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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

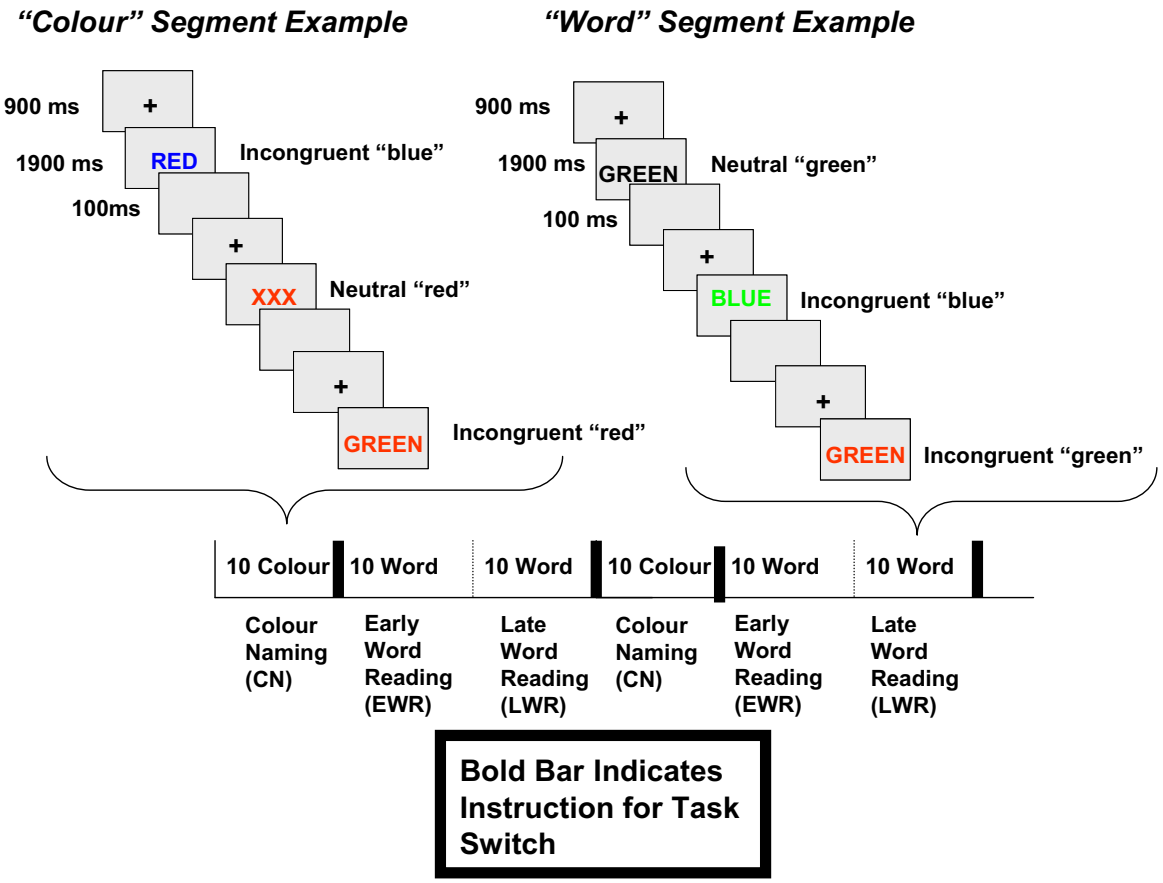

Fig. 1. Visual depiction of the experimental run, adapted from Woodward et al. (2006). The insets provide examples of color naming (CN) and word reading trials. In total, 60 color naming and 120 word reading trials were presented. The instructions for a task switch consisted of "WORD" and "COLOR". We refer to the first 10 word-reading trials following a switch from color naming as early word reading (EWR), and the last 10 word-reading trials following a switch from color naming as late word reading (LWR).

combinations and presented in the same order for all participants. For the color-naming neutral stimuli, a string of four Xs was displayed in red, green, yellow or blue font. For the word-reading neutral stimuli, the words "RED", "GREEN", "YELLOW", or "BLUE" were displayed in black font. Two instruction screens containing the phrases "WORD" or "COLOR", displayed in black font on a gray background, were used to instruct the participants to switch tasks. A "+" character in black font was used as a fixation point prior to the display of instructions or stimuli.

Prior to scanning, participants completed a 15-min training session, to learn the following key-response mapping: left index finger RED, left middle finger GREEN, right index finger YELLOW, and right middle finger BLUE. Feedback for errors ("Incorrect") or slow responses exceeding 1300 ms ("Too slow") appeared on the screen for 2 s before the next color word was presented. Each subject completed 15 min of training, and all subjects had extinguished incorrect and slow responses upon completion. A practice run was completed in the scanner consisting of 10 word reading trials (five neutral and five incongruent words in random order) followed by 10 color naming trials (five neutral and five incongruent in random order) and 60 word reading trials (30 neutral and 30 incongruent in random order).

2.2.2. *Image acquisition and pre-processing*

Before each scanning session, standardized instructions were read to the participants: "You will now be required to either press for word, or press for the colors of ink in which the words are written. Instructions on the screen will tell you whether to press for word or press for colors. Please respond as quickly and as accurately as possible." fMRI scanning was performed in a darkened room, with stimuli presented on a rear projection screen mounted at the entrance to the magnet bore. Participants viewed the screen by means of a mirror system attached to the head coil.

