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Altered balance of functional brain networks in Schizophrenia

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ABSTRACT

Activity in dorsal attention (DAN) and frontoparietal (FPN) functional brain networks is linked to allocation of attention to external stimuli, and activity in the default-mode network (DMN) is linked to allocation of attention to internal representations. Tasks requiring attention to external stimuli shift activity to the DAN/FPN and away from the DMN, and optimal task performance depends on balancing DAN/FPN against DMN activity. The current functional magnetic resonance imaging (fMRI) study assessed the balance of DAN/FPN and DMN activity in 13 schizophrenia patients and 13 healthy controls while they were engaged in a task switching Stroop paradigm which demanded internally directed attention to task instructions. The typical pattern of reciprocity between the DAN/FPN and DMN was observed for healthy controls but not for patients, suggesting a reduction in the internally focussed thought important for maintenance of instructions and strategies in schizophrenia. The observed alteration in the balance between DAN/FPN and DMN in patients may reflect a general mechanism underlying multiple forms of cognitive impairment in schizophrenia, including global processing deficits such as cognitive inefficiency and impaired context processing.

1. Introduction

Schizophrenia is associated with a wide range of cognitive deficits, affecting memory, attention, and processing speed (Forbes et al., 2009; Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009). Many of the theoretical accounts attempting to explain these impairments have focussed on individual brain regions, notably the dorsolateral prefrontal cortex (DLPFC; Barch and Ceaser, 2012; Callicott et al., 2000; Potkin et al., 2009). Increasingly, however, cognitive neuroscience research is focusing on networks rather than individual regions. For example, aspects of the DLPFC are known to link with the superior parietal cortex and other regions to form the frontoparietal network (FPN; Yeo et al., 2011). Isolated study of the DLPFC may oversimplify interpretation of brain functioning (Whitman et al., 2013; Woodward et al., 2015). Other configurations of functional links between frontal and parietal brain regions have been labeled the multiple demands network (Duncan and Owen, 2000; Duncan, 2010), central executive network (Seeley et al., 2007), dorsal attention network (DAN; Yeo et al., 2011), and ventral attention network (Yeo et al., 2011). Aspects of all of these networks are active when engaged in tasks requiring allocation of attention to external stimuli.

Task-based activity in these frontoparietal network configurations is reciprocally related to activity in the default mode network (DMN; Raichle, 2011). The DMN includes ventral and posterior cingulate cortex, medial frontal regions, and inferior temporo-occipito-parietal regions such as the angular gyrus. The DMN is linked to attending to internal representations (Mason et al., 2007; Sestieri et al., 2011; Smallwood et al., 2013). Importantly, effective task performance requires flexible shifts between attention to external stimuli and attention to internal representation of task context and instructions, and thus an optimized balance between the FPN and DMN activity. DMN activity has been found to correlate with “mind wandering” (Mason et al., 2007), which is linked to poor performance on a concurrent task in healthy people and schizophrenia patients (Christoff et al., 2009; Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009). However, often overlooked is the fact that DMN activity is not limited to a “resting state” or “mind wandering”; for example, it increases activity when instructions are provided to attend to or ignore scanner noise during otherwise task-free scans (Benjamin et al., 2010), so activity may enhance performance when attention to internal representations of task context are important for task execution.

An optimized balance between FPN and DMN activity is likely

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to be particularly important for tasks that involve responding to ambiguous stimuli that cue more than one task in the current task set (Shallice, 1994). Bivalent stimuli cue two responses in the task set, and trivalent stimuli cue three (Allport and Wylie, 2000; Pashler, 2000). A classic example of bivalent stimuli is Stroop stimuli, for which one stimulus dimension cues color naming and the other word reading. Switching between tasks involving bivalent stimuli requires balancing internal and external attentional resources; that is, attending to internal representations of the task context (e.g., instructions) while also attentionally selecting appropriate external stimulus information to control task execution (Meier et al., 2009; Metzak et al., 2013; Woodward et al., 2003a). This creates an ideal task context for observing relative contributions of the FPN and DMN in schizophrenia relative to healthy controls.

Although schizophrenia patients show impairment when switching tasks (Meiran et al., 2000) and when responding to incongruent Stroop stimuli (Heinrichs and Zakzanis, 1998; Henik and Salo, 2004), to date, task switching in response to Stroop stimuli has not been studied in schizophrenia. In the current study, we compare FPN/DMN activity balance in schizophrenia patients to that in healthy controls using functional magnetic resonance imaging (fMRI) while switching between color naming and word reading in response to bivalent Stroop stimuli. To measure the task-related activity of the FPN and DMN, we employed group constrained principal component analysis for fMRI (group fMRI-CPCA; Metzak et al., 2013; Whitman et al., 2013; Woodward et al., 2003a,b; Lavigne et al., 2015; Woodward et al., 2015), which allows quantification of task-dependent functional networks and comparison of activation in these networks between groups and conditions. We hypothesized that patients with schizophrenia would show decreased activity in the FPN and DMN and/or reciprocity with the DMN, mapping onto imbalanced allocation of external and internal attentional resources, and that this would be associated with performance deficits caused by interference from incongruent Stroop stimuli.

2. Methods

2.1. Participants

Thirteen outpatients with schizophrenia and thirteen healthy controls participated in the study. Demographic data was missing for three control subjects, so these subjects are not included in the age, sex and handedness calculations. The schizophrenia sample had 6 females (mean age=34.2; SD=10.3) and the control sample had 5 females (mean age=33.5; SD=11.9). All except one participant from each group were right-handed (Annett, 1970). No group differences were observable for age, $t(21)=-0.16$, $p>0.05$, or sex, $\chi^2(1, 23)=0.34$, $p>0.05$. All participants had 20/20 or corrected to 20/20 vision and normal color vision. Screening for MRI compatibility was performed and informed consent was obtained for all participants prior to the start of the experiment. The study was approved by the University of British Columbia (UBC) and UBC Hospital Clinical Research Ethics Committees.

The exclusion criteria for both groups included: (1) history of neurological disorder, traumatic brain injury with loss of consciousness for more than 5 minutes, and any cognitive sequalae resulting from loss of consciousness; or (2) diagnosis of substance abuse/dependence. History of psychiatric disorder (self or immediate family) warranted exclusion from the control group. All diagnoses were confirmed via diagnostic interview by an independent psychiatrist using Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (American Psychiatric Association, 2000) criteria.

2.2. Design and procedure

Participants completed a task switching version of the Stroop task (Woodward et al., 2006). The stimuli used were incongruent or neutral Stroop stimuli. Incongruent Stroop stimuli are color words printed such that the ink color in which each word is printed does not agree with the meaning of the word (e.g., GREEN printed in red ink). The neutral color condition was XXXX printed in colored letters (no word dimension), and the neutral word condition was the color word written in black ink (no task-relevant color dimension). Stroop stimuli are frequently employed in cognitive psychology for the study of the "Stroop effect", whereby word reading interferes with color naming due to the relative dominance of the word-reading task (MacLeod, 1991; Stroop, 1935). It is assumed that the longer response times (RTs) when processing the incongruent Stroop stimuli relative to the neutral Stroop stimuli reflect cognitive processes involving selective attention to the task-relevant stimulus dimensions and away from the task-irrelevant stimulus dimension. Congruent Stroop stimuli are color words printed such that the color ink in which each word is printed agrees with the meaning of the word (e.g., GREEN printed in green ink), and are used in many Stroop studies to demonstrate facilitation. However, congruent Stroop stimuli were not used in this study because, as with the seminal task switching studies using Stroop stimuli (Allport et al., 1994; Allport and Wylie, 2000), the cognitive operations underlying conflict but not facilitation were of primary interest here, and under task switching conditions, the facilitation effect may be absent (Rogers and Monsell, 1995, p. 215, Fig. 2, Congruent Switch condition; Woodward, 1999, p. 62).

The experiment consisted of 180 trials: 10 color-naming trials followed by 20 word-reading trials, all repeated 6 times. Each block of 10 trials consisted of five neutral and five incongruent stimuli in random order. We refer to the first 10 word-reading trials following a switch from color naming (CN) as early word-reading (EWR), and the last 10 word-reading trials following a switch from color naming as late word-reading (LWR). EWR is expected to produce slower response times (RTs) than LWR due to the conflict carry over from CN trails, and by LWR trials this conflict is expected to be depleted. On any given trial, either a task-appropriate neutral or incongruent stimulus was selected with a probability of 50%. Each time the task was to be switched, an instruction screen was displayed. In total, 30 incongruent and 30 neutral CN trials and 60 incongruent and 60 neutral word-reading trials were presented. Example trials are presented in Fig. 1. See past work (Woodward et al., 2006) for a more detailed description of the task, and CN, EWR and LWR effects.

2.2.1. Stimuli and conditions

All stimuli were displayed in 38-point Helvetica font on a computer monitor, centered on screen against a gray background. Stimuli were presented using in-house software (Visual Auditory Presentation Package, or VAPP; http://nrc-iol.org/vapp). Two commercially-available MRI compatible fiber optic response devices with two buttons each were used for the participants' responses. For each trial, a fixation point was presented for 900 ms, immediately followed by the relevant stimulus for 1900 ms, and then by a blank screen for 100 ms. The response was recorded within the 1900 ms that the stimulus remained on the screen.

The experimental conditions consisted of either neutral or incongruent color- or word-reading, and were presented in three blocks of 10 trials (i.e., CN, EWR, LWR). For the incongruent color-naming and word-reading conditions, the words "RED", "GREEN", "YELLOW", or "BLUE" were displayed on-screen in incongruent font colors red, green, yellow or blue. Presented stimuli were randomly selected from different incongruent word/font color