White Noise Improves Learning by Modulating Activity in Dopaminergic Midbrain Regions and Right Superior Temporal Sulcus

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Abstract

■ In neural systems, information processing can be facilitated by adding an optimal level of white noise. Although this phenomenon, the so-called stochastic resonance, has traditionally been linked with perception, recent evidence indicates that white noise may also exert positive effects on cognitive functions, such as learning and memory. The underlying neural mechanisms, however, remain unclear. Here, on the basis of recent theories, we tested the hypothesis that auditory white noise, when presented during the encoding of scene images, enhances subsequent recognition memory performance and modulates activity within the dopaminergic midbrain (i.e., substantia nigra/ventral tegmental area, SN/VTA). Indeed, in a behavioral experiment, we can show in healthy humans that auditory white noise—but not control sounds, such as a sinus tone—slightly improves recognition memory. In an fMRI experiment, white noise selectively enhances stimulus-driven phasic activity in the SN/VTA and auditory cortex. Moreover, it induces stronger connectivity between SN/VTA and right STS, which, in addition, exhibited a positive correlation with subsequent memory improvement by white noise. Our results suggest that the beneficial effects of auditory white noise on learning depend on dopaminergic neuromodulation and enhanced connectivity between midbrain regions and the STS—a key player in attention modulation. Moreover, they indicate that white noise could be particularly useful to facilitate learning in conditions where changes of the mesolimbic system are causally related to memory deficits including healthy and pathological aging. ■

INTRODUCTION

The ability to perceive a weak signal can be improved by adding an optimal level of white noise (WN; i.e., a random signal with equal power at any frequency in a given bandwidth). This form of enhanced information processing is known as "stochastic resonance" (or "stochastic facilitation") and has been demonstrated in tactile, visual, auditory, and cross-modal perception (McDonnell & Ward, 2011; Moss, Ward, & Sannita, 2004). Although the effects of WN have been studied in a wide range of biological systems, their underlying neural mechanisms remain incompletely understood.

Recent studies have extended the long tradition of research on stochastic resonance in perception by demonstrating facilitating effects of WN on higher cognitive functions. For instance, during arithmetic tasks, auditory WN fastens RTs indicating improved memory retrieval (Usher & Feingold, 2000). Moreover, in children with attention-deficit hyperactivity disorder (ADHD), WN—when presented during encoding of words—enhances subsequent free recall (Söderlund, Sikström, & Smart, 2007). Because ADHD is characterized by imbalanced dopaminergic functioning (Solanto, 2002), this finding suggests a close link between dopaminergic neuromodulation and improved learning by WN (Sikström & Söderlund, 2007; Söderlund et al., 2007). Although such a relationship has been formally expressed in the moderate brain arousal (MBA) model (Sikström & Söderlund, 2007; Söderlund et al., 2007), empirical evidence in healthy human adults is sparse.

The main source of dopamine neurons can be located to the substantia nigra/ventral tegmental area (SN/VTA; Duzel et al., 2009; Fields, Hjelmstad, Margolis, & Nicola, 2007). This midbrain region projects to different target sites, such as the medial-temporal lobe (MTL; including hippocampus and parahippocampal cortex), where it regulates learning and synaptic plasticity (Morris, 2006; Jay, 2003). For instance, the late phase of hippocampal long-term potentiation is dopamine-dependent (Morris, 2006; Frey & Morris, 1998), and the dopamine precursor levodopa improves hippocampus-dependent long-term memory formation (Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Duzel, 2012; Knecht et al., 2004). These and other (Bunzeck, Guitart-Masip, Dolan, & Duzel, 2013; Bunzeck & Duzel, 2006) studies have led to the notion that SN/VTA dopamine neurons and the hippocampus form

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a functional loop controlling the entry of novel information into long-term memory (i.e., the "hippocampal–VTA loop"; Lisman, Grace, & Duzel, 2011; Lisman & Grace, 2005).

Functionally, SN/VTA dopamine neurons can be tonically active or in a phasic burst firing mode. Importantly, to achieve and maintain balanced dopamine levels, reduced tonic activity has been suggested to lead to enhanced stimulus-dependent phasic firing; increased tonic dopamine activity, on the other hand, is supposed to lead to reduced phasic firing (Grace, 1991). Although altered tonic dopamine activity has been related to neural instability and psychiatric diseases, such as schizophrenia or ADHD, the MBA model suggests that WN can modulate tonic and associated phasic activity via perceptual brain regions (see Discussion; Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010; Söderlund et al., 2007). Boosted phasic dopamine release into the hippocampus, in turn, may increase the likelihood of successful long-term memory encoding (Duzel et al., 2009; Lisman & Grace, 2005). Indeed, computational modeling of hippocampal networks (Kawaguchi, Mino, & Durand, 2011; Mino & Durand, 2010; Yoshida, Hayashi, Tateno, & Ishizuka, 2002) and direct cell recordings in CA1 (Stacey & Durand, 2001) have shown that noise enhances hippocampal signal detection and information transmission, which might relate to long-term memory performance (Yoshida et al., 2002).

Following this rationale, we tested the hypothesis that auditory WN, as presented during encoding, improves subsequent recognition memory by differentially modulating sustained and stimulus-driven hemodynamic responses in the SN/VTA. More precisely, we predicted WN-dependent reduced tonic and (at the same time) enhanced stimulus-driven phasic activity, as well as strengthened functional connectivity between the SN/VTA and interconnected brain regions. The latter hypothesis is based on the notion that stochastic resonance can be achieved by neural synchronization within and between brain regions, as demonstrated for auditory perception (Ward, MacLean, & Kirschner, 2010).

METHODS

The study consisted of two experiments: Experiment 1 was a behavioral experiment, and Experiment 2 included fMRI as well as behavioral measures.

Participants

In total, 66 healthy volunteers participated (Experiment 1: 26 women and 12 men, mean age = 24.8 years, *SD* = 4.2 years; Experiment 2: 14 women and 14 men, mean age = 24.6 years, *SD* = 3.5 years). All were right-handed, had normal or corrected-to-normal visual acuity, and gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Council Hamburg.

Task

Behavioral testing was divided into an encoding and a retrieval phase for Experiments 1 and 2 and an additional familiarization phase in the beginning of Experiment 2. In Experiment 1, all phases were performed on a computer screen, whereas in Experiment 2, familiarization and encoding phases were carried out in the MRI scanner.

