the space of Talairach and Tournoux (1988; Ashburner and Friston 1999). Finally, to allow for anatomical variation between as well as within the 2 age groups (Good et al. 2001); see (Morcom et al. 2003), the time series was smoothed with a 10-mm full width half maximum isotropic Gaussian kernel.

First Level Models

The fMRI effects reported pertain to the memory encoding phase. Population inferences were made using a 2-stage "summary statistic" procedure (Holmes and Friston 1998). In the first stage, the volumes acquired for each participant were modeled as a continuous time series. Trials at study were classified according to SM performance, that is, responses *in the test phase*. There were thus 3 main event types: studied items that attracted a "remember" decision (R items), those that attracted a "know" decision (K items), and those that attracted a "new" decision (forgotten or F items). Those items wrongly classified during the study phase were modeled as events of no interest in the fMRI analysis, as were the 2 types of study task cues preceding each of the mini-blocks. The hemodynamic response to the onset of each event type of interest was modeled with 2 basis functions: a canonical hemodynamic response function (HRF; Friston et al. 1998), and a delayed HRF (Henson et al. 2000), shifted 2.5 s later in time than the canonical HRF (see Morcom et al. 2003 for a similar approach). This approach does not assume that event-related responses fit the "canonical" shape. We also employed "early" and "late" response functions specifically because aging may affect the shape and/or timing of the hemodynamic response as a result of cerebrovascular changes ([although we note that studies to date have not revealed consistent such effects (D'Esposito et al. 1999; Huettel et al. 2001; Aizenstein et al. 2004; Ances et al. 2009]). Thus, event-related responses with a different shape or timing in the 2 age groups could be detected and distinguished from event-related responses of different magnitudes.

Sequences of delta functions representing the onsets of events for each trial type were convolved with the early and the late response functions to form the covariates in a general linear model, together with a constant term for each participant. The covariates for the late HRF were orthogonalized with respect to those for the early HRF using a Gram-Schmidt procedure, giving priority to the early covariate (Andrade et al. 1999). Variance common to the early and late covariates was thus attributed to the early covariate, so that loadings on the orthogonalized late covariate accounted only for residual variance in the data unexplained by the early covariate. This avoided variance being "lost" due to collinearity and meant that early covariate effects were interpretable as canonical event-related responses. Parameter estimates for each covariate were calculated from the weighted least squares fit of the model to the data, following prewhitening based on an AR(1) plus white noise model to remove autocorrelations in the time series (Friston et al. 2002). The data for each session were proportionally scaled to a global mean of 100. Using a discrete cosine basis set fitted as part of the model, the data were high-pass filtered to a maximum of 1/128 Hz. Twelve covariates were also included for each session to capture residual movement-related artifacts (the 3 rigid body translations and rotations determined from the realignment stage, and their

between-scan differences). Planned linear contrasts of parameter estimates were then computed for the combinations of conditions specified in the Results section, for both early and late covariates. These contrast images were stored separately for each participant, and entered into second level or "random effects" models, which permit inferences about condition effects across subjects and between groups that generalize to the population.

Second Level Models and Analysis Strategy

Group level models and covariates. The group level analyses focused on drug modulations of activity at encoding predicting SM, and on age-related differences and commonalities in these drug modulations. An ANCOVA model was constructed with the categorical factors of group (young, old) and drug (Sulpiride, Placebo, Bromocriptine). Because the relationship between brain activity and individual memory performance was of interest, Pr measures were also entered into the second level designs as predictors using 6 covariates (see Introduction for rationale, and Results and Discussion: Behavioral findings for details of measures). Covariates for each drug condition across age groups were constructed in 3 columns. Covariates for age group × Pr were constructed by mean correcting score vectors for young and older subjects separately, weighting the young group values positively and the older group values negatively, and then combining them in a single column for each drug condition. To account for possible confounding effects of Br, these measures were entered into the models in the same fashion, but were not analyzed further. In order to interpret the drug effects in terms of baseline age-related differences, analyses were first conducted for the Placebo condition alone.

All of these second level analyses were conducted using first level SM contrast images as dependent measures. These were formed from the difference between the estimated activity at each voxel for items later judged "remembered" and those forgotten (R – F). In this way, the activity specifically associated with encoding leading to later recollection in both groups was contrasted with that associated with unsuccessful encoding. The contrasts were defined in this way so that between-groups comparisons of SM effects would not be confounded with differing levels of recollection for remembered items, recollection being expected to be lower in the old group (Yonelinas 2001). However, the use of R, not K, items to form SM effects was not intended to isolate encoding leading to later recollection from that leading to later familiarity, because, depending on the processing model, at least some recollected items are likely also to be familiar (see Yonelinas and Jacoby 1995). Effects elicited by items later judged "known" are not reported because K responses are likely to reflect a mixture of familiarity and guessing, the rate of the latter varying according to response criterion (which here showed drug effects, see Results; Yonelinas et al. 1996). SM-related activity was not assessed separately for the 2 different study (stimulus attribute decision) tasks because there were not enough trials to do this reliably given the variability in memory performance (see online Supplementary Material for analysis of effects under Placebo). All models were estimated using a weighted least squares procedure that accounted for nonsphericity. Contrasts of second level parameter estimates produced SPMs of F or t statistics at each voxel, subsequently transformed to the unit normal Z distribution.

Thresholding strategy and region identification. To minimize the number of statistical tests at each voxel, effects were in general detected using (nondirectional) F-tests, then further delineated using specific 1- and 2-sample t-tests where appropriate. To control the false positive rate across voxels, a region of interest (ROI) mask was defined combining regions from the AAL template using WFU PickAtlas (Tzourio-Mazoyer et al. 2002; Maldjian et al. 2003). This comprised bilateral medial temporal lobes (hippocampus and parahippocampal gyrus), bilateral lateral PFC (inferior and middle frontal gyri but not orbitofrontal cortex), and bilateral striatum (caudate, putamen and lentiform nucleus). Also included was the region defined by Aron et al. (2004) to include the ventral tegmental area (a 15-mm sphere centered on $x = 0$, $y = -15$, $z = -9$). These ROIs were chosen because the MTL and the lateral PFC are the regions of primary interest in the study of episodic memory, and specifically in the study of episodic memory and ageing

