Neuropsychologia 51 (2013) 2469–2477

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Reprint of: DAT genotype modulates striatal processing and long-term memory for items associated with reward and punishment ☆, ☆☆

Bianca C. Wittmann [a,b,c,*], Geoffrey C. Tan [a,d,e], John E. Lisman [f], Raymond J. Dolan [a], Emrah Düzel [g,h,i]

[a] Wellcome Trust Centre for Neuroimaging, University College London, London, WC1N 3BG, UK
[b] Helen Wills Neuroscience Institute, University of California, Berkeley, CA 94720, USA
[c] Department of Psychology, University of Giessen, 35394 Giessen, Germany
[d] Psychiatry Residency Programme, National Healthcare Group/Ministry of Health, Singapore, Singapore
[e] Agency for Science, Technology and Research, Singapore, Singapore
[f] Department of Biology and Volen Center for Complex Systems, Brandeis University, Waltham, MA 02454, USA
[g] Institute of Cognitive Neuroscience, University College London, London, W1CN 4AR, UK
[h] Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University, 39120 Magdeburg, Germany
[i] German Centre for Neurodegenerative Diseases (DZNE), Standort, Magdeburg, Germany

ARTICLE INFO

Keywords:
Episodic memory
Reward
Dopamine
Hippocampus
Striatum

ABSTRACT

Previous studies have shown that appetitive motivation enhances episodic memory formation via a network including the substantia nigra/ventral tegmental area (SN/VTA), striatum and hippocampus. This functional magnetic resonance imaging (fMRI) study now contrasted the impact of aversive and appetitive motivation on episodic long-term memory. Cue pictures predicted monetary reward or punishment in alternating experimental blocks. One day later, episodic memory for the cue pictures was tested. We also investigated how the neural processing of appetitive and aversive motivation and episodic memory were modulated by dopaminergic mechanisms. To that end, participants were selected on the basis of their genotype for a variable number of tandem repeat polymorphism of the dopamine transporter (DAT) gene. The resulting groups were carefully matched for the 5-HTTLPR polymorphism of the serotonin transporter gene. Recognition memory for cues from both motivational categories was enhanced in participants homozygous for the 10-repeat allele of the DAT, the functional effects of which are not known yet, but not in heterozygous subjects. In comparison with heterozygous participants, 10-repeat homozygous participants also showed increased striatal activity for anticipation of motivational outcomes compared to neutral outcomes. In a subsequent memory analysis, encoding activity in striatum and hippocampus was found to be higher for later recognized items in 10-repeat homozygotes compared to 9/10-repeat heterozygotes. These findings suggest that processing of appetitive and aversive motivation in the human striatum involve the dopaminergic system and that dopamine plays a role in memory for both types of motivational information. In accordance with animal studies, these data support the idea that encoding of motivational events depends on dopaminergic processes in the hippocampus.

1. Introduction

Reward improves episodic memory formation in humans (Shohamy & Adcock, 2010). Functional imaging studies have shown that memory encoding of reward-associated stimuli involves a network of dopaminergic midbrain areas, ventral striatum and hippocampus (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Callan & Schweighofer, 2008; Krebs, Schott, Schutze, & Duzel, 2009; Wittmann et al., 2005). Evidence from animal studies suggests that this reward-related modulation of long-term memory could be mediated by dopamine release in the hippocampus (Bethus, Tse, & Morris, 2010; for a review of dopamine effects on hippocampal long-term potentiation, see Lisman, Grace, & Duzel, 2011; Otmakhova, Duzel, Deutch, & Lisman, 2013; Rossato, Bevilaqua, Izquierdo, Medina,

DOI of original article: http://dx.doi.org/10.1016/j.neuropsychologia.2013.07.018

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*Corresponding author at: Department of Psychology, University of Giessen, 35394 Giessen, Germany. Tel.: +49 641 99 26160; fax: +49 641 99 26169.
E-mail address: bianca.wittmann@psychol.uni-giessen.de (B.C. Wittmann).

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http://dx.doi.org/10.1016/j.neuropsychologia.2013.09.031

& Cammarota, 2009). This is supported by studies in humans indicating that dopamine binding potential in the hippocampus is correlated with memory performance (Backman et al., 2000; Cervenka, Backman, Cselenyi, Halldin, & Farde, 2008; Takahashi et al., 2007, 2008).

In contrast to the memory effects of monetary reward, little is known about the effects of monetary punishments on episodic memory formation. For emotional stimuli, it has been shown that negative emotional events are remembered better than emotionally neutral events, and that this effect involves the amygdala (for a review see Murty, Ritchey, Adcock, & LaBar, 2010). For aversive motivation, there have been inconsistent reports across a range of human memory tasks. Whereas aversive electrical stimulation impaired memory in a human version of the Morris water maze (Murty, LaBar, Hamilton, & Adcock, 2011), threat of shocks enhanced memory for scene images when participants were tested 24 h later, an effect that was based on amygdala-hippocampal interaction at encoding (Murty, LaBar, & Adcock, 2012). When monetary rewards and punishments were dependent on memory performance, threat of monetary loss enhanced source memory retrieval in a similar manner to reward when tested immediately after learning (Shigemune, Tsukiura, Kambara, & Kawashima, 2013). This was associated with a correlation of activity in striatum and hippocampus during successful source retrieval. In contrast, punishment cues during an incidental memory task had no effect on item recollection or recognition when tested immediately after learning (Mather & Schoeke, 2011). These contrasting results suggest that the effect of punishment on memory may be dependent on contextual influences. The current study investigated whether monetary punishment affects memory consolidation through a dopaminergic network.

Appetitive and aversive motivation have been suggested to be processed in opponent brain systems, with rewards eliciting dopaminergic activity and punishments eliciting serotonergic activity (Daw, Kakade, & Dayan, 2002). More recent data indicate that punishments can also induce firing of dopaminergic neurons in rats (Brischoux, Chakraborty, Brierley, & Ungless, 2009) and monkeys (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Matsumoto & Hikosaka, 2009), although other data suggest that punishment-responsive SN/VTA neurons are GABAergic (Cohen, Haesler, Vong, Lowell, & Uchida, 2012). By combining fMRI with genetics, the current study investigated transmitter specificity of midbrain signals in humans. In humans, striatal activity has been shown to correlate with aversive predictions (Carter, Macinnes, Huettel, & Adcock, 2009; Delgado, Li, Schiller, & Phelps, 2008; Seymour et al., 2004; Seymour, Daw, Dayan, Singer, & Dolan, 2007). Current models propose that the interaction of appetitive and aversive motivation in the dopamine and serotonin systems could depend on the overall motivational value of the context and on action requirements (Boureau & Dayan, 2011; Cools, Nakamura, & Daw, 2011). A recent study supports these models by demonstrating the relevance of action requirements for activation of SN/VTA and the striatum in humans (Guitart-Masip et al., 2011). Thus, when investigating the effects of dopamine-related polymorphisms on episodic memory for appetitive and aversive events, it is important to stratify and match populations for polymorphisms that influence serotonergic neurotransmission. After non-synaptic sources, transporter concentration is the most important factor in neurotransmitter homeostasis (Pendyam, Mohan, Kalivas, & Nair, 2012). The genes for the serotonin transporter, SLC6A4/SERT, and the dopamine transporter, SLC6A3/DAT1, both contain length variations in their promoter regions that regulate expression of their respective transporters. As transporters both influence speed of reuptake from the synapse and increase presynaptic neurotransmitter availability, they may be expected to shape phasic neuromodulation seen in reward and punishment.

The current study investigated (i) whether anticipation of monetary punishments modulates episodic memory, (ii) whether reward and punishment related anticipation and memory are modulated by dopamine transporter genotype under conditions when groups are matched for serotonin transporter genotype, and (iii) the common and dissociable fMRI correlates of these processes. Subjects were genotyped for common polymorphisms in the dopamine transporter (DAT1 VNTR) and serotonin transporter (5-HTTLPR) and scanned during a motivational anticipation task, followed one day later by a memory test outside the scanner. In line with previous studies (Adcock et al., 2006; Wittmann et al., 2005; Wittmann, Schiltz, Boehler, & Duzel, 2008), we expected reward-predicting stimuli to activate the SN/VTA system and enhance episodic memory. Based on reports of activations in the dopaminergic system for aversive stimuli, we hypothesized that punishment prediction would also activate the mesolimbic system. Increased dopaminergic transmission was expected to lead to improved episodic memory performance.

2. Experimental procedures

2.1. Participants

A total of 24 healthy adults (all right-handed, mean age [± SD] 25.3 ± 3.9 years; 8 men) participated in the study. They were screened for neurological conditions and past psychiatric disorders using the Mini International Neuropsychiatric Inventory (Sheehan et al., 1998) and provided blood samples for genotyping. The study was designed to compare DAT 9-repeat carriers and 10-repeat homozygotes based on previous reports of a role of the DAT VNTR in dopaminergic modulation of memory (Bertolino et al., 2008; Schott et al., 2006). We here report comparisons of the DAT 10-repeat homozygotes with DAT 9/10-repeat heterozygotes. There were no DAT 9-repeat homozygotes in the participant sample. The two DAT groups were matched for age, gender and 5-HTTLPR genotype. In relation to 5-HTTLPR, only short allele homozygotes (SS) and long allele homozygotes (LL) were included in this study. The final sample included 12 participants from each DAT group. Half of the participants in each group were SS homozygotes and half were LL homozygotes. The majority of participants were invited based on their genotype. Additionally, some participants were genotyped after scanning and excluded if they were heterozygous for 5-HTTLPR (seven participants). Because the overall sample was non-random, we did not calculate Hardy–Weinberg equilibrium statistics. Twenty-one participants were Caucasian, three participants were Asian (two 10-repeat homozygotes, one 9/10-repeat heterozygous). To address possible effects of ethnicity, second-level analyses were performed excluding the three Asian participants. Since there was no significant change in the result, we report analyses of the combined group. All participants gave written informed consent, and the study was approved by the local ethics committee.

2.2. Behavioural task

We obtained fMRI data while participants were completing alternating blocks of a reward and punishment task (modified from Wittmann et al., 2005). Before entering the scanner, participants received written instructions and completed a practice version of each block type. The anticipation task was presented in alternating blocks of reward and punishment. In each block, motivational stimuli were randomly mixed with neutral stimuli in an event-related design. This design allowed a contrast of each motivational category with corresponding neutral items from the same block as well as a direct contrast of appetitive and aversive motivational processes. At the beginning of each block, participants were informed of the motivational block type (reward/punishment). At the beginning of each trial, the motivational status of the trial (motivational/neutral) was indicated by the category of a picture on