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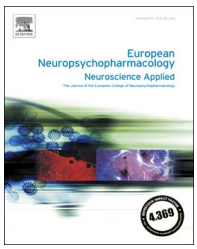

Noradrenaline transporter blockade increases fronto-parietal functional connectivity relevant for working memory

Dennis Hernaus[a,*], Marta M[a] Casales Santa[b], Jan Stefan Offermann[b], Thérèse Van Amelsvoort[b]

[a]*University of Maryland School of Medicine, Department of Psychiatry; Maryland Psychiatric Research Center, MD, USA*
[b]*Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, School for Mental Health and NeuroScience MHeNS Maastricht University, Maastricht, The Netherlands*

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Abstract
Experimental animal work has demonstrated that dopamine and noradrenaline play an essential role in modulating prefrontal cortex-mediated networks underlying working memory performance. Studies of functional connectivity have been instrumental in extending such notions to humans but, so far, have almost exclusively focussed on pharmacological agents with a predominant dopaminergic mechanism of action. Here, we investigate the effect of a single dose of atomoxetine 60 mg, a noradrenaline transporter inhibitor, on working memory performance and associated functional connectivity during an n-back task in 19 healthy male volunteers. Atomoxetine increased functional connectivity between right anterior insula and dorsolateral prefrontal cortex, precentral gyrus, posterior parietal cortex and precuneus during the high-working memory load condition of the n-back task. Increased atomoxetine-induced insula-dorsolateral prefrontal cortex functional connectivity during this condition correlated with decreased reaction time variability and was furthermore predicted by working memory capacity. These results show for the first time that noradrenaline transporter blockade-induced increases in cortical catecholamines accentuate fronto-parietal working memory-related network integrity. The observation of significant inter-subject variability in response to atomoxetine has implications for inverted-U frameworks of dopamine and noradrenaline function, which could be useful to predict drug effects in clinical disorders with variable treatment response.

*Correspondence to: Department of Psychiatry; Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228 USA.
E-mail address: dhernaus@mprc.umaryland.edu (D. Hernaus).

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1. Introduction

Cortical dopamine (DA) and noradrenaline (NA) play an essential role in orchestrating neural networks underlying working memory and attention (Goldman-Rakic, 1995). While a wide range of brain networks underlie these executive functions, they most consistently depend on contributions from prefrontal cortex (PFC)-mediated networks that among others include dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex and insula (Niendam et al., 2012). A better understanding of DA and NA's action in PFC-mediated networks could improve pharmacological treatment of mental disorders associated with cognitive deficits such as schizophrenia (Glahn et al., 2005; Zhang et al., 2016) and attention-deficit hyperactivity disorder (Hart et al., 2013) (ADHD). Here, we investigate for the first time how NA transporter blockade modulates frontal cortical functional connectivity (FC) in healthy volunteers during a working memory paradigm, how this relates to task performance and how inter-individual differences predict these effects.

The ability of catecholamines to sculpt neuronal networks is directly related to their signal-to-noise modulating properties: DA receptor subtype 1 (D1) activation selectively decreases resource allocation to 'noise' processing (Arnsten, 2011; Vijayraghavan et al., 2007), thought to facilitate a state of focused attention (Seamans et al., 2001). In contrast, D1 blockade markedly decreases delayed working memory performance (Sawaguchi and Goldman-Rakic, 1994) and D2 stimulation increases activity in response-related networks thought to underlie a more flexible form of attention (Arnsten, 2011). Modulation of γ-aminobutyric acid (GABA)ergic interneuron excitability is one essential mechanism by which DA tunes PFC-mediated neural networks (Seamans et al., 2001), with these GABAergic interneurons projecting onto pyramidal neurons. In comparison, NA optimizes PFC-mediated networks by increasing 'signal' processing, rather than decreasing noise (Arnsten, 2011); stimulation of α2A-adrenoceptors increases activity of neural ensembles that fire for similar preferred directions during a spatial working memory task. In contrast, pharmacological blockade of these receptors impairs working memory performance and decreases overall PFC functionality (Wang et al., 2007). Correspondingly, pharmacological agents that increase extracellular cortical DA and NA have been shown to increase signal *and* decrease noise-related firing of neurons (Gamo et al., 2010).

While the notion that catecholamines are essential regulators of PFC-mediated networks has been extensively validated in experimental animals, evidence in humans stems from indirect sources. Studies of FC – a neuroimaging technique that assesses task-dependent correlations between brain areas (O'Reilly et al., 2012) – have played an important role in unraveling how catecholaminergic activity reorganizes functional brain networks in man. However, the majority of these studies have focused on the DA system. For example, D2 agonism (Bloemendaal et al., 2015) and D1 antagonism (Rieckmann et al., 2012) modulate FC of working memory networks involving dlPFC, a region essential for working memory performance and part of a task-positive network (Niendam et al., 2012). Moreover, levodopa, which increases extracellular DA over and above NA (Dolphin et al., 1976; Everett and Borcherding, 1970), and D2 antagonist haloperidol exert opposing effects on frontal cortico-striatal FC at rest (Cole et al., 2013).

How selective NA transporter blockade affects the integrity of functional brain networks that subserve executive functions is less clear. In Parkinson's disease, atomoxetine – a potent NA transporter inhibitor that increases extracellular cortical DA and NA (Bymaster et al., 2002) - increases resting-state FC between dlPFC and anterior cingulate cortex, which correlates with a measure of drug-induced cognitive improvement (Borchert et al., 2016). Moreover, atomoxetine weakens FC within the default-mode network (van den Brink et al., 2016), a task-negative network in which activity decreases with increasing task demands (i.e. task-related deactivation). In the current study, we investigated how a single dose of atomoxetine impacted FC of PFC regions during a well-validated working memory task. We predicted that NA transporter blockade, similar to studies of DA agonism, would I) preferentially accentuate FC between PFC regions relevant for task performance, and, II) that drug-induced changes in FC correlated with task performance parameters sensitive to changes in catecholamine function.

Importantly, however, considerable variation exists in the effect of catecholamine-enhancing agents on cognition-related brain activity and cognitive performance, which can be predicted by surrogate markers of catecholamine function such as catechol-o-methyl transferase (COMT) genotype (Mattay et al., 2003) (although also see (Wardle et al., 2013)) and baseline working memory capacity (Kimberg et al., 1997; Mehta et al., 2004). We therefore additionally hypothesized that the extent to which atomoxetine modulated FC within task-relevant PFC regions is dependent on baseline catecholamine function. To these aims, we obtained a measure of working memory capacity which has previously shown to predict the effect of methylphenidate on working memory-related brain function (Mehta et al., 2000), cognitive performance (Mehta et al., 2004) and DA synthesis capacity (Cools et al., 2008). In accordance with previous work (Cools et al., 2008; Kimberg et al., 1997; Mehta et al., 2004), we hypothesized that individuals with the lowest working memory capacity would show the greatest increase in task-positive PFC FC following atomoxetine administration.

2. Experimental procedures

2.1. Participants

Twenty-two healthy male right-handed non-smokers between 18–30 years were recruited from a student population (M=23.26,

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