Neuropsychologia 56 (2014) 263–270

Contents lists available at ScienceDirect

Neuropsychologia

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

Dissociable and common effects of methylphenidate, atomoxetine and citalopram on response inhibition neural networks

L. Sanjay Nandam [a], Robert Hester [b], Mark A. Bellgrove [c,*]

[a] Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
[b] School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia
[c] Monash University, School of Psychology and Psychiatry, Melbourne 3800, Victoria, Australia

ARTICLE INFO

Article history:
Received 13 July 2013
Received in revised form
27 January 2014
Accepted 31 January 2014
Available online 8 February 2014

Keywords:
Methylphenidate
Atomoxetine
Citalopram
Go no-go
Response inhibition
fMRI

ABSTRACT

Response inhibition is an executive function that allows the detection and modification of unwanted actions. Its underlying neurochemistry and neurobiology have been explored by combining classic neuropsychological paradigms, such as the go/no-go task (GNG), with targeted pharmacology and functional neuroimaging. We sought to further this literature by using single doses of methylphenidate (30 mg), atomoxetine (60 mg), citalopram (30 mg) and placebo to probe dopaminergic, noradrenergic and serotonergic aspects of response inhibition. Twenty-seven (27) healthy, right-handed males participated in a randomised, double blind, placebo-controlled, within subject, crossover fMRI study to examine stop-related BOLD activation correlates of a modified GNG task.

Methylphenidate demonstrated activation versus placebo in the pregenual cingulate (dorsal anterior cingulate), right inferior frontal, left middle frontal, left angular and right superior temporal gyri and right caudate. Atomoxetine demonstrated activation versus placebo across a broad network of cortical regions. Both methylphenidate and atomoxetine, but not citalopram, activated superior temporal, right inferior frontal and left middle frontal clusters. Citalopram only activated the left inferior occipital lobe.

Taking the above as functionally defined regions of interest, we examined the specificity of stop-related drug activity by comparing mean activations across the four conditions. Only methylphenidate demonstrated drug-specific effects with increased activation of the pregenual cingulate and decreased activation of the caudate.

Direct comparison of methylphenidate and atomoxetine showed broad recruitment of prefrontal regions but specific effects of methylphenidate in the pregenual cingulate and caudate revealing dissociable modulations of response inhibition networks.

1. Introduction

Methylphenidate and atomoxetine are two of the most widely prescribed and efficacious treatments for attention deficit hyperactivity disorder (ADHD). Both medications also ameliorate deficits of response inhibition, an executive function that modifies the automatic tendency to act in a given situation, in both adult and child ADHD populations (Aron, Dowson, Sahakian, & Robbins, 2003; Chamberlain, Del Campo et al., 2007; Gau & Shang, 2010; Overtoom et al., 2003). These clinical findings have provided impetus for investigating the underlying neurobiology of response inhibition, especially when response inhibition deficits are thought to be prototypical of ADHD (Crosbie & Schachar, 2001). Importantly, methylphenidate and atomoxetine have also been shown to augment response inhibition in wild-type animals (Eagle, Tufft, Goodchild, & Robbins, 2007; Robinson et al., 2008) and healthy adults (Chamberlain, Muller, Cleary, Robbins, & Sahakian, 2007; Nandam et al., 2011), suggesting that these agents are modulating evolutionarily conserved, and therefore fundamental, response inhibition neurobiology. This work has been driven by the clinical need for a robust foundational model of response inhibition, not least because inhibitory impairments extend beyond ADHD. Indeed response inhibition deficits have also been observed in obsessive-compulsive disorder (Menzies et al., 2007), schizophrenia (Bellgrove et al., 2006), cocaine dependence (Hester & Garavan, 2004), antisocial and borderline personality disorders (Vollm et al., 2004) and major depression (Langenecker et al., 2007). Importantly, these deficits in executive function have been linked to adverse clinical outcomes (Field & O'Keefe, 2004). Yet progress towards a coherent neurobiological

* Corresponding author. Tel.: +61 3 9902 4200; fax: +61 3 9905 3948.
E-mail address: mark.bellgrove@monash.edu (M.A. Bellgrove).

http://dx.doi.org/10.1016/j.neuropsychologia.2014.01.023
0028-3932

model remains limited due to the inherent difficulty of combining data from heterogeneous study populations, varied drug doses and differing response inhibition paradigms.

Classical neuropsychology asserts that response inhibition is not a singular construct but instead has dissociable components that can be tested through specific paradigms (Eagle, Bari, & Robbins, 2008). One such paradigm is the go/no-go task (GNG), which requires a motor response to be made to a dominant stimulus or withheld to a less frequent one. The GNG assesses a component of response inhibition known as 'action restraint', in contrast to 'action cancellation', which is assessed by paradigms such as the stop signal task (SST) (Eagle et al., 2008). It has been suggested that the GNG and SST represent distinct forms of response inhibition that have different evolutionary purposes, and could therefore have different underlying neurobiology (Aron, 2011). In support of this, a meta-analysis of functional magnetic resonance imaging (fMRI) studies showed distinct, though partially overlapping, neural circuits underpinning response inhibition during the GNG and SST (Swick, Ashley, & Turken, 2011). GNG inhibition was distinguishable from SST inhibition by greater activation of the right middle frontal gyrus, right inferior parietal lobule/precuneus and the right inferior frontal gyrus (Swick et al., 2011). These cortical areas receive and are modulated by ascending dopaminergic, noradrenergic and serotonergic projections (Eagle et al., 2008). In addition to being established treatments for ADHD, the ability of methylphenidate and atomoxetine to modulate catecholamine levels has made them prime candidates for pharmacoimaging studies of GNG and SST inhibition.

