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Left anterior cingulate activity predicts intra-individual reaction time variability in healthy adults

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ABSTRACT

Within-subject, or intra-individual, variability in reaction time (RT) is increasingly recognised as an important indicator of the efficiency of attentional control, yet there have been few investigations of the neural correlates of trial-to-trial RT variability in healthy adults. We sought to determine the neural correlates of intra-individual RT variability during a go/no-go response inhibition task in 27 healthy, male participants. We found that reduced trial-to-trial RT variability (i.e. greater response stability) was significantly associated with greater activation in the left pregenual anterior cingulate. These results support the role of the left anterior cingulate in the dynamic control of attention and efficient response selection. Greater understanding of intra-individual RT variability and top-down attentional control in healthy adults may help to inform disorders that impact executive/attentional control, such as attention deficit hyperactivity disorder and schizophrenia.

1. Introduction

The ability to maintain consistent attention to a task at hand is critical to all aspects of human learning and performance. Although fluctuations in attention can arise as a result of external distractors and fatigue, there is also inherent, internal fluctuation in our capacity to exert control over performance. Inherent fluctuations in neuronal activity occur both at rest and during cognitive tasks; this intrinsic variability in neuronal activity is a thought to be a primary driver of trial-to-trial behavioural variation (MacDonald et al., 2009b; Weissman et al., 2006). The variability in brain activity during cognitive tasks is thought to reflect the allocation of attentional resources at structural, functional, and neurochemical levels, which drives the subtle variation in an individual's trial-to-trial behavioural response (MacDonald et al., 2009b).

Trial-to-trial variability in behavioural response, often referred to as intra-individual variability, is thought to be a hallmark of attention deficit hyperactivity disorder (ADHD; Bellgrove et al., 2005; Castellanos et al., 2006; Mullins et al., 2005) and other disorders that impact attention, such as schizophrenia and dementia (MacDonald et al., 2009b). Individuals with ADHD show greater intra-individual variability across a range of cognitive tasks, and this measure is more robust in differentiating ADHD from healthy control subjects compared to other indices, for instance, mean RT, directional errors, omission errors, or rates of inhibition on tasks such as the Continuous Performance Task and go–no go tasks (Castellanos et al., 2006; Klein et al., 2006; Mullins et al., 2005). In disorders such as ADHD, greater intra-individual variability may reflect inefficient response selection, greater frequency of lapses in attention or difficulty maintaining attention to the task, which may manifest as a greater proportion of trials with prolonged reaction times (RT; Castellanos et al., 2006). Intra-individual RT variability may therefore be an important indicator of efficient attentional control, rather than simply random noise.

Despite intra-individual RT variability being recognised as a hallmark of impaired cognitive control, there has been relatively little attention given to investigating its neural correlates. Research that has examined RT variability has largely focused on contrasting performance between clinical and control groups (Bellgrove et al., 2005; Castellanos et al., 2006; Klein et al., 2006; MacDonald et al., 2009a), however intra-individual variability within a healthy population is under-examined. Investigating fluctuations in RT in healthy individuals is essential to advancing both theoretical and clinical understandings of effective attentional control. It is well established that the timing of the haemodynamic response is correlated to an individual's RT on a given task (Esterman et al., 2013; Fox et al., 2006; Yarkoni et al., 2009). However, it is

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necessary to decompose the relationship between RT variability and its neural correlates according to specific executive function contexts, such as response inhibition, response conflict, working memory, or motor planning, because intra-individual RT variability has been shown to vary across domains (Castellanos et al., 2006; Yarkoni et al., 2009). Studies have examined the functional neural correlates of RT variability in healthy adults across cognitive domains including response inhibition (Bellgrove et al., 2004; Connolly et al., 2005; Esterman et al., 2013, 2014), global/local selective attention (Weissman et al., 2006), set shifting (MacDonald et al., 2009a), spatial attention (Hahn et al., 2007) or working memory and emotion processing tasks (Yarkoni et al., 2009). In assessing the relationship between neural activation and RT variability, the approach has been either to correlate global variability measures, such as coefficient of variability of RT, with brain activation (Bellgrove et al., 2004; Connolly et al., 2005), or alternatively, examine neural correlates of trial-to-trial RT fluctuations (Esterman et al., 2013; Weissman et al., 2006; Yarkoni et al., 2009). Of studies that have assessed intra-individual RT variability during response inhibition tasks, Connolly et al. (2005) used an anti-saccade task but only examined activation in the frontal and supplementary eye fields and intraparietal sulcus, rather than whole brain activation. Bellgrove et al. (2004) used a go/no-go task to examine the relationship between intra-individual RT variability and whole brain task-related activation in non-clinical adults, which revealed correlations between bilateral middle frontal areas and right inferior parietal and thalamic regions. Similar findings were reported in children (Simmonds et al., 2007). Previously our group has found that RT variability was inversely related to successful response inhibition, indicating that RT variability may be an important indicator of effective attentional control (Bellgrove et al., 2004). However this approach only informs us about global variability, rather than trial-to-trial fluctuations in response. Esterman et al. (2013) assessed whole brain correlates of trial-to-trial fluctuations in RT using a sustained attention task and found that low RT variability was associated with greater activation of the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), both part of the default mode network (DMN), whereas higher RT variability was associated with greater FEF activation. Rapid, dynamic control of attention over trials is important to efficient cognitive control. Therefore to further elucidate brain regions that may play an important role in the dynamic top down control of attention in healthy adults, we sought identify brain regions whose activity showed a relationship with trial-to-trial RT variability during a go/no-go task using whole brain fMRI analysis.