Encoding

Experiment 1. During encoding, volunteers were presented with 200 grayscale photographs (time of presentation = 1.5 sec, intertrial interval [ITI] = 1.5 sec), and they had to indicate their indoor and outdoor status (100 indoor, 100 outdoor images) by button press. Concurrently, background noise could be presented in blocks according to the following conditions: WN (20–5000 Hz), no noise (NoN), a sinus tone (100 Hz), or the sound of a running horse played backward (this sound was chosen because it is meaningless, i.e., it could not be recognized by the participants and covered a similar frequency range as WN). Each sound was played at ~70 dB via headphones. There was one block of each "noise" condition (in total four blocks in random order, 50 items per block) and a fixation delay of 10 sec between blocks.

Experiment 2. Before the encoding phase, participants were familiarized with three indoor and three outdoor scene images, which were presented eight times each. During encoding, these familiarized scene images were intermixed with 144 new ones, and all items were presented in random order (time of presentation = 1.5 sec, ITI = 1.5 sec). The six familiar scenes were randomly presented across blocks (24 times each, in total 144 presentations of familiar scenes). As in Experiment 1, participants indicated the indoor/outdoor status of each image while listening to blocks of different background noise conditions: WN (20–5000 Hz), NoN, or a sinus tone (100 Hz). In this experiment, "horse noise" was not included because it had no effect on memory in Experiment 1 (see Results) and to reduce the number of conditions. Participants were presented with 12 scenes per block (six novel, six familiar). One session consisted of six "noise" blocks (two blocks of each "noise" condition in random order, 72 items per session) that were separated by a fixation delay of 10 sec; each volunteer participated in four sessions (i.e., 288 items in total, 144 novel and 144 familiar items). Importantly, within each noise block, an equal number of familiar and novel items were presented in random order, allowing us to dissociate the hemodynamic responses associated with each trial type (even in the absence of a temporal jitter). NoN was presented during the familiarization phase. The goal of including the novel/familiar condition was to identify those brain regions responsive to the novelty status of the images (i.e., SN/VTA, MTL; Bunzeck et al., 2013;

Bunzeck & Duzel, 2006) and test for possible interactions with noise.

Retrieval

Experiments 1 and 2. About 20 min after encoding, participants had to perform an incidental recognition memory test using the "remember/know" procedure (Tulving, 1985). Here, images that were presented during encoding (only "new" but not "familiar" images) were intermixed with novel distractor images (50 in Experiment 1, 48 in Experiment 2), and participants were asked to make two choices per image. First, they had to judge whether an image was presented during encoding ("old") or not ("new"). Following a "new" response, they had to specify whether they were confident ("certainly new") or unsure ("unsure"). Following an "old" response, participants indicated whether they were able to remember something specific about seeing the scene at study ("remember" response), just felt familiarity without any recollective experience ("familiar" response), or were unsure that the picture was an old one ("guess" response). Participants had 4 sec to make each of both judgments (ITI = 1.5 sec). To make the participants familiar with this procedure, a training session was performed before the retrieval phase. For an overview of the experimental design and task, see Table 1 and Figure 1.

We employed a remember/know paradigm because we expected the effect of WN to be driven by dopamine, which is known to be released into the hippocampus and surrounding parahippocampal cortex to a different extent. For instance, in rodents the projection from the VTA to the entorhinal cortex is richer in dopamine neurons compared with the VTA–hippocampus projection (Fields et al., 2007). In humans, on the other hand, D2 receptor expression is higher in the hippocampus compared with the parahippocampal cortex, which is in line with strong effects of reward anticipation (which releases dopamine) on hippocampus-dependent memory (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Wittmann et al., 2005). Together with the notion of dual process models of recognition memory, suggesting that recollection depends on the integrity of the hippocampus, whereas familiarity-based recognition rather relates to the parahippocampal cortex (Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, Yonelinas, & Ranganath, 2007), we therefore hypothesized that a remember/know procedure might be much more sensitive to capture the effects of WN.

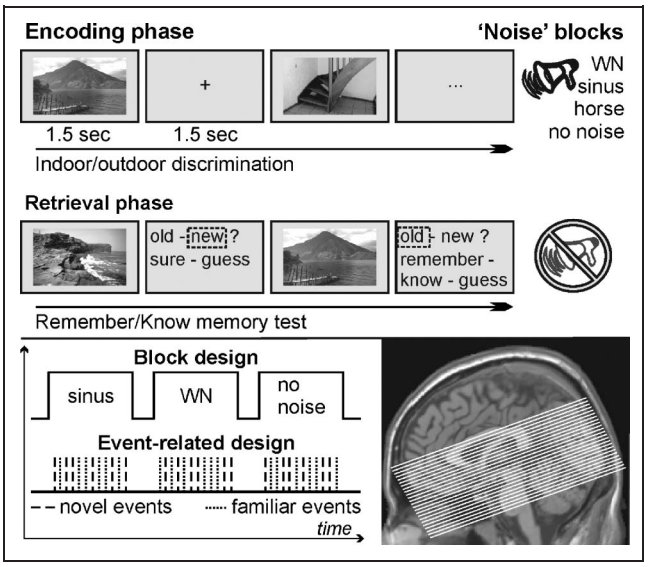

Figure 1. Experimental design, analysis design, and EPI image acquisition. Top: During encoding, participants were asked to indicate the indoor and outdoor status of scene images by pressing a button. Concurrently, they were listening to blocks of WN, NoN, or control sounds, such as the sound of a horse running played backward (horse, Experiment 1 only) or a sinus tone (sinus). Twenty minutes after encoding, participants had to perform a recognition memory test according to the remember/know procedure (for details, see Methods section). NoN was applied during retrieval. Lower left: Sustained effects of "noise" were analyzed by using a block design, event-related effects of "novelty" and "noise" were tested by using an event-related design (see Methods). Lower right: During fMRI scanning (Experiment 2), a partial volume was acquired including auditory cortex, MTL, and midbrain (see text).

fMRI Methods

In Experiment 2, fMRI was performed on a 3-T MR scanner (Siemens TRIO, Erlangen, Germany) with EPI. In the

