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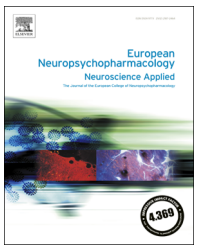

Nicotine-dopamine-transporter interactions during reward-based decision making

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Abstract
Our everyday-life comprises a multitude of decisions that we take whilst trying to maximize advantageous outcomes, limit risks and update current needs. The cognitive processes that guide decision making as well as the brain circuits they are based on are only poorly understood. Numerous studies point to a potential role of dopamine and nicotine in decision making but less is known about their interactions. Here, 26 healthy male subjects performed the Iowa Gambling Task (IGT) in two sessions following the administration of either nicotine or placebo. Striatal dopamine transporter (DAT) binding was measured by single-photon emission computed tomography (SPECT). Results indicate that lower DAT levels were associated with better performance in the IGT (p=0.0004). Cognitive modelling analysis using the prospect valence learning (PVL) model indicated that low DAT subjects' performance deteriorated following nicotine administration as indicated by an increased learning rate and a decreased response consistency. Our results shed light on the neurochemistry underlying reward-based decision making in humans by demonstrating a significant interaction between nicotine and the DAT. The observed interaction is consistent with the hypothesized associations between DAT expression and extracellular dopamine levels, suggestive of an inverted U-shape relationship between baseline dopamine and magnitude in response to a pro-dopaminergic compound. Our findings are of particular interest in the context of psychiatric disorders where aberrant decision making represents a part of the core symptomatology, such as addiction, schizophrenia or depression.

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1. Introduction

Decision making represents a higher-level cognitive ability involving multiple basal cognitive functions such as learning from past experiences, representing available options or internal needs, selecting actions as well as evaluating outcomes (Rangel et al., 2008). Understanding the cognitive and motivational factors that underlie decision making as well as their neurobiological underpinnings is central to understanding human behaviour, not only in healthy individuals but also in psychiatric patients where aberrant decision making frequently represents a core of the symptomatology (Maia and Frank, 2011; Montague et al., 2012; Lee, 2013).

Multiple studies have implicated dopaminergic neurotransmission in reward based decision making especially in the striatum (Everitt and Robbins, 2005; Schultz, 2007). At the same time nicotine seems to assert effects on individuals' choice behaviour (Xiao et al., 2008; Buelow and Suhr, 2014) by modulating dopaminergic circuits (Brody et al., 2004, 2009; Scott et al., 2007; Takahashi et al., 2008). However, little is known about the interplay of dopaminergic and nicotinergic circuits in the moderation on reward-based decision making.

The Iowa Gambling Task (IGT) represents a well investigated experimental paradigm to model real-life decision making in a controlled laboratory setting (Bechara et al., 1994). Subjects are instructed to select cards from four available decks while trying to maximize reward. The cognitive and motivational processes underlying decision making in the IGT can be disentangled with the help of cognitive modelling (Yechiam et al., 2005; Ahn et al., 2008). The prospect valence learning model (PVL model) represents one of the most recently formulated models of the IGT (Ahn et al., 2008, 2011). It decomposes participants' choice behaviour into four latent variables that are hypothesized to guide decision making: learning rate, sensitivity to gains, sensitivity to losses and response consistency. Importantly, cognitive models of the IGT such as PVL allow the identification of clinical populations that show specific changes in decision making such as increased sensitivity to rewards in amphetamine abusers (Ahn et al., 2014).

The IGT has successfully been employed to demonstrate the role of dopamine (DA) for reward-based decision making. A recent PET study reported an association of D2/D3-receptor binding potential in the striatum and IGT performance in healthy subjects, suggesting better performance in subjects with high striatal DA levels (Linnet et al., 2010). The major determinant of striatal DA levels is the presynaptically located dopamine transporter (DAT) which enables reuptake of DA from the synaptic cleft into the presynaptic neuron. A role of the DAT in reward processing has been demonstrated in subjects with attention deficit hyperactivity disorder (ADHD) (Volkow et al., 2011) as well as in a rodent model of the IGT (Van Enkhuizen et al., 2014).

At the same time nicotine has been found to influence IGT performance (Xiao et al., 2008; Buelow and Suhr, 2014). Lower IGT scores have been reported in subjects who smoked in the past seven days (Xiao et al., 2008) and in smokers who stayed abstinent over night (Buelow and Suhr, 2014) but not in smokers compared to non-smokers (Businelle et al., 2008). In general, acute nicotine administration exerts positive effects on cognitive functions that underlie decision making such as attention, short-term episodic memory or working memory (Heishman et al., 2010). On the molecular level nicotine binds to the nicotinic acetylcholine receptor (nAChR), although some of nicotine's cognitive effects likely result from an interplay of cholinergic agonism with downstream dopaminergic neurotransmission (Jacobsen et al., 2006; Zhu and Reith, 2008). Specifically, administration of cholinergic substances such as nicotine leads to an increase of dopamine levels in the striatum (Brody et al., 2004, 2009; Scott et al., 2007; Takahashi et al., 2008) probably via binding to nAChR of dopaminergic neurons located in the striatum and the ventral tegmental area (Nisell et al., 1994; Ferrari et al., 2002).

Thus, recent results indicate a significant role of striatal DA and nicotine during reward-based decision making. While on the molecular level the interplay of nicotine and dopamine has been demonstrated, their mutual effects during reward-based decision have – to the best of our knowledge – not been investigated so far. We, therefore, administered nicotine and placebo to healthy volunteers before they performed the IGT to measure the compound's effects on decision making. We also obtained single-photon emission computed tomography (SPECT) scans of striatal DAT in order to investigate whether this key molecule in striatal dopamine neurotransmission is related to IGT performance and its modulation by nicotine.

2. Experimental procedures

2.1. Participants

In the present study twenty-six healthy, non-smoking, male volunteers were recruited (mean age=26.68 years, SD=2.91). Participants were screened for possible psychiatric diseases by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and excluded in case of a psychiatric condition, a first-degree relative with psychosis, a history of neurological illness or another severe medical condition, head injury with loss of consciousness of >5 min, lifetime history of alcohol or substance abuse or dependence, visual impairments, obesity (body mass index>30), intake of any medications which act on the CNS. Verbal IQ was estimated with a standardized German vocabulary test, the Mehrfachwahl-Wortschatz-Intelligenztest-B (Lehrl, 2005). Approval of the ethics committee of the Faculty of Medicine of the University of Munich was obtained. Participants provided written informed consent before inclusion.

2.2. Experimental design

Prior to the study all participants took part in a baseline session including a health check in form of questionnaires, blood-testing, electrocardiography and electroencephalography to exclude cardiovascular or metabolic disorders that might have put participants at risk following nicotine administration. Participants were then tested in two separate sessions using a double-blind, placebo-controlled counterbalanced within-subjects design.

Nicotine (NiQuitin Clear 7 mg, GlaxoSmithKline, Germany) and placebo (Fink and Walter GmbH, Germany) patches were applied on the participants' right upper back by a research assistant who was not involved in any further testing in order to ensure double blindness. Following a 3-hour waiting period to allow for stable peak plasma levels of nicotine (Petrovsky et al., 2013; http://www.pharmazie.com/graphic/A/35/1-23135.pdf), participants performed the IGT.

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