(see Introduction). The striatum is commonly assumed to be involved in procedural, rather than episodic, memory, but is both a central part of the DA system and the region in which an age-related decline is dopaminergic markers has most clearly been demonstrated in humans (see Introduction). The dopaminergic midbrain is also of potential functional relevance particularly in the light of recent findings of Schott et al. (2006). An uncorrected threshold of $P < 0.001$, and > 5 contiguous voxels was adopted across this search volume of 8855 voxels (using a Bonferroni correction at alpha = 0.05, 9 false positive voxels would be expected—however, given the smoothness of the data, there are fewer observations than voxels, so this is a conservative estimate; see Nichols and Hayasaka (2003). Second level contrasts were evaluated at all voxels within the ROIs. The locations of maxima of suprathreshold regions were established by rendering them onto the volunteers' normalized structural and mean EPI images, and the MNI reference brain (Cocosco et al. 1997). They were labeled using the nomenclature of Talairach and Tournoux (1988) and anatomical designations of Brodmann (1909). Results from the late covariate are not reported here because in no case did they add meaningfully to the findings from the early covariate; they are available from the first author on request.

Effect combination and masking strategy. In the case of all but the highest level interaction, exclusive masking was employed to discount any voxels where there were higher order effects, thresholded at $P < 0.05$ uncorrected (e.g., age group and drug effects were exclusively masked with interactions of age group × drug and interactions involving drug × Pr). To assess effects common to both age groups, however, a strict criterion was adopted that the effect should be reliable in *both* groups at $P < 0.001$, uncorrected. This was implemented by inclusively masking t-statistic maps from the young with those from the old. When reporting masked contrasts, the Z values refer to the outcome of the masked contrast only.

Results

Behavioral Findings

Study Phase

The stimulus attribute decision tasks were performed with an average accuracy of 90% and 89% (SDs = 7% and 8%) by young and older subjects, respectively. There were no reliable effects of age group or drug on the proportion of correct responses, and no effect of these factors nor of SM on response times (RTs; means in young and old = 1130 and 1148 ms, SDs = 276 and 148 ms; performance at study also did not differ between the 2 study tasks: see online Supplementary Material).

Test Phase

Old/new item discrimination. Memory test performance is summarized in Figure 1 and the indices used are described in the Materials and Methods. There was a reliable main effect of drug on the ability to discriminate old from new items ($F_{2.0,48.8} = 4.20$, $P < 0.05$), item recognition increasing with increasing D2-like stimulation across both groups. However, neither drug effect was individually significant against Placebo (for Sulpiride versus Placebo, $t(26) = 1.79$, $0.05 < P < 0.1$; for Bromocriptine versus Placebo, $t(26) < 1$). Also, although the drug × age group interaction was not significant ($F_{2.0,48.8} = 1.49$), the main effect of drug was only reliable in the old when the groups were considered separately. Given the imaging results, further analyses also tested for drug effects on memory discrimination that varied according to individual baseline discrimination performance: a correlation of the discrimination index Pr on Placebo with the linear increase in Pr across drug conditions yielded no significant
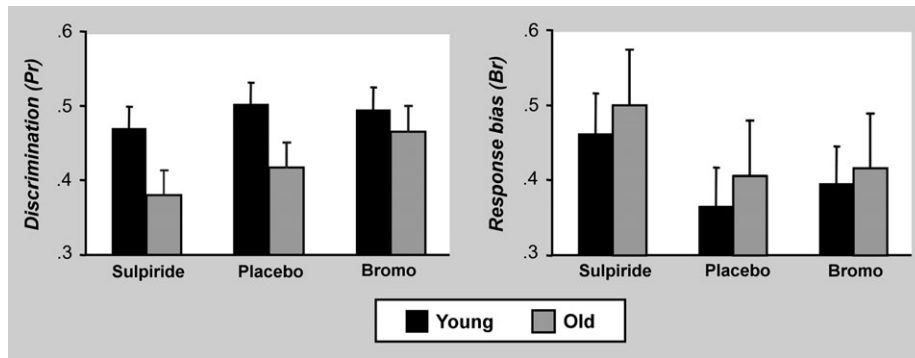
Figure 1. Plots of behavioral data showing mean discrimination of old from new items (indexed by Pr) and mean response bias (indexed by Br) according to age group and drug condition. For details of measures, see Materials and Methods: Behavioral procedures. Error bars represent the standard errors of the mean.

results for either age group or between age groups (all $F < 1$). Analyses of response bias, test phase RTs, and differences between the 2 study tasks on Pr are given in the online Supplementary Material: none of these showed any evidence of memory-specific drug effects (see also Supplementary Table S1).

Recollection and familiarity. There were no reliable effects of age group or drug on the level and relative proportions of memory based upon recollection and familiarity, although recollection was somewhat lower in the older group (mean corrected R proportion = 0.36/SE 0.03 and 0.28/0.04 for young and old; see online Supplementary Table S1 for full details). However, on Sulpiride, subjects were more likely to classify items as "known" regardless of whether they were old or new, in keeping with Sulpiride's effect on response criterion (for main effect of drug, $F_{1.6,38.9} = 3.95$, $P < 0.05$; see Table S1). The orienting task used at study also affected the level of recollection, as for overall recognition, but here there was only a trend to a group difference, which reflected a tendency for group differences in the probability of later recollection to be greater for the deep than for the shallow task (for main effect of deep vs. shallow, $F_{1,25} = 204.66$, $P < 0.001$; for interaction, $F_{1,25} = 3.23$, $0.05 < P < 0.1$; mean R discrimination = 0.43 for deep study task, and 0.21 for shallow (for young 0.48 deep/SE 0.03 and 0.23/0.04 for shallow; for old 0.38/0.04 and 0.19/0.04]).

Other Measures

Subjects' subjective reports suggested that they could not consciously determine when they had received a drug. The Apathy analog rating scales and the Judgment of Line Orientation tests also did not reveal any reliable effects of the drugs (see online Supplementary Material).

fMRI Findings

We compared activity elicited by subsequently recollected (R) items with that elicited by subsequently forgotten (F) items, that is, those later afforded "remember" versus "new" judgments. This comparison (later remembered vs. later forgotten) will be referred to as SM-related activity. The analysis strategy is described in full in Materials and Methods: fMRI scanning and data analysis. In brief, we first examined drug-free effects in the 2 age groups, under Placebo, and then went on to characterize the drug effects and the effects across the 3 drug conditions. These analyses were conducted using an ANCOVA model of SM-related activity. Under Placebo, we analyzed baseline age-related differences (main effect of age group) and commonalities (overlapping effects in young and old) in SM-related activity. We tested for the following effects across the 3 drug conditions: drug modulations that differed according to age (age group × drug interactions), commonalities between the groups in drug modulations of SM-related activity (overlapping drug main effects in young and old), group differences in SM-related activity across drug conditions (main effect of group), and activity common to both age groups (overlapping effects in young and old across drug conditions). Importantly, higher order group differences and commonalities involving the additional factor of Pr were also assessed in both sets of analyses. We describe the higher order effects first. For clarity with respect to the direction of SM-related activity, the findings are reported in terms of *SM effects*—greater activity associated with items later recollected than forgotten (R > F)—and *subsequent forgetting effects*—greater activity for items later forgotten than recollected (R < F). All analyses were performed within all regions of interest within medial temporal lobes, lateral PFC, striatum and midbrain (no reliable effects were seen in the midbrain ROI at the threshold set).

Analyses of the Placebo Condition

Group differences in Placebo condition effects. There were group differences in activity predicting SM in left posterior MTL, in anterior left inferior and middle frontal gyri, and in bilateral dorsal striatum (see Table 1 and Fig. 2). In general, these were crossover interactions, with SM effects in the young and subsequent forgetting effects in the old. Follow-up tests of simple effects indicated that the effects in the young were the more robust in most regions (see Table 1). In MTL, however, subsequent forgetting effects in the old were prominent. Interactions of group × Pr on Placebo were not significant.

Effects common to both age groups. No ROI showed either SM or subsequent forgetting effects common to both age groups. In addition, no ROI showed a reliable effect of Pr on SM-related activity that was common to both groups.

Follow-up analyses were done in the groups separately to clarify the pattern of findings, The forgoing section and Table 1 detail the main regions in which there were SM effects in the young and subsequent forgetting effects in the old, of those showing age group × SM interactions. It is also of interest that although the age group × SM interaction in left middle frontal gyrus (at $y = 21$) appeared mainly driven by SM effects in the

Table 1
Group differences in SM-related activity on Placebo. Regions showing a main effect of age group are shown (contiguous clusters of ≥5 voxels at $P < 0.001$, uncorrected)

Location (x, y, z)	Peak Z (n)	Region	Brodmann area	R > F significant in young group	R < F significant in old group
−15, 6, 24	4.16 (18)	Left body of caudate	—	P < 0.001	(P < 0.005)
18, 27, 0	3.50 (11)	Right head of caudate	—	P < 0.001	(P < 0.005)
−33, 6, 27	3.38 (7)	Left precentral gyrus	BA 6	P < 0.001	—
−30, −42, −6	3.33 (6)	Left posterior parahippocampal gyrus/hippocampus	BA 19/37/—	(P < 0.005)	P < 0.001
−39, 21, 24	3.25 (6)	Left middle frontal gyrus	BA 46	P < 0.001	—
−36, 33, −12	3.12 (6)	Left inferior frontal gyrus	BA 47	(P < 0.005)	—

Note: N refers to the number of significant voxels in each cluster; Z refers the Z statistic value for each peak or subpeak; and x, y, and z refer to distances in millimeter from the origin in MNI space (see Materials and Methods). Follow-up tests assessed SM (R > F) and subsequent forgetting (R < F) effects in the 2 groups; only those that yielded significant results are shown. For these, findings from comparisons using more lenient thresholds are also shown in brackets to indicate trends. **Indicates reliable at $P < 0.001$; *indicates reliable at $P < 0.005$
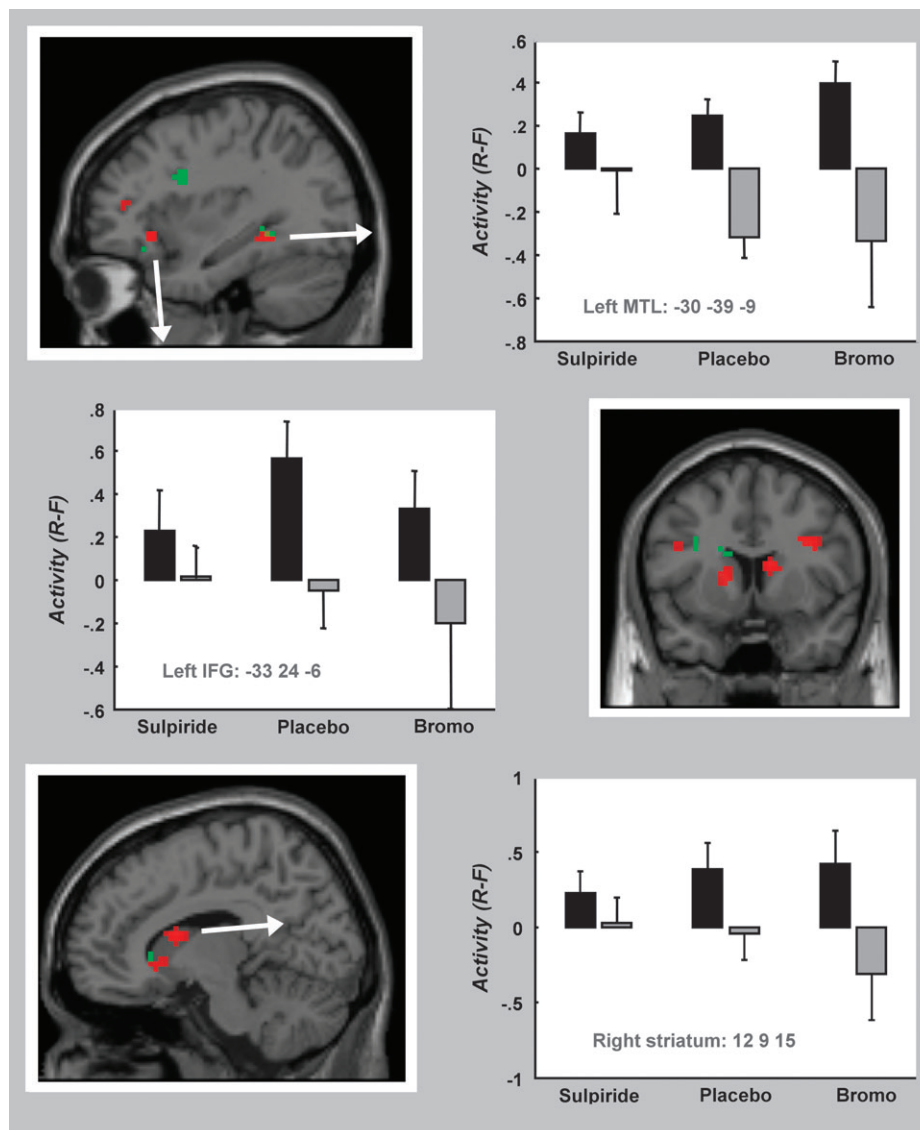