Table 1. Experimental Design

	Familiarization		*Encoding*		*Retrieval*	
	Number of Items	*"Noise"*	*Number of Items*	*"Noise"*	*Task Design*	*"Noise"*
Experiment 1	–	–	4 blocks à 50 items	Sinus, WN, Horse, NoN, presented in blocks, each condition once	Rem./know	–
Experiment 2	6 items, presented 8 times each	–	6 blocks à 12 items (6 novel, 6 fam.) per session; 4 sessions	Sinus, WN, NoN, presented in blocks, each condition twice per session	Rem./know	–

For details, see Methods section. Sinus = a sinus tone; WN = white noise; Horse = the sound of a running horse played backward; NoN = no noise; Rem. = remember; fam. = familiar.

functional session, T2*-weighted images (EPI sequence) with BOLD contrast were obtained (matrix size = 108 × 108 mm, spatial resolution = 2 × 2 × 2 mm, repetition time [TR] = 1440 msec, echo time [TE] = 25 msec). Here, a partial volume of the brain was acquired with slices parallel to the hippocampus; it included MTLs, midbrain, auditory cortex, occipital cortex, and BG (Figure 1). For each participant, fMRI data were acquired in four scanning sessions containing 200 volumes. Six additional volumes were acquired at the beginning of each series to allow for steady state magnetization; they were subsequently discarded from further analysis. Ten whole head EPI images were recorded for each participant for the purpose of coregistration.

Anatomical images of each participant's brain were collected using multiecho 3-D FLASH for mapping proton density (TR = 24 msec, TE = 2.2–24 msec), T1 (TR = 19 msec, TE = 2.2–15 msec), and magnetization transfer (MT; TR = 24 msec, TE = 2.2–20 msec) at 1-mm resolution (Helms, Draganski, Frackowiak, Ashburner, & Weiskopf, 2009) at the end of the experiment.

The MRI data were preprocessed and analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, University College London, UK) and MATLAB 7.7 (The MathWorks, Inc., Natick, MA). The first image of the first session was coregistered to the first whole brain volume. To correct for motion artifacts, all functional images and two whole brain functional images were realigned to the first volume and corrected for the interaction of motion and distortion. After segmenting the first whole brain image, all functional images were normalized and smoothed with an isotropic 8-mm FWHM Gaussian kernel.

The fMRI data were high-pass filtered (cutoff = 128 sec) and whitened using an AR(1) model. For each participant, a mixed event-related/block design was employed (Figure 1) by creating a stick function for the events (duration = 0 sec) and a boxcar function for the blocks (duration = 36 sec), which were convolved with the canonical hemodynamic response function. The following regressors were included as events: WN novel, WN familiar, Sinus novel, Sinus familiar, NoN novel, NoN familiar, errors. The block conditions included the following: Sinus block, WN block, NoN block. To capture residual movement-related artifacts, six covariates were included (the three rigid body translation and three rotations resulting from realignment) as regressors of no interest.

The resulting contrast images were entered into a second-level random-effects analysis. For the event-related part of the model, the hemodynamic effects of each condition were assessed using a 2 × 3 ANOVA with the factors Novelty (novel, familiar) and Noise (WN, Sinus, NoN). This model allowed us to test for main effects of Novelty, main effects of Noise, and the interaction between both. Sustained effects of WN were analyzed by a one-way ANOVA with the factor Noise Block (WN block, Sinus block, NoN block).

The anatomical localization of significant activations was assessed with reference to the standard stereotaxic atlas by superimposition of the SPM maps on one of two group templates. A T1-weighted and an MT-weighted group template were derived from averaging all participants' normalized T1 or MT images (spatial resolution of 1 × 1 × 1 mm). Whereas the T1 template allows

Table 2. Mean Correct Responses (Hit Rate) of Indoor/Outdoor Discrimination (Accuracy) and Mean RTs during Encoding (RT in msec)

	Experiment 1	*Experiment 2 Novel*	*Experiment 2 Familiar*
Sinus			
Accuracy	.98 (.02)	.98 (.02)	.97 (.05)
RT	661 (99)	697 (101)	648 (84)
WN			
Accuracy	.98 (.02)	.99 (.02)	.98 (.04)
RT	653 (83)	700 (91)	651 (82)
NoN			
Accuracy	.99 (.02)	.98 (.03)	.97 (.04)
RT	660 (90)	692 (104)	657 (95)
Horse			
Accuracy	.97 (.03)	–	–
RT	663 (102)	–	–

Numbers in brackets indicate one standard deviation. *Sinus* = a sinus tone of 100 Hz; WN = white noise; NoN = no noise; horse = the sound of a running horse played backward; novel = novel items; familiar = familiar items.

Table 3. Mean Corrected Hit Rates for Each Condition

	Experiment 1	*Experiment 2*
Sinus		
Remember	.12 (.08)	.13 (.09)
Know	.14 (.12)	.09 (.12)
Guess	.05 (.07)	.01 (.06)
WN		
Remember	.13 (.10)	.12 (.06)
Know	.16 (.08)	.12 (.11)
Guess	.05 (.08)	.02 (.04)
NoN		
Remember	.12 (.09)	.13 (.08)
Know	.14 (.09)	.11 (.12)
Guess	.03 (.07)	.01 (.06)
Horse		
Remember	.12 (.08)	–
Know	.13 (.08)	–
Guess	.04 (.07)	–

Numbers in brackets indicate one standard deviation. Sinus = a sinus tone of 100 Hz; WN = white noise; NoN = no noise; Horse = the sound of a running horse played backward.

anatomical localization outside the midbrain, on MT images the SN/VTA region can be distinguished from surrounding structures as a bright stripe while the adjacent red nucleus and cerebral peduncle appear dark (Bunzeck et al., 2007; Bunzeck & Duzel, 2006; Eckert et al., 2004).

Reported results are corrected for multiple comparisons across the whole brain or after small volume correction (SVC)—corresponding masks were defined by using the WFU-Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003)—using family-wise error (FWE) correction as implemented in SPM8 at a threshold of $p < .05$. For display purposes, figures show results with a $p < .001$ (uncorrected) and with an extend threshold of $k = 15$.

RESULTS

Only correct responses (indoor/outdoor; new/old) were included in the analysis of the behavioral data. Analysis of recognition data was based on corrected (corr.) hit rates: These were calculated by subtracting the false alarm rate (proportion of "old" responses to distractors) from the hit rate (proportion of "old" responses to old items) for each condition and "remember," "know," and "guess" separately.

SPM coordinates are given in MNI space. Color bars indicate *t* values; error bars denote the *SEM* unless otherwise indicated (*$p < .05$; **$p < .01$; ***$p < .001$).

Experiment 1

Accuracy and RTs

Accuracy for indoor/outdoor discrimination during encoding was high (mean ± *SD* correct responses, Experiment 1, 98.1 ± 2.3%, Table 2), and there was no significant main effect of Noise (one-way ANOVA with the factor Noise [Sinus, WN, NoN, and Horse], $F(3, 148) = 1.5$, $p > .05$, Table 2). Another one-way ANOVA revealed no main effect of Noise on RTs, $F(3, 148) = .084$, $p > .05$ (Table 2).

Recognition Memory

A 3 × 4 ANOVA with the factors Memory (remember/know/guess) and Noise (Sinus, WN, NoN, Horse) revealed a main effect of Memory, $F(2, 444) = 59.5$, $p < .001$ (Table 3), which was driven by higher corrected know rates (in contrast to remember and guess). The ANOVA showed no main effect of Noise, $F(3, 444) = 0.761$, $p > .05$, and no significant interactions (Memory × Noise, $F(3, 444) = 0.236$, $p > .05$). Given the absence of an interaction Memory × Noise, we summed the corrected hit rates for remember, know, and guess responses and performed a one-way ANOVA, which again showed no effect of Noise on memory performance (one-way ANOVA with the factor Noise [Sinus, WN, NoN, and Horse], $F(3, 148) = 0.87$, $p > .05$). However, given our specific a priori hypothesis of a beneficial effect of WN, we directly compared conditions using *t* tests. As depicted in Figure 2A (Experiment 1; Table 3), there was significant better memory for items encoded in the context of WN in contrast to NoN (WN > NoN, paired *t* test, $t(37) = 2.306$, $p = .027$, two-tailed). This effect was also significant when

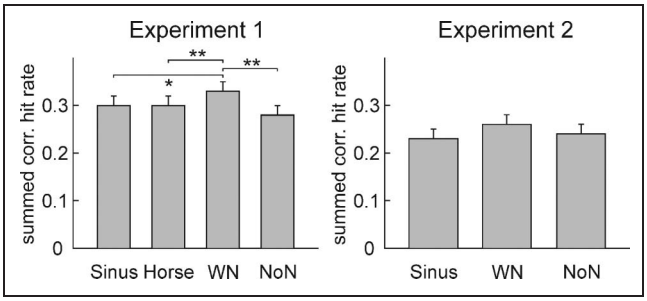

Figure 2. Effects of WN on recognition memory. In the behavioral version of the experiment (Experiment 1), WN selectively enhanced subsequent recognition memory. Although not significant, the same trend was observed when encoding was performed in the fMRI scanner (Experiment 2). Bar graphs depict mean values of the summed corrected (corr.) hit rates (remember, know, and guess) of every condition ± *SEM*. Paired *t* test, *$p < .05$ one-tailed, **$p < .05$ two-tailed. Sinus = a sinus tone; Horse = the sound of a running horse played backward; WN = white noise; NoN = no noise.

comparing WN with the other two conditions (paired t test, WN > Sinus, $t(37) = 1.793$, $p = .04$, one-tailed; WN > Horse, $t(37) = 2.502$, $p = .017$, two-tailed). No effect was found for the control sounds (paired t test, Sinus > NoN, $t(37) = 1.026$; Horse > NoN, $t(37) = 0.783$; both p's > .05).

Experiment 2

Behavioral Data—Accuracy and RTs

Accuracy for indoor/outdoor discrimination during encoding was high (mean ± *SD* correct responses, Experiment 2, 97.9 ± 2.3%, Table 2), but there were no differences between conditions as revealed by a 2 × 3 ANOVA with the factors Novelty (novel, familiar) and Noise (Sinus, WN, NoN): no main effects (factor Novelty, $F(1, 162) = 2.398$, $p > .05$; factor Noise, $F(2, 162) = .357$, $p > .05$) and no significant interactions (Novelty × Noise, $F(2, 162) = .033$, $p > .05$). Another 2 × 3 ANOVA on RTs revealed a main effect of Novelty that was driven by faster responses to familiar items, $F(1, 162) = 9.76$, $p = .002$ (Table 2); there was no main effect of Noise, $F(2, 162) = .017$, $p > .05$, and no significant interactions (Novelty × Noise, $F(2, 162) = .104$, $p > .05$).

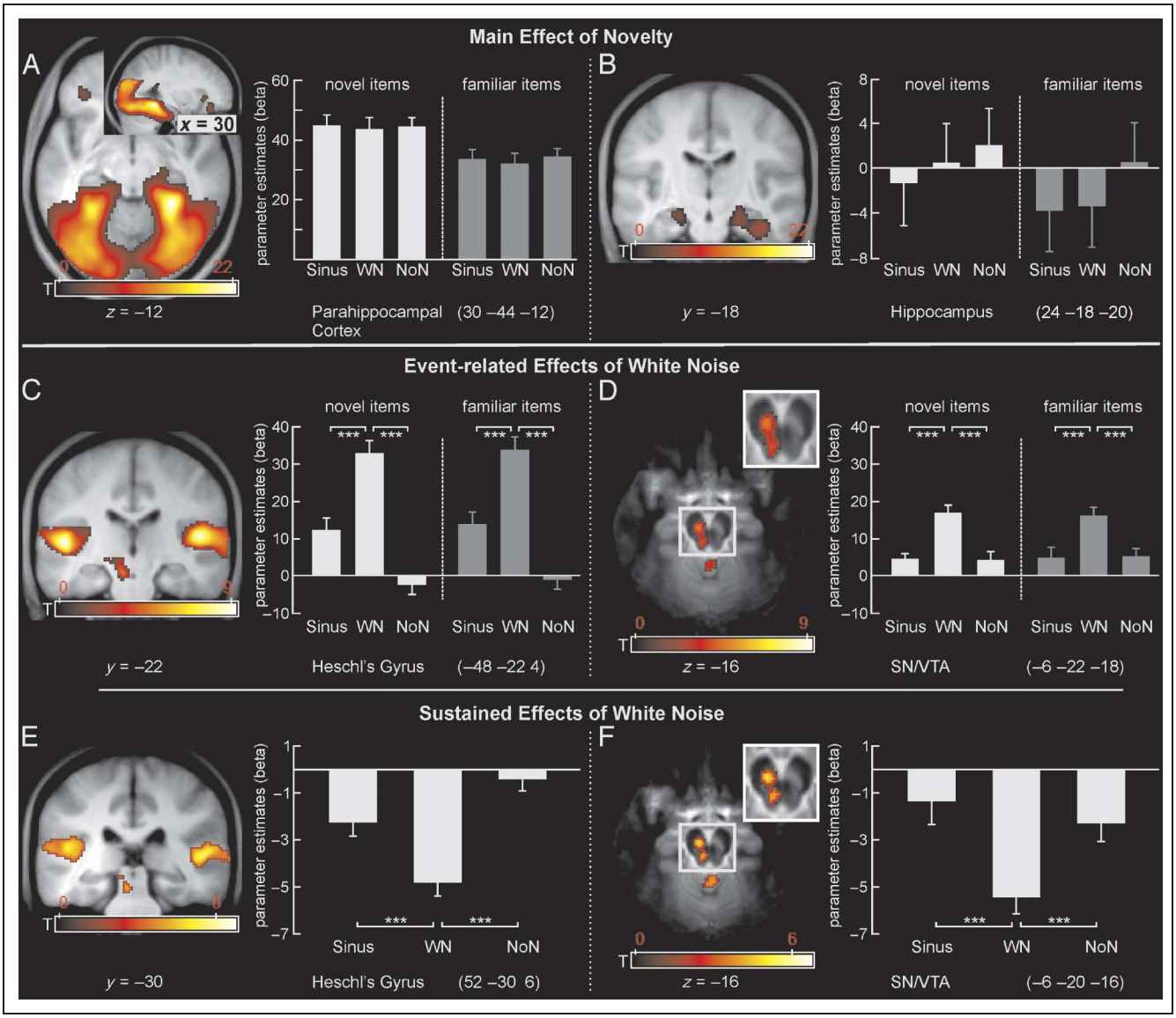

Figure 3. Neuronal effects of novelty and WN. (A + B) Increased hemodynamic responses to novel items (vs. familiar items) were found bilaterally in the visual system, including occipital cortex and ventral visual system (A), extending into both MTLs including parahippocampal cortices (A) and hippocampi (B). (C + D) Event-related effects of WN expressed by increased hemodynamic responses were found bilaterally in the auditory cortex (C) and left SN/VTA (D, inset shows an enlarged view of the SN/VTA). Decreased hemodynamic response in the auditory cortex and the SN/VTA was observed as a sustained effect of WN (E, F). Bar graphs illustrate the mean parameter estimates ± *SEM* of every condition from the voxel assigned below each graph. Paired t test, ***, $p < .001$ two-tailed; results displayed at $p < .0001$ (uncorrected), extent threshold 15 voxels. Sinus, a sinus tone; WN, white noise; NoN, no noise.

Table 4. fMRI Results

Anatomical Structure	*Hemisphere*	*Clustersize [Voxel]*	*FWE-corrected p Value*	*t Value*	*Peak Coordinates MNI (mm)*		
					x	*y*	*z*
A. Novel > Familiar							
Fusiform gyrus/occipital lobe	L/R	22193	<.001	22.23	30	−44	−12
Inferior frontal gyrus	R	177	.001	5.64	26	32	−14
Inferior frontal gyrus	L	194	.074	4.60	−34	32	−16
Medial frontal gyrus	L	201	.086	4.56	−8	28	−18
Parahippocampal gyrus	L	83	.23	4.24	−16	−14	−22
White matter	R	56	.277	4.17	26	−38	20
Vermis	L/R	19	.714	3.73	0	−56	−34
White matter	R	34	.747	3.69	30	24	0
Anterior cingulate cortex	L/R	34	.882	3.53	0	10	−10
B. Event-related WN > Sinus + NoN							
Primary auditory cortex	L	1436	<.001	9.16	−48	−22	4
Primary auditory cortex	R	1628	<.001	8.78	50	−22	8
Dorsal midbrain	L	256	.015	5.04	−10	−28	−8
including a peak in SN/VTA[a]			.026	4.90	−6	−22	−18
Cerebellum	L	118	.193	4.30	−24	−54	−26
Vermis	R	49	.789	3.65	4	−50	−14
Inferior frontal gyrus	R	18	.888	3.52	40	28	−6
Secondary auditory cortex	R	24	.890	3.52	58	10	−4
C. Sustained WN < Sinus + NoN							
Primary auditory cortex	R	1161	<.001	6.71	52	−30	6
Primary auditory cortex	L	838	.001	6.44	−44	−26	6
SN/VTA[a]	L	111	.104	4.83	−6	−20	−16
Inferior frontal gyrus	R	33	.326	4.38	38	30	−6
Cerebellum	L	48	.621	4.04	−20	−52	−22
Cerebellum	R	71	.724	3.93	4	50	−20
D. Regression							
Superior temporal sulcus[a]	R	46	.602	4.58	56	−44	0
Striatum	R	59	.855	4.21	20	22	4
E. PPI							
Secondary auditory cortex	R	40	.635	4.26	64	−28	4
Thalamus	L	17	.68	4.20	−12	−2	4
Medial frontal gyrus	R	59	.75	4.10	16	42	−14
Primary auditory cortex	L	19	.763	4.09	−42	−24	0
Superior temporal sulcus[a]	R	22	.782	4.06	56	−54	14
Thalamus	R	43	.881	3.88	12	−2	8

Regions activated for the contrasts "novel > familiar items" (A), "WN > Sinus and NoN" (B), "WN block < Sinus block and NoN block" (C), "Regression of memory improvement by WN and brain activity during encoding in the WN condition" (D), and "PPI modeled by WN with SN/VTA as seed region" (E). Data are thresholded at $p < .001$ (uncorrected) and $k = 15$.

[a]Survived SVC (see text).

Recognition Memory

A 3 × 3 ANOVA with the factors Memory (remember/know/guess) and Noise (Sinus, WN, NoN) on corrected hit rates revealed a significant main effect of Memory, $F(2, 243) = 39.417$, $p < .001$, which was driven by relatively low corrected guess rates in comparison with corrected remember and know rates. No significant main effect for Noise and no interaction was observed (Noise, $F(2, 243) = 0.174$; Memory × Noise, $F(2, 243) = 0.505$; both ps $> .05$). A one-way ANOVA on summed corrected hit rates for each condition revealed no effect of Noise (Sinus, WN, NoN, and Horse), $F(2, 81) = 0.328$, $p > .05$. Similarly, there was no significant effect in the planned direct comparisons (t tests) between summed corrected hit rates for each condition (WN > NoN, $t(27) = .691$, $p > .05$; WN > Sinus, $t(27) = 1.063$, $p > .05$; Table 3, Figure 2B, Experiment 2). No effect was found for the control sound (paired t test, Sinus > NoN, $t(27) = -0.68$, $p > .05$).

fMRI Data

For the event-related effects, fMRI data were analyzed on the basis of a full factorial 2 × 3 ANOVA with the factors Novelty (novel, familiar) and Noise (Sinus, WN, NoN). We found a main effect of Novelty (t contrast: novel > familiar) bilaterally in the visual system, including the occipital cortex and ventral visual system, extending into both MTLs including the hippocampi (peak at [30 −44 −12], $p < .05$ whole brain FWE-corrected; Figure 3A, B, Table 4). An effect of Noise (t contrast: WN and Sinus > NoN) was detected bilaterally in the superior temporal gyrus and lateral sulcus extending into Heschl's gyrus (i.e., auditory cortex; peak at [48 −26 8] and [−48 −22 4], $p < .05$ whole brain FWE-corrected) and in the midbrain (peak at [−8 −28 −6], $p < .05$ whole brain FWE-corrected). An effect of WN (WN > Sinus and NoN) was observed bilaterally in the auditory cortex (peak at [−48 −22 4], $p < .05$ whole brain FWE-corrected, Figure 3C) and left SN/VTA (peak at [−6 −22 −18], $p < .05$ whole brain FWE-corrected; Figure 3D, Table 4).

Sustained effects of WN were analyzed by using a one-way ANOVA with the factor Noise Block (Sinus block, WN block, NoN block). An effect of Noise (t contrast: WN and Sinus < NoN) was detected bilaterally in the superior temporal gyrus and lateral sulcus extending into Heschl's gyrus (i.e., auditory cortex; peak at [−46 −24 6] and [52 −26 4], $p < .05$ whole brain FWE-corrected) and in the left superior colliculus (peak at [−6 −26 −6], $p < .05$ whole brain FWE-corrected). An effect of WN (t contrast: WN < Sinus and Noise) was observed bilaterally in the auditory cortex (peak at [−48 −22 4], $p < .05$ whole brain FWE-corrected, Figure 3E) and left SN/VTA (peak at [−6 −22 −18]), which survived SVC using a combined MTL/midbrain mask ($p = .008$; Figure 3F, Table 4). The mask included hippocampus, parahippocampal cortex, and midbrain.

Note that the effects of WN on midbrain activity could be replicated when using a conjunction null conjunction of simple main effects (WN > NoN and WN > Sinus) for event-related and (WN < NoN and WN < NoN) for sustained effects, respectively ($p = .035$ for event-related effects and $p = .048$ for sustained effects, both FWE-corrected using an MTL/midbrain mask).

Importantly, the decreases in sustained SN/VTA [−6 −20 −16] activity correlated negatively with the event-related SN/VTA increases [−6 −22 −18], as revealed by a correlation analysis including beta values from both peak voxels (Figure 4). This relationship was evident for both event-related responses to novel ($r = 0.903$, $p < .001$) and familiar items ($r = 0.925$, $p < .001$).

The midbrain effects of WN could be replicated when using smaller smoothing kernels (6 mm: for event-related effects [WN > Sinus and NoN] $p = .004$ and for sustained effects [WN < Sinus and NoN] $p = .037$ whole brain FWE corrected; 4 mm: event-related effects $p = .006$ and sustained effects $p = .004$ FWE corrected using an MTL/midbrain mask).

In a next step, we used simple regression analysis to investigate the relationship between the effects of WN at the behavioral and hemodynamic level. Here, we first calculated individual contrast images for the difference between novel items in the WN versus novel items in the NoN condition. At the second level, these contrast images were regressed against the memory improvement by WN (i.e., the difference between summed corrected hit rates for images presented with WN vs. summed corrected hit rates in the NoN condition). This analysis revealed a cluster in the right posterior STS (peak at [56 −46 0]), which did not survive whole brain FWE correction ($p > .05$; Table 4). It was driven by a positive correlation between both parameters ($r = 0.668$; Figure 5A).

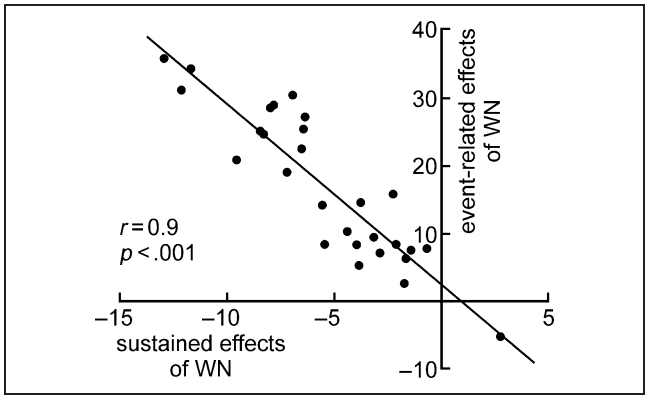

Figure 4. Negative correlation between event-related and sustained effects of WN in the SN/VTA. Hemodynamic activity (parameter estimates, beta) of the SN/VTA during encoding of novel items in the context of WN (event-related, x axis) was regressed against the hemodynamic activity of the SN/VTA during WN blocks (sustained, y axis). The graph shows the individual betas (dots) and the regression line (Pearson's correlation).

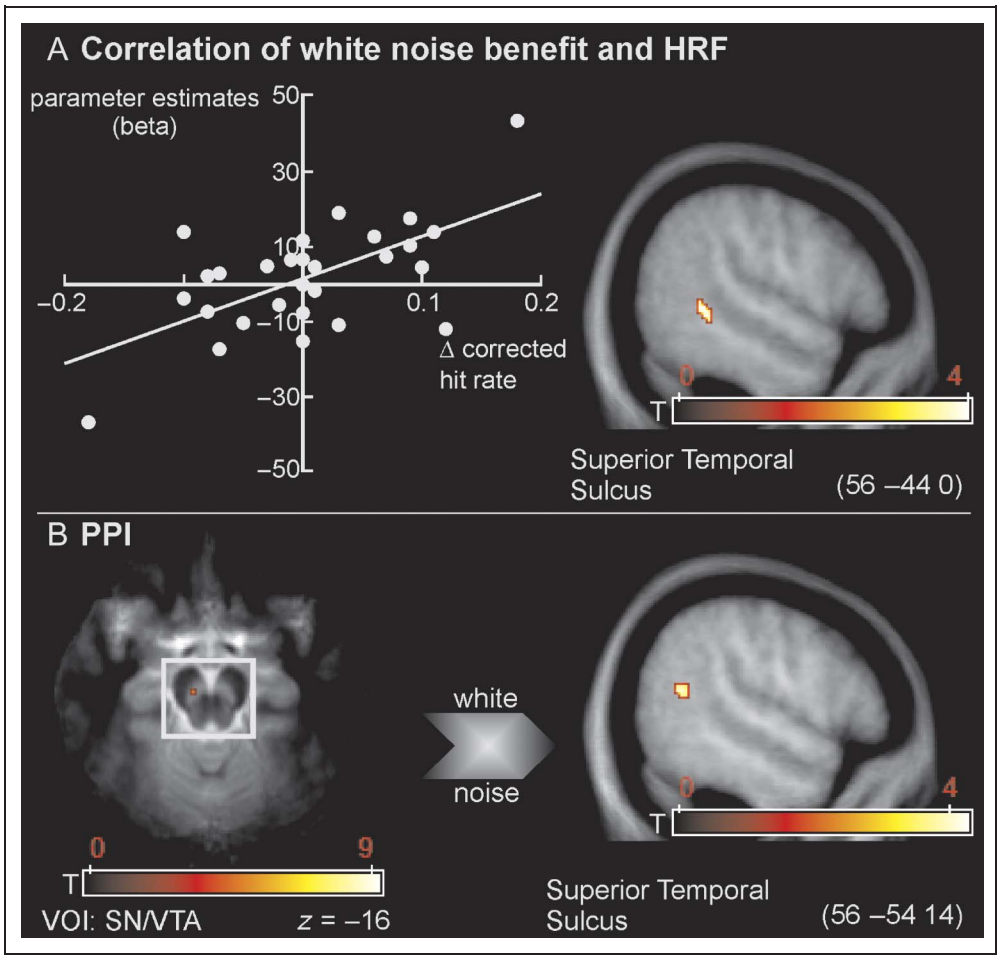

Figure 5. WN increases connectivity between brain regions. (A) Hemodynamic activity in the STS during encoding (i.e., activity to novel items in the context of WN vs. NoN; parameter estimates, beta) correlated with the memory improvement by WN (i.e., the difference in corrected hit rate for novel items in the context of WN vs. NoN; Δ corrected hit rate). The graph shows the individual values (dots) and the regression line (Pearson's correlation). (B) Psychophysiological interaction between SN/VTA and the STS modeled by WN showing increased functional connectivity between both regions (seed: SN/VTA). Results are displayed at $p < .001$ (uncorrected), extent threshold 15 voxels (except B: $p < .05$, whole brain FWE).

The posterior STS is part of the TPJ and plays a critical role in attention processing (see Discussion). See Table 4 for a list of all activated brain regions.

Finally, a psychophysiological interaction (PPI) analysis was performed to investigate the effects of WN on functional connectivity. This method allows to detect brain regions in which connectivity to a predefined seed region is modeled by an experimental factor (in this case, WN; Friston et al., 1997). Here, as a seed region we used the SN/VTA cluster showing an event-related main effect of WN (peak at [−6 −22 −18]). The PPI analysis revealed positive effects (i.e., increased functional connectivity) in several brain regions (Table 4), including the posterior STS (Figure 5B), but none of them survived whole brain FWE correction ($p > .05$). This positive effect indicates increased functional connectivity between the SN/VTA and the STS in relation to WN (see Discussion).

Moreover, the STS is known as a key player in audio-visual integration (Hein & Knight, 2008). Indeed, both STS clusters (i.e., revealed by PPI and regression analysis) survived SVC when using a box of 20 × 20 × 20 mm centered around [50, −50, 12] ($p = .047$ FWE-corrected for the regression; $p = .025$ FWE-corrected for the PPI). This center coordinate was derived from a meta-analysis on the function of the STS (Hein & Knight, 2008), revealing an STS cluster that appears to be particularly relevant for integrating audio-visual signals (see Discussion).

DISCUSSION

In one behavioral and one fMRI experiment, we investigated whether WN can improve learning and aimed to identify neuronal correlates of its beneficial effect. There are four main results of this study: first, auditory WN, when presented during encoding outside the MRI scanner, slightly improves subsequent recognition memory. Second, at the neural level, WN decreases sustained activity and, at the same time, increases stimulus-driven responses in the auditory cortex and SN/VTA. Third, the beneficial effect of WN on memory performance is positively correlated with hemodynamic responses in the STS and the striatum, a dopaminergic output region of the SN/VTA. And fourth, WN increases functional connectivity between SN/VTA and STS.

During perception, WN can improve information processing, as shown across modalities and species (for a review, see McDonnell & Ward, 2011; Moss et al., 2004). For instance, the perception of a weak or subthreshold visual (Piana, Canfora, & Riani, 2000; Simonotto et al., 1997), auditory (Behnam & Zeng, 2003; Zeng, Fu, &

Morse, 2000), or tactile (Ivey, Apkarian, & Chialvo, 1998; Collins, Imhoff, & Grigg, 1996) stimulus can be enhanced by adding WN. Although the underlying mechanisms still remain debated, one possibility is that WN enhances the weak signal's amplitude, which, as a result, exceeds the perception threshold (Moss et al., 2004).

Apart from its effects on perception, there is also evidence that WN can enhance more cognitive functions. In children with ADHD (Söderlund et al., 2007) and healthy monkeys (Carlson, Rämä, Artchakov, & Linnankoski, 1997) adding auditory WN during learning increased memory performance and in healthy humans, WN can increase the retrieval speed in simple arithmetical tasks (Usher & Feingold, 2000). Our data extend these findings by demonstrating that auditory WN slightly but selectively enhances memory performance when presented during encoding. That means, other forms of auditory noise, such as a sinus tone or the noise of a running horse played backward, did not induce such an effect. This is important to note because it further underlines the specificity of WN on cognition rather than being an unspecific effect of auditory stimulation, which could not be excluded on the basis of some previous studies.

Dopamine is a critical neuromodulator for synaptic plasticity (Tritsch & Sabatini, 2012; Morris, 2006; Jay, 2003) and has recently been linked with the effects of WN on learning (Pålsson, Söderlund, Klamer, & Bergquist, 2011; Sikström & Söderlund, 2007). More precisely, the work by Söderlund and colleagues demonstrates that, in inattentive or children with ADHD, WN improves learning possibly by compensating low tonic dopamine levels (Söderlund et al., 2010; Sikström & Söderlund, 2007). Our findings strongly implicate that—in healthy adults—adding moderate levels of WN reduces tonic dopamine activity (i.e., reduced sustained effects in the SN/VTA), which boosts phasic dopamine release in response to external stimulation (i.e., increased event-related effects in the SN/VTA). Importantly, the negative correlation between sustained and event-related SN/VTA activity (Figure 4) further supports this claim and concords with the account by Grace (1991), suggesting that finely tuned interactions between tonic and phasic dopamine activity may be the basis to maintain balanced dopamine levels. Specifically, through presynaptic autoreceptors high tonic dopamine levels are supposed to down-regulate stimulus-driven phasic responses and, conversely, low tonic dopamine concentrations lead to increased phasic activity. Functionally, the latter (i.e., increased phasic dopamine release) could drive memory performance through enhanced synaptic plasticity in downstream brain regions (Lisman et al., 2011; Lisman & Grace, 2005).

One potential caveat of this interpretation relates to the fact that BOLD fMRI is only an indirect marker of neural activity and associated neurotransmitter release. However, there is some evidence indicating that fMRI activity in the SN/VTA correlates with ventral striatal dopamine release (Schott et al., 2008). One may further address this open question by combining our or similar tasks with psychopharmacological means or PET.

How can WN modulate activity in neurotransmitter systems? According to the MBA model, facilitated information processing in the dopaminergic system could be induced through inputs from perceptual brain regions (Sikström & Söderlund, 2007). Moreover, Ward et al. (2010) have demonstrated that auditory WN facilitates perception and increases neuronal synchronization within and between brain regions, such as the auditory cortex and superior frontal gyrus, suggesting that increased connectivity is one of the underlying neural mechanisms. Indeed, we not only observed differential sustained and event-related responses in the auditory cortex that mimic those observed in the SN/VTA but also stronger connectivity between the SN/VTA and the posterior STS. Importantly, STS activity also correlated with the beneficial effects of WN on learning, suggesting a causal relationship.

Functionally, one prominent role of the posterior STS relates to the modulation of attentional demands (Corbetta, Patel, & Shulman, 2008). More precisely, the STS is part of the TPJ cortex, which, together with the supramarginal gyrus and parts of the ventral pFC, forms a ventral frontoparietal attention network that is involved in detecting salient information as well as in reorienting toward behaviorally relevant stimuli (Corbetta et al., 2008). Because dopamine not only plays a role in synaptic plasticity and learning but also attention (Nieoullon, 2002), we take these findings to suggest that WN enhances phasic dopamine release, which, in turn, increases the salience/relevance of externally presented items (via the ventral attention network) and therefore improves encoding and memory formation. Physiologically, this view is further supported by the fact that D1 receptors are expressed in the STS (Black, Hershey, Gado, & Perlmutter, 2000). Moreover, participants with higher extracellular dopaminergic levels (because of a homozygote Met158 allele polymorphism in the COMT and thus lower COMT activity) showed improved memory performance (Goldberg et al., 2003) and increased cortical thickness in the STS compared with participants with lower dopamine levels (Cerasa et al., 2010).

Alternatively, the increased connectivity between SN/VTA and posterior STS could relate to increased demands to integrate visual scene information with the auditorily presented WN. Indeed, the location of the STS activity is in the vicinity of a brain region that Hein and Knight (2008) characterized to be involved in audiovisual integration (see Results). However, future studies are needed to further investigate whether and how increased audiovisual integration might contribute to enhanced subsequent memory performance.

We observed neural novelty signals in the MTL (including hippocampus and parahippocampal gyrus) but, unexpectedly, not SN/VTA (Bunzeck et al., 2013; Bunzeck & Duzel, 2006; Lisman & Grace, 2005). One speculation is that the absence of novelty effects and the absence of improved subsequent recognition memory by WN (in

Experiment 2) might be because of an interaction between the MRI scanning procedure and additional noise presentation. It is known that MRI environments can raise stress and cortisol levels (Tessner, Walker, Hochman, & Hamann, 2006), which could have interfered with memory formation (Tessner et al., 2006) and possibly the responsiveness of the SN/VTA to novelty. This view receives some support from the fact that memory performance for the WN condition was significantly better in Experiment 1 (i.e., when encoding and retrieval was performed outside the MRI) as compared with Experiment 2 (i.e., when items were encoded inside the MRI; $t(64) = 2.964$, $p = .009$, two-sample t test); however, it is difficult to directly compare both experiments because they also differed in the number of noise conditions (four in Experiment 1 and three in Experiment 2), the number of trials per condition, and the fact that there were familiar items in Experiment 2 but not Experiment 1. Nevertheless, overall memory performance (i.e., across all conditions) was significantly better in Experiment 1 in contrast to Experiment 2 ($t(234) = 3.614$, $p < .001$), which also supports the notion of a negative impact of the scanner environment on memory formation.

On a similar note, we acknowledge that the behavioral effect of WN seems to be rather weak even in the absence of MRI scanner noise (i.e., Experiment 1). Nevertheless, it concords well with previous reports of beneficial effects of WN on cognitive functions, including memory performance (McDonnell & Ward, 2011; Moss et al., 2004), which formed the basis for our a priori hypotheses. Under the assumption that dopaminergic neuromodulation is a key factor for the observed effects, future studies may further investigate the mediating role of genetic polymorphisms or personality traits, such as novelty seeking or reward dependence.

Taken together, we can show that auditory WN slightly enhances subsequent memory performance and differentially modulates sustained and event-related neural activity in the auditory cortex and SN/VTA. Together with enhanced functional connectivity between the SN/VTA and STS, these findings concur with the notion of a causal relationship between dopamine and the facilitating effects of WN on cognition. Specifically, we suggest that enhanced phasic dopamine release by WN modulates STS activity, which drives attention and therefore improves encoding and memory formation. From a more general perspective, our results point toward nonpharmacological strategies for treating memory impairments associated with healthy and pathological aging that are characterized by a degeneration of the dopaminergic system.

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