Images were acquired with a clinical GE 1.5 T whole body MRI system fitted with a Horizon echo speed upgrade. Conventional spin-echo T_1 weighted sagittal localizers were used to view the positioning of the participant's head and to graphically prescribe the functional image volumes. Functional image volumes were collected with a gradient echo (GRE) sequence (TR/TE 3000/40 ms, 90° flip angle, FOV 24×24 cm^2, 64×64 matrix, 62.5 kHz bandwidth, 3.75×3.75 mm^2 in plane resolution, 5.00 mm slice thickness, 29 slices, 145 mm axial brain coverage). The participant's head was firmly secured using a custom head holder. In the experimental run, 220 images of the entire brain were collected in a period of 660 s for each participant (TR = 3). The run was preceded by a 12 s rest condition, allowing T1 effects to stabilize. The four brain volumes collected during this period were not included in any subsequent analyses.

Functional images were reconstructed offline and pre-processed using Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Centre for Neuroimaging, UK). All images were realigned and normalized to the Montreal Neurological Institute (MNI) brain template (voxel size = $2 \times 2 \times 2$), and spatially smoothed with an $8 \times 8 \times 8$ mm full width at half maximum Gaussian filter. Translation and rotation corrections did not exceed 3 mm or 3° for any of the participants. fMRI-CPCA analyzes only variance that is predictable from task timing, greatly reducing the potential impact of movement artefacts. However, as a precautionary measure, head movement was regressed out of the blood-oxygen level dependent (BOLD) time series prior to fMRI-CPCA analysis to ensure that it

would not substantially influence the results presented below.

2.3. Data analysis

2.3.1. Behavioral analysis

Group differences in response time (RT) and errors were examined using a $2 \times 3 \times 2$ mixed-model analysis of variance (ANOVA), with RTs as the dependent variable, Congruency (incongruent vs. neutral) and Task (CN, EWR, LWR) as within-subjects variables, and Group (healthy controls vs. schizophrenia patients) as a between-subject variable. Significant interactions were interpreted with analyses of simple main effects and lower order interactions. Only factors that interacted with Group are reported in this manuscript. The full set of interactions and main effects is available by contacting the corresponding author. For examination of correlation of brain activity and cognitive performance, an interference RT was computed as the average of the Stroop effect (incongruent – neutral RT for CN) and reverse Stroop effect (incongruent – neutral RT for EWR and LWR).

2.3.2. Functional connectivity

fMRI data analysis was carried out using constrained principal component analysis for fMRI (fMRI-CPCA) with orthogonal rotation (Metzak et al., 2011; Metzak et al., 2013; Whitman et al., 2013; Woodward et al., 2003a,b; Lavigne et al., 2015). The theory and proofs for CPCA are detailed in previously published work (Takane and Hunter, 2001; Takane and Shibayama, 1991). Briefly, fMRI-CPCA combines multivariate multiple regression analysis and principal component analysis into a unified framework to reveal multiple orthogonal sources of post-stimulus fluctuations in brain activity. Whole-brain BOLD signal activity variance is partitioned into task-related and task-unrelated fluctuations using multivariate multiple regression. Orthogonal sources (components) of task-related BOLD activity fluctuations are then captured using principal component analysis (PCA). Functional brain networks associated with each temporally orthogonal source of BOLD variance are spatially interpreted by examining the voxels whose activity dominated each component/network, and temporally interpreted by statistically assessing the hemodynamic response (HDR) shape associated with each component. fMRI-CPCA is able to (1) identify multiple functional brain networks simultaneously involved in executing a cognitive task, (2) estimate the post-stimulus time course of coordinated BOLD activity fluctuations associated with each functional network, and (3) statistically test the effect of experimental manipulations and group differences on BOLD activity in each functional brain network. The fMRI-CPCA application is available online, free of charge (www.nitrc.org/projects/fmricpca).

2.3.3. Reliability of functional brain networks

Group fMRI-CPCA produces predictor weights for each combination of post-stimulus time point, condition, and participant. These weights, which provide estimates of the engagement of functional networks at each post-stimulus time point, can be used to statistically determine whether or not these values reflect a HDR shape (and do not simply vary randomly around zero), as well as to examine differences in the engagement of these networks between groups and/or conditions. A significant effect of post-stimulus time combined with a biologically plausible HDR shape provides evidence that the component reflects a reliable BOLD response to the task. These analyses were carried out as a $2 \times 6 \times 3 \times 2 \times 2$ mixed model ANOVA, with the within-subjects factors of Component (2 components were extracted from fMRI-CPCA, see Results below), Post-stimulus Time (6 whole-brain scans after the onset of each stimulus were estimated in the finite impulse response model), Task (CN vs. EWR vs. LWR), Congruency (Incongruent vs. Neutral), and the between-subjects factor of Group (healthy controls vs. schizophrenia patients). With the exception of the main effect of Post-stimulus Time, which provided a reliability check, only factors that interacted with Group are reported in the text of this manuscript.

2.3.4. Functional reciprocity and relation to behavior

The relationship between activity levels in DAN/FPN and DMN was assessed by correlating peak and post-peak intensity of functional network responses (either activity increases or decreases) indexed by the predictor weights. Peak and post-peak values were examined separately because they can reflect different task-related cognitive operations and therefore reveal distinct functional interactions between networks. In order to promote clarity in reporting results, reciprocity was assessed averaged over Task and Congruency. Baseline-to-peak activity was computed as the mean of time points 2 and 3 (with time point 1 excluded as no reliable activity is expected at the early stage). Post-peak activity was computed as the mean of time points 4, 5, and 6. Since the DAN/FPN is defined by activations (positive loadings overlaid on brain images) and DMN by deactivations (negative loadings overlaid on brain images), positive correlations between DAN/FPN and DMN predictor weights indicate that the level of intensity of DAN/FPN *activity* corresponds with the level of intensity of DMN *deactivity*; therefore, a strong positive correlation between DAN/FPN and DMN predictor weights indexes strong functional reciprocity. Correlations between behavioral measures and baseline-to-peak and post-peak activity in DAN/FPN and DMN were also computed.