Figure 2. Cross-section images of group main effects under Placebo (green) and group × drug × Pr effects (red), with parameter estimate (R–F) plots, showing key regions in which both effects are present. The cross-sections shows significant clusters (at $P < 0.001$, uncorrected, cluster size ≥5), superimposed on the SPM5 canonical T_1 image (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). The plots shows the mean differences in the parameter estimates for the early covariate between remembered (R) and forgotten (F) items, across subjects for each age group and drug condition, at the peak voxel of the cluster indicated by the relevant white arrow. Error bars represent the standard error of this difference.

young, there was a subsequent forgetting effect in the old in a region only just anterior to this (32 voxels, peak $Z = 3.64$; $x = -27$, $y = 36$, $z = 18$). Most notably, in the reverse contrasts, the older group did not show any reliable activity positively predicting SM in the ROIs at the threshold set. In the young, a single area in right inferior frontal gyrus manifested subsequent forgetting effects (20 voxels, peak $Z = 3.98$; $x = 48$, $y = 42$, $z = -3$). This overlapped with the interaction of age group × drug (see below).

Analyses of Drug Effects

Group and individual differences in drug effects. The most striking drug modulations of SM effects within the ROIs not only differed between age groups, but also varied according to individuals' level of recognition memory, as indexed by Pr. These interactions of age group × drug × Pr for SM measures were elicited in left posterior MTL, left inferior frontal gyrus, left anterior PFC, bilateral posterior lateral frontal cortex and bilateral dorsal striatum, and are summarized in Table 2 and Figure 2. In the older group, the baseline subsequent forgetting effects seen on Placebo became more pronounced on Bromocriptine in the poorer performers. In the young, if anything, poorer individual performance tended to be associated with more pronounced SM effects in frontostriatal regions. As on Placebo, the young consistently showed SM rather than subsequent forgetting effects in these regions. Follow-up tests indicated that Bromocriptine was the main determinant of the group differences; however, the overall picture suggests a contribution of both agonist and antagonist (see Table 2). There were differential linear trends in the 2 age groups in the drug effects on the association between SM measures and memory performance (linear drug × Pr interactions). Positive linear trends in the older group indicated that D2 stimulation increased the *negative* association between memory discrimination performance and the magnitude of subsequent *forgetting* effects. In the young, drug × Pr effects were not reliable at the threshold set, although there were negative linear trends (see Table 2). The predominance of agonist effects in the old and antagonist effects in the young may reflect a lower baseline level of DA stimulation in the older group, consistent with "inverted U" models of dopamine function (see Williams and Castner 2006).

The most striking interaction of age group × drug × Pr was in left posterior MTL. This cluster also overlapped that showing the group × SM interaction under Placebo. However, inspection of the data supporting this correlation between behavior and SM-related activity suggested that it could have been influenced by 2 outlier older subjects (see Fig. 3). One had a low Pr due to a high rate of "Know" false alarms, and another a particularly marked drug effect (using an outlier criterion of 2 standard deviations from the mean). Using this conservative procedure, re-analysis of the data ($N = 15$, 10) still gave rise to a reliable drug × group × Pr interaction in the posterior L MTL region (19 voxels, peak $Z = 4.26$; $x = -27$, $y = -42$, $z = -6$), with an additional voxel in the posterior right PFC region ($x = 30$, $y = 6$, $z = 30$). Analyses of a subset of subjects with the order of drug administration exactly matched between age groups are also given in the Supplementary Material.

Average group differences in drug effects. The contrast of the interaction of age group × drug revealed a single region in right inferior prefrontal gyrus (RIFG; 16 voxels, peak $Z = 3.77$, $x = 39$, $y = 27$, $z = 6$). Effects in this region are illustrated in Figure 4, which suggests a reversal by S of a baseline pattern of crossover group differences: on P, the young showed SM effects and the old subsequent forgetting effects (see ANCOVA under P, below for similar effects in other regions). Follow-up analyses comparing each drug condition with P confirmed a drug × group interaction for S versus P within this regions, but none for P versus B. Tests in the different drug conditions separately also showed a group × SM interaction on S which overlapped the group × drug effect. Unlike on Placebo, SM-related activity in the old on S took the form of a SM, as opposed to a subsequent forgetting, effect (the effect in the young was not significant). The simple effect of S versus P was not reliable in the old group separately, but was present in the young at a more lenient threshold ($P < 0.005$, uncorrected).

Drug effects common to both age groups. There were no significant drug effects common to both age groups.

Discussion

We sought to identify process- and region-specific changes in brain responses to episodic encoding in healthy ageing, and

Table 2

Group and individual differences in drug modulations of SM-related activity

Location (x, y, z)	Peak Z (n)	Region	Brodmann area	Follow-up contrasts significant for group differences	Follow-up contrasts significant in young group	Follow-up contrasts significant in old group
−30, −39, −9	4.39 (26)	Left posterior parahippocampal gyrus/hippocampus	BA 37/19/—	O > Y lin	—	Overall, Pos lin
33, 6, 27	4.31 (31)	Right precentral/inferior frontal gyrus	BA 6/44	O > Y lin, B vs. P	(Neg lin at 0.005)	Overall, B vs. P
12, 9, 15	4.21 (33)	Right caudate body	—	O > Y lin, B vs. P	(Neg lin at 0.005)	Overall, Pos lin, B vs. P
−15, 15, 9	4.11 (71)	Left caudate body	—	O > Y lin, B vs. P	—	Overall, Pos lin, B vs. P
15, 21, −3	3.75 (17)	Right caudate head	—	O > Y lin	(Neg lin at 0.005)	Overall, Pos lin
−33, 24, −6	3.70 (13)	Left inferior frontal gyrus (anterior)	BA 47	O > Y lin, B vs. P	—	Overall, Pos lin
−42, 3, 27	3.60 (19)	Left inferior frontal gyrus	BA 9	O > Y lin, B vs. P	—	B vs. P
−33, 42, 12	3.29 (5)	Right anterior middle frontal gyrus	BA 10	B vs. P	(B vs. P at 0.01)	(B vs. P at 0.01)