The mixed noradrenaline and dopamine reuptake inhibitor, methylphenidate, improves GNG performance in both ADHD (Vaidya et al., 1998) and non-clinical individuals (Vaidya et al., 1998) and remains the gold standard pharmacological treatment for ADHD. Yet interpreting the available methylphenidate fMRI data has been complex, with improved performance associated with reduced caudate/putamen activity in non-clinical participants but increased caudate/putamen activity in ADHD patients (Vaidya et al., 1998). Further, acute dosage studies have suggested that methylphenidate modulates striatal activity during GNG inhibition (Rosa-Neto et al., 2005; Rubia et al., 2011), as well as down regulating activity in the inferior frontal gyrus during SST inhibition (Pauls et al., 2012).

Atomoxetine is a non-stimulant noradrenaline reuptake inhibitor that increases noradrenaline and dopamine levels in the cortex without affecting subcortical dopamine (Chamberlain, Del Campo et al., 2007). In contrast to methylphenidate, atomoxetine has been associated with an up regulation of right inferior frontal gyrus activity during SST inhibition in healthy adults (Chamberlain et al., 2009; Graf et al., 2012). Up regulation of inferior frontal gyrus activity has been reported during both improved and impaired SST performance (Chamberlain et al., 2009; Graf et al., 2012). These seemingly opposing results might be due to the differing atomoxetine doses used in the two studies (40 mg versus 80 mg), suggesting an inverted U dose–response curve (Pauls et al., 2012). There is less information available on the neural correlates of GNG inhibition following acute dosage atomoxetine in healthy adults. In a recent study of children with ADHD two parallel groups took either methylphenidate or atomoxetine, but no placebo, for 54 days and then completed a GNG task during fMRI acquisition (Schulz et al., 2012). For both drugs comparable clinical and task improvements was associated with bilateral decreases in motor cortex activation (Schulz et al., 2012). There were, however, differences between drug conditions in the right inferior frontal gyrus, left anterior cingulate cortex/supplementary motor area and bilateral posterior cingulate cortex (Schulz et al., 2012). Interestingly, and in contrast to other studies of children with ADHD, methylphenidate failed to modulate striatal activity suggesting that acute and chronic dosing of the same compound may produce different neurobiological activations.

In addition to the interest in ADHD pharmacotherapies, the presence of inhibitory deficits in major depression (Langenecker et al., 2007), obsessive compulsive disorder (Menzies et al., 2007) and personality disorder populations (Vollm et al., 2004) has prompted analogous studies using serotonergic antidepressants. Citalopram, a highly selective serotonin reuptake inhibitor, has been shown to increase activation in the lateral orbitofrontal cortex and attenuate activation in the medial orbitofrontal cortex during GNG inhibition in healthy participants (Del-Ben et al., 2005). Similar activations were found following chronic dosing of escitalopram in patients with major depression during a GNG task (Langenecker et al., 2007). There was, however, no behavioural effect on GNG performance in either study (Del-Ben et al., 2005; Langenecker et al., 2007), and citalopram does not appear to affect SST performance (Chamberlain et al., 2006; Nandam et al., 2011). Yet citalopram remains a treatment of interest for disorders that exhibit impulsivity and aggression (Kamarck et al., 2009) providing clinical impetus to keep exploring its neurobiology in response inhibition.

Here we used fMRI to contrast the neural correlates of acute doses of methylphenidate (30 mg), atomoxetine (60 mg) and citalopram (30 mg) during GNG inhibition. A within-subject cross over design was employed to control for individual differences in neurochemistry and thus allow the direct comparison of drug specific fMRI activation patterns. These direct comparisons are difficult to make in studies that use differing cohorts and testing paradigms. Our study was restricted to healthy adult subjects to maximise the applicability of findings towards foundational neurobiology. For each drug condition we expected that there would be distinct but over lapping fMRI activation patterns associated with successful inhibition, when contrasted to placebo. Methylphenidate was predicted to modulate activity in the striatum, right inferior frontal gyrus, and dorsal anterior cingulate; atomoxetine was predicted to modulate the right inferior frontal gyrus, dorsal anterior and posterior cingulate; and citalopram was predicted to regulate activity in the lateral and medial orbitofrontal cortex.

To assess response inhibition we employed the Error Awareness Task (EAT), a modified GNG task in which participants are required to indicate their conscious awareness of performance errors. In the EAT the no-go stimuli is either repeating or font-colour congruent words, which increase its complexity when compared to classical GNG paradigms that only use a single no-go condition. We have previously published on error-related brain activity elicited by this task as a function of drug condition (Hester et al., 2012). Here we present the pharmacoimaging analysis associated with successful GNG inhibition.

2. Methods and materials

2.1. Participants

Twenty-seven healthy (27), right-handed, 18–35 year old male participants were recruited via advertisements at The University of Queensland and Griffith University, Queensland, Australia. A consultant psychiatrist (LSN) excluded any participants with a history of psychiatric or neurological illness, acquired brain injury, psychotropic medication use, or significant illicit drug use. For further detail please see Hester et al. (2012).

2.2. Drug administration

The study employed a randomised, double blind, placebo-controlled, within subject, crossover design. Participants attended one testing session a week for four (4) consecutive weeks. At each session, in a randomised order and in identical capsules, they took either methylphenidate 30 mg, atomoxetine 60 mg, citalopram