3. Results

3.1. Behavioral results

Mean RT and accuracy results for each condition are shown in Table 1, and RT results are displayed in Fig. 2. Group differences on manual RTs and errors were examined using a $2 \times 3 \times 2$ mixed-model ANOVA with Congruency (incongruent vs. neutral) and Task (CN, EWR, LWR) as within-subjects variables, and Group (healthy controls vs. schizophrenia patients) as a between-subject variable. Analysis of errors showed that no interactions or main effects involving Group were significant (all $ps > 0.15$), so are not discussed further. Analysis of the RTs showed a significant three-way interaction, $F(2,46)=4.29$, $p < 0.05$. This was interpreted by analyzing incongruent and neutral stimulus conditions separately with 3×2 mixed-model ANOVAs, employing Task as a within-subjects variable, and Group as a between-subject variable. This analysis resulted in a significant Task × Group interaction for neutral stimuli, $F(2,46)=4.79$, $p < 0.05$, but not for incongruent stimuli, $F(2,46)=0.01$, $p=0.99$. Polynomial contrasts for the Task × Group interaction (condition order: CN, EWR, LWR) for neutral stimuli showed a significant quadratic effect interaction with Group, $F(1,23)=6.94$, $p < 0.05$, but not a linear effect interaction with Group, $F(1,23)=2.18$, $p < 0.15$, indicating that the effect was driven by responses to neutral stimuli differing between groups. At the basis of this effect was that, for neutral stimuli, patients outperformed controls on EWR only (RT = 768 vs. 787 ms, respectively, see Table 1). For incongruent stimuli, the main effect of Group was not significant, $F(1,23)=0.54$, $p=0.47$, and polynomial contrasts showed that the linear effect was highly significant, $F(1,23)=46.25$, $p < 0.001$, and the quadratic effect was not, $F(1,23)=3.53$, $p=0.07$. This indicated that for incongruent stimuli, as was expected based on past work (Woodward et al., 2006), RT decreased in a primarily linear fashion for both groups, (RTs = 951, 910 and 808 ms for CN, EWR and LWR, respectively, averaged over groups).

Table 1
Reaction time (RT; standard deviations in parentheses) and accuracy (% correct) for healthy controls and schizophrenia patients on all experimental conditions.

Variable	Healthy Controls ($n=13$)		Schizophrenia Patients ($n=12$)*	
	RT (ms)	Accuracy % Correct	RT (ms)	Accuracy % Correct
Color-Naming (CN)				
Neutral	754 (107)	96% (4.4)	839 (179)	90% (15.0)
Incongruent	937 (126)	90% (8.7)	965 (137)	82% (14.4)
Early Word-Reading (EWR)				
Neutral	787 (79)	96% (6.7)	768 (147)	90% (13.6)
Incongruent	896 (86)	83% (12.7)	924 (111)	82% (11.3)
Late Word-Reading (LWR)				
Neutral	724 (113)	94% (9.9)	761 (169)	90% (11.1)
Incongruent	792 (87)	92% (13.2)	824 (132)	93% (7.7)

Note.
* Reaction Time (RT) and accuracy data were missing for one patient.

3.2. fMRI-CPCA results

3.2.1. Functional connectivity

Inspection of the scree plot of singular values (Cattell, 1966, 1977) suggested a two-component solution, and this was confirmed by observation of biologically plausible HDR shapes and statistical tests for these components reported below. A significant effect of Post-stimulus Time, $F(5,120)=35.43$, $p<0.001$, did not interact with Component ($p=0.28$), suggesting that a HDR shape was present for both components (see Fig. 3B and C), and was reliable over participants for both components. The percentage of task-related variance accounted for by each rotated component was 18.62% and 8.61% for Components 1 and 2, respectively. A complete list of statistical tests for all main effects and interactions are reported in Table 2.

The brain regions associated with Component 1 are displayed in Fig. 3A (red/yellow), with anatomical descriptions in Table 3. Relating Component 1 to the recently proposed 7-network brain parcellation derived from resting state data (Yeo et al., 2011), most frontal and parietal peaks were located on the DAN, but some frontal and parietal peaks were located on the FPN. The dACC/supplementary motor area (SMA) peak was located on the ventral attention network. The brain regions associated with Component 2 are displayed in Fig. 3A (blue/green), with anatomical descriptions in Table 4. Component 2 was characterized by a functional network of decreasing activity (negative loadings on brain images displayed in blue/green) in regions overlapping with the DMN (Buckner et al., 2008), such as ventral anterior cingulate and anterior prefrontal regions (BA 9, 10, 32), posterior cingulate regions (BAs 30, 23), bilateral hippocampi, and bilateral temporo-occipital regions (BA 37, 39). Relating Component 2 to the recently proposed 7-network brain parcellation derived from resting state data (Buckner et al., 2011; Yeo et al., 2011; Choi et al., 2012), all deactivated regions in the current data indexed on the 7-network brain parcellation map were located on the DMN, including the caudate and cerebellum (subthreshold). Components 1 and 2 overlaid on the cortical surface templates of resting state networks (Yeo et al., 2011) are provided in Fig. 4.

Analysis of the HDR shapes with a $2\times6\times3\times2\times2$ mixed model ANOVA, using the within-subjects factors of Component, Post-stimulus Time, Task, and Congruency, and the between-subjects factor of Group, showed a significant Component × Congruency × Group interaction, $F(1,24)=4.12$, $p=.05$, suggesting that group differences in Congruency depended on Component, but not on Post-stimulus Time or Task. This was followed up by separate 2×2 repeated measures ANOVAs for each Group, with Component and Congruency as the within-subjects factors. For schizophrenia patients, there was a significant Component × Congruency interaction, $F(1,12)=4.82$, $p<0.05$, such that the Congruency effect (incongruent > neutral) was significant for

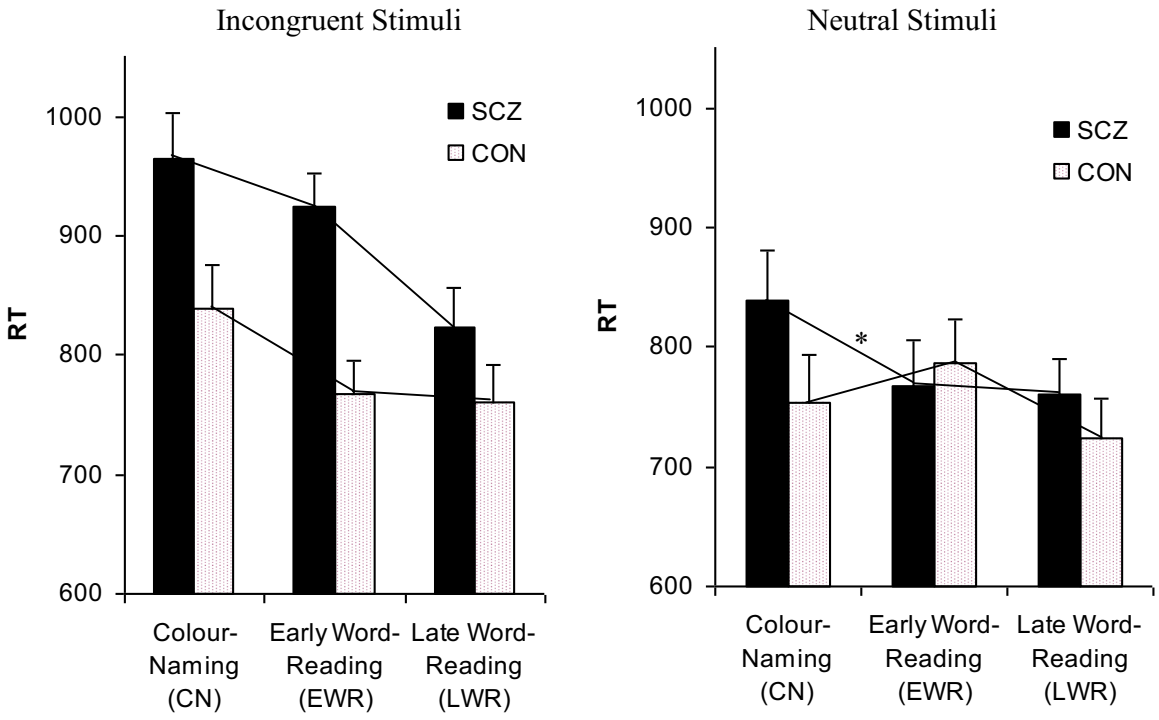

Fig. 2. Mean response time (RT) plotted as a function of task condition, stimulus type and group. The significant Task × Group interaction for neutral stimuli, $F(2,46)=4.79$, $p<0.05$, but not for incongruent stimuli, $F(2,46)=0.01$, $p=0.99$, was caused by neutral stimuli showing a significant quadratic effect interaction with Group, $F(1,23)=6.94$, $p<0.05$, but not a linear effect interaction with Group, $F(1,23)=2.18$, $p<0.15$ (condition order: CN, EWR, LWR). At the basis of this effect was that, for neutral stimuli, patients outperformed controls on EWR only. * signifies the significant interaction between the quadratic effect (the difference between EWR and the other conditions) and Group. The lines have been added to emphasize the linear and quadratic patterns in the mean changes. Error bars are standard errors. SCZ = schizophrenia. CON = controls.

