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Conflict and error processing in an extended cingulo-opercular and cerebellar network in schizophrenia

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ABSTRACT

The loss of cognitive control is a prominent feature of schizophrenia. Relevant for adaptive control, individuals with schizophrenia often show impairments in their ability to monitor their ongoing behavior, and to adjust their responses based on advance information or feedback. By conducting a systematic examination of the behavioral adjustments after error and conflict and of activity within and between brain regions sensitive to the need to increase control (i.e. error commission, conflict presentation) in individuals with schizophrenia ($n = 38$) compared to healthy controls, we aimed to 1) shed light on the role of diverse brain regions previously associated with adaptive cognitive control, and 2) contribute to our understanding of the nature of the cognitive deficits present in individuals with schizophrenia. Our results show that error- and conflict-related behavioral adjustments are relatively intact during the performance of a change-signal task. Similarly, individuals with schizophrenia demonstrated intact error- and conflict-related effects in the dorsal anterior cingulate cortex, as well as in a number of other key regions including the bilateral anterior prefrontal cortex (PFC), bilateral insula, right inferior parietal lobule during error processing, and bilateral inferior parietal lobule and thalamus, right anterior PFC, left insula, and left lateral and inferior cerebellum during conflict processing. Given that a critical characteristic of our experimental design was the use of tasks that explicitly provide information about errors and conflict, we interpret our results as suggesting that the error- and conflict-detection systems are still somewhat functional in individuals with schizophrenia, but that a compromise in the ability to represent task relevant information that allow for the generation of an error representation may lead to the alterations in error- and conflict-processing documented in the schizophrenia literature.

1. Introduction

Cognitive dysfunction is a core feature of schizophrenia. Recent models propose that alterations in a common mechanism, specifically in cognitive control, underlie the widely documented deficits present in a range of cognitive domains as well as the enduring difficulties in adaptive functioning seen in individuals with schizophrenia (Barch, 2009; Lesh et al., 2011; Minzenberg and Carter, 2012; Minzenberg et al., 2009). One component of cognitive control, namely the psychological and neural mechanisms involved in actively maintaining goals to guide appropriate behavior, has been the focus of extensive investigations, both in the normative and in the schizophrenia literature. However, to satisfy the changing demands of the environment, cognitive control requires flexibility. Performance monitoring is an aspect of cognitive control that supports such flexibility, enabling the updating of relevant action rules and goals based on outcomes and ongoing experience (Carter et al., 1998; Cohen et al., 1990). Although such mechanisms have received a great deal of attention in the normative literature, the psychological and neural mechanisms underlying this process have received relatively less attention in the schizophrenia literature.

The dorsal anterior cingulate cortex and adjacent medial superior frontal cortex (dACC/msFC) has been repeatedly implicated as a major player in performance monitoring, though the precise nature of its involvement is still under debate. Some models propose that the dACC/msFC detects the co-activation of incompatible responses (with errors being an extreme case of conflict) and recruits regions in the prefrontal cortex (PFC) involved in control processes to resolve discrepancies or conflict (Botvinick et al., 2001). Alternatively, other models stress the predictive role of the dACC/msFC in signaling unexpected outcomes (Brown and Braver, 2005, 2007; Holroyd and Coles, 2002; Holroyd et al., 2005; Jessup et al., 2010). Some authors propose that such evaluative signals lead to the engagement of proactive control based on a learned task context, such as the likelihood of making an error (Brown and Braver, 2005, 2007).

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Individuals with schizophrenia often show impairments in their ability to monitor their ongoing behavior (Frith and Done, 1989; Malenka et al., 1982, 1986), and to adjust their responses based on advance information or feedback (Elliott et al., 1995). Given that the dACC/msFC is thought to play a central role in performance monitoring through its sensitivity to conflict or unexpected outcomes, there has been a great interest in examining the neural mechanisms of error-processing in schizophrenia. Studies using evoked response potentials (ERP) and functional magnetic resonance imaging (fMRI) consistently report diminished correlates of error commission (i.e. error related negativity (ERN) and blood-oxygenation level dependent [BOLD] responses in the dACC/msFC) in individuals with schizophrenia compared to controls (Alain et al., 2002; Bates et al., 2002; Becerril et al., 2011; Botvinick et al., 2001; Kerns et al., 2005; Kopp and Rist, 1999; Krawitz et al., 2011; Laurens et al., 2003; Mathalon et al., 2002; Morris et al., 2006; Polli et al., 2008). In contrast to the consistency of the neurophysiological evidence, typical behavioral adjustments observed after error-commission have been studied with mixed results in schizophrenia, with a number of studies reporting intact post-error slowing (Alain et al., 2002; Mathalon et al., 2002; Morris et al., 2006; Polli et al., 2006), but others reporting significantly less slowing of reaction time after error commission in individuals with schizophrenia compared to healthy controls (Becerril et al., 2011; Kerns et al., 2005; Kopp and Rist, 1999; Carter et al., 2001). Closer attention to individual differences in clinical symptoms of schizophrenia may shed light on the mixed behavioral results. For example, some authors have proposed that decrements in error-related BOLD responses reflect the interaction between a motivational deficit associated with the negative clinical symptoms of schizophrenia (i.e. alogia, flat affect, amotivation) and performance monitoring (Laurens et al., 2003), though at least one group has reported an inverse correlation between the magnitude of the ERN and the severity of negative symptoms (Bates et al., 2002).

The evidence reviewed above indicates that error-related responses in the dACC/msFC are frequently diminished in individuals with schizophrenia, while evidence regarding post-error behavioral adjustments in schizophrenia is mixed. In addition, it remains unclear whether flexible responses in the dACC/msFC based on task-context (e.g. error likelihood) are also impaired. Moreover, how specific clinical symptoms impact adaptive cognitive control and behavioral adjustments in schizophrenia is still unclear. Furthermore, performance monitoring is a complex function, requiring the coordination of activity between many regions outside of the dACC/msFC. Thus, it is important to extend the examination of error and conflict related responses to other brain regions that have also been implicated in active, adaptive online control. A growing body of research shows that, in addition to the dACC/msFC, a set of regions spanning the cingulo-opercular and cerebellar networks as well as regions in the inferior parietal lobule respond to errors. This set of regions includes portions of the dACC/msFC, anterior insula/frontal operculum (aI/fO), inferior parietal lobule (IPL) and thalamus, and in addition, cerebellum regions that also show robust responses to errors (Becerril et al., 2011; Dosenbach et al., 2006, 2007; Stevens et al., 2009; Zhang and Li, 2011).

To examine error-related responses at a network level, our previous work compared BOLD responses associated with error commission during a working memory (WM) task in individuals with schizophrenia and healthy controls in the regions described above previously identified to show robust error-related responses in the normative literature. We found evidence that: 1) brain activity in individuals with schizophrenia is altered compared to controls in these other regions known to show robust error-related activity, 2) post-error slowing is compromised in individuals with schizophrenia, with the magnitude of dACC/msFC activation positively correlating with post-error slowing, and 3) the integration of this network of regions differed between groups, with the cerebellar regions and the dACC less connected to the rest of the regions in individuals with schizophrenia compared to controls (Becerril et al., 2011). Thus, our previous findings suggest that individuals with schizophrenia fail to respond appropriately to errors, and that alterations in adaptive behavior are primarily linked to anomalies in dACC function. However, in the context of a WM task, to have a sense of whether an error occurred, participants need to be able to maintain information about the stimuli in WM and to use this task representation information to generate an internal error representation for themselves, as this information is not necessarily available in the external environment if the task does not provide explicit feedback. As such, individuals may be unaware that they made an error if their representations of information in WM are impaired. As such, the behavioral and neurophysiological alterations that we found could reflect a compromise in the ability of individuals with schizophrenia to properly construct a task representation in WM, and not a deficit in performance monitoring per se. Therefore, in this study we utilized a task where information about errors and conflict is more directly provided by the task structure (i.e. change-signal task (Brown and Braver, 2005)), and examined group differences in behavioral performance and brain activation related to error- and conflict-processing at a network level between individuals with schizophrenia and healthy controls.