2. Materials and methods

2.1. Participants and task design

Detailed methods describing participants, task and procedures have been previously reported (Hester et al., 2012), therefore a summary of the study's methodology is presented here. All participants were recruited in accordance with the principles of the Declaration of Helsinki and ethical guidelines of the University of Queensland and the Wesley Hospital (Brisbane, QLD, Australia).

Twenty-seven right-handed, male subjects (mean age, 22 years; range, 18–35 years) were recruited for this study via advertisements at the University of Queensland (Brisbane, QLD, Australia). Exclusion criteria for the study included any reported history of psychiatric or neurological illness, including head injury, previous usage of psychotropic medication, or significant drug use (Hester et al., 2012). All participants were screened prior to commencing the study by a consultant psychiatrist who also

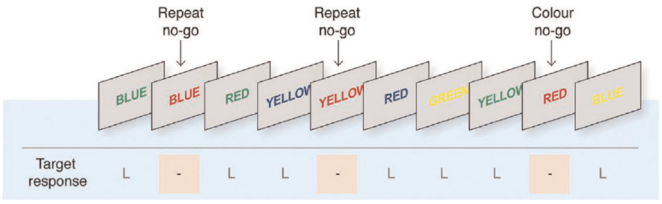

Fig. 1. Participants responded to each of the words with a single "go" trial by pushing the button under their index finger (left button, L) whenever the word and colour were different, and withheld their response when either the same word was presented on two consecutive trials ("repeat no-go") or if the word and its font colour matched ("colour no-go"). Only correct go-trials were used to assess intra-individual reaction time variability; all no-go trials, correct inhibitions on no-go trials and not withholding responses during no-go trials were excluded from the analysis. Figure adapted from Hester et al. (2012). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

administered the Mini-International Neuropsychiatric Interview screen (Sheehan et al., 1998) and the Kessler Psychological Distress Scale (K10; Kessler et al., 2003). Participants did not consume caffeine on the day of testing.

Participants were administered the "error awareness task" (EAT) which has been described elsewhere (Fig. 1; (Hester et al., 2012)). Briefly, this task is a motor go/no-go task in which subjects are presented with a serial stream of single colour words, with the word presented for 800 ms followed by a 700 ms inter-stimulus interval; the order of presentation was the same across subjects. Participants responded to each of the words with a single "go-trial" button press with their right index finger, using an MR-compatible response box; participants withheld their response in accordance with two competing types of response inhibition rules: (1) the same word was presented on two consecutive trials ("repeat no-go") or (2) if the word and its font colour matched ("colour no-go"). If participants were aware that they had made a mistake, on the next trial they ignored their regular go-trial button response and instead to made a non-speeded "error awareness" response with an alternative button using their index finger. Before the MRI session, participants practiced two novel blocks of the task to ensure they understood the task instructions. Six consecutive blocks consisting of 225 trials (200 go-trials, 25 no-go trials), were presented during the MRI session. This yielded a total of 1350 trials (1200 go-trials, 150 no-go trials). Stimulus presentation and response recording was controlled by E-Prime software (version 1.1; Psychology Software Tools) on a laptop computer, interfaced with the MR scanner.

All participants performed the EAT under 4 different drug conditions (methylphenidate [30 mg]; atomoxetine [60 mg], citalopram [30 mg] or placebo [dextrose]), according to a placebo-controlled, double-blind, randomised cross-over methodology as described in Hester et al. (2012). Data presented here are from the placebo condition only.

2.2. fMRI parameters

Scanning was performed on a whole-body 1.5 T Siemens Sonata scanner at the Wesley Hospital (Auchenflower, Brisbane, QLD, Australia) (Hester et al., 2012). Signals were acquired using the quadrature transmit-receive radiofrequency head coil. A total of 174 echo planar images (EPI) volumes were collected for each of the six functional runs, per participant; EPI were acquired using a gradient-echo pulse sequence and sequential slice acquisition (TR, 2000 ms; TE, 30 ms; flip angle, 90°; 29 contiguous slices of 3 mm thickness; 10% gap; in-plane resolution of 3.6×3.6 pixels in a FOV of 384 mm). Task-associated activation changes were registered to high-resolution T1-weighted isotropic ($1\ mm^3$) structural MPRAGE images, which were acquired at the beginning of the scanning