Note: Regions showing an interaction of age group × drug × Pr are shown (contiguous clusters of ≥5 voxels at $P < 0.001$, uncorrected, see Methods). N refers to the number of significant voxels in each cluster; Z refers to the Z statistic value for each peak or subpeak; and x, y, and z refer to distances in millimeter from the origin in MNI space (see Materials and Methods). The results of follow-up contrasts are also shown. These tested interactions of drug × Pr in the 2 groups together for each drug versus Placebo separately, that is, Sulpiride versus Placebo, and Bromocriptine versus Placebo (S vs. P and B vs. P). Further tests assessed positive and negative linear forms of this contrast in the groups separately, and group differences in these effects: Pos lin and Neg lin indicate weightings of the Pr covariate with [−1 0 1] and [1 0 −1] respectively across the Sulpiride, Placebo, and Bromocriptine conditions, and O > Y indicates a linear effect that is more positive in the old than in the young (see text in Results section and Materials and Methods). For the follow-up tests, findings from comparisons using more lenient thresholds are shown in brackets to indicate trends.
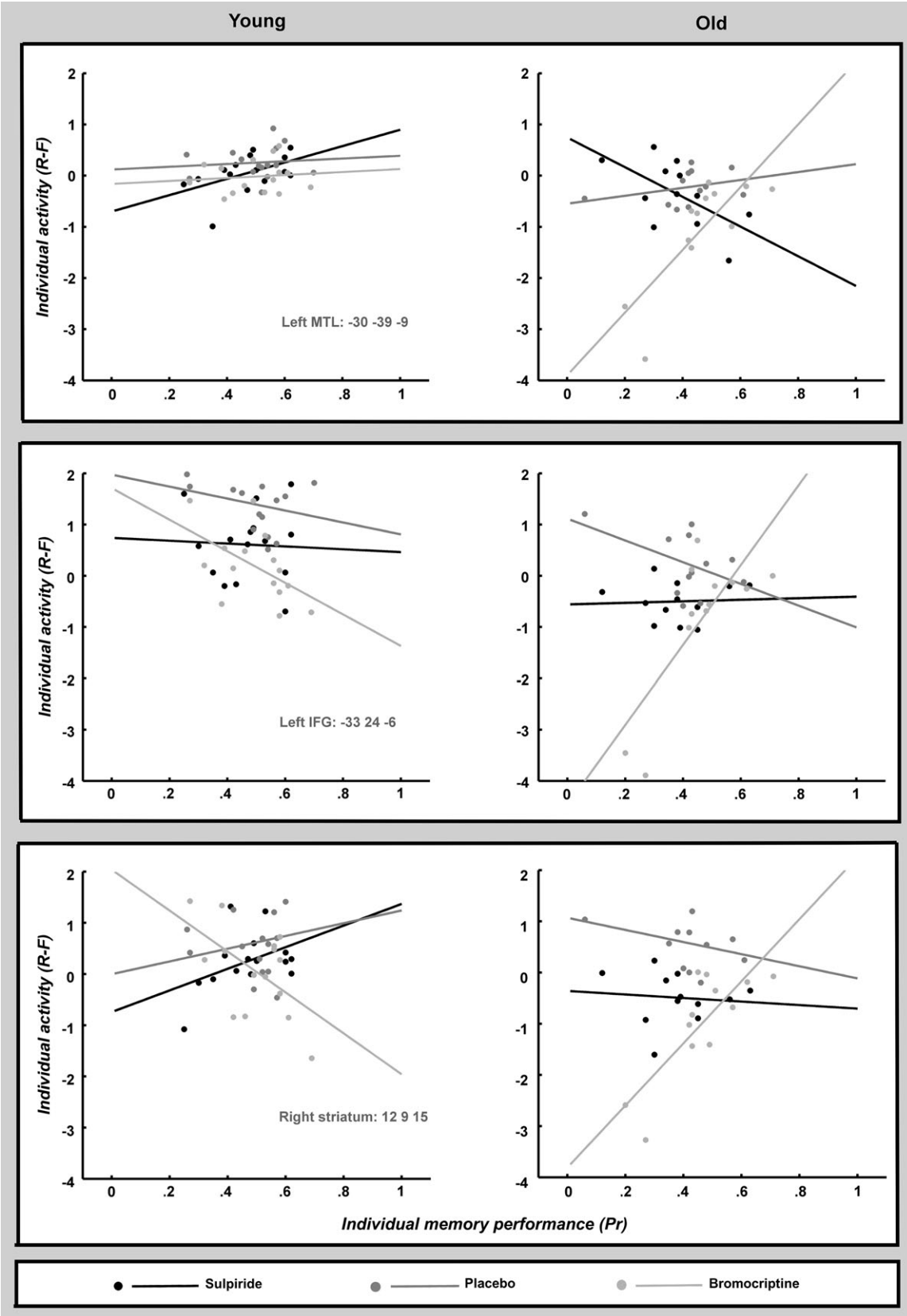
Figure 3. Plots of parameter estimates (R–F) against memory performance (Pr) in regions showing an interaction of age group × drug × Pr. Point plots with fitted regression lines illustrate activity–performance relationships for peak voxels in MTL, left inferior PFC, and striatum. The x-axis shows Pr for each subject and drug condition; the y-axis shows the differences in the parameter estimates for the early covariate between remembered (R) and forgotten (F) items. The point plots were generated from individual values extracted from the peak voxels for each subject, and adjusted for confounding effects of Br using the regress function in MATLAB 6.5 (http://www.mathworks.com/), and plotted against Pr. The best fit lines to indicate the linear effects of drug at each voxel were computed separately, also using the regress function, and are plotted on the same axes.
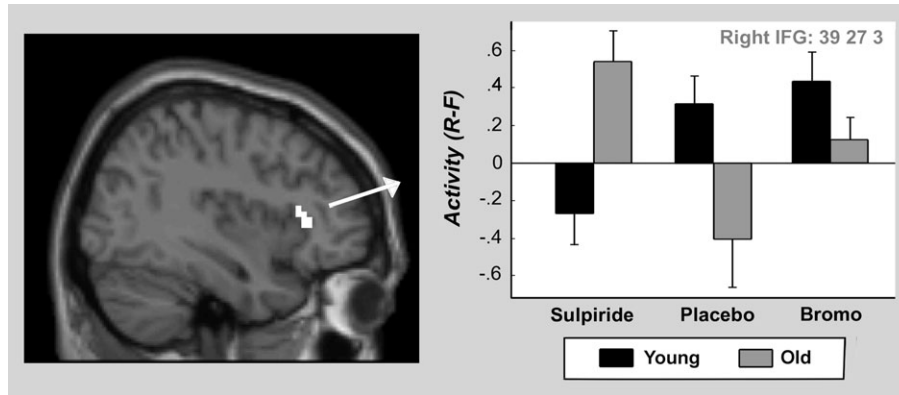
Figure 4. Cross-section image of age group × drug interaction in right PFC, with parameter estimate (R–F) plot. For details of sections and plots, see legend to Figure 2.