We predicted that compared to healthy controls, if individuals with schizophrenia had deficits in performance monitoring itself, individuals with schizophrenia would demonstrate: 1) reduced post-error/conflict behavioral adjustments, 2) reduced brain activation elicited by error-commission and conflict in a distributed network that includes regions in the ACC, anterior insula, anterior prefrontal cortex, inferior parietal lobule, thalamus, and cerebellum, and 3) reduced modulation of brain activation in these regions in response to implicit cues that predict the likelihood of making a mistake. In addition, we examined the relationship of obtained behavioral and fMRI measures to clinical symptoms of schizophrenia. Based on previous research associating greater negative symptoms with deficits in performance monitoring, we expected that greater negative symptom scores would be associated with diminished error and conflict related dACC/msFC activity, and with reduced post-error slowing.

2. Material and methods

2.1. Participants

Participants were recruited through the clinical core of the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St. Louis, and included: 1) 38 individuals meeting criteria for DSM-IV schizophrenia and 2) 39 healthy control participants. Exclusion criteria included (a) substance abuse or any type of dependence within the past three months; (b) the presence of any clinically unstable or severe medical disorder; (c) present or past head injury with documented neurological sequelae, and/or causing loss of consciousness; (d) meeting DSM-IV criteria for mental retardation; and (e) pregnancy, or any contraindication to MR. Controls were excluded if they had any lifetime history of, or first-order family member with, an Axis I psychotic disorder, or any personal current mood or anxiety disorder other than specific phobias. This study received Washington University IRB approval, and all participants provided written informed consent in accordance with Washington University Human Subjects Committee's criteria. The groups did not significantly differ in age, ethnicity, handedness, or parental education. However, there was a significant difference in the gender ratio, and matrix reasoning scores between groups (*see* Table 1). All individuals with schizophrenia were taking medications at the time of participation in the study. For details on clinical assessment and symptom ratings please see Supplemental material.

2.2. Tasks and materials

Participants performed a "change-signal task" (CST) (Brown and Braver, 2005), an adaptation of the classical Stop-Signal Task (Logan et al., 1984). In this task participants are presented with a "go" signal consisting of an arrow pointing either left or right, and are instructed

Table 1
Demographic information.

Group	CON (n = 39)	SCZ (n = 38)
Age (SD)	36.6 (9.2)	37.5 (9.1)
Gender* %		
Female	56.4	28.6
Male	43.6	64.7
Ethnicity %		
Asian	2.6	3
Black or African American	63.2	66.7
Caucasian	34.2	30.3
Handedness %		
Left	10.5	15.8
Right	89.5	84.2
Years of school (SD)	14.3 (2.1)	14.6 (7.5)
Parental years of school (SD)	13.1(1.9)	13.3 (3.6)
Matrix reasoning test scaled score (SD)*	11.6 (2.6)	10.3 (3.1)
Average positive symptoms score (SD)	.03 (.16)	3.34 (2.78)
Average negative symptoms score (SD)**	1.44 (2.2)	7.58 (3.12)
Average disorganization score (SD)*	1.26 (1.25)	3.18 (2.92)

Note: CON = control group; SCZ = individuals with schizophrenia; SD = standard deviation.
** $p < .001$.
* $p < .05$.

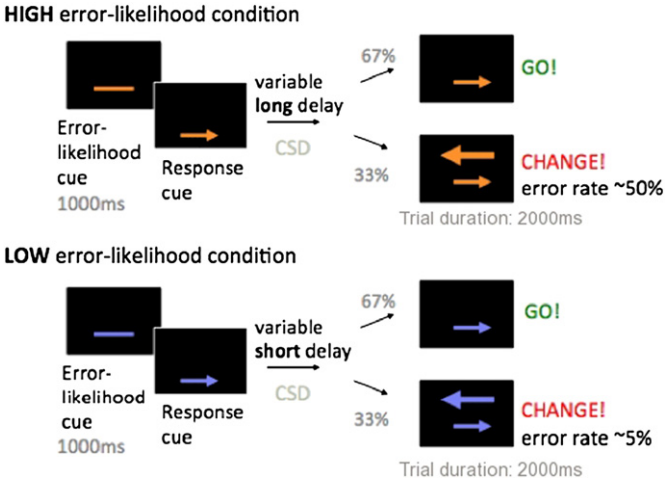

Fig. 1. Change-signal task diagram.

to indicate with a button-press the direction in which the arrow is pointing. In one third of the trials, a "Change" signal, consisting of a second, bigger arrow pointing in the opposite direction appears on top of the first arrow. In such cases, participants are instructed to indicate with a button press in which direction the second, bigger arrow is pointing. Importantly, the delay between the onset of the first arrow and of the "Change" signal can be manipulated. The longer the delay, the more likely subjects are to give a wrong response to the first, smaller arrow instead of to the second, bigger arrow appearing on "Change-trials". Thus, error-likelihood increases as the change-signal delay (CSD) increases. All trials initiated with an error-likelihood cue (i.e. a horizontal line in one of two colors) displayed for 1000 ms, followed by a response cue (i.e. the "go" signal in the same color as the initial cue) that was displayed for an additional 1000 ms. While the response cue is displayed, a "Change" signal may (or may not) appear at variable delays. Thus, the total duration of each event-trial always equaled 2000 ms. We used a stair-step algorithm designed to maintain the error rate of each participant at a specific target level (by adjusting the CSD based on performance) and created two target error rates for Change trials, High = 50% and Low = 5%. (See Fig. 1 for task diagram). Arrows in the High and Low conditions differed in color, so that color served as an implicit cue for error-likelihood (EL), as participants were not told of differences between task conditions. This task allowed us to differentiate responses associated with error-commission (i.e. incorrect vs. correct trials), conflict (i.e. correct Change trials vs. correct Go trials), and error-likelihood (i.e. correct High EL Go trials vs. correct Low EL Go trials). Participants were presented with 6 runs of the CST, each including 108 task trials (36 Change; 72 Go; half High and half Low error-likelihood randomly intermixed).

Participants completed 6 task runs, all of which included 4 initial and 6 final fixation trials, which consisted of a black screen with a white cross hair in the center (meant for participants to fixate their gaze on). These appeared at the beginning and at the end of each block, and allowed for signal stabilization, and were not included in data analysis. All trials, that is task (i.e. participant saw stimuli and made a response), no-event (black screen with no stimuli and no response), and fixation trials had a 2 second duration, in line with our TR. Mixed with task trials (always lasting 2 s), we interleaved 1 to 3 no-events (i.e. black screens appearing for 2, 4 or 6 s). Presenting no-events between task-trials introduces a "jitter" or variation in the inter-trial-interval (ITI), which allows the sampling of many more timepoints than using a fixed ITI, allowing us to estimate the shape of the BOLD response without assuming a canonical HRF (please see Miezin et al. (2000) for more details).

Visual stimuli were generated using e-Prime (Psychology Software Tools Inc., Pittsburg), and projected onto a computer screen behind the subject's head within the imaging chamber. Participants saw the screen through a mirror positioned approximately 8 cm above their face.

2.3. Behavioral data acquisition, processing and analysis

A fiber-optic, light-sensitive key press interfaced with a response button box was used to record subjects' accuracy and reaction time (RT) while they performed the task in the scanner. To examine the effect of accuracy and of conflict on RT, we categorized data into correct and incorrect response trials; post-correct or post-incorrect response trials (to examine post-error slowing); and post-conflict or post-non-conflict trials (to examine post-conflict slowing). We calculated error rates and RTs for each of these trial types. For median RT calculations, we excluded trials with RTs shorter than 300 and longer than 1600, as these were likely to represent noise. Cut-off points were determined based on histogram inspection, and are presented in Fig. S1 the Supplemental materials. For behavioral adjustment analyses, the first trial of each block was excluded and only correct, non-conflict (i.e. Go or congruent) trials were considered.

2.4. fMRI data acquisition, processing and analysis

2.4.1. Acquisition and pre-processing

Images were acquired on a Siemens 3 T Tim Trio system using standard acquisition procedures. During each run, sets of 33 contiguous axial images with isotropic voxels (4 mm^3) were acquired parallel to the anterior–posterior commissure plane. Acquisition time for each volume was 2000 ms. For event trials, stimuli were pseudorandomly jittered at 1, 2 and 3 MR frames (i.e. 2, 4, and 6 s.) (Miezin et al., 2000). All data preprocessing and further analysis was conducted using in-house developed software (FIDL, Washington University School of Medicine). MR data was reconstructed into images, and normalized across runs by scaling whole-brain signal intensity to a fixed value (mode of 1000), and removing the linear slope on a voxel-by-voxel basis to counteract effects of drift. MR data was aligned to correct for head motion using 6 parameter rigid-body rotation and translation correction algorithms (Friston et al., 1994; Snyder, 1996; Woods et al., 1998), and registered to a common space (Talairach and Tournoux, 1988) using 12 parameter linear (affine) transformations of the participant's average MP-RAGE image into a target image in Talairach atlas space, and then using the T2 images to align the T2* and T1 images. The fMRI images were spatially smoothed with a 6 mm FWHM Gaussian kernel. There was no difference

Table 2
Accuracy and RT in change signal task.

Group	CON (n = 37)		SCZ (n = 35)	
A. Accuracy	Mean accuracy (SD)			
	High EL	Low EL	High EL	Low EL
Change trials	.65 (.14)	.92 (.07)	.66 (.19)	.91 (.16)
Go trials	.96 (.05)	.96 (.05)	.95 (.09)	.95 (.08)
B. Reaction time (RT)	Median RT in ms (SD)			
	High EL	Low EL	High EL	Low EL
Correct Go	664.0 (133.5)	663.6 (131.6)	712.7 (163.2)	712.3 (166)
Correct Change	870.7 (110.7)	700.2 (95.3)	914.3 (131.6)	764.7 (140.8)
C. Behavioral adjustments				
Error-related				
	Mean accuracy (SD)			
	CON (37)		SCZ (n = 34)	
Current trial type	Post correct	Post error	Post correct	Post error
Correct Go (collapsing High and Low EL)	.993 (.006)	.988 (.03)	.989 (.01)	.986 (.03)
	Median RT in ms (SD)			
	CON (n = 37)		SCZ (n = 34)	
Correct Go (collapsing High and Low EL)	662.7 (131.0)	677.2 (161.7)	706.3 (162.1)	722.9 (148.4)
Conflict-related				
	Mean accuracy (SD)			
	CON (n = 37)		SCZ (n = 35)	
Current trial type	Post non-conflict	Post conflict	Post non-conflict	Post conflict
Correct Go (collapsing High and Low EL)	.993 (.010)	.990 (.014)	.991 (.01)	.986 (.017)
	Median RT in ms (SD)			
	CON (n = 37)		SCZ (n = 35)	
Correct Go (collapsing High and Low EL)	644.9 (129)	715.4 (149.9)	696.0 (161.9)	751.3 (165.3)

between groups in the signal to noise ratio (SNR), as the average RMS movement per frame during bold runs was of 0.19 for controls and .21 for individuals with schizophrenia ($t(68) = .67$, $p = .50$), and the mean voxelwise SD was of 13.27 for controls and 12.44 for individuals with schizophrenia ($t(68) = -1.2$, $p = .12$). To further reduce motion artifacts, frames with a displacement greater than .5 were also excluded. The average percentage of frames included was 90.6 for the control group and 89.5 for the schizophrenia group. To allow signal stabilization, the first 4 frames of each BOLD run were excluded from analyses.

2.4.2. fMRI analysis of accuracy, conflict and error-likelihood effects

Each subject's fMRI data was analyzed using General Linear Models (GLMs). Event types were modeled including 10 frames. We estimated the percent signal change at each time-point, thus calling for a "parameter" for the event type at each time point in the timecourse of each event type (a total of 20 s given the 2 second TR), making no assumption about the shape of the hemodynamic response. This is akin to modeling the hemodynamic response with a series of delta functions. The estimates from the individual subject GLMs were analyzed using repeated measures ANOVAs (as described in the Results section) that treated participants as a random factor and included timepoint within trial (frames 1–10) as within a subject factor.

2.4.3. Individual difference analyses

To examine the relationship between brain activity in response to error commission and conflict and behavioral adjustments, we conducted linear regression analyses using group and the difference in behavior between conditions (i.e. error minus correct, or conflict minus non-conflict) in step 1, and group × difference in behavioral measure in step 2 to predict activation in regions showing group effects. In addition, we created average scores of positive symptoms, negative symptoms and disorganization symptoms based on validated clinical symptoms scales (Andreasen, 1983a, 1983b). We then examined whether symptom scores predicted the difference in RT or activation in regions showing group effects (i.e. error–correct, or conflict–non conflict).

2.4.4. Regions of interest identification

To test our hypotheses, we defined as a priori regions of interest (ROIs) regions within the cingulo-opercular and cerebellar networks, previously shown to demonstrate robust error-related activity across a wide variety of tasks (Dosenbach et al., 2006, 2007). We created a ROI mask by taking the coordinates reported by Dosenbach et al. (2007) as the center of spheres with a 15 mm diameter (*see* Supplemental Table S2). To maximize the power of this approach, we conducted repeated measures ANOVAs using each ROI as a whole.

3. Results

3.1. Behavioral results

3.1.1. Overall task performance

Two control participants and one individual with schizophrenia were excluded from analyses due to poor performance (i.e. respectively, overall mean accuracy [.68; .63; .43] and accuracy in Go trials [.63, .53; .40] that was more than two standard deviations (SDs) below mean group accuracy). Another individual with schizophrenia was excluded due to technical difficulties in behavioral acquisition. Table 2 shows the mean accuracy and median RTs according to trial-type. A repeated

measures ANOVA using EL (High; low) and trial-type (change/conflict; go/non-conflict) as within-subject factors and group (CON; SCZ) as between-subject factor confirmed that there was a significant interaction between EL and trial-type, $F(1, 70) = 265.1$, $p < .001$ that did not further interact with group. This reflects the fact that, as planned, error rates for Change trials differed significantly according to target between EL conditions in both groups, although error rates were somewhat lower than expected in the High EL condition (see Table 2). A repeated measures ANOVA on RT in correct trials using the same factors revealed a trendlevel main effect of group, $F(1, 70) = 2.9$, $p = .092$, as participants with schizophrenia were overall slower, and a significant interaction between EL and trial-type, $F(1, 70) = 377.6$, $p < .001$, as RT was significantly greater in change compared to Go trials, and significantly greater in Change (but not go) trials in the High versus Low EL. There were no further interactions with group.

3.1.2. Error-related behavioral adjustments

To examine the effect of error on subsequent performance, we conducted a repeated measures ANOVA on accuracy in Go trials (collapsing across High and Low EL conditions) using accuracy in the preceding trial-type (prior correct; prior incorrect) as a within-subject factor and group (CON, SCZ) as a between-subject factor. One participant with schizophrenia made no errors and was excluded. Please see Table 2 for mean accuracy values following correct versus incorrect responses. This analysis revealed no significant main effects or interactions. A repeated-measures ANOVA on correct Go trial RTs (collapsing across High and Low EL conditions) using accuracy in previous trial as a within-subject factor, and group as a between-subject factor revealed a trend-level effect of accuracy in previous trial, $F(1, 69) = 3.0$, $p = .089$, but no main effect or interaction with group. As shown in Table 2, both groups showed a tendency toward greater RTs following an incorrect compared to a correct response.

3.1.3. Conflict-related behavioral adjustments

Similarly, to examine the effect of conflict on subsequent trials, we conducted a repeated measures ANOVA on accuracy in Go trials (collapsing across High and Low EL conditions) using conflict in the preceding trial-type (prior conflict; prior non-conflict) as a within-subject factor and group (CON, SCZ) as a between-subject factor. We found a significant main effect of previous conflict that did not further interact with group, $F(1, 70) = 5.8$, $p = .02$. As shown in Table 2, accuracy in Go trials was better following another Go compared to a Change trial. A repeated-measures ANOVA on correct Go trial RTs (collapsing across High and Low EL conditions) using conflict in previous trial as a within-subject factor, and group as a between-subject factor revealed a significant effect of conflict in previous trial, $F(1, 70) = 94.3$, $p < .001$ that did not further interact with group. As shown in Table 2, both groups demonstrated greater RTs following a conflict compared to a non conflict trial.

Table 3
Z-scores in ROIs demonstrating a statistically significant interaction with time in accuracy analysis in CST.

Brain region	Accuracy × time	Group × time	Accuracy × group × time
dACC/msFC	9.34	2.21	
L. ant. prefrontal cx.	1.96		
R. ant. prefrontal cx	5.35		
L. inf. parietal lob.	7.92		3.9
R. inf. parietal lob.	7.53		
L. ant. insula	11.83		
R. ant. insula	10.96		
L. ant. Thalamus	6.1		4.32
R. ant. Thalamus	7.06		4.66
L. lat. cerebellum	3.09		
R. lat. cerebellum		2.87	
L. inf. cerebellum			
R. inf. cerebellum	2.69		2.3

Note: L = left; R = right; ant = anterior; inf = inferior; lat = lateral; dACC/msFC = dorsal anterior cingulate cortex/medial superior frontal cortex.

3.2. Behavioral performance and clinical symptoms of schizophrenia

In a linear regression analysis using scores of positive symptoms, negative symptoms or disorganization, no clinical symptom score predicted the difference in accuracy or RT between correct and incorrect trials or between conflict and non-conflict trials within the schizophrenia group.

3.3. Neuroimaging results

3.3.1. Error-related brain activity

To examine the effect of errors on brain activity, we conducted a repeated measures ANOVA in each of our a priori ROIs in which we included accuracy (correct, incorrect) and timepoint within trial (1–10) as within-subject factors, and group as a between-subject factor. So that the effects of accuracy observed would be over and above conflict, we restricted analysis to conflict trials so that the effect of conflict was held constant across correct and incorrect trials. As shown in Table 3, all of our a priori selected regions in the Cingulo-Opercular network and regions in the left lateral cerebellum and right inferior cerebellum demonstrated a significant timepoint (i.e. frame within trial) × accuracy effect. As expected, all of these regions showed greater activity in error compared to correct trials (*see* Fig. S1 in Supplemental material). Regions in the dACC/msFC, and right lateral cerebellum also demonstrated a significant group × time interaction (see Table 3). Timecourses for regions showing a group × time interaction are shown in Fig. 2 along with their accuracy-related timecourses. To examine the source of the interaction, we conducted the same analysis described above, but included only timepoints 3 and 4 (to examine response peak differences) or timepoints 7 and 8 (to examine response undershoot differences). At response peak, we found a trend-level effect of group, $F(1, 67)_{3+4} = 1.75$, $p = .08$ in the dACC/msFC, and a trend-level accuracy × group interaction in the cerebellum, $F(1, 67)_{3+4} = 1.72$, $p = .08$. We found no group main effects or interactions at response undershoot in either region. In addition, the left inferior parietal lobule, thalamus bilaterally and right inferior cerebellum demonstrated a three-way accuracy × time × group interaction. Timecourses for each of these regions are shown in Fig. 3. In the left inferior parietal lobe and right inferior cerebellum, there was a significant group × time × accuracy interaction both at response peak, $F(1, 67)_{3+4} = 2.87$, $p = .004$ and $F(1, 67)_{3+4} = 2.43$, $p = .02$ respectively, and at response undershoot, $F(1, 67)_{7+8} = 1.98$, $p = .04$ and $F(1, 67)_{7+8} = 2.7$ $p = .006$, respectively. In the thalamus, a significant group × time × accuracy interaction was present only at response undershoot, $F(1, 67)_{7+8} = 3.19$, $p = .001$ (left) and $F(1, 67)_{7+8} = 3.9$ $p < .001$ (right).

3.3.2. Conflict-related brain activity

To examine conflict and error likelihood effects, we estimated responses to correct change (i.e. conflict) and to correct Go (i.e. non-conflict) trials, creating separate estimates for High EL and Low EL conditions. We included EL (High, low) and trial type (conflict, non-conflict) as within-subject factors in a repeated measures ANOVA (in addition to timepoint within trial), and group as a between-subject factor. As shown in Table 4 and Fig. S3 in Supplemental materials, regions in the right anterior PFC, left inferior parietal lobule, left insula, bilateral thalamus and left inferior and lateral cerebellum demonstrated a conflict by timepoint interaction that did not further interact with error likelihood or group, showing greater activity during incongruent compared to congruent trials. Regions in the dACC/msFC, right inferior parietal lobule and right anterior insula showed a conflict × error likelihood × time interaction (see Table 4). As shown in Fig. S4 in Supplemental materials, change but not Go trials elicited greater activation in the High EL compared to the Low EL condition in these regions. Regarding interactions with group, the dACC/msFC, right inferior parietal lobule, left anterior

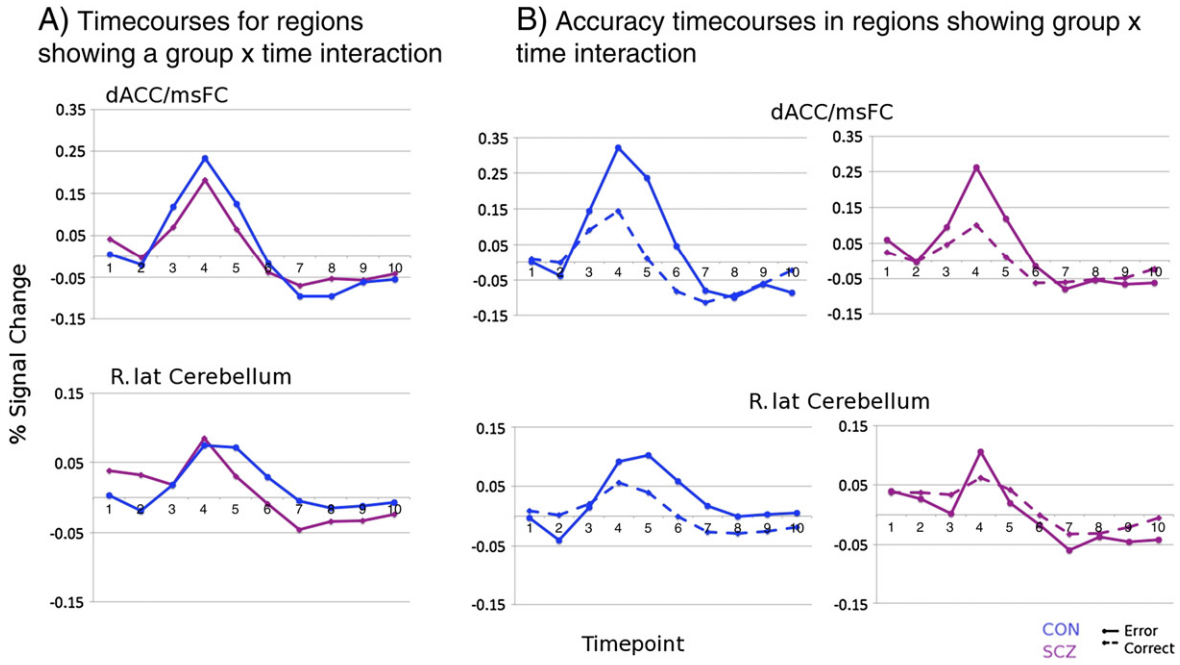

Fig. 2. Timecourses for regions showing a group × time interaction in accuracy analysis in CST.

insula, and thalamus bilaterally showed a significant group × time interaction (see Table 4, and Fig. 4). To examine the source of the interaction, we again conducted analyses that included only timepoints 3 and 4 (to examine response peak differences) or timepoints 7 and 8 (to examine response undershoot differences). The dACC/msFC demonstrated a trend-level main effect of group both at response peak and undershoot, $F(1, 68)_{3+4,\ 7+8} = 1.77$, $p = .08$. The right inferior parietal lobule, left insula and thalamus did not demonstrate group differences at response peak. However, we found a significant group × time interaction at response undershoot in the right inferior parietal lobule, $F(1, 68)_{7+8} = 2.1$, $p = .04$, and thalamus bilaterally, $F(1, 68)_{7+8} = 2.56$, $p = .01$ (left), and $F(1, 68)_{7+8} = 3.11$, $p = .002$ (right). Further, the right anterior insula demonstrated a significant conflict × group × timepoint interaction (see Table 4, Fig. 5B). We found no significant group differences at response peak in this region, but found evidence of a significant conflict × group interaction, $F(1, 68)_{7+8} = 2.9$, $p = .004$, as well as a significant time × group interaction, $F(1, 68)_{7+8} = 2.6$, $p = .01$ at response undershoot.

3.3.3. Error-likelihood effects

The right anterior PFC demonstrated an interaction between error likelihood, group and timepoint (see Table 4, Fig. 5A). Post-hoc analysis showed a significant main effect of group at response peak, $F(1, 68)_{3+4} = 2.01$, $p = .04$, but no differences between groups at response undershoot.

3.4. Brain activity and task performance relationship

We conducted linear regression analyses using group and the difference in RT between conditions (i.e. error minus correct, or conflict minus non-conflict) in step 1, and group × difference in behavioral measure in step 2 to predict overall activation in regions showing group effects. This analysis yielded a significant model for RT differences predicting activity differences in the right thalamus in the CST in step 1, F Change $(2,67) = 7.14$, $p = 0.009$. Adding the interaction between group and RT difference in step 2 did not account for any significant increase in variance, step 2, F Change $(1,66) = 6.99$, $p = .41$, indicating a

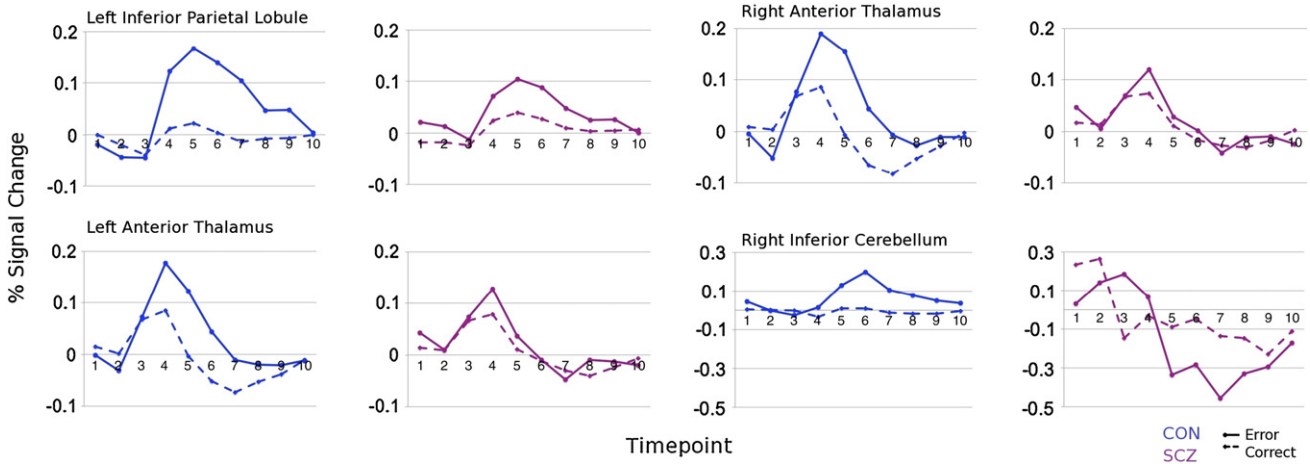

Fig. 3. Timecourses for regions showing an accuracy × time × group interaction in accuracy analysis in CST.

Table 4
Z-scores in ROIs Demonstrating a statistically significant interaction with time in conflict analysis in CST.

Brain region	Cnfct × time	EL × time	Cnft × EL × time	Group × time	Group × time × EL	Cnfct × group × time
dACC/msFC			2.04	2.41		
Left ant prefrontal cx						
Right ant prefrontal cx	3.36				2.48	
Left inf parietal lob	7.43					
Right inf parietal lob			2.24	2.73		
Left ant insula	8.3	3.76		2.49		
Right ant insula						1.96
Left Thalamus	6.05			2.64		
Right Thalamus	5.61			3.32		
Left lat cerebellum	3.7					
Right lat cerebellum						
Left inf cerebellum	2.96					
Right inf cerebellum						

Note: L = left; R = right; ant = anterior; inf = inferior; lat = lateral; dACC/msFC = dorsal anterior cingulate cortex/medial superior frontal cortex; cnfct = conflict; EL = error likelihood.

positive relationship between post-error slowing and the difference in activation in incorrect compared to correct trials in the thalamus in both groups. Although the model for the dACC/msFC was not significant, we followed up with the planned correlation analysis within each group given the main focus of this region. In the schizophrenia group, greater post-error slowing correlated with greater difference in activation in incorrect compared to correct trials in the dACC/msFC, $R^2 = .245$, $p = .005$. This was not the case within the control group, $R^2 = .039$, $p = .24$. In addition, we examined the correlation between the clinical measures (positive, negative and disorganization scales) and the difference in activation (error–correct, or conflict–non conflict) in regions showing group effects within the schizophrenia group. We found that in the CST, greater avolition scores in the schizophrenia group predicted greater difference in activity (error–correct) in the dACC/msFC, $R^2 = .144$, $p = .035$.

4. Discussion

In this study we examined group differences in behavioral performance and brain activation related to error- and conflict-processing between individuals with schizophrenia and healthy controls. We extend previous findings in the literature in two important ways: 1) we examined neural responses to error and conflict beyond the dACC/msFC, including a set of regions previously identified to show robust error-related responses in the normative literature and 2) we utilized a task that explicitly provides information about error and conflict, in contrast to previous studies relying on the participant's self-generated task representation. Contrary to our predictions, individuals with schizophrenia demonstrated intact post-error and post-conflict behavioral effects, as well as error- and conflict-related effects comparable to those of healthy controls in the dACC/msFC, and in a number of other key regions. Taken together, our results indicate that when information about errors and conflict is provided by the task structure itself, error- and conflict-processing is relatively preserved in individuals with schizophrenia, suggesting that a compromise in task representation may contribute to the behavioral and neural alterations related to error- and conflict-processing documented in the schizophrenia literature. Below we expand on how our findings relate to previous research, and elaborate on their implications.

4.1. Error-related activity

In the present study, we found no significant differences between groups in post-error slowing in the context of a change-signal task (CST). Previous studies examining behavioral adaptations after error-commission in individuals with schizophrenia have produced conflicting results, with a number of studies reporting comparable post-error slowing between groups (Alain et al., 2002; Laurens et al., 2003; Mathalon et al., 2002; Morris et al., 2006; Polli et al., 2006), but other studies indicating a compromise in individuals with schizophrenia (Becerril et al., 2011; Carter et al., 2001; Kopp and Rist, 1999). The tasks used have varied widely across studies, most studies had small sample sizes, in many cases the proportion of overall errors is relatively low and performance between groups was frequently not matched. Thus, making comparisons between studies is difficult. However, abnormal error-related neural responses in individuals with schizophrenia have been reported more consistently, even in the absence of behavioral alterations (Becerril et al., 2011; Carter et al., 2001; Kerns et al., 2005; Krawitz et al., 2011; Laurens et al., 2003; Polli et al., 2008). Our results stand in contrast to these findings. In the context of a CST, we found similar error-related effects in both groups in the dACC/msFC, as well as in other key regions including bilateral anterior PFC, bilateral insula, right inferior parietal lobule, right inferior cerebellum, and left lateral cerebellum.

Although on the surface our findings seemingly contradict previous literature, a careful examination of the tasks used and brain activation reveals interesting patterns. An important difference in the current study is the utilization of tasks in which information about errors is directly provided by the task structure, as opposed to requiring the generation of an error representation by participants from memory. Most fMRI studies examining error processing in schizophrenia have used tasks in which information about whether an error was made needs to be generated by the participant based upon their internal representation of the task structure and demands, as opposed to contained in the task structure or feedback (Becerril et al., 2011; Carter et al., 2001; Kerns et al., 2005; Polli et al., 2008). For example, some studies have used working memory tasks such as the n-back or antisaccade tasks, in which participants need to keep in mind a given cue or a set of stimuli. In these, the ability to maintain the cues of the stimuli in working memory is necessary in order for an individual to know whether they made an error. If such maintenance mechanisms are impaired, they may be unaware that they committed an error. In all of these studies error-related activity in the dACC is diminished in individuals with schizophrenia compared to healthy controls (Becerril et al., 2011; Carter et al., 2001; Kerns et al., 2005; Polli et al., 2008). In contrast, studies in which information about errors was provided by the task structure, such as in a Go/NoGo task where the task stimulus itself gives feedback regarding accuracy after responses are executed, individuals with schizophrenia demonstrate an interesting dissociation in regions sensitive to error commission within the dACC/msFC. Specifically, the more ventral and anterior portions of the dACC/msFC – typically associated with affect and motivation – demonstrate abnormal responses in individuals with schizophrenia, while the more dorsal portions – typically associated with performance-monitoring – demonstrate comparable activation between groups (Krawitz et al., 2011; Laurens et al., 2003). Moreover, this same pattern has been found in a recent topographic analysis of individual activation patterns associated with error commission in individuals with schizophrenia (Stern et al., 2009). Thus, although

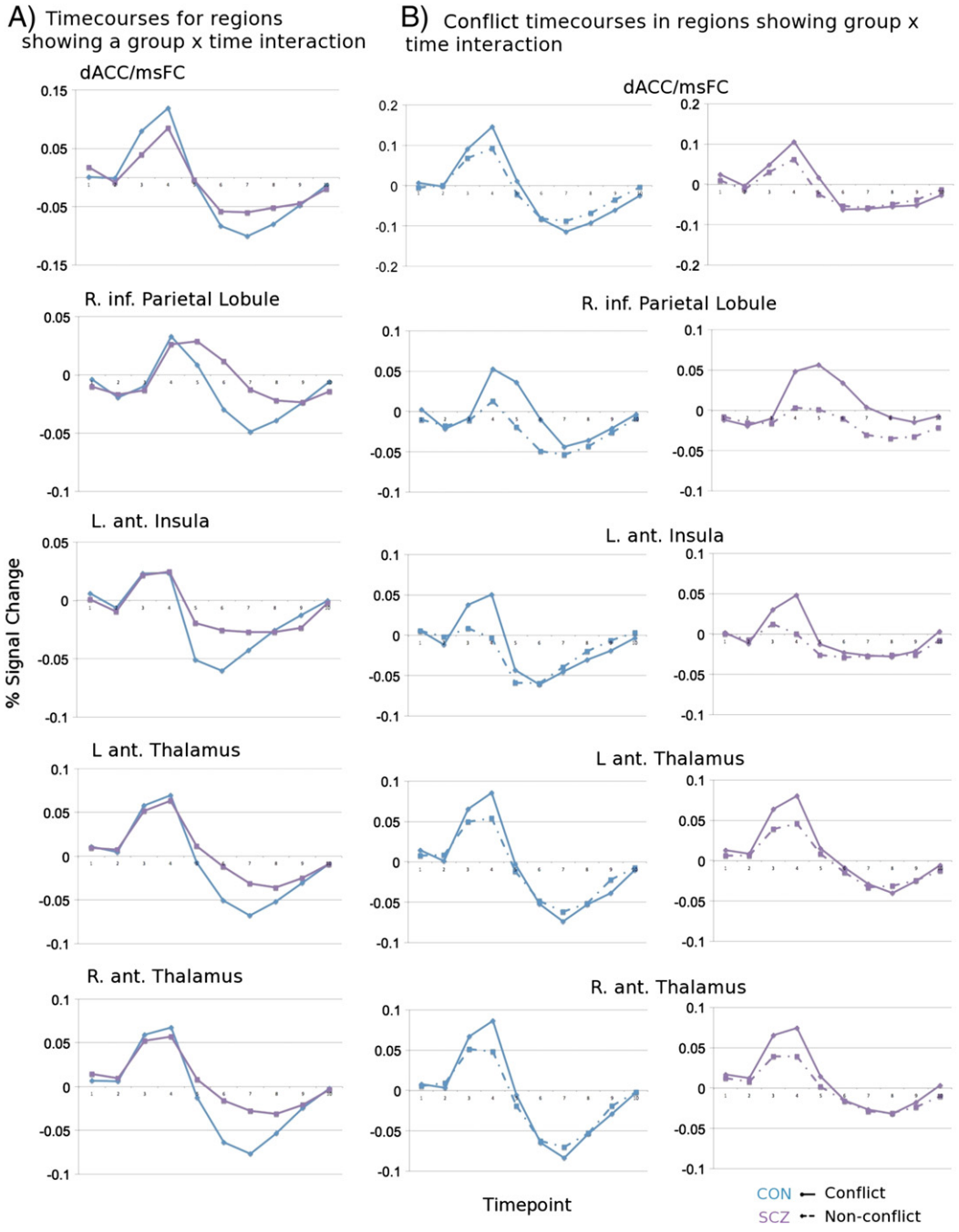

Fig. 4. Timecourses for regions showing a group × time interaction in conflict analysis in CST.

our present findings are contrary to our initial expectations, they are in line with the hypothesis that the behavioral and neurophysiological alterations reported in performance-monitoring tasks in individuals with schizophrenia may reflect, at least in part, a compromise in the ability to construct or maintain task relevant representations, rather than a compromise in error-detection per se. Further, an emergent pattern in the literature indicates that altered error-related responses may be associated with impaired affective responses to errors. Lastly, this interpretation of our results is also consistent with recent data suggesting that individuals with schizophrenia show abnormal ERN responses when internally generated feedback is needed, but normal feedback related responses (FRN) to externally generated feedback (Horan et al., 2012; Morris et al., 2011).

That being said, even though the dACC/msFC did not show significant differences in error-related activity in this study, which is consistent with the relatively intact behavioral response to errors and conflict, we did find evidence of an overall reduction in dACC/msFC activation in schizophrenia. Blunted responses in the medial PFC in individuals with schizophrenia compared to controls have been previously observed even when performance is matched (Koch et al., 2008). The significance of this finding remains an empirical question, and more research is needed to clarify the functional impact that the level of engagement of the dACC/msFC and other brain regions has in performance monitoring when differential responses to errors is intact.

In contrast to the dACC/msFC, the left inferior parietal lobe, the thalamus bilaterally, and the right inferior cerebellum did demonstrate significantly diminished error-related activity in individuals with schizophrenia compared to healthy controls. Studies in healthy controls have associated error-related activity in the inferior parietal lobe with attentiveness (Hester et al., 2004). Under that framework, blunted responses in parietal regions may suggest diminished

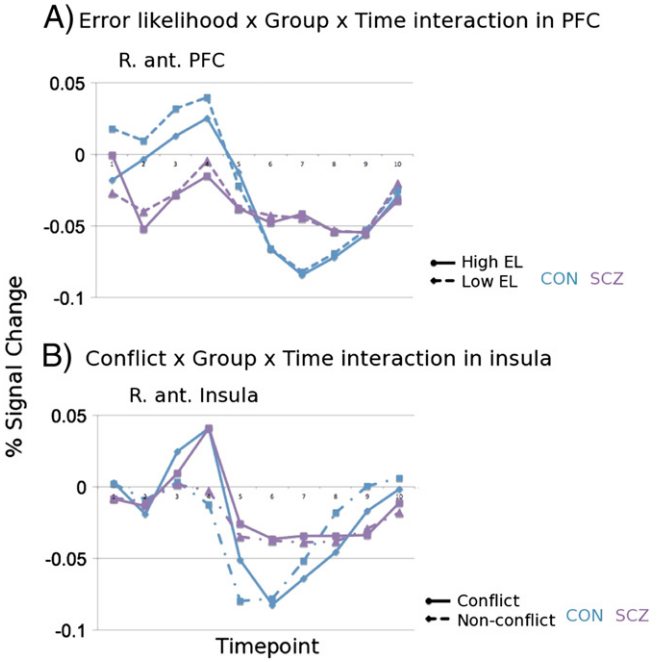

Fig. 5. Timecourses for regions showing a 3-way interaction in conflict analysis in CST.

attentiveness in individuals with schizophrenia compared to healthy controls.

The role of the thalamus in error-processing remains unclear. Studies in patients with thalamic lesions have shown that the "error-related negativity" evoked related potential, a neurophysiological correlate associated with error-commission (Gehring et al., 1993) is diminished in these patients compared to healthy controls, as is error awareness and post-error slowing (Peterburs et al., 2011; Seifert et al., 2011). Previous literature suggests that the thalamus is organized into functional areas according to its connections to specific cortical regions (Jones, 1998). In primates, projections from the ACC terminate primarily in the anterior and ventral portion of the thalamus (Carmichael and Price, 1996). While our methods did not afford the fine-grained spatial resolution that allowed us to distinguish between different thalamo-cortical loops, it is worth mentioning that the coordinates which served as the focus of our analysis are centered in the anterior portion of the thalamus. Peterburs et al. (2011), propose that input from the thalamus may inform the cingulate cortex about ongoing movements in the form of an efference copy to allow monitoring processes. In the light of the well known alterations in dopamine in schizophrenia, it is interesting to note that dopamine is thought to modulate the activity and plasticity of the basal ganglia (Hikida et al., 2010; Reynolds and Wickens, 2002). Thus, one may speculate that reduced thalamic responses in schizophrenia are not specific to error-processing, but instead relate to alterations in the fast relay of information regarding nature of the planned or ongoing response, with potential implications for action selection.

In contrast to thalamic findings, timecourses in the cerebellum among individuals with schizophrenia were not particularly well-formed and thus could indicate some signal artifact. For example, greater cross-subject variability in activation patterns in the schizophrenia group may be contributing to this result.

4.2. Conflict-related activity

As with our error-related analyses, we found no group differences in behavioral adjustments after conflict trials. We found common conflict-related effects across groups in the right anterior PFC, left inferior parietal lobule, left insula, thalamus bilaterally, and left lateral and inferior cerebellum regions. Moreover, the dACC/msFC and the right inferior parietal lobule demonstrated a further interaction of conflict with error-likelihood in both groups. These results support the hypothesis that when information about conflict is provided by the environment or task-structure, individuals with schizophrenia demonstrate relatively intact conflict-related effects. Thus a compromise in the ability to properly construct or maintain task relevant representations may be at the core of the deficits observed in performance monitoring in schizophrenia.

