Mesolimbic Novelty Processing in Older Adults

Normal aging is associated with neuronal loss in the dopaminergic midbrain (substantia nigra/ventral tegmental area, SN/VTA), a region that has recently been implicated in processing novel stimuli as part of a mesolimbic network including the hippocampus. Here, we quantified age-related structural degeneration of the mesolimbic system using magnetization transfer ratio (MTR) and correlated it with mesolimbic hemodynamic responses (HRs) to stimulus novelty. Twenty-one healthy older adults between 55 and 77 years performed a visual oddball paradigm allowing to distinguish mesolimbic HRs to novelty from rareness, negative emotional valence, and targetness using functional magnetic resonance imaging (fMRI). The HRs in the right SN/VTA and the right hippocampus to novelty were positively correlated both with the SN/VTA MTR and hippocampus MTR but not amygdala MTR. However, the HR of the amygdala to negative emotional valence correlated with the amygdala MTR but not with the MTR in SN/VTA or the hippocampus. The results establish a structure-function relationship in support of a hippocampal-SN/VTA loop of mesolimbic novelty processing by showing that the hemodynamic activation in SN/VTA and hippocampus for novelty is selectively affected by age-related degeneration of these structures.

Keywords: fMRI, hippocampus, mesolimbic system, novelty, substantia nigra/VTA

Introduction

There is converging evidence that dopamine plays a role not only in reinforcement learning but also in hippocampus-dependent episodic memory formation (Lisman and Grace 2005). In animals, dopamine promotes hippocampal long-term potentiation (Otmakhova and Lisman 1996; Li et al. 2003; Lemon and Manahan-Vaughan 2006) and long-term depression (Lemon and Manahan-Vaughan 2006) in area CA1 and improves hippocampus-dependent learning (Gasbarri et al. 1996; Bach et al. 1999; Lemon and Manahan-Vaughan 2006). Intrahippocampal application of dopaminergic agents (such as amphetamine) improves spatial memory in water maze tasks (Packard et al. 1994). Intraventricular injections of selective dopamine D1/D5 receptor antagonists lead to an impaired habituation of exploratory behavior when animals are reexposed to an initially novel environment (Lemon and Manahan-Vaughan 2006). In humans, pathological alterations in the dopaminergic system can be associated with memory deficits (Backman et al. 2000).

Functional anatomical evidence for the role of dopaminergic midbrain in episodic encoding comes from recent functional magnetic resonance imaging (fMRI) findings. Reward-related activation of the substantia nigra/ventral tegmental area (SN/VTA), a region where mesolimbic dopaminergic neuromodulation originates, is associated with improved hippocampus-dependent long-term memory formation and possibly consolidation (Wittmann et al. 2005; Adcock et al. 2006). Encoding-related midbrain activation also occurs independently of reward (Schott et al. 2006). The anatomical inference that this functional response of the SN/VTA is related to dopaminergic neurotransmission has been strengthened by recent genetic evidence showing that an encoding-related activation profile in this region is modulated by a functional variable number of tandem repeat polymorphism in the dopamine transporter (DAT1) gene (Schott et al. 2006). It has been suggested that the functional relationship between SN/VTA and the hippocampus is driven by stimulus novelty (Lisman and Grace 2005). Reward-coding dopaminergic midbrain neurons in animals also respond to novelty and habituate when stimuli become familiar without reinforcement (Schultz 1998). Using fMRI, we recently observed that also the human SN/VTA responds to stimulus novelty, while other forms of stimulus salience such as rareness (or contextual deviance), negative emotional valence, or targetness of familiar stimuli are less effective (Bunzeck and Duzel 2006). These data provide evidence in favor of a recent model suggesting a functional hippocampal-SN/VTA loop of novelty processing and encoding (Lisman and Grace 2005). They clarify that in the absence of apparent reward, activation of this loop is driven by stimulus novelty rather than other forms of stimulus salience. Together with the aforementioned evidence linking SN/VTA activity to successful encoding even in the absence of reward (Schott et al. 2006), these findings suggest a link between novelty responses in the hippocampal-SN/VTA and successful episodic memory formation.

Dopaminergic neurotransmission undergoes age-related changes that are relevant for episodic memory. Human autopsy data indicate a 3% age-related decrease in dopamine D1 (Seeman et al. 1987; Cortes et al. 1989; Rinne et al. 1990) and D2 receptors (Seeman et al. 1987) per decade. In the SN, there is a loss of dopaminergic neurons of 6% per decade in the medial portion and 2% in the lateral ventral portion (Fearnley and Lees 1991). In a correlation of antemortem fluorodopa positron emission tomography and postmortem neuronal cell counts in the SN, the neuronal loss was strictly proportional to the decrease in striatal dopamine availability (Snow et al. 1993). In older adults, deficits in episodic memory are better accounted for by D2 receptor binding than by age (Backman et al. 2000).

The hippocampal-SN/VTA model predicts that the response magnitude of the human SN/VTA and hippocampus to novelty in older adults should be jointly determined by the integrity within the SN/VTA and the hippocampus. In contrast, given that the amygdala does not directly contribute to hippocampal-SN/VTA novelty processing (Lisman and Grace 2005; Bunzeck and...
Duzel 2006), neither hippocampal nor SN/VTA novelty responses should be correlated with integrity within the amygdala. We tested this hypothesis using the same novelty paradigm that reliably elicited hemodynamic responses (HRs) in the SN/VTA and hippocampus in young adults (Bunzeck and Duzel 2006) in a group of healthy older adults. The structural integrity of the SN/VTA, hippocampus, and amygdala of all participants was measured using magnetization transfer imaging (MTI). Magnitization transfer in tissue relates to the exchange of proton magnetization between mobile water protons and protons that are immobilized by macromolecules (Wolff and Balaban 1989). To achieve MTI, the magnetization of macromolecular protons is partially saturated using appropriate off-resonance irradiation during standard proton density-weighted imaging. The interaction of these partially saturated macromolecular protons with the protons of mobile water in their direct surrounding attenuates the observed water signal in the images. This signal reduction depends on tissue properties such as the concentration, structure and/or chemistry of macromolecules, and water content as well as on image sequence parameters. If 2 consecutive measurements with (magnetization transfer [MT]) and without (no magnetization transfer [noMT]) magnetization transfer are acquired, the so-called magnetization transfer ratio (MTR) can be calculated on a voxel by voxel basis according to:

\[
\text{MTR} = \frac{\text{noMT} - \text{MT}}{\text{noMT}}.
\]

Hippocampal reductions of MTR have been reported in Alzheimer's disease (Hanyu, Asano, Iwamoto, et al. 2000; Hanyu, Asano, Kagure et al. 2002) and to a lesser extent in Lewy body dementia (Hanyu et al. 2005). The specific pathophysiology that underlies the hippocampal MTR reductions in these cases is not yet clear, but MTR reductions in patients with multiple sclerosis provide some clues. They suggest that reductions in MTR can be observed even if other imaging modalities, such as \(T_2\) and \(T_1\)-weighted imaging, show no abnormality making it particularly sensitive in detecting early abnormalities of normal-appearing tissues including white matter (Iannucci et al. 2000; Traboulsee et al. 2002; Audoin et al. 2004; Fernando et al. 2005) and cortical (Fernando et al. 2005) as well as deep gray matter (Audoin et al. 2004). MTR reductions in normal-appearing white matter might be due to astrocytic proliferation, perivascular inflammation, demyelination (Rademacher et al. 1999), and loss of axonal density (van Waesberghe et al. 1999) as well as vascular insults (Fazekas et al. 2005). MTR reductions in normal-appearing gray matter could be due to transsynaptic morphological abnormality secondary to afferent demyelinating lesions, and this possibility was recently supported by the finding that visual cortical MTR is reduced after an isolated incident of optic neuritis (Audoin et al. 2006). Interestingly, these patients also had reduced MTRs in the hippocampus, superior temporal gyrus, lenticular nuclei, and cerebellum, suggesting that MTR is sensitive to transsynaptic neuronal degeneration and cortical synaptic morphological changes in normal-appearing gray matter after remote afferent white matter lesions (Audoin et al. 2006).

MTR reductions have also been observed in the SN in patients with Parkinson's disease (PD) (Eckert et al. 2004; Seippi and Schocke 2005). The reason for SN MTR reduction in PD is not fully understood. PD is characterized by a selective depletion of dopaminergic, neuromelanin-containing neurons of the SN (pars compacta). Neuromelanin is the dark insoluble macromolecule that confers the black color to the SN. Neuronal loss as well as degradation of the neuromelanin macromolecule scaffolding (Fasano et al. 2006) could lead to a reduction of MTR. It is conceivable that both mechanisms could also lead to some reduction in MTR in apparently healthy older adults who do not have clinical signs of PD.

Finally, in healthy older adults, MTR of the cortex shows a negative correlation with age, and the age-related reduction is stronger than that of white matter, suggesting that MTR is sensitive to age-related changes in gray matter structures (Ge et al. 2002; Fazekas et al. 2005; Benedetti et al. 2006). However, data on the relationship between MTR and cognitive functioning in aging are scarce (e.g., Deary et al. 2006), and there are, to our knowledge, no data available on age-related changes of MTR in the mesolimbic system.

### Materials and Methods

#### Subjects

Twenty-one healthy, right-handed adults (age range: 55–77 years; mean = 65.3 years; standard deviation \(SD = 6.3\) years; 11 females and 10 males) were recruited for paid participation in the study, which was approved by the local ethics committee of the Otto-von-Guericke University of Magdeburg, Germany. According to self-report, none of the subjects had a history of neurological, psychiatric, or medical disorders or any current medical problems. All subjects scored within a normal range at the Geriatric Depression Scale (GDS [Yesavage JA et al. 1982]; mean GDS = 1.4, SD = 1.1; GDS \(\leq 4\) for all subjects; GDS ranges from 0–15; scores of higher than 11 indicate depression) and the Mini-Mental State Examination (MMSE [Folstein ME et al. 1983]; mean MMSE = 29.5, SD = 0.75; MMSE \(\geq 28\) for all subjects; MMSE ranges from 0–30; scores of lower than 25 are pathological). Further, all subjects had a normal blood pressure, and none of them was obese (mean body mass index = 27.1, SD = 5.1). Taken together, the self-reports, questionnaires, and medical examinations indicate age appropriate health. In order to assess whether there is age-related reduction in MTR, we included anatomical MRI data from 24 young adults (age range: 21–30 years; mean = 23.25 years; SD = 2.21 years; 16 females and 8 males). None of these young adults reported a history of neurological, psychiatric, or medical disorders or any current medical problems.

#### Experimental Design and Task

The older subjects completed 8 blocks of a modified visual oddball paradigm reported in Bunzeck and Duzel (2006). In each block, there were 80 standards, 10 target oddballs, 10 neutral trials, 10 emotional oddballs, and 10 novel oddballs, yielding a total of 80 stimuli per oddball class in the entire experiment (Fig. 1A). To avoid category-specific habituation and allow for generalization of our findings over different categories of visual stimuli, we presented pictures of male faces in one half of the session and pictures depicting outdoor scenes in the other half (counterbalanced across subjects). We chose these categories instead of abstract images to make stimulus exploration biologically relevant. The target stimulus was presented prior to the experimental session for 4.5 s, and subjects were required to make a simple button press to each of its subsequent appearance in the experiment using their right index finger. No motor responses were associated with any of the other stimulus classes. During the experiment, the pictures were presented for 500 ms followed by a white fixation cross on a gray background (gray value = 127) using an interstimulus interval (ISI) of 2.7 s. ISI was jittered between -300 and +300 ms (uniformly distributed). The order of stimuli was optimized for efficiency with regards to estimating stimulus-related HRs (Hinrichs et al. 2000).

All stimuli were taken from Bunzeck and Duzel (2006). The scalp hair and ears of faces were removed artificially, and the outdoor scenes did not include faces. All pictures were gray scaled and normalized to a mean gray value of 127 and an SD of 75. The pictures were projected onto the center of a screen, and the participants watched them through a mirror mounted on the head coil, subtending a visual angle of about 8°. The pictures were taken from different sources (neutral faces: "The Psychological Image Collection at Stirling," http://pics.psych.stir.ac.uk/; the negative emotional face: Ekman and Friesen 1976); and the negative emotional scene: the international affective picture system [Lang et al. 2000].

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The negative emotional scene picture depicted a negatively rated car accident (without any persons). The performance of target detection was assessed by analyzing the hit rate (correct responses to the target) and false alarm rate (responses to nontarget pictures).

**fMRI Methods**

As in Bunzeck and Duzel (2006), fMRI was performed on a 3-Tesla whole-body MRI system (Siemens Magnetom Trio, Erlangen, Germany) with echo planar imaging (EPI) using an 8-channel head coil. Acquisition protocol and data analysis were as in Bunzeck and Duzel (2006). Slices were acquired parallel to the brainstem in an odd–even interleaved direction. In the functional session, 24 T2* -weighted images (EPI sequence) per volume with blood oxygenation level-dependent contrast were obtained (matrix size: 64 × 64; 24 slices per volume; field of view [FoV]: 192 × 192 mm; spatial resolution: 3 × 3 × 3 mm; gap = 0.3 mm; time echo [TE] = 30 ms; time repetition [TR] = 1500 ms; and flip angle = 75°). These partial volumes covered the hippocampus, amygdala, and brainstem (including diencephalon, mesencephalon, pons, and medulla oblongata) and parts of the prefrontal cortex and cerebellum (Fig. 1B). For each older subject, functional data were acquired in 4 scanning sessions containing 440 volumes per session. Six additional volumes per session were acquired at the beginning of each functional session and subsequently discarded from the analysis to allow for steady-state magnetization. Images of each subject’s entire brain were collected by T1-weighted inversion recovery-prepared EPI (IR-EPI) sequences (matrix size: 64 × 64; 60 slices; FoV: 192 × 192 mm; spatial resolution: 3 × 3 × 3 mm; gap = 0.3 mm; TE = 33 ms; TI = 1450 ms; and TR = 15000 ms).

For both the young and older adults, a T1-weighted anatomical image (3D spoiled gradient-echo sequence; matrix size: 256 × 256; 124 slices; FoV: 250 × 250 mm; spatial resolution: 0.98 × 0.98 × 1.5 mm; TE = 8 ms; TR = 24 ms; and flip angle = 30°) and 2 proton density-weighted images (spin-echo sequence; matrix size: 256 × 256; 48 slices; FoV: 250 × 250 mm; spatial resolution: 0.98 × 0.98 × 3 mm; TE = 20 ms; and TR = 2600 ms) were acquired for each subject’s entire brain. One proton density-weighted image was acquired with a preparing saturation pulse (1200 Hz off-resonance, 16 ms) resulting in a MT image (Fig. 2A) and one was acquired without a preparing saturation pulse resulting in a noMT image (Fig. 2B). Subsequently, the MTR maps for each subject (Fig. 2C) were calculated according to the following equation: MTR = (noMT − MT)/noMT. To improve the identification of the SN/VTA and the red nucleus, the MT images of all 21 older subjects were spatially normalized to the standard Montreal Neurological Institute (MNI) template supplied by SPM99 and averaged across subjects to create an MT template of the older subjects group (Fig. 2D) and false alarm rate (responses to nontarget pictures).

The fMRI data were preprocessed and statistically analyzed as in Bunzeck and Duzel (2006) by the general linear model approach (Friston et al. 1994) using SPM99 software package (The Wellcome Department of Cognitive Neurology, University College, London, UK) and MATLAB 6.1 (The MathWorks, Inc., Natick, MA). All functional images were corrected for odd–even slice intensity differences with reference to the middle slice acquired in time, corrected for motion artifacts by realignment to the first volume, and spatially normalized to a standard T1-weighted statistical parametric map (SPM) template (Ashburner and Friston 1999). The normalization was realized by warping the subject’s anatomical IR-EPI to the SPM template and applying these parameters to the functional images. The images were...
resampled to $2 \times 2 \times 2$ mm and smoothed with an isotropic $4$-mm full-width half-maximum Gaussian kernel. The time-series fMRI data were high-pass filtered (cut-off $120$ s) and globally scaled over voxels and scans within each session. A statistical model for each subject was computed by applying a canonical response function and its temporal derivatives (Friston et al. 1998). To capture residual movement-related artifacts, 6 covariates per session were included (the 3 rigid body translations and 3 rotations determined from initial realignment). Regionally specific condition effects were tested by employing linear contrasts for each subject and different conditions. The resulting contrast images were submitted to a second-level random effects analysis. Here, one-sample t-tests were used on images obtained for each subject's volume set and different conditions. Given our a priori hypotheses, the results were thresholded at $P < 0.005$ (uncorrected) and $k = 3$ voxel. To verify the anatomical localization of SN/VTA and red nucleus responses, the activation maps were superimposed on the MT template. The anatomical localization of significant activations outside of the midbrain was assessed with reference to the standard stereotaxic atlas by superimposition of the SPM maps on a standard brain template (MNI) provided by SPM99.

To test the effects of structural changes of the mesolimbic system on novelty processing, hippocampus and amygdala were defined as regions of interest (ROI) using the individual $T_1$-weighted images, and the SN/VTA ROI was defined using the individual MT image. Subsequently, the ROIs were transferred to the individual MTR image, and the mean value (across voxels) of each ROI was extracted resulting in the SN/VTA MTR, hippocampus MTR, and amygdala MTR. In second-level simple regression analyses age, SN/VTA MTR, hippocampus MTR, and amygdala MTR were entered as regressors for the comparison of interest (e.g., novel oddballs vs. neutral oddballs).

Results

Behaviorally, 92.1% ($SD = 2.1$) of all targets were detected with a mean reaction time of 558 ms ($SD = 68$), and only 2.32% ($SD = 2.1$) of all other stimulus classes were falsely responded to as targets.

In a first fMRI-data analysis, the HRs within the midbrain were assessed for the different conditions of interest. Statistical parametric maps show that within the midbrain, stimulus novelty (novel oddballs vs. neutral oddballs) elicited a prominent response in the right SN/VTA (Fig. 3A-C, Supplementary Table S1A) but rareness per se (neutral oddballs vs. standards) and negative emotional valence (negative emotional oddballs vs. neutral oddballs) did not. At the statistical threshold of $P = 0.005$ (uncorrected) targetness (target oddballs vs. neutral oddballs) was associated with a strong activation across the entire midbrain including bilateral SN/VTA and bilateral red nucleus. However, at a threshold of $P = 0.05$ (corrected), only the left red nucleus (Fig. 3H) revealed activation (Supplementary Table S1D).

In the rest of the scanned volume, stimulus novelty was associated with a strong bilateral response in the hippocampus (Fig. 3D,E) and parahippocampal cortex (Fig. 3F and Supplementary Table S1A). Negative emotional valence (negative emotional oddballs vs. neutral oddballs) elicited activation in the right amygdala (Fig. 3F, and Supplementary Table S1B), rareness (neutral oddballs vs. standards) activated the left hippocampus (Fig. 3G) and bilateral parahippocampal cortex (Supplementary Table S1C), and targetness was associated with activation in many regions of the scanned partial volume including both hippocampi. However, at a more conservative threshold ($P = 0.05$, corrected), the activation pattern for targetness was restricted to the right cerebellum, left thalamus, bilateral inferior frontal cortex, bilateral basal ganglia, bilateral insula, right cingulate gyrus, and left postcentral gyrus (Supplementary Table S1D). Finally, novelty, rareness, and targetness but not negative emotional valence activated several regions within the prefrontal cortex (Supplementary Table S1).

Figure 3. fMRI activation patterns. Novelty processing (novel oddballs vs. neutral oddballs) was associated with activation in SN/VTA (A–C), hippocampus, and parahippocampal cortex (D, E). Negative emotional valence (negative emotional oddballs vs. neutral oddballs) activated the right amygdala (F) and rareness (neutral oddballs vs. standards) activated the hippocampus (G). Both negative emotional valence and rareness did not activate the SN/VTA. Targetness (target oddballs vs. neutral oddballs) activated the left red nucleus (H). Activation maps were superimposed on an MT template in (A, B, C, and H) (see Materials and Methods) and on the $T_1$-weighted standard MNI brain in (D, E, F, and G). Activation maps were thresholded at $P = 0.005$ (uncorrected) except from (H) were activations were thresholded at $P = 0.05$ (corrected).
**MTR Analysis**

A correlation analysis within the group of older adults (all reported correlations are two-tailed Pearson’s correlations unless stated otherwise) with the variables SN/VTA MTR, hippocampus MTR, amygdala MTR, and age revealed a positive correlation between SN/VTA MTR and hippocampus MTR ($r = 0.542, P = 0.011$) but no correlation between any other variables (Table 1). To further assess the effects of aging on structural changes, the SN/VTA MTR and hippocampus MTR were compared between the 24 young and 21 older adults using an independent sample’s $t$-test. There was a significant reduction of the SN/VTA MTR in older adults (two-tailed, degrees of freedom [df] = 43, $P = 0.008$, $T = 2.8$), while there was only a trend (two-tailed, df = 43, $P = 0.17$, $T = 1.4$) for hippocampus MTR reduction (Fig. 4).

In order to assess the relationship between novelty processing and structural integrity—as expressed by the MTR—and novelty processing and age, simple regression analyses for the novelty-contrast (‘novel oddballs vs. neutral oddballs’) were performed using the regressors SN/VTA MTR, hippocampus MTR, amygdala MTR, and age. SPMs revealed that the SN/VTA MTR correlated positively with the novelty HR in the SN/VTA (Fig. 5A) and the right hippocampus (Supplementary Table S2A), the hippocampus MTR correlated positively with the novelty HR in the right hippocampus (Fig. 5F) and Supplementary Table S2B), and age was negatively correlated with the novelty HR in the right hippocampus (Supplementary Table S2C). There was no correlation between the amygdala MTR and novelty HR in either the hippocampus or SN/VTA (Supplementary Table S2D).

A closer examination of the peak voxel in the SN/VTA (Fig. 5A) ($x, y, z = 0, -14, -12$) that exhibited a correlation between novelty HR and SN/VTA MTR and the peak voxel in the hippocampus (Fig. 5F) ($10, -2, 24$) that exhibited a correlation between novelty HR and the hippocampus MTR was then performed. The novelty HR in the SN/VTA correlated positively not only with the SN/VTA MTR (Fig. 5B) but also with hippocampus MTR (Fig. 5C), while showing no correlation with age (Fig. 5D) or amygdala MTR (Fig. 5E). The novelty HR in the right hippocampus (Fig. 5F) correlated positively not only with hippocampus MTR (Fig. 5H) but also with SN/VTA MTR (Fig. 5G), while showing a negative correlation with age (Fig. 5I), and no correlation with the amygdala MTR (Fig. 5J).

Furthermore, hippocampus HR and SN/VTA HR to novelty correlated positively ($r = 0.375, P = 0.047$, one-tailed), but there was no correlation between the amygdala HR to novelty and the SN/VTA HR or hippocampus HR to novelty (both $P > 0.39$). In a subsequent partial correlation using age as control variable, the correlations between novelty HR in SN/VTA and SN/VTA MTR ($r = 0.62, P = 0.004$), novelty HR in SN/VTA and hippocampus MTR ($r = 0.48, P = 0.03$), novelty HR in the hippocampus and SN/VTA MTR ($r = 0.43, P = 0.055$), and novelty HR in the hippocampus and hippocampus MTR ($r = 0.63, P = 0.003$) remained significant or approached significance level (novelty HR in hippocampus and SN/VTA MTR).

The structure-function relationship between SN/VTA MTR and hippocampal MTR is unlikely to be a mere reflection of a global age-related gray or white matter process as neither the SN/VTA MTR nor the hippocampal MTR showed a correlation with the global gray or white matter volume of the older adults (all $P$ values > 0.3). The individual global gray and white matter volumes were extracted based on the subject’s $T_1$-weighted image using standard SPM brain segmentation algorithms (Ashburner and Friston 2000).

In order to analyze the characteristics of the HR in the amygdala for negative emotional oddballs, simple regression analyses using the contrast “negative emotional oddballs vs. neutral oddballs” and the different MTRs and age as regressors were performed. Neither of these SPM analyses revealed a significant correlation at the significance level of 0.005 (uncorrected). However, a closer examination of the HR of the peak voxel within the right amygdala for negative emotional valence ($x, y, z = 28, 0, -22$; see Supplementary Table S1B) and the right amygdala MTR revealed a correlation between both variables at a one-tailed level of significance ($r = 0.376, P = 0.046$, one-tailed). In contrast, the HR in this peak voxel to negative emotional valence did not correlate with SN/VTA MTR, hippocampus MTR, or age (all $P > 0.34$).

Unlike our recent observations in healthy young adults (Bunzeck and Duzel 2006), target detection and the associated motor response were associated with a prominent bilateral HR not only in the red nucleus but also the SN/VTA, including those SN/VTA voxels that showed peak responses to novelty. Unlike novelty, however, targetness HRs of these voxels did not correlate with SN/VTA MTR ($P \geq 0.5$) but did correlate negatively with the subject’s reaction times to targets ($r = -0.42, P = 0.056$). Furthermore, the novelty HR in the SN/VTA did not correlate with reaction time ($r = 0.16, P = 0.5$), and there was no correlation between SN/VTA HR to targetness and age ($P \geq 0.5$).

Table 1. Coefficients (Pearson correlation) for the correlations between SN/VTA MTR, hippocampus MTR, amygdala MTR, and age

<table>
<thead>
<tr>
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<th>SN/VTA MTR</th>
<th>Hippocampus MTR</th>
<th>Amygdala MTR</th>
<th>Age</th>
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<tbody>
<tr>
<td>SN/VTA MTR</td>
<td>1</td>
<td>0.542* (0.011)</td>
<td>0.325 (0.151)</td>
<td>-0.179 (0.438)</td>
</tr>
<tr>
<td>Hippocampus MTR</td>
<td>0.542* (0.011)</td>
<td>1</td>
<td>0.193 (0.402)</td>
<td>-0.343 (0.128)</td>
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<tr>
<td>Amygdala MTR</td>
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<td>0.193 (0.402)</td>
<td>1</td>
<td>-0.053 (0.821)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.179 (0.438)</td>
<td>-0.343 (0.128)</td>
<td>-0.053 (0.821)</td>
<td>1</td>
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*Significant correlation at $P = 0.05$ (two-tailed). Numbers in brackets indicate the statistical significance ($P$ values).

**Figure 4.** MTR comparison between young and older adults. While the SN/VTA MTR was significantly higher in the population of young adults (two-tailed comparison, $P = 0.008$, $T = 2.8$) (indicated by the star), the hippocampi MTR did not differ significantly between both populations but tended to be higher in the sample of young adults (two-tailed comparison, $P = 0.17$, $T = 1.4$). Error bars indicate the standard error of the mean.
Discussion

The hippocampal-SN/VTA model predicts that the response magnitude of the human SN/VTA and hippocampus to novelty in older adults should be jointly determined by the integrity within the SN/VTA and the hippocampus. In contrast, given that the amygdala does not directly contribute to hippocampal-SN/VTA novelty processing, neither hippocampal nor SN/VTA novelty responses should be affected by integrity within the amygdala. This is exactly the pattern that we observed. When considering MTRs of SN/VTA, amygdala, and hippocampus, we observed a selective structure–function relationship between SN/VTA and hippocampus for novelty processing. Novelty responses in SN/VTA and hippocampus were correlated, and they were correlated with their respective MTRs (Fig. 5B,H). More importantly, hippocampal novelty responses were also correlated with the MTR of the SN/VTA (Fig. 5G), and the novelty responses in the SN/VTA were correlated with the MTR of the hippocampus (Fig. 5C). This interregional structure–function relationship is unlikely to reflect a regionally unspecific effect of MTR changes because the MTR of the amygdala was not correlated with the novelty response of either the SN/VTA (Fig. 5E) nor the hippocampus (Fig. 5J). There was, however, a weak correlation between MTRs in the amygdala and the HR to negative emotional valence in the amygdala in the absence of any correlation with MTR changes in the SN/VTA and the hippocampus. These findings of a selective structure–function relationship within the SN/VTA and hippocampus for novelty processing provide strong support for a hippocampal-SN/VTA loop in novelty processing (Lisman and Grace 2005).

The SN/VTA MTR of the older adults was significantly lower than in our young control group (Fig. 4), suggesting that our
findings go beyond an interregional correlation and are relevant to understand age-related changes in memory. However, this SN/VTA MTR reduction in the older adults did not translate into a correlation between age and MTR in our study. One plausible explanation for this is the relatively narrow age range of our sample of older subjects. It is known, for instance, that hippocampal volumes also do not show a correlation with age in narrow age samples (Szentkuti et al. 2004; Schiltz et al. 2006) but do show a correlation with samples ranging from the 20s to the 80s (Raz and Rodriguez 2006). It is conceivable that with an age range starting in the 20s and ranging to the late 80s, our finding of a significant reduction in older adults would also translate into a correlation between age and SN/VTA MTR.

Our findings raise the question whether structural and functional changes in the SN/VTA and the hippocampus are causally related. Anatomical data favor such a possibility. First, the SN/VTA projects directly to the hippocampus (Lisman and Grace 2005). Second, although the hippocampus does not project directly to the SN/VTA, it is the main and perhaps the sole origin of a novelty signal to the SN/VTA (Lisman and Grace 2005). This is because other medial temporal regions that have been implicated in novelty detection (Brown and Aggleton 2001), such as the perirhinal cortex, have very weak projections to the ventral striatum (Friedman et al. 2002) and are therefore not believed to provide an effective novelty signal to the SN/VTA (Lisman and Grace 2005).

As in healthy young adults (Bunzeck and Duzel 2006), the SN/VTA was more responsive to stimulus novelty than to rareness or negative emotional valence. However, unlike our previous findings in healthy young adults (Bunzeck and Duzel 2006), SN/VTA was significantly activated by targetness and its associated motor response in older adults. The HR to targetness was negatively correlated with reaction time, suggesting that the allocation of processing resources associated with SN/VTA structures into making behavioral responses to targets might reflect compensatory mechanisms for mild motor problems. It should be noted, however, that at a higher statistical threshold we observed the same qualitative pattern both within and outside the midbrain as in healthy young adults (Bunzeck and Duzel 2006). Particularly, within the midbrain, targetness responses were confined to the red nucleus (Fig. 3H). Thus, it seems that the allocation of SN/VTA into targetness responses in healthy older adults reflects a quantitative change particularly in those older adults with slow reaction times but not a qualitative change in the response of the midbrain to targetness. In a recent postmortem analysis of SN neuronal density, healthy older adults without PD showed neuronal loss in the SN, and this loss was correlated with mild parkinsonian signs such as bradykinesia and gait imbalance (Ross et al. 2004). It is possible that slowed reaction times reflect a mild bradykinesia, which in turn is associated with an increased drive to the SN/VTA in an attempt to compensate. Importantly, it should be noted that it remains to be determined whether or not a task that required a “mental count” or “mental registration” of targets in the absence of an overt motor response would lead to a different midbrain HR to targets in young and in old adults.

The hippocampus and the amygdala of older adults appeared to retain their response properties observed in healthy young adults (Strange and Dolan 2001; Yamaguchi et al. 2004; Crottaz-Herbette et al. 2005). As in young adults (Bunzeck and Duzel 2006), the hippocampus was less selective than the SN/VTA because it responded to novelty (Fig. 3D,E) as well as rareness (Fig. 3G). The amygdala, on the other hand, was the only region that significantly responded to negative emotional valence (Fig. 3F). Previous studies in older adults have shown that novel fearful faces compared with familiar neutral faces are associated with a robust activation of the amygdala in healthy older adults (Wright et al. 2006). The present data extend this finding by showing that in healthy older adults there is also robust activation of the amygdala to familiar fearful stimuli (faces and scenes) when compared with familiar neutral stimuli (faces and scenes).

A number of previous studies have investigated age-related changes in novelty processing using event-related potentials (ERPs). When allowed to voluntarily allocate attention to novel visual images during self-paced viewing, high-performing older adults show no sign of diminished novelty-related P300 responses (Daffner et al. 2006). In fact, their P300 amplitudes can even be enhanced possibly suggesting more effortful orienting to novel stimuli in older adults (Daffner et al. 2006). This notion is compatible with lesion studies suggesting that lateral prefrontal cortex participates in the generation of the novelty P300 (Soltani and Knight 2000) and that healthy older adults often show less hemispheric lateralization in cognitive tasks such as episodic encoding possibly indicating effortful compensatory mechanisms (Dolcos et al. 2002). Our data are compatible with such an account of ERP studies of novelty processing as they show diminished mesolimbic novelty responses in older adults with less intact SN/VTA and hippocampi. It is possible that older adults compensate for diminished mesolimbic novelty responses by more effortful prefrontal orienting to novel stimuli. If true and if the P300 novelty response in older adults is related to such effortful orienting, one would predict that novelty P300 in these subjects should increase in amplitude with decreasing MTR in the SN/VTA and hippocampus. Importantly, this assumes that the integrity of the prefrontal cortex during normal aging allows for compensation of a decline in mesolimbic functioning. However, this might not be the case if there is a correlation between the loss of prefrontal cortical and mesolimbic functioning and/or integrity.

A well replicated abnormality in novelty processing in healthy older adults is that of a diminished habituation of the novelty P300 by repetition (Friedman et al. 1998; Daffner et al. 2006; Weisz and Czigler 2006). Our data show that mesolimbic novelty responses are per se diminished in relation to structural changes in the SN/VTA and the hippocampus, but we have not studied habituation given that the novel oddballs in our study were not repeated. Our data are thus neutral with respect to the possibility that in addition to being diminished with lower MTRs in SN/VTA and hippocampus, the novelty responses in these regions also show diminished habituation.

Apart from the temporal lobe, a wide range of electrophysiological recordings, patient studies (Baudena et al. 1995; Daffner et al. 2000), and imaging studies (Opitz et al. 1999; Clark et al. 2000) have highlighted the role of the prefrontal and orbitofrontal cortices (Rule et al. 2002) in novelty processing (Yamaguchi et al. 2004). While the HRs to novelty, rareness, and targetness were anatomically different within our limited imaging volume, the role of the frontal cortex in novelty processing is beyond the scope of this paper. A full volume of acquisition is necessary to assess the functional relationship between prefrontal and orbitofrontal cortices and mesolimbic structures during novelty processing.

To summarize, the pattern of age-related structural and functional changes observed here within the mesolimbic system.
provide support for a hippocampal-SN/VTA loop of novelty processing. It now remains to be determined how the structural and functional changes in this loop affect episodic memory performance in older adults. Furthermore, these findings implicate that older adults with low SN/VTA MTRs and diminished mesolimbic responses to novelty might benefit from dopaminergic substitution. The dopamine precursor levodopa (L-DOPA) is mostly taken up and converted by dopaminergic neurons and then can be phasically released into the synaptic cleft, whereas dopamine agonists will exert a more tonic activation of postsynaptic dopamine receptors. Thus, L-DOPA is a particularly interesting drug to enhance phasic dopamine release in response to novelty. It has already been shown to enhance learning of new vocabulary through repetitions in healthy young adults (Knecht et al. 2004; Breitenstein et al. 2006) and memory processing of words (Newman et al. 1984) as well as motor memory formation in healthy older subjects (Floel et al. 2005, 2006). Pharmacological studies are needed to assess the benefits of L-DOPA and dopamine agonists in older adults with low MTRs in the SN/VTA.

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

Notes
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