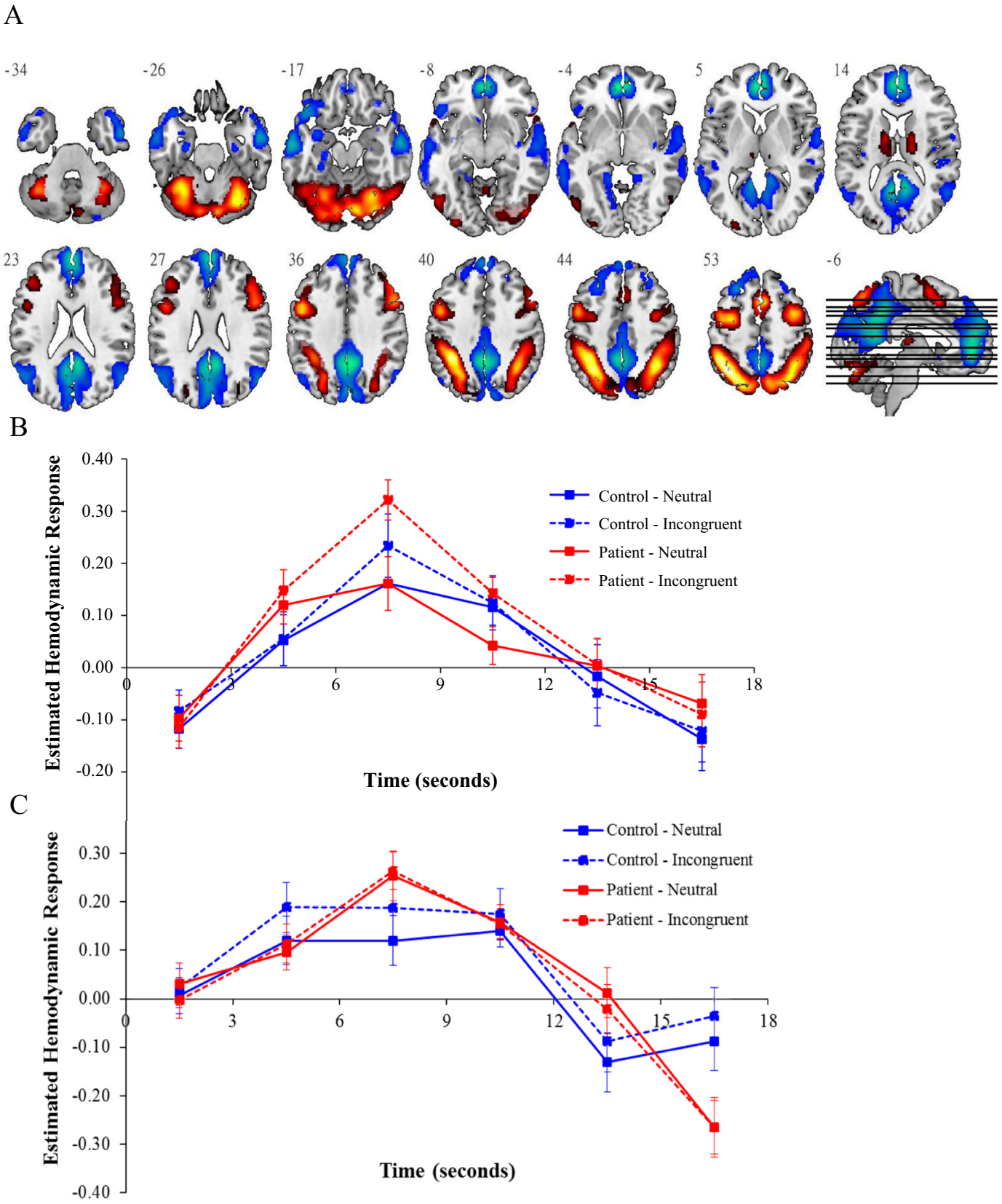

Fig. 3. (A) Dominant 10% of component loadings for Component 1 (red/yellow = positive loadings; threshold = 0.28, max = 0.40; no negative loadings passed threshold) and Component 2 (blue/green = negative loadings, negative threshold = −0.20, min = −0.34; no positive loadings passed threshold). Axial slices are located at the MNI *Z*-axis coordinates listed above brain slices. (B) Mean finite impulse response (FIR)-based predictor weights for component 1 (dorsal attention network/frontoparietal network; DAN/FPN) for neutral and incongruent trials in each group, plotted as a function of post-stimulus time. (C) Mean FIR-based predictor weights for component 2 (default mode network; DMN) for neutral and incongruent trials in each group, plotted as a function of poststimulus time.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Statistical test of all effects and interactions. Reported p values are based on uncorrected degrees of freedom for tests of violations of sphericity. *df* refers to degrees of freedom.

Effect	*df*	*F* statistic	*p* value
Component	1, 24	0.52	0.48
Component × Group	1, 24	0.80	0.38
Task	2, 48	16.87	< 0.001
Task × Group	2, 48	4.14	< 0.05
Condition	1, 24	9.93	< 0.005
Condition × Group	1, 24	0.80	0.38
Time	5, 120	35.43	< 0.001
Time × Group	5, 120	1.66	0.15
Component × Task	2, 48	1.12	0.33
Component × Task × Group	2, 48	1.10	0.34
Component × Condition	1, 24	0.22	0.64
Component × Condition × Group	1, 24	4.12	=0.05
Task × Condition	2, 48	0.15	0.86
Task × Condition × Group	2, 48	0.42	0.66
Component × Task × Condition	2, 48	2.25	0.12
Component × Task × Condition × Group	2, 48	1.59	0.22
Component × Time	5, 120	1.27	0.28
Component × Time × Group	5, 120	1.20	0.32
Task × Time	10, 240	3.15	< 0.001
Task × Time × Group	10, 240	1.21	0.29
Component × Task × Time	10, 240	2.63	< 0.01
Component × Task × Time × Group	10, 240	0.38	0.95
Condition × Time	5, 120	7.65	< 0.001
Condition × Time × Group	5, 120	2.01	0.08
Component × Condition × Time	5, 120	3.20	< 0.05
Component × Condition × Time × Group	5, 120	1.61	0.16
Task × Condition × Time	10, 240	1.36	0.20
Task × Condition × Time × Group	10, 240	0.84	0.60
Component × Task × Condition × Time	10, 240	0.61	0.80
Component × Task × Condition × Time × Group	10, 240	1.49	0.14

Component 1 (DAN/FPN; activation increases), $F(1,12)=5.98$, $p<0.05$, but not Component 2 (DMN; activation decreases), $F(1,12)=0.27$, $p=0.61$. For healthy controls, the Component × Congruency interaction was not significant, $F(1,12)=0.90$, $p=0.36$, and the Congruency main effect was significant, $F(1,12)=6.86$, $p<0.05$. This 3-way interaction is displayed in Fig. 5 using peak values of the HDR shapes depicted by the predictor weights. There was also a significant Task × Group interaction, $F(2,48)=4.14$, $p<0.05$, characterized by a (non-significantly) increased intensity (both activation and suppression) for schizophrenia patients during EWR collapsed over Component and Congruency, $F(1,24)=2.63$, $p=0.12$, but near equivalence in CN and LWR, ($p>0.8$ and 0.9, respectively).

3.2.2. Functional reciprocity and relation to behavior

Healthy reciprocity was observed for controls as a significant correlation between baseline-to-peak DAN/FPN increases and post-peak DMN decreases, $r(12)=0.63$, $p<0.05$. In other words, the level of early DAN/FPN *activity* was associated with the level of late DMN *deactivity*. This reciprocity was absent for patients, $r(12)=-0.05$, $p=0.88$. Cooperation (as opposed to reciprocity) was observed for patients and controls between post-peak DAN/FPN and DMN decreases, $r(12)=-0.79$, $p=0.001$; $r(12)=-0.67$, $p=0.01$, respectively. That is, for both patients and controls, a slow return to baseline for the DAN/FPN was associated with a rapid return to baseline (or reversal to activation) for the DMN.