to assess the impact of a dopaminergic manipulation on these age-related changes. We made a number of important observations. Key regions—medial temporal lobes, striatum, and PFC—showed age- and drug-related effects on brain responses to episodic encoding. In the old, unlike in the young, activity in these regions was not associated with subsequent successful remembering. Dopaminergic drug effects differed across groups in a network of regions including MTL, and these group differences varied according to individual performance differences among older subjects. In these regions, Bromocriptine accentuated subsequent forgetting effects in older subjects, having the greatest impact in individuals with the poorest recognition memory. Sulpiride, on the other hand, was associated with an attenuation of subsequent forgetting effects. In younger subjects, Bromocriptine accentuated SM effects and Sulpiride attenuated or reversed them, notably in right PFC. The findings demonstrate age-related changes in the neural underpinnings of encoding. They further show that the system is differentially sensitive to dopaminergic perturbation in old and young subjects. The accentuation by Bromocriptine of age-related differences in SM effects does not support our specific predictions regarding neural inefficiency. However, critically, many of these effects are correlated with underlying memory performance: older individuals with the lowest levels of performance show the most pronounced drug effects. This is in keeping with our predictions. Below, we consider these findings in more detail, focusing on medial temporal and frontostriatal patterns of activity.

Drug Effects in Medial Temporal Lobes

In the young, words later remembered elicited greater activity in MTL than those later forgotten. SM effects are thought to reflect processing that directly or indirectly promotes memory formation (Rugg et al. 2002). The reverse was seen in the old. The fact that our earlier study and some others have shown age-invariant SM effects within MTL suggests that these age-related differences may be modulated by factors such as encoding task, and we consider this further below (Morcom et al. 2003; Gutchess et al. 2005; Dennis et al. 2007b). But why might activity become detrimental to performance? Theoretical accounts of hippocampal function emphasize the importance of pattern separation mechanisms for memory trace encoding (Marr 1982; O'Reilly and McClelland 1994; Treves and Rolls 1994). Thus, MTL-mediated processes may endow memory traces with a uniqueness that facilitates subsequent recall. If

such processes are suboptimal in the old, undifferentiated memory traces could be formed, with retrieval failure due to representational overlap and a paradoxical detrimental effect of MTL involvement at the encoding stage (Wagner and Davachi 2001). According to Gluck and Myers (1993), MTL may contribute to dual and opposing effects: "redundancy compression," which inhibits stimulus-specific memory, and "predictive differentiation," which promotes such memory. This might explain why activity in the same region appeared beneficial in one group but detrimental in the other. The enhancement by Bromocriptine of subsequent forgetting effects, in poorer performing older subjects, suggests that D2 stimulation potentiated this detrimental tendency. In keeping with this view, aging animals are thought to fail "…to encode new contexts with sufficient distinction from already stored memories" (Wilson et al. 2006). Sulpiride, on the other hand, seems to dissociate MTL activity from subsequent behavioral sequelae in both groups. A reduction in the distinctiveness of neural representations has also been reproduced in network models which perform similarly to older adults on associative memory tests. These simulate a deficiency in neuromodulation and reduction in neural signal-to-noise (Servan-Schreiber et al. 1990; Li et al. 2005); see also (Abrams and Taylor 1987; Rypma and D'Esposito 2000; Li et al. 2001).

The drug effects within MTL may reflect dopaminergic inhibition of the direct cortical pathway to CA1 (Otmakhova and Lisman 1998) and effects on signaling in entorhinal cortex (Pralong and Jones 1993; Caruana et al. 2006). The direction of these effects may be sensitive to the level of stimulation as well as to pre- and postsynaptic factors (Caruana et al. 2006). This pathway is thought to regulate the gating of sensory input to the hippocampus, and to interact with novelty detection mechanisms, and so may impact on the effectiveness with which sensory information is incorporated into a new memory trace (Lisman and Otmakhova 2001).

Drug Effects in Striatum and PFC

The interactions of drug with age group and SM in PFC and striatum were similar in form to those observed in MTL. Bromocriptine tended to enhance SM effects in the young, and subsequent forgetting effects in the poorer performing older subjects. Thus, as in MTL, increasing D2 stimulation increased the coupling between activity and subsequent behavior in a way that depended on individual differences amongst the older subjects. The pattern of baseline age differences also

paralleled those in MTL, but SM effects in the young, rather than subsequent forgetting effects in the old, were prominent. left inferior frontal gyrus (LIFG) is known to be critical for encoding in young adults (Wagner et al. 1999). However, previous studies comparing SM effects in LIFG across age groups have not shown the differences observed here (Morcom et al. 2003; Gutchess et al. 2005; Dennis et al. 2007b). These baseline age-related differences are considered further below. SM effects within striatum are not commonly examined, but PFC and striatum form parts of a circuit (Voorn et al. 2004; Leh et al. 2007) known to support episodic encoding via top-down inputs to MTL (Wagner et al. 1999; Fernandez and Tendolkar 2001; Addis and McAndrews 2006; Summerfield et al. 2006; Kopell and Greenberg 2008). Thus the parallel pattern of findings in striatum and PFC is perhaps not surprising. A parsimonious interpretation of the effects of dopamine manipulation on MTL is therefore that it is secondary to direct actions on frontostriatal circuitry, most likely via striatal D2-like receptors (see also Goto and Grace 2008). Consistent with this, imaging of working memory in the young have shown D2-like drug effects in striatum (see Mehta et al. 2003). Computational models and animal studies implicate striatal DA in the maintenance of a balance between updating working memory representations and stabilizing them against noise (Crofts et al. 2001; Frank et al. 2001; Gruber et al. 2006; Hazy et al. 2006). A somewhat speculative possibility is that by modifying representational stability, DA may also influence whether activity in frontostriatal circuits supports or hinders the formation of long-term memory traces. This may be analogous to, or contribute to, undifferentiated memory trace formation in MTL (see above). Recent evidence suggests that these drugs' actions in striatum may be primarily presynaptic (Frank et al. 2006; Mehta et al. 2008), but the locus of the difference between age groups is not necessarily the same and presumably relates to the interaction of the drugs with baseline differences in signaling. An alternative possibility is that frontostriatal drug effects were secondary to actions within MTL that reduced the efficacy of top-down inputs, giving rise to parallel drug effects "upstream." This could also, as noted, account for the baseline subsequent forgetting effects in the old seen in MTL.