As in our error analyses, we found evidence for an overall reduction in dACC/msFC activity in schizophrenia. This group × time effect was also present in the right inferior parietal lobule, left anterior insula, and thalamus bilaterally. In addition, the right anterior insula demonstrated a significant conflict × time × group interaction. In all of these cases, group differences were apparent at response undershoot, with individuals with schizophrenia failing to deactivate to the same extent as controls, but no significant effects at response peak. Thus, rather than a lack of sensitivity to conflict, the pattern of differences in brain activity that we observed suggests alterations in the disengagement of brain regions sensitive to conflict-effects in individuals with schizophrenia compared to healthy controls, though the exact meaning of reductions in response undershoot among individuals with schizophrenia needs further research.

4.3. Error-likelihood effects

We found an error-likelihood effect in the left insula in both groups, and an abnormal error-likelihood effect in the right anterior PFC in individuals with schizophrenia compared to healthy controls. Previous studies examining error likelihood effects in the normative literature have been for the most part focused on the dACC/msFC. However, results have been inconsistent, with some studies reporting a significant error-likelihood effect in this region (Alexander and Brown, 2010; Brown and Braver, 2005), but other studies failing to replicate the effect (Becerril and Barch, 2012; Brown, 2009; Nieuwenhuis et al., 2007). Error-likelihood effects beyond the dACC have only been reported in two studies to our knowledge. Results have also been inconsistent, with one study reporting error likelihood effects in regions in the dorsolateral PFC, inferior parietal lobule and cerebellum (Brown and Braver, 2005), and another study failing to identify error likelihood effects in any of the regions shown to demonstrate robust error-related effects (Becerril and Barch, 2012). Of note, this error-likelihood effect has been associated with increased risk-taking behaviors (Brown and Braver, 2007). Thus, individual differences in personality traits may represent a confound.

To examine error-likelihood effects in individuals with schizophrenia, Krawitz et al. (2011), administered a modified version of the CST in which participants also completed a delayed match to sample task based on the response cue. Krawitz et al. (2011), found no evidence of error-likelihood effects at response cue in the dACC/msFC across groups, but reported a greater error-likelihood effect in bilateral regions of the dACC/msFC when controls were compared to individuals with schizophrenia, suggesting alterations in this region in signaling the predicted likelihood of an error occurring in response to a given task condition. In contrast to Krawitz et al. (2011), we found no evidence of altered error likelihood effects in the dACC in individuals with schizophrenia. Notably, in our task, the response cue carried no information that needed to be retrieved at a later point in the trial, whereas the task used by Krawitz et al. (2011) did. Thus, differences in encoding or maintenance of information may explain the lack of error-likelihood effects in the dACC/msFC. However, our results suggest that in a simpler paradigm, individuals with schizophrenia do show alterations in prediction mechanisms of response-outcome evaluations, but that these are apparent in prefrontal regions rather than the dACC. Consistent with literature indicating abnormal prefrontal cortex function in schizophrenia, it is possible that in the context of a simpler task with explicit information about errors, the compromise in individuals with schizophrenia lies in the utilization of error signals by prefrontal regions for the implementation

of outcome predictions. On the other hand, the error likelihood effect observed in both groups in the insula may reflect an intact response to the saliency of more demanding task conditions (Nelson et al., 2010; Seeley et al., 2007).

4.4. Brain behavior relationships

In the schizophrenia group, greater post-error slowing correlated with greater difference in activation in incorrect compared to correct trials in the dACC/msFC. This result is consistent with previous findings in the normative literature (Botvinick et al., 2001; Kerns et al., 2004). Although the relationship between brain activity in specific regions and behavioral adjustments has not received much attention in the schizophrenia literature, one of our previous studies also showed that stronger dACC/msFC responses in individuals with schizophrenia were associated with greater post-error slowing in the context of a working memory task where no feedback about performance was provided (Becerril et al., 2011). Taking a slightly different angle, Polli et al. (2008), reported a negative relationship between activity in the dACC/msFC and error commission during an antisaccade task where, again, no feedback about performance was provided. Taken together, these findings support the role of the dACC/msFC in cognitive control and online behavioral adjustments. Further, they suggest that irrespective of whether feedback regarding errors is provided or not, the level of engagement of the dACC/msFC can predict performance and error-related behavioral adjustments in individuals with schizophrenia. In addition, we found that greater post-error slowing was associated with a greater difference in activation in incorrect compared to correct trials in the thalamus in both groups, suggesting that greater error-processing activity at early information processing stages results in a greater impact of error on behavioral correlates.

4.5. Limitations and future directions

As with many studies in this field, a limitation here is that all participants with schizophrenia were taking antipsychotic medications at the time of the study, which may interact with task performance and brain activity. In addition, patients in our sample were taking different antipsychotic medications, and at different doses, which precluded post-hoc analyses examining the role of medication that were sufficiently powered. However, there is evidence that neurophysiological correlates of error-processing are diminished in unmedicated individuals with schizophrenia (Bates et al., 2004). Furthermore, an important proportion of individuals with schizophrenia are chronically medicated, thus, we believe it is important to assess the functioning of patients on medications if this is their typical state. Ideally, studies like this one should be complemented with examinations in first-episode or medication naïve patients, as well as in unaffected siblings that possess genetic liability to schizophrenia but no medication exposure.

Another limitation in this study is that we did not manipulate the availability of task-representation, and we did not directly compare the patterns of brain activity and behavior elicited by tasks providing explicit information about errors and conflict versus tasks that require a task representation to be generated by participants. As such, our hypotheses about the sources of differences in the results of the current study versus previous studies are speculative. Future studies that allow a "head to head" comparison of results between types of tasks within the same individuals will provide more conclusive evidence to distinguish between alterations due to a compromise in task representation versus error and conflict monitoring in schizophrenia. Finally, future studies that examine effective functional connectivity relationships between key regions associated with the implementation of cognitive control will shed light on the temporal dynamics in brain activation, and help further clarify the role of the diverse regions involved in performance monitoring.

4.6. Conclusions

Although alterations in dACC/msFC function related to cognitive control in schizophrenia have been explained in terms of compromises in error detection (Polli et al., 2008) or conflict monitoring (Kerns, 2008) during performance monitoring, our results suggest a new interpretation of findings. In both of our tasks, individuals with schizophrenia demonstrated intact error- and conflict-related effects in the dACC/msFC, as well as in a number of other key regions including the bilateral anterior PFC, bilateral insula, right inferior parietal lobule during error processing, and bilateral inferior parietal lobule and thalamus, right anterior PFC, left insula, and left lateral and inferior cerebellum during conflict processing. With the exception of the inferior cerebellum, the pattern of activity in all of our a priori selected regions of interest is consistent with previous studies showing that individuals with schizophrenia demonstrate blunted (but not absent) error- and conflict-related activity. Given that a critical difference in our experimental design was the use of tasks that explicitly provide information about errors and conflict, our results raise the hypothesis that the error- and conflict-detection systems are still somewhat functional in individuals with schizophrenia, but that a compromise in the generation or maintenance of task relevant information leads to the alterations in error- and conflict-processing documented in the schizophrenia literature. An intriguing hypothesis is that a faulty task representation in schizophrenia would not provide the necessary signals that mechanisms involved in performance-monitoring utilize at later information processing stages.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2013.09.012.

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