Relating baseline-to-peak and post-peak measures to behavior, for the full sample of both controls and patients (with the group variable partialled out of the interference RT measure, thereby removing the influence of shared group differences in RT and on the correlations), both DAN/FPN and DMN post-peak activity levels were correlated with interference RT, $r(24)=-0.46$, $p<0.05$; $r(24)=0.42$, $p<0.05$, respectively, but correlations with baseline-to-peak predictor weights were not significant. This result implies that weak DAN/FPN activity and strong DMN deactivity post-peak led to more interference impact on an individual. Weak DAN/FPN activity and strong DMN deactivity both imply reduced engagement of these networks in external and internal attentional processes, respectively.

Table 3
Cluster volumes for the most extreme 10% of Component 1 (dorsal attention network/frontoparietal network; DAN/FPN), with anatomical descriptions, Brodmann's areas (BAs), and Montreal Neurological Institute (MNI) coordinates for the peaks within each cluster.

Cortical regions	Cluster volume (mm^3)	BAs for peak locations	MNI coordinates for peak locations		
			x	*y*	*z*
Cluster 1: Bilateral	76,128				
Superior parietal lobule		7	−36	−58	54
Supramarginal gyrus, posterior division		40	−36	−46	42
Superior parietal lobule		40	−42	−50	52
Superior parietal lobule		40	36	−52	46
Lateral occipital cortex, superior division		7	34	−62	52
Supramarginal gyrus, anterior division		2	50	−34	50
Cluster 2: Bilateral	71,472				
Cerebellar VI		n/a	26	−64	−20
Cerebellar VI		n/a	−30	−56	−26
Cerebellar Crus I		n/a	−12	−78	−22
Occipital fusiform gyrus		18	−24	−82	−18
Lateral occipital cortex, inferior division		37/19	48	−64	−16
Lateral occipital cortex, inferior division		19	44	−78	−12
Temporal occipital fusiform cortex		37	−46	−58	−18
Inferior temporal gyrus, temporooccipital part		37	−48	−60	−16
Cerebellar V		n/a	0	−56	−10
Occipital pole		18	−28	−92	4
Cluster 3: Left Hemisphere	25,256				
Precentral gyrus		6	−38	−4	56
Precentral gyrus		44	−50	6	34
Middle frontal gyrus		45	−44	30	26
Cluster 4: Right Hemisphere	23,640				
Middle frontal gyrus		6	36	−2	58
Precentral gyrus		44	50	12	32
Middle frontal gyrus		45	48	28	32
Cluster 5: Bilateral	12,328				
Supplementary motor area		6	0	4	60
Cluster 6: Left Hemisphere	2688				
Thalamus		n/a	−8	−20	10
Cluster 7: Right Hemisphere	2536				
Thalamus		n/a	16	−14	14
Cluster 8: Left Hemisphere	680				
Temporal pole		38	−58	12	−4
Cluster 9: Right Hemisphere	624				
Temporal pole		38	52	18	−8

4. Discussion

DAN/FPN activity is linked to allocation of external attention, and DMN activity is linked to internally oriented processing, which benefits task performance when it supports application of instructions under ambiguous task conditions. Optimal task performance depends on balancing DAN/FPN against DMN activity, or balancing expenditure of external and internal attentional

resources under ambiguous task conditions. The current study used a challenging task set requiring internally focussed attention to task instructions in order to switch between color naming and word reading of ambiguous Stroop stimuli that cued both responses. A typical pattern of balanced reciprocity between the DAN/FPN and DMN was observed for healthy controls, whereby increased attentional demand from external stimuli led to an increase in DAN/FPN activity and a reduction in DMN activity, and reduced attentional demand from external stimuli led to a decrease in DAN/FPN activity and an increase in DMN activity (presumably due to increased internally oriented processing). However, for patients with schizophrenia, DMN activity was not increased during periods when internally oriented processing was expected. This result suggests a reduction in the internally oriented processing important for maintenance of instructions and strategies in favor of external allocation of attentional resources.

Although DMN activity is sometimes associated with "mind wandering" at rest (Mason et al., 2007; Christoff et al., 2009), it has also been shown to increase when attention is allocated to internal representation of instructions (Benjamin et al., 2010), and other aspects of perceptually decoupled task-related thought (Smallwood et al., 2013). Therefore, task-related DMN activity would be expected to benefit performance overall when it supports rehearsing and applying task instructions, as is required when responding to ambiguously cued stimuli, such as incongruent Stroop stimuli. Thus, DMN activity could be associated with slower word reading, particularly under easier conditions (e.g., responding to neutral Stroop stimuli), due to slowing induced by attention to internal representations, exposed in the absence of the need to respond to incongruent stimuli (Woodward et al., 2003a; Meier et al., 2009; Metzak et al., 2013). In the current study, we observed decreased DMN activity and fast RTs for neutral word reading (relative to incongruent word reading) in schizophrenia, interpreted as a reduction in internal reflectiveness manifesting as faster responding (Woodward et al., 2003a; Meier et al., 2009; Metzak et al., 2013). Reciprocity was also measured directly, and it was observed that, at the level of individual differences, high initial DAN/FPN *activity* was echoed by strong DMN *deactivity* for healthy controls but not patients.

An altered balance between the DAN/FPN and DMN in schizophrenia, alongside neglect of internally directed attention to instructions and context, unifies a number of other concepts put forward to explain cognitive deficits in schizophrenia. For example, the account of cognitive inefficiency, whereby an increase in cognitive resources is required for schizophrenia patients to achieve the performance levels of healthy controls (Callicott et al., 2000; Potkin et al., 2009), could be explained by altered balance between DAN/FPN and DMN, assuming that an optimal balance is required for efficient brain functioning. Another example is impairment in context processing (or proactive control), defined as the ability to actively represent and apply instructions and goal information in working memory to guide behavior (Cohen et al., 1999; Lesh et al., 2011; Barch and Ceaser, 2012). Contextual processing (e.g., recalling and rehearsing task instructions) was assumed to be represented in the current study by activity in the DMN. The schizophrenia patients' hyper-deactivation of the DMN, most observable during neutral relative to incongruent word-reading trials, suggests difficulty attending to contextual information. This account appears to contrast with an account linking DMN "overactivity" during task state to mind wandering, assumed to adversely affect performance (Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009). However, these accounts can be unified in that DMN activity *during the task state* may index mind wandering during straight-forward tasks, but maintenance and application of rules and contextual information when responding to ambiguous stimuli.

Table 4
Cluster volumes for the most extreme 10% of Component 2 loadings (default mode network; DMN), with anatomical descriptions, Brodmann's areas (BAs), and Montreal Neurological Institute (MNI) coordinates for the peaks within each cluster.

Cortical regions	Cluster volume (mm^3)	BAs for Peak Locations	MNI coordinates for peak locations		
			x	*y*	*Z*
Cluster 1: Bilateral	81,368				
Precuneus cortex		23	2	−52	36
Posterior cingulate gyrus		30	6	−52	20
Precuneus cortex		18	−8	−58	14
Cuneal cortex		18	0	−78	32
Precuneus cortex		5	−4	−46	60
Cluster 2: Bilateral	48,728				
Paracingulate gyrus		10	−4	48	−6
Paracingulate gyrus		32	−2	52	14
Middle frontal gyrus		8	−28	26	50
Superior frontal gyrus		9	−20	38	48
Frontal Pole		8	−6	42	52
Cluster 3: Right Hemisphere	38,600				
Middle temporal gyrus, posterior division		21	58	−8	−18
Middle temporal gyrus, anterior division		20	54	−2	−26
Lateral occipital cortex, superior division		39	52	−66	28
Lateral occipital cortex, superior division		37	54	−62	18
Temporal pole		38	48	16	−30
Planum temporale		48	62	−6	4
Frontal orbital cortex		47	34	30	−20
Middle temporal gyrus, temporooccipital part		21	66	−44	0
Planum temporale		41	46	−30	14
Middle temporal gyrus, temporooccipital part		37	62	−56	4
Cluster 4: Left Hemisphere	38,416				
Middle temporal gyrus, posterior division		21	−60	−10	−18
Frontal orbital cortex		38	−46	24	−16
Lateral occipital cortex, superior division		39	−52	−64	22
Middle temporal gyrus, temporooccipital part		21	−64	−48	0
Middle temporal gyrus, posterior division		21	−66	−38	−2
Temporal pole		20	−48	4	−40
Lateral occipital cortex, inferior division		37	−60	−64	10
Frontal orbital cortex		47	−28	30	−18
Inferior frontal gyrus, pars triangularis		45	−54	24	2
Cluster 5: Right Hemisphere	2088				
Middle frontal gyrus		9	30	30	48
Cluster 6: Left Hemisphere	2072				
Hippocampus		30	−26	−16	−24
Parahippocampal gyrus, posterior division		37	−30	−34	−14
Cluster 7: Left Hemisphere	1640				
Amygdala		48	−34	0	−18
Cluster 8: Right Hemisphere	680				
Hippocampus		36	26	−14	−26
Cluster 9: Left Hemisphere	392				
Superior temporal gyrus, posterior division		22	−50	−32	4
Cluster 10: Right Hemisphere	368				
Insular cortex		48	38	−10	−10
Cluster 11: Left Hemisphere	336				
Insular cortex		48	−36	−20	10
Cluster 12: Right Hemisphere	208				

Table 4 (*continued*)

Cortical regions	Cluster volume (mm^3)	BAs for Peak Locations	MNI coordinates for peak locations		
			x	*y*	*z*
Cerebellar Crus II		n/a	28	−86	−36
Cluster 13:Right Hemisphere	168				
Temporal pole		38	32	6	−22
Cluster 14: Left Hemisphere	88				
Subcallosal cortex		25	−8	16	−10

One limitation of the current study is low power due to the relatively small number of subjects per group. Likely as a result of this, despite slower RTs for patients in all incongruent Stroop conditions, this difference did not reach statistical significance, although it was predicted based on past work (Heinrichs and Zakzanis, 1998; Henik and Salo, 2004). In addition, power may be a concern when assessing the significance of high-order interactions, and a larger sample size would be particularly beneficial in that it would allow the patients to be split on symptom types. For example, it would be of interest to compare patients with symptoms of disorganization to those without, as it has been observed that severity of disorganization is associated with performance on a Stroop task (Barch et al., 1999a; Barch et al., 1999b; Henik and Salo, 2004; Moritz et al., 2001; Woodward et al., 2003b). Another limitation is that the current results could be confounded to the extent that the cognitive processes studied here are affected by antipsychotic medication. However, this is unlikely, because the administration of antipsychotic medication has little effect on neurocognitive abilities (e.g., attention and memory) in schizophrenia (Keefe et al., 2007), including the Stroop effect (Henik and Salo, 2004). Finally, the manual response would increase the working memory load over that required for verbal responses, but

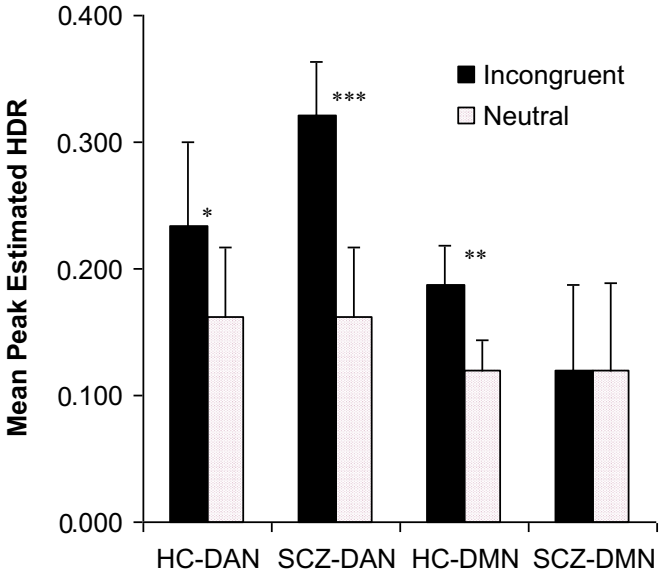

Fig. 5. Peak finite impulse response (FIR)-based predictor weights, plotted as a function of group (HC=healthy control; SCZ=schizophrenia), component (DAN=dorsal attention/fronto-parietal network; DMN=default-mode network) and condition (incongruent and neutral trials). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for incongruent versus neutral *t*-test ($df = 1, 12$), two-tailed, averaged over task. Error bars are standard errors.

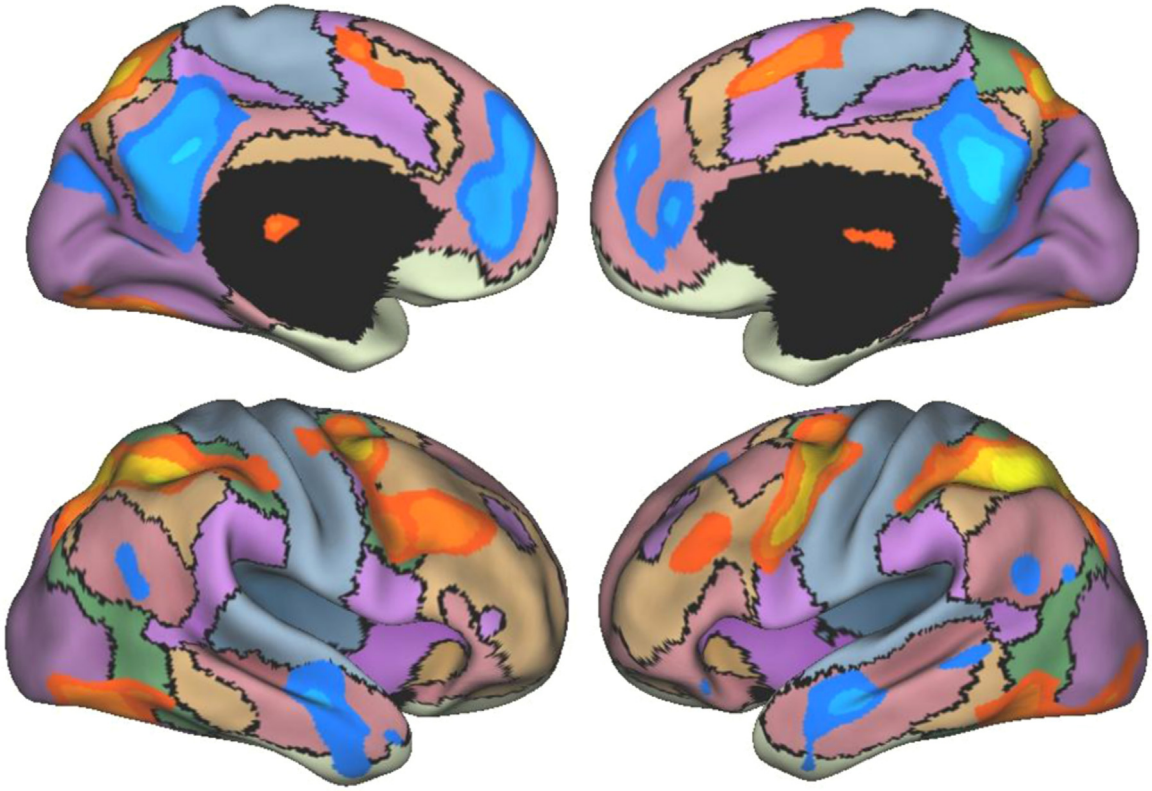

Fig. 4. Dominant 10% of component loadings for Component 1 (red/yellow=positive loadings; threshold=0.28, max=0.40; no negative loadings passed threshold) and Component 2 (blue/green=negative loadings, negative threshold=−0.20, min=−0.34; no positive loadings passed threshold) superimposed on the 7-network cortex brain parcellation derived from resting state data (Yeo et al., 2011), as follows: visual (purple); somatosensory (blue/gray); dorsal attention (green); ventral attention (violet); limbic (pale green); frontoparietal (orange); default (red).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

is required for fMRI due to task-timing-related increased head movement associated with verbal responses. Since working memory is largely attention to internal representations, it is not possible with these data to determine whether group differences are due to working memory, or internal-attention-specific cognitive processes.

5. Conclusion

This set of results suggests that for healthy controls, activity in the DAN/FPN and DMN was balanced such that the increase in DAN/FPN demand from incongruent relative to neutral Stroop stimuli was paralleled by a corresponding decrease in DMN activity. In contrast, this reciprocal DAN/FPN-DMN activity balance was not observed in schizophrenia patients, for whom increased DAN/FPN demand from incongruent relative to neutral Stroop stimuli was not paralleled by a corresponding decrease in DMN activity. This reduced DMN activity may signify a decrease in the self-reflective thought important for maintenance of instructions and strategies in favor of external allocation of attentional resources. Faster RT for patients was also observed for neutral early word reading, presumably reflecting an absence of cautiousness normally induced by attention to internal representations of task instructions. An altered balance between DAN/FPN and DMN may contribute to general cognitive impairment in schizophrenia, reflecting a quantifiable brain mechanism for previously proposed "black-box" conceptual explanations such as cognitive inefficiency, and impaired proactive control processes/maintenance of context.

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