The interaction of drug with age group in right inferior frontal gyrus (RIFG) was different in that it was predominantly an effect of Sulpiride and driven mainly by drug effects in the young. In contrast to the LIFG, the RIFG is thought to be important in nonverbal aspects of encoding (Brewer et al. 1998; Golby et al. 2001). Thus, reduced D2 signaling in the young apparently interfered with this region's contribution to encoding. This is in keeping with the tendency of D2-blockade in other regions to reduce their apparent impact on later remembering.

Baseline Age-Related Differences

The baseline group differences in SM and forgetting effects differed in key respects from expectation based on earlier data. These differences are themselves of potential interest in understanding age-related memory decline. The majority of prior studies have reported age-invariant SM effects in LIFG (Morcom et al. 2003; Gutchess et al. 2005; Dennis et al. 2007a; Miller et al. 2008; Stevens et al. 2008; Duverne et al. 2009). However a reduction in SM effects in this region in older adults encoding faces has been observed by Dennis et al. (2008) (see also Logan et al. 2002). Findings within the MTL have been less consistent, with age-invariance in some studies (Morcom et al. 2003; Miller et al. 2008; Stevens et al. 2008; Duverne et al. 2009), but larger SM effects in the young in others (Gutchess et al. 2005; Dennis et al. 2007b, 2008). Only one earlier study showed MTL subsequent forgetting (R < F) effects specific to an older group; that of Gutchess et al. (2005). Their Figure 4 indicates that, as here, an interaction of group × SM reflected SM effects in the young, and subsequent forgetting effects in the old, in bilateral regions slightly posterior and medial to the L sided cluster reported here ($x = \pm21$ to 24; $y = -48$ to -51). In 3 separate studies, Dennis et al. (2007a,b, 2008) have also reported an age-related reduction in SM effects in similar L-sided posterior MTL regions (negative SM effects were not analyzed, thus could have been present).

A possible contribution to this cross-study variability within MTL, and to the present baseline group differences, is the use of shallow (nonsemantic) as opposed to deep (semantic) study tasks. An exploratory analysis (see online Supplementary Material) of SM effects by orienting task suggested that SM effects were positive in both age groups for the living/nonliving task in both MTL and LIFG, and reversed in MTL only for the syllable (shallow) task. The stimuli and procedure used by Gutchess et al. (2005) differed from ours in several respects but this study, unlike most earlier ones, employed a shallow visual orienting task (with stimuli being scenes) at study. Dennis et al. (2008) also used N-back matching of faces, and found group differences in LIFG; noted above. This supports the possibility that the age-related differences in the effectiveness with which MTL, and perhaps LIFG, mechanisms were engaged reflected the nonsemantic orienting task. As already noted, active but ineffective processing at the time of encoding may engender subsequent forgetting effects. We assume, in keeping with the depth of processing principle (Craik and Lockhart 1972) that elaborative, meaningful processing in general is more likely to lead to effective pattern separation and therefore retrievable memory traces. It has been suggested that such processing is less likely spontaneously to be engaged with aging (Craik 1983; Logan et al. 2002; Naveh-Benjamin et al. 2005). However another possibility is that with a reduction in the efficiency of MTL pattern separation, a *greater* specificity of meaningful processing is required in older adults to achieve the same level of encoding as the young. We therefore hypothesize that in a shallow study task, where meaningful links between items and context are weak and incidental, processing items in the orienting task may become detrimental to episodic encoding. Clearly, further data are required to resolve this issue but this hypothesis offers a possible explanation for the baseline findings that is also consistent with the drug effects we report.

Drug Effects on Other Processes

So far, we have considered only drug actions on episodic encoding. However, drug effects on other aspects of processing engaged during the orienting task, but not specifically involved with encoding, could have impacted the SM modulations we observed.

Another aspect of the encoding task procedure that differed from previous studies (e.g., Morcom et al. 2003) was the use of separate runs of trials for 2 different study tasks. Irrespective of whether the subsequent forgetting effects in the older group were truly shallow task-specific, it is possible that the groups

differed in the state-related effects associated with these runs of trials, and that there was differential modulation of these effects according to age and drug. Two prior studies in young adults have shown state-related encoding effects in LIPFC that differ in kind or direction from item-related effects (Otten et al. 2002; Reynolds et al. 2004). In a study using semantic encoding of words, Dennis et al. (2007b) examined sustained as well as item-related activity that predicted SM, and found that this was reduced in older adults in posterior and dorsolateral PFC relative to the young. Such a group difference might have contributed to the under-recruitment of PFC here (and in other studies that employed only a single encoding task); however, it was not seen in LIFG nor in MTL, and subsequent forgetting effects were not assessed. Further investigations comparing task-set related effects across age groups are therefore needed to resolve this issue.

It is also possible that the encoding-related effects were secondary to drug effects at the time of retrieval. If recollection were impaired by a drug, only the most strongly encoded items might later be "Remembered." If so, the differential activity between these and forgotten items—SM effects—could be enhanced. It is possible that, in addition to or instead of acting on encoding, Bromocriptine impaired later recollection, and Sulpiride tended to enhance it, in both age groups. Given the direction of the drug effects on memory performance, this is less likely than an effect on encoding. However, further studies employing memory stage-specific pharmacological interventions are required in order to confirm this. Effects on either or both stages of episodic memory are of substantial interest in furthering understanding of age-related memory decline.

Drug Effects on Brain and Behavior

The importance of the drug effect on old/new item discrimination across both age groups is difficult to assess, and appeared to be driven mainly by an effect in the older group. This finding differs from that in a group of comparable age in a pilot behavioral study (unpublished data).

There have been other recent findings of variable dopaminergic drug effects on performance in long-term memory (as well as other) tasks in humans. In young adults, sustained administration of a D1/D2-like agonist (pergolide) has been shown to impair associative learning (Breitenstein et al. 2006), whilst in another, levodopa (L-dopa) improved new word learning (Knecht et al. 2004), and in a third, bromocriptine improved spatial delayed learning (Mehta et al. 2001); see also (Mehta et al. 2005, 2008; Mehta and Riedel 2006). In older animals and adults, DA agonist effects can be similar to those in the young, but are sometimes attenuated, consistent with a relative insensitivity to postsynaptic effects (Arnsten et al. 1994, 1995; Cai and Arnsten 1997; Turner et al. 2003; Peretti et al. 2004). Clearly, future work is needed on the reasons for this variability: however, the present findings, as well as work on genetic polymorphisms such as catechol-O-methyltransferase (e.g., Bertolino et al. 2006), suggest that individual differences in DA transmission are likely to play a critical role in the young and in aging.

In the fMRI data, but not the behavioral data, group differences rather than commonalities predominated: within the ROIs, the main effect of the drugs on memory was accompanied by age-related differences in their effects on neural activity. Thus, the relationship between drug effects on brain activity and behavior appears to differ qualitatively in the 2 age groups. The memory improvement may have reflected a separate age-invariant drug effect, linked for example to an increase in activity in unexamined regions. Alternatively, the apparently opposite neural effects in the 2 groups may both have been associated with an increase in overall encoding efficacy. Bromocriptine tended to enhance the group differences on Placebo, inducing tighter coupling between regional activity and SM in both age groups (SM and forgetting effects). Potentially, an interaction of drug with age group could reflect a modulation of the strength of this coupling, as opposed to its direction. However, it seems implausible that encoding efficacy, and thus the effect on performance, would not depend on the direction of coupling. This would also be at odds with reversal of group differences in the direction of this coupling by Sulpiride in RIFG. Most importantly, an age-invariant mechanism for the principal fMRI and behavioral effects does not account for the dependence of the former on individual differences within the older group.

As the foregoing caveats suggest, the absence of clear cut behavioral effects of the drugs renders their neural effects more complex to interpret. However, these neural effects are themselves no less interpretable than behavioral effects, and indeed some potential confounds between brain activity and performance are avoided (Honey and Bullmore 2004; Wilkinson and Halligan 2004). Put more simply and generally, there are not prima facie reasons why an observed effect on one outcome variable (brain imaging) is less interpretable when there is no measurable effect on another outcome variable. Indeed, the existence of brain changes in the face of apparently unchanged behavioral observations is the basis for the notions of the value of endophenotypes. Of course, in order to account for age-related cognitive decline, age-related differences in brain activity must ultimately be connected to age-related changes in performance. The present link between the effects of the drugs on SM effects and individual differences in memory within the old group is critical in this regard and allows us to interpret the drug effects as a correlate of age-related memory decline.

DA, Aging, and Neural Efficiency

As already noted, the findings are consistent with some of our predictions but not others. Within RIFG, Sulpiride appeared to de-couple activity from later memory performance so that patterns of SM-related activity in the young resembled those in the old at baseline in RIFG and in LIFG. However, Sulpiride did not have parallel effects in LIFG, and thus did not consistently render activity in the young more like that in the old. Bromocriptine, conversely, was expected to render activity in the old more like that in the young, and we did not find evidence of this. If anything, it tended to enhance rather than attenuate the average group differences in neural activity. The implications of this for the notion of age-related neural inefficiency linked to DA depletion are mixed. The baseline group differences we observe appear to reflect MTL activity that gives rise to ineffective rather than effective encoding in the old (see Drug effects in medial temporal lobes). Importantly, this coupling between activity and ineffective memory encoding in the old was enhanced by D2 stimulation. This does not fit the prediction of an amelioration of age-related processing and neural impairment with dopaminergic stimulation. A possible mechanism for the Bromocriptine effects we

observe is an increased (relative) sensitivity to D2 presynaptic effects in aging, perhaps linked to postsynaptic receptor downregulation (see Drug effects on brain and behavior). Thus the present results present a more complex picture of dopamine aging than a simple reduction in neural efficiency. They do, however, do support the prediction of the dopamine aging hypothesis that the greatest effects of DA stimulation in the older group would be in those with the poorest memory—those with the greatest potential degree of underlying dopaminergic decline. This is considered further in the next section.

Individual Differences in Drug Effects

The fMRI findings indicate that dopamine perturbation alters the efficacy with which neural activity supports later remembering. Importantly, the age-related differences in the effects of this perturbation interacted with individual differences. Within the older group only, individual vulnerability to drug effects varied according to the level of memory performance: dopaminergic modulation of SM effects was most pronounced in those with the poorest memory. Individual differences in the neural substrates of episodic memory in older adults were unmasked by D2 receptor stimulation, which accentuated the differences in neural activity between the young, and the old poorer performers. Thus, critically, age-related variance in memory performance accounted for variance in specific encoding-related activity in key regions. This suggests that changes in DA systems with normal aging contribute to, or are a marker of, age-related memory decline.

Conclusions

Our findings indicate an association between the well-documented age-related decline in dopaminergic neurotransmission, and the decline in episodic memory. This goes beyond the established "correlative triad" between age, DA, and cognition (Backman et al. 2006) in 2 ways. First, it shows that in adults of different ages, DA perturbation differentially affects the brain activity that predicts whether information will later be remembered or forgotten. Second, it identifies a link between dopamine, memory networks, and performance variability amongst older adults. Similar effects across a network of medial temporal and frontostriatal regions are consistent with several possible underlying mechanisms. A speculative conclusion, and a hypothesis to be tested in future studies, is that changes in DA signaling mediate an impairment of distinct memory trace formation in the aging hippocampus. It will be critical to establish the extent to which these age-related neuromodulatory changes impact on other cognitive processes, and the extent to which they are specific to dopamine systems. On the basis of the present data, however, it is clear that age-related changes in dopaminergic neuromodulation are important and relevant to memory function.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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