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Sustained and Transient Reward Effect on Cognitive Control in Schizophrenia: The Relevance of Negative Symptoms

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by

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List of Abbreviations

BA: Broadmann's Area

BCXT: Baseline-Context trials cued by "XX" in baseline blocks

BG: Basal ganglia

BOLD: blood oxygenation level dependency

DLPFC: dorsolateral prefrontal cortex

DA: dopamine

fMRI: functional magnetic resonance imaging

HC: healthy controls

OFC: orbitofrontal cortex

PFC: prefrontal cortex

RC: Reward-Cue trials cued by "*XX*" in reward blocks

RCXT: Reward-Context trials cued by "*$20*" in reward blocks

ROI: Region of interest

SCZ: schizophrenia

VS: Ventral striatum

WB: Whole brain

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ABSTRACT OF THE DISSERTATION

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Doctor of Philosophy in Psychology

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Professor Deanna M. Barch, Chair

Schizophrenia (SCZ) is characterized by severe cognitive impairments and amotivation, generally referred to as negative symptoms, including anhedonia and/or avolition. Amotivation tends to exist in prodromal patients and persist over the illness course regardless of successful antipsychotic medications, which are known to reduce positive symptoms, including hallucination and delusions (e.g., (Horan, Blanchard, Clark, & Green, 2008; Tarbox et al., 2013). Importantly, amotivation is a promising predictor for later social functioning in SCZ, even after accounting for patients' cognitive impairments (e.g., (Evensen et al., 2012; Faerden et al., 2010). Despite this crucial impact on functioning outcome in SCZ, to date, no study has systematically investigated neural mechanism underlying amotivation in SCZ.

To date, it has been well documented that many of cognitive impairments in SCZ may reflect a core deficit of non-emotional context processing, supported by the dorsolateral prefrontal cortex (DLPFC), and defined by the ability to maintain non-emotional context information necessary to regulate upcoming behavioral response towards goal-directed behavior (e.g., (Cohen, Barch, Carter, & Servan-Schreiber, 1999). Recent evidence from both animal and healthy human neuroimaging work suggests that the DLPFC plays a crucial role in representing and integrating reward-related context information. However, it has been unexplored whether individuals with SCZ can represent and integrate reward-related contextual

information to modulate cognitive control function implicated in the DLPFC.

Thirty-six individuals with SCZ and twenty-seven healthy controls (HC) underwent behavioral and fMRI data collection at 3Tsela while performing a modified response conflict processing task under two contexts, that is, no-reward baseline and reward contexts. Participants first performed baseline conditions without any knowledge regarding the future potential for incentives (Baseline-Context; BCXT). Each trial started with a baseline cue, "*XX*" that was pre-instructed to participants as being irrelevant to the task. After each cue, "*XX,*" either a house or building picture (with overlaid words that are either congruent or incongruent) was presented to each participant one at a time. The job of the task was to categorize each picture as either a house or a building by pressing a certain button while ignoring the overlaid word. Following the baseline condition, participants performed additional reward blocks on which they were told that they could win money on some trials by performing fast (faster than their median correct reaction times (RT) in the baseline and accurately). Each trial was then preceded either by a "*$20*" cue (Reward-Cue; RC), indicating that a fast and correct response would be rewarded or by a "*XX*" cue (Reward-Context; RCXT), indicating zero money would be possible on the trial. After the target stimulus, participants received immediate feedback regarding the reward points they earned on the trials, as well as their cumulative earning in points.

As such, this response conflict task paradigm enabled examination of: (1) reward *context* effects by comparing performance and brain activity when the cue, "XX" was presented in the *baseline* context versus in the *reward* context (BCXT vs. RCXT trials cued by the same cue, "*XX*") and (2) reward *cue* effects by comparing performance during RC (cued by "*$20"*) versus RCXT (cued by "*XX"*) within reward blocks. Importantly, by employing a mixed state-item fMRI design, I investigated both sustained (block-based) context-dependent and transient (trial-by-trial) reward-related cue activity at both behavioral and neural levels.

The behavioral data revealed two main patterns: contrary to our prior behavioral work

(Mann, Footer, Chung, Driscoll, & Barch, 2013), like the HC, individuals with SCZ also showed faster response on the Reward-Context trials within reward contexts ("*XX*", zero money) compared to Baseline-Context trials ("*XX*" in baseline blocks), which we refer to as the reward context effect. On the other hand, the SCZ showed a trend-level of reduced reward cue effect relative to the HC, as evidenced by less reduction in reaction times (RT) from RCXT ("*XX*", zero money) to RC ("*$20*") within reward blocks.

The neuroimaging data revealed four main patterns of results. First, in terms of sustained context-dependent effect, contrary to my prediction, individuals with SCZ showed intact pattern of increased sustained activity during reward contexts in the bilateral DLPFC at a group level like the HC. Secondly, in terms of transient trial-by-trial reward-predicting cue-related activity, different from the HC, patients showed blunted VS activity to the cue regardless of its type ("*XX*" or "*$20*"). During the target phase, the SCZ showed blunted target-related activity in the right DLPFC (BA9) while HC showed reduced activity on RC and RCXT relative to BCXT across condition-type. These results might be suggestive of patients' reduced ability to represent reward-related contextual information supported by the right DLPFC in motivationally salient situations. Lastly, regarding the relation to negative symptoms in SCZ, in the right DLPFC (BA9: +42, +16, +29) where both group showed the same pattern of increased sustained activity during reward vs. baseline context, we found that more sustained activity during reward vs. baseline blocks at an individual level was associated with lower amotivation scores. Also, transient cue-related activity during RC vs. RCXT in the DLPFC was significantly associated with individual difference in negative symptoms scores. These results suggest that patients' motivational impairments (i.e., anhedonia, avolition) are closely related to DLPFC function to integrate reward-related information in motivationally salient situations. Taken together, current behavioral and fMRI results may suggest patients' abnormalities of both DA-related right DLPFC and subcortical systems (i.e., ventral striatum) during reward processing despite intact behavioral pattern of reward context effect.

Introduction

Overview. Schizophrenia (SCZ) is one of the most debilitating neuropsychiatric disorders that afflict approximately one in every 100 young people (American Psychiatric Association, 1994). Since Kraepelin (Kraepelin, 1919), cognitive and motivational impairments have been considered as fundamental clinical features of this illness (Meehl, 2001; Rector, Beck, & Stolar, 2005). In SCZ literature, amotivation is generally categorized as a negative symptom, which also includes anhedonia, asociality, avolition, alogia, and blunted affect (e.g., (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Negative symptoms often occur before the onset of psychosis and persist over the course of illness even when antipsychotic treatment is successfully in relieving symptoms such as hallucinations and delusions (e.g., (Horan et al., 2008; Tarbox et al., 2013)). Notably, converging data show that the negative symptom domain (e.g., amotivation and/or apathy) is a prominent predictor of functional outcomes in first-episode (e.g., (Evensen et al., 2012; Faerden et al., 2010) and chronic patients (e.g., (Kiang, Christensen, Remington, & Kapur, 2003) across the illness course even after accounting for cognitive impairments. However, despite the potentially crucial impact of motivational impairments on functional outcomes in SCZ, little is known about the neural mechanisms underlying negative symptoms in SCZ.

To date, independent lines of research have shown that individuals with SCZ display deficits in cognitive control function (e.g., (Cohen et al., 1999), and both intact and impaired aspects of dopamine (DA)-related reward processing (Gold, Waltz, Prentice, Morris, & Heerey, 2008). Deficits in cognitive control functions are thought to reflect impairments in the lateral prefrontal cortex (PFC), which is hypothesized to have dysregulated input from the midbrain dopamine (DA) system in SCZ (Braver, Barch, & Cohen, 1999; Cohen & Servan-Schreiber, 1992); Cohen, 1999). Recent evidence suggests that the lateral PFC plays a crucial role in integrating cognitive and reward-related information (Jimura, Locke, & Braver, 2010; Sakagami & Watanabe, 2007; Watanabe & Sakagami, 2007). However, despite a body of literature

suggesting cognitive control impairments associated with impaired lateral PFC function in SCZ (Glahn et al., 2005; Goldman-Rakic & Selemon, 1997; Van Snellenberg, Torres, & Thornton, 2006), little is known about whether individuals with SCZ can use reward-related information to modulate cognitive control function. As such, the purpose of this study is to investigate the influences of motivational (monetary) incentives on cognitive control function in SCZ at both behavioral and neural levels.

Emerging evidence from neurophysiological studies in non-human primates and neuroimaging studies in humans suggest that the lateral PFC is involved in encoding reward-related information, which is used to enhance cognitive control functions (Kouneiher, Charron, & Koechlin, 2009; Krawczyk, Gazzaley, & D'Esposito, 2007; Szatkowska, Szymanska, Marchewka, Soluch, & Rymarczyk, 2011). This enhanced cognitive control function, potentially via internal representations of reward value, is referred to as “motivated” cognitive control. For example, many neurons in primate lateral PFC showed differential visual responses to reward-predicting cue stimuli compared to other no-reward predicting cue stimuli (Sakagami & Watanabe, 2007). Consistent with findings in primates, human neuroimaging studies provide evidence suggesting that reward incentives modulate cognitive control function in various task paradigms. For example, when healthy individuals performed a conflict-processing task under reward and no-reward conditions, conflict processing was significantly reduced on reward trials relative to no-reward trials, as evidenced by faster reaction times during reward conditions (Padmala & Pessoa, 2011). Furthermore, reward-predicting cues during the reward condition increased neural activity in several brain regions related to cognitive control function, often referred to as the Cognitive Control Network (CCN), as well as in reward-related regions including the dorsal and ventral striatum. More importantly, increased reward cue-related responses during reward versus no-reward trials were associated with decreased conflict-related responses in the medial PFC, suggesting that the presence of rewarding cues enhances cognitive control function by decreasing conflict processing (Padmala & Pessoa, 2011). Interestingly, more recent work from

human neuroimaging provides evidence that the representation of reward-related context information impacts cognitive control function. For example, according to (Locke & Braver, 2008), healthy individuals showed faster and better behavioral performance as measured by the *AX* variant of the Continuous Performance Test (AX-CPT) during reward blocks in which incentives were available on some trials compared to when they performed the same task with no knowledge of the potential incentives. This effect, as referred to as the reward context effect, indicates the reward enhancement of cognitive control in the presence of incentives, which facilitates representing and preparatory processing of the upcoming target-related information. The reward context effect has been associated with increased sustained activations in several cognitive control regions such as the lateral PFC at the neural level (e.g., (Jimura et al., 2010; Locke & Braver, 2008). Taken together, this line of prior findings has suggestive evidence for the motivational enhancement of cognitive control function both at the behavioral and neural levels.

However, relatively little is known regarding the effect of motivation on cognitive control function in SCZ, despite a body of literature on cognitive control function in this illness (e.g., (J. D. Cohen et al., 1999). Mixed and complex findings exist in the reward processing literature in SCZ depending on the demands of the tasks used. On the one hand, individuals with SCZ show relatively intact reward-related experiences at the time of reward-related outcomes, which may not require the internal representation of reward value (Kirsch, Ronshausen, Mier, & Gallhofer, 2007; Maher, 1972; Simon et al., 2010; Waltz et al., 2010). For example, individuals with SCZ showed intact brain responses during reward receipt (e.g., monetary incentive) in tasks with low cognitive requirements in regions such as the ventral striatum, midbrain, and frontal cortex (Dowd & Barch, 2012). On the other hand, some studies have found that patients with this illness show reduced neural responses to reward-predicting cues in reward-related regions such as the ventral striatum (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Kapur, 2003; Kirsch et al., 2007; Robbins, 1976; Schlagenhauf et al., 2008).

These findings provide evidence that motivational deficits in SCZ may come from impairment of representing reward value internally. Taken together, these recent works suggest the possibility that abnormalities of motivational behavior in SCZ may be related to patients' deficiency of integrating reward-related information in the motivational context rather than reward-related experiences *per se* (Gold et al., 2012; Gold et al., 2008; Strauss et al., 2011).

In this context, the primary aim of this study was to examine the effect of reward on cognitive control in SCZ and its relationships to negative symptoms by using a response conflict task paradigm previously validated (Padmala & Pessoa, 2011). In this task, compound picture-plus-word stimuli were presented to participants. The images are either overlaid with a matching word (e.g., "*BLDNG*" on a building; congruent trials), a non-matching word (e.g., "*HOUSE*" on a building; incongruent trials) or a row of five red *X*s (e.g., "*XXXXX*"; neutral trials) (see Figure 1 and 2 for task stimuli and paradigm). The job of participants was to categorize images as either houses or buildings while ignoring the overlaid words. Participants first performed non-incentive baseline conditions in the absence of knowledge regarding the future potential for incentives. Following the baseline condition, participants performed blocks on which they were told that they could win money on some trials by performing fast (faster than their median correct RT in the baseline) and accurately. Each trial was then preceded either by a cue ("*$20*") indicating that a fast and correct response would be rewarded or by a cue ("*XX*") indicating no reward would be possible on that trial. After the target stimulus, participants received immediate feedback regarding the reward points they earned on the trials, as well as their cumulative earning in points. Participants were told that they could earn money up to $20 in addition to the base pay given that the accumulated money points would be converted to cash at the end of experiment. As such, this response conflict task paradigm allowed us to examine whether reward-related information can enhance cognitive control function in motivational contexts, by enabling the examination of: (1) a reward *context* effect, isolated by comparing performance and brain activity during non-incentive baseline versus no-reward trials (cued by "*XX*"); and (2) a reward

cue effect, isolated by comparing performance during reward (cued by "*$20"*) versus no-reward trials (cued by "*XX"*). To address these reward effects at neural level, I employed a hybrid experimental design, which allowed me to investigate both sustained and transient components of "motivated" cognitive control function in SCZ. Sustained components of the design correspond to events that are maintained for the duration of the blocks, as referred to as reward context effect. At the same time, transient components of the design correspond to events associated with the processing of briefly presented incentive cue within a block, as referred to as reward cue effect. Therefore, a mixed event and blocked fMRI design was employed, that enabled examination of which aspects of reward effect (cue, context) on cognitive control function are impaired in SCZ. Specific aims are as follows:

Specific Aim 1: Behavioral Study

To examine the behavioral effect of motivational context on conflict processing in SCZ using a response conflict processing task (Padmala & Pessoa, 2011)

Specific Aim 2: Neural Study

To investigate neural mechanism that lead to impaired reward context effect on cognitive control processing.

Specific Aim 3: Relation to Negative Symptoms

To examine the relationship between negative symptoms and both behavioral and neural indices of the reward context effect.

The first two sections below contain an overview of the literature in each area related to current study from both animal and healthy human studies: (i) cognitive control function and (ii) the reward enhancement of cognitive control function ("motivated" cognitive control) in the lateral PFC. The next third and fourth sections review SCZ research in each relevant area: (iii) dysfunctional context processing and (iv) both intact and impaired aspects of reward processing

in SCZ.

I. Cognitive Control Function In the Lateral Prefrontal Cortex

Cognitive control refers to a resource-limited cognitive system that provides top-down support for task-relevant processes in accordance with internal goals (Miller & Cohen, 2001). Most voluntary and complex human behaviors require a high-degree of cognitive control function, which allows us to represent task-relevant goal internally and inhibit task-irrelevant information (Miller & Cohen, 2001). Several studies using functional Magnetic Resonance Imaging (fMRI) have related cognitive control function to activity in several brain regions, that is often referred to as the Cognitive Control Network (CCN). The CCN consists of several subregions of the lateral PFC including dorsolateral PFC, anterior cingulate cortex, dorsal premotor cortex, anterior insular cortex, inferior frontal junction, and posterior parietal cortex (Cabeza & Nyberg, 2000; Cole & Schneider, 2007; Duncan & Owen, 2000; Rolls & Grabenhorst, 2008).

The PFC, specifically DLPFC, has been long thought to be involved in processing of non-emotional "context" information, or context processing (Cohen & Servan-Schreiber, 1992; MacDonald, Goghari, et al., 2005; Servan-Schreiber, Cohen, & Steingard, 1996). Since the term, "context" was first introduced by (Pribram, 1971), a robust literature provides evidence showing the involvement of the DLPFC in processing of cognitive "context" via top-down regulation (Braver et al., 1999; Braver & Cohen, 1999; MacDonald, 2008; MacDonald & Carter, 2003; MacDonald, Goghari, et al., 2005; Miller & Cohen, 2001). To be specific, the "context" information is defined as the "*information that has to be held actively in mind in such a form that it can be used to mediate an appropriate behavioral response*." (p.1105, (Servan-Schreiber et al., 1996)). Thus, context processing is a crucial component of cognitive control since it requires flexible behavioral adjustments along with internal representation of task-relevant goal.

II. Reward Enhancement of Cognitive Control Function in the Lateral PFC

A. Transient Cue-Driven Effects On Cognitive Control

Evidence from later neurophysiological studies in nonhuman primates and neuroimaging works in humans suggest that the lateral PFC is involved in processing reward-related context as well as cognitive context information (Barch, Moore, Nee, Manoach, & Luck; Kouneiher et al., 2009; Sakagami & Watanabe, 2007). The lateral PFC receives projections from sensory areas and sends outputs to the higher-order motor cortices such as premotor and supplementary motor areas (Tompkins, Goldman, & Axelrod, 1995). In addition, the lateral PFC also receives projections from other parts of brain such as the orbitofrontal cortex (OFC) (Peters & Buchel, 2010; Rolls & Grabenhorst, 2008) and the striatum that are thought to help encode neural representation of value (Kimura, Yamada, & Matsumoto, 2003; Samejima, Ueda, Doya, & Kimura, 2005). According to single unit studies in the lateral PFC with nonhuman primates, the majority of neurons in the lateral PFC encode the representation of the response relating to reward value (Sakagami & Watanabe, 2007). For example, when monkeys were trained to make go or no-go responses to the physical features of cue stimulus such as colors, most neurons in the lateral PFC showed differential visual responses only to rewarding cues regardless of the physical features of the cue stimulus (Watanabe & Sakagami, 2007).

In line with neurophysiological studies in nonhuman primates, more recent studies in humans provides strong evidence that reward-predicting cues exert enhancing effects on cognitive control functions thought to be supported by the lateral PFC across various cognitive control paradigms. For example, a task-switching paradigm is one of the frequently used cognitive control function tasks since reprioritizing task goals during task switching heavily depends on cognitive control function (Kiesel et al., 2010). The magnitude of the switch cost when task sets change is a good index of cognitive control (Kleinsorge & Rinkenauer, 2012). In (Savine, Beck, Edwards, Chiew, & Braver, 2010), healthy individuals completed a cued task-switching paradigm with knowledge about potential monetary incentives for their correct and fast

responses. Healthy individuals' performance was faster on incentive trials relative to no-incentive trials, showing decreased switch costs, referred to as the incentive cue effect.

The demand on cognitive control function increases in situations where there are competing stimulus dimensions in tasks. In typical conflict processing paradigms, for example, the Stroop Color and Word test (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006), task-irrelevant stimuli are usually presented to participants, which produces conflicts with task-relevant stimuli (e.g., naming the word "red" printed in blue colors). A wealth of behavioral and neuroimaging data in humans provides strong evidence showing that incentive cue can enhance cognitive control by decreasing conflict processing on reward trials (Krebs, Boehler, & Woldorff, 2010). For example, in neuroimaging work by (Padmala & Pessoa, 2011), healthy individuals performed a conflict processing task both on reward trials cued by "*$20*" or no-reward trials cued by "*$0*" with the instruction saying that correct and fast performance on "*$20*" trials would be rewarded by getting additional money up to $20. Consistent with prior studies showing reward enhancement of cognitive control (Engelmann, Damaraju, Padmala, & Pessoa, 2009; Small et al., 2005), they found a reward cue-related facilitation effect on cognitive control both at the behavioral and neural levels. Conflict was reduced on reward trials relative to no-reward trials, as evidenced by faster response time (Padmala & Pessoa, 2011). At the neural level, the incentive cue-related neural responses were increased in several fronto-parietal regions including reward-related subcortical regions such as the nucleus accumbens and caudate. Furthermore, conflict-related responses in the medial PFC during the reward versus no-reward conditions were decreased (Padmala & Pessoa, 2011).

In addition to conflict processing and task-switch processing, monetary incentives enhance visual attention processing via top-down control (Easterbrook, 1959; Engelmann & Pessoa, 2007; Mogg, Bradley, Hyare, & Lee, 1998). That is, cues associated with reward value capture attention, which leads to attentional modulation, as evidenced by decreased reaction time and enhanced neural activity in attentional processing networks (e.g., (Bradley, Mogg,

White, Groom, & de Bono, 1999; Pourtois & Vuilleumier, 2006). For example, (Small et al., 2005) conducted a covert attention task (Posner, 1980) under three incentive conditions: win-money, lose-money, and neutral. In all three conditions, the presentation of targets was preceded by a directional cue (valid trial), a cue to the opposite side (invalid trial), or neutral, non-directional (central) cues. The job of participants was to respond to a target stimulus as soon as possible (e.g., peripheral *X*s) but not to non-target stimulus (e.g., +s). The neutral condition was always performed first so that the mean reaction time to non-directional trials could be used as a cut-off. In the win-money condition, participants got monetary incentives for faster responses than this cut-off while in the lose-money condition, they were given $25, base money and lost money for slower responses than the cut-off. As a result, they found that monetary incentives showed a facilitation effect on directionally cued trials, as participants were faster on directionally cued trials in the incentive conditions compared to neutral condition, with no significant differences in reaction times between win- versus lose-money conditions for any of the trial types (Small et al., 2005). The degree to which the valid cue enhanced performance (e.g., faster reaction times on directional cues compared to non-directional cues) was associated with neural responses within the attentional network including the posterior cingulate cortex and medial prefrontal cortex (Small et al., 2005). Taken together, prior findings from neurophysiological studies in nonhuman primates and neuroimaging works in human provide ample evidence showing that reward-predicting cues have salient motivational value, which leads to facilitating task performance across various cognitive control function task paradigms.

B. Sustained State-Dependent Context Effects On Cognitive Control

While a wealth of nonhuman and human studies provides strong evidence suggesting incentive cue-related facilitation effect on cognitive control, as reviewed above, state-dependent incentive context effects has been relatively less explored until recent years (e.g., (Pessoa, 2009). Interestingly, reward incentives have been recently observed to modulate task

performance in a sustained fashion as well as in a transient cue-driven fashion. In other words, reward incentives have been associated with a sustained increase in lateral PFC activity in regions implicated in cognitive control functions (Engelmann, Damaraju, Padmala, & Pessoa, 2009; Jimura et al., 2010; Locke & Braver, 2008; Pessoa, 2009). For example, when accurate working memory performance on tasks such as the *n*-back tasks was associated with high monetary incentives, there was an increase in sustained activity in the DLPFC [Broadmann area (BA) 9/46] observed in healthy individuals compared to when the same task was associated with no monetary reward (Pochon et al., 2002). These findings suggest that cognitive control functions supported by the lateral PFC are modulated by the representation of reward-related context information during an ongoing task. In other work by (Engelmann et al., 2009) using a Posner-type task in which cues indicated the location of the face target stimulus in 70% of the trials, motivation was manipulated in a blocked fashion by varying the valence (e.g., winning, avoiding-loss), and the magnitude of a monetary incentive associated with task performance (e.g., winning of $1, $4, or avoid losing $2.5, and $0). The job of participants was to report the target location as quickly and accurately as possible by pressing a button using either index finger when the target was on the left or using their middle finger when the target was on the right. Consistent with prior findings, a greater magnitude of incentives led to cue-related response modulations. Importantly, (Engelmann et al., 2009) also found that sustained neural responses through the block increased as a function of the magnitude of incentive, referred to as context effect. The sustained state-related context effects in several brain regions are associated with attentional processing, suggesting that both transient and sustained fMRI signals modulate task performance (Engelmann et al., 2009).

More recent work by (Jimura et al., 2010) extended prior findings by showing that even no-reward trials can lead to better task performance when embedded in the context of being able to earn rewards. To be specific, when healthy individuals completed a working memory task under no-reward versus a reward context in which the magnitude of reward randomly

varied (high, low, or none), they showed faster performance on reward trials relative to no-reward trials, consistent with prior findings (e.g., (Padmala & Pessoa, 2011). Interestingly, their performance even on neutral trials in the reward condition (no reward) was faster compared to the same trials conducted in non-incentive baseline condition with no knowledge of monetary incentives, which is referred to as the incentive context effect. Importantly, this behavioral incentive context effect was associated with an increase in the activity in the right lateral PFC (BA 9/46) that was sustained across both reward and non-reward trials in the task blocks (Jimura et al., 2010).

Taken together, along with the evidence suggesting that the lateral PFC (BA 4/96) supports context processing, existent findings suggest that the lateral PFC integrates task information imbued with reward value in both a sustained and transient fashion when the information is internally represented, maintained, and updated depending on task demand (Engelmann et al., 2009; Gilbert & Fiez, 2004; Locke & Braver, 2008; Pessoa, 2009). To be specific, the presence of reward-predicting cues is associated with transient neural activity in the lateral PFC and other reward-related regions. However, more recent work also demonstrates that the representation of reward-related context information modulates cognitive control function through an increase in sustained activity in the lateral PFC, which persists across the entire reward condition (both reward and non-reward trials) (Engelmann et al., 2009; Gilbert & Fiez, 2004; Locke & Braver, 2008; Pessoa, 2009). These findings suggest a possibility that reward value may modulate cognitive control via a common neural mechanism of context processing thought to be supported by the lateral PFC.

C. Dysfunctional Context Processing in Schizophrenia

In SCZ literature, a very robust literature shows that individuals with SCZ have cognitive impairments in a number of domains including working memory (Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005), episodic memory (Achim & Lepage, 2005) and inhibition (see (Westerhausen, Kompus, & Hugdahl, 2011), with recent meta-analyses evidence (see

(Fioravanti, Bianchi, & Cinti, 2012) for a meta-analysis of general cognitive deficits in SCZ, reviewed in (Barch & Ceaser, 2012; Burbridge & Barch, 2007; Cohen et al., 1999; Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996; Vohringer et al., 2013) and symptoms of SCZ are associated with a disturbance of cognitive control function in the DLPFC (Braver et al., 1999; Braver & Cohen, 1999; Kerns, Nuechterlein, Braver, & Barch, 2008; Kravariti, Dixon, Frith, Murray, & McGuire, 2005; Mahurin, Velligan, & Miller, 1998). Many of these cognitive impairments seem to reflect deficits in cognitive control due to abnormal dopamine function in the lateral PFC (e.g., (Braver et al., 1999; Cohen & Servan-Schreiber, 1992)). More specifically, it has been argued that the cognitive control deficits especially reflect deficits in connect processing, or the ability to represent and maintain non-emotional context information necessary to guide upcoming goal-directed behavior, as referred to as context processing (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Braver et al., 1999; Cohen et al., 1999; McClure, Barch, Flory, Harvey, & Siever, 2008).

Context processing in SCZ has been widely investigated using several task paradigms. A clear demonstration of context processing abnormalities can be found in language performance for SCZ. When early sentence components provide context information, which affects the comprehension of later sentence components, individuals with SCZ make poor use of context information (Maher, 1972). In particular, poor use of context in SCZ is found to be more pronounced when there is a temporal range over which individuals with SCZ have to process linguistic context (Salzinger, Portnoy, & Feldman, 1964). For example, in a lexical disambiguation task (Cohen et al., 1999), pairs of sentences were presented to participants who were then asked to respond to a visually presented probe. The probe was a letter string (e.g., SH_FT) that could be completed to make either of two words (e.g., dominant: SHIFT, subordinate: SHAFT). Given that two possible words have different frequencies (dominant versus subordinate meaning, the less frequent meanings), the completion of the letter string is determined by the context provided by one of the two preceding sentences favoring either the

dominant (more frequent) or the subordinate (less frequent) completion. Furthermore, there was a delay manipulation by presenting context in either the first or the second of the two preceding sentences. Therefore, it is expected that persons with impaired context processing would show less context-dependent interpretation of the probe, especially when the context occurred in the first sentence, requiring maintenance of that context across the second sentence. As predicted, several studies found that individuals with SCZ had fewer context-mediated responses in both the subordinate and dominant context conditions (e.g., (Cohen et al., 1999; Cohen & Servan-Schreiber, 1992; Cohen & Servan-Schreiber, 1992). Further, the deficits of context processing were greater when the delay between context and probe is lengthened.

In a similar vein, the expectancy AX task modified by (J. D. Cohen et al., 1999) from the original AX Continuous Performance Test (AX-CPT; (Servan-Schreiber et al., 1996) has been frequently used to examine context processing in SCZ (e.g., (Cohen et al., 1999; MacDonald, 2008; MacDonald, Pogue-Geile, Johnson, & Carter, 2003; McClure et al., 2008; Servan-Schreiber et al., 1996). In this task, participants were presented with a series of letters one at a time and then, asked to make a target response to the letter *X* only when it follows the letter *A*. Therefore, the cue, whether an *A* or non-*A* letters such as *B*, serves as the context that should be internally represented and maintained for a subsequent target response decision. However, due to the high proportion of the *AX* trials (leading to the expectation of an *X* probe following an *A* cue), people with intact context processing ability tend to make more errors on *AY* trials relative to *BX* trials. In contrast, people with impaired context processing, which is hypothesized to be present in SCZ, tend to make more errors on *BX* trials than *AY* trials (MacDonald, Goghari, et al., 2005; Servan-Schreiber et al., 1996), as they are less able to use the context information provided by the B (i.e., non-A) cue to inhibit a tendency to want to respond target to the X. By manipulating the delay between contextual cue and response, a body of studies using the AX-CPT confirmed a specific deficit of processing context information in SCZ when the task-appropriate response was context-dependent and there was a temporal delay between

contextual cue and response, which required individuals with SCZ to maintain the context internally represented over time (Cohen et al., 1999; MacDonald, 2008; MacDonald et al., 2003; McClure et al., 2008; Servan-Schreiber et al., 1996). Furthermore, behavioral deficits in context processing have been consistently found to be associated with decreased activity in the DLPFC in individuals with SCZ (Cohen et al., 1999; MacDonald, Carter, et al., 2005) and their relatives (MacDonald et al., 2003).

The Dot Pattern Expectancy task (DPX) is a variant of the AX-CPT optimized for clinical use. The format of the DPX is the identical to that of the AX-CPT except that instead of letters, visuospatial stimuli comprised of specific dot patterns are used as cue-probe stimuli (Barch et al., 2009; MacDonald, Goghari, et al., 2005). Compared to the AX-CPT, the DPX has fewer trials and shorter inter-stimulus interval, which makes easier to administer in clinical settings. Consistent with prior work using the AX-CPT, work using the DPX has found that individuals with SCZ show a specific deficit of context processing (e.g., more errors on BX trials than AY trials) with the evidence of good reliability (Chung & Barch, 2011; Henderson et al., 2012; Jones, Sponheim, & MacDonald, 2010; MacDonald, Goghari, et al., 2005).

Taken together, this line of studies provides strong evidence that individuals with SCZ have deficits in representing and maintaining non-emotional context information over time, associated with reduced activity in the lateral PFC. However, despite emerging evidence that representation of reward-related context information can enhance cognitive control function in the lateral PFC, it has been unexplored whether patients with SCZ can represent reward-related context information during reward processing.

IV. Intact and Impaired Aspects of Reward Processing In Schizophrenia: Behavioral and Neural Evidence

With recent increased attention on the relevance of reward processing to positive (Barch et al.; Koch et al., 2010) and negative symptomatology of SCZ (e.g., (Gold et al., 2012; Gold et al., 2008)); see (Kring & Barch, 2014) for a recent review), the extant findings provide mixed

evidence suggesting both intact and impaired aspects of reward processing in SCZ. Reward processing comprises multiple dissociable psychological components of hedonic impact, "liking," motivational impact of "wanting," and learning (predictive associations and cognitions) incentive salience" (Berridge & Robinson, 1998, 2003). In the next sections, I summarize each relevant area of reward processing with behavioral and neural evidence.

A. Relatively Intact "Liking" Pleasure in SCZ

The "hedonics or liking" component of reward processing refers to the ability to enjoy pleasurable experiences or responses to rewarding stimulus or event in the moment (e.g., (Barch & Dowd, 2010), see (Kring & Barch, 2014; Kring & Elis, 2013) for a recent review). Contrary to limited experiences of positive emotion in SCZ measured by interview-based clinical assessments (e.g., Horan et al., 2006), interestingly, converging data from behavioral studies shows that individuals with SCZ have similar pattern of intact pleasurable experience and/or responses to various pleasurable stimuli as healthy controls did (e.g., (Burbridge & Barch, 2002, 2007), see (Cohen & Minor, 2010; Yan et al., 2012) for recent meta-analysis).

In line with findings from behavioral studies (Kring & Moran, 2008), neuroimaging work using various reward task paradigms suggests that at least some aspects of "liking" experience appear not to be impaired as expected, as proven by intact neural responses associated with the magnitude of secondary rewards (e.g., monetary outcomes) regardless of typical or atypical antipsychotic medication status (Kirsch et al., 2007; Simon et al., 2010; Waltz et al., 2010; Weiler, Bellebaum, Brune, Juckel, & Daum, 2009), despite some non-monetary studies showing reduced responses to primary rewards (e.g., juice deliveries) (e.g., (Waltz et al., 2009)) or emotionally-evocative olfactory stimuli (e.g., pleasant or unpleasant odors) in the insula and the orbital frontal cortex (OFC) (e.g.,(Plailly, d'Amato, Saoud, & Royet, 2006; Schneider et al., 2007). For example, the Monetary Incentive Delay (MID) task (Knutson, Fong, Adams, Varner, & Hommer, 2001) is a commonly used task designed to measure reward processing associated reward anticipation and receipt. In the MID task, different types of visual cues (shapes) predict

monetary reward (gain), punishment (loss), and no monetary outcome depending on a rapid performance on a simple reaction time by pressing a button during the brief presentation of a visual target stimulus. Individuals with SCZ showed normal sensitivity to the magnitude of monetary outcomes (e.g., $2.50, $10. $15) in the ventral striatum to healthy controls (Waltz et al., 2010).

However, as (Dowd & Barch, 2012) pointed out, the majority of task paradigms used in reward processing literature include cognitive demands to some extent, which may have confounded patients' pure reward-related responses. In this context, they extended prior findings by using a passive Pavlovian reward paradigm in which patients passively viewed reward-predicting cues followed by reward outcomes (e.g., monetary incentives) (Dowd & Barch, 2012). They found that patients with SCZ exhibited intact neural responses in reward-related regions such as bilateral caudate at the time of monetary receipt with no requirement of response selection and execution (Dowd & Barch, 2012) suggesting that patients have intact reward-related experiences in the moment per se. Consistent with these findings, a meta-analysis of neuroimaging work about emotional processing in SCZ also shows that individuals with SCZ show comparable amount of activation in the amygdala during positive vs. baseline conditions compared with the HC (Anticevic, Van Snellenberg, et al., 2012).

B. Impairments of "Wanting" or Anticipatory Pleasure in SCZ

If individuals with SCZ experience relatively intact hedonic experience "in-the-moment" like other individuals without SCZ, as reviewed above, where do motivational impairments in SCZ come from? Hedonic responses to rewarding stimulus in the moment are not enough to lead to motivated goal-directed behaviors. Another key component of reward processing that appears to show more pronounced impairments in SCZ is "wanting" or anticipatory pleasure (i.e., reward anticipation in the future). The animal literature distinguishes "liking" ("in-the-moment" pleasure) from "wanting"/anticipatory pleasure, which presumably comes from the internal

representation of motivational incentive value mediated by DA systems (Berridge, 2004; Berridge & Robinson, 1998, 2003).

Different from relatively hedonic reward experiences or responses in SCZ at a group level, emerging evidence from several neuroimaging work suggests impairments of “wanting” /anticipatory pleasure in SCZ (reviewed in (Kring & Barch, 2014). For example, several neuroimaging studies using a variant of monetary incentive delay task in comparison of the HC found less ventral striatal activation during the presentation of reward-predicting cues in unmedicated individuals with SCZ (Esslinger et al., 2012; Ghuman, van den Honert, & Martin, 2013; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wustenberg, et al., 2006; Schlagenhauf et al., 2009) as well as in those with typical antipsychotic mediations (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Kirsch et al., 2007; Schlagenhauf et al., 2008). In another reward task paradigm, a prediction-error task, different card stimuli were used as reward-predicting cues and reward stimulus (e.g., money) was either presented or omitted. Thus, participants’ predictions could be either correct or incorrect. Using this task paradigm, (Morris et al., 2012) found that neural activity in the ventral striatum of individuals with SCZ taking atypical antipsychotics was not driven by expected or unexpected reward value while neural activity in the same region of healthy controls differentiated between expected and unexpected events, suggesting that patients’ attenuated prediction error may reflect a deficiency of representing reward value (Morris et al., 2012). Similar pattern was observed in unmediated individuals with SCZ showing reduced VS activation elicited by prediction errors (Schlagenhauf et al., 2013).

Importantly, an increasing number of studies found the relationship between negative symptom severity of SCZ and reduced ventral striatum response to reward predicting cues (e.g., (Gold et al., 2012). For example, reduced neural activity in the ventral striatum during reward-predicting cues versus neutral cues was inversely correlated with the severity of negative symptoms, suggesting that the greater in the severity of negative symptoms, the more decrease

in neural response in the reward-related brain regions (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Simon et al., 2010; Waltz et al., 2010). In more recent work, even when patients were asked to passively view reward-predicting cues without any requirements, patients having high anhedonia symptoms showed reduced activity in the ventral striatal and ventromedial PFC during reward anticipation (Dowd & Barch, 2012), which may come from a deficiency of representing reward value in SCZ. Taken together, these results suggest a possibility that negative symptoms of SCZ, in particular, anhedonia and/or avolition may be related to a specific aspects of reward processing, "wanting" pleasure, not necessarily relating to reward-related experiences per se (Gold et al., 2012).

C. Impairments In Reward-driven Learning Towards Goal-directed Behavior

Even though people are motivated by having positive prediction of upcoming stimuli, this motivational state does not necessarily lead to goal-directed behavior that maximizes reward or positive outcomes. The goal-directed behavior requires computation of reward value and flexible adjustment of action plans by updating internalized reward value that is associated with better-than-expected outcomes given a reward-related context.

In addition to impaired reward prediction in SCZ, as summarized above, in the past decade, there is has been a resurgence of interest in the relevance of reinforcement learning deficits and symptoms of SCZ in the literature (e.g., (Barch & Dowd, 2010; Gold et al., 2012; Heinz & Schlagenhauf, 2010)). To be specific, when individuals with SCZ are asked to translate internalized reward value to their response selection and execution towards goal-directed behavior, individuals with this illness exhibit impaired reward processing, as evidenced by their difficulty in choosing a stimulus previously associated with a higher reward value (Gold et al., 2012; Strauss et al., 2011; Waltz, Frank, Robinson, & Gold, 2007; Weiler et al., 2009). For example, (Gold et al., 2012) used a probabilistic reinforcement learning paradigm, in which participants were presented four pairs of landscape items, one pair at a time of which two pairs involved monetary gain and the other pairs involved loss-avoidance learning. The correct choice

of the optimal stimulus in rewarding pairs was associated with probabilistic outcome (e.g., money receipt) while the correct choice in the loss-avoidance pairs results in no reward (a zero outcome).

Following the initial acquisition phase of the task with feedback about their response, participants completed a transfer test phase in which novel pairs were included in addition to the original pairs without additional feedback. Importantly, some items of novel pairs were items previously associated with monetary gain and the other items were items previously associated with loss-avoidance pair. The job of participants was to choose the "best" item in the pair based on their earlier learning. Therefore, if participants are sensitive to the expected reward outcome of their response execution, they should show preference for the action with monetary gain over the action with a zero outcome. They found that patients with high negative symptoms had less tendency to learn from gains relative to learning loss-avoidance whereas healthy controls and patients with low negative symptoms showed to some extent preference for learning from gains (Gold et al., 2012).

Summary

In parallel with a body of work suggesting abnormalities in representing and processing non-emotional context information in SCZ, which is crucial component of cognitive control supported by the lateral PFC, emerging evidence suggests that individuals with SCZ show impairments in specific components of reward processing. Surprisingly, individuals with SCZ show relatively intact reward-related experiences ("liking") to a range of rewarding outcomes, including monetary incentives. Specifically, when reward outcomes are presented in the external environment and do not require internal representations, individuals with SCZ show intact reward-related experiences at a group level (Heerey, Bell-Warren, & Gold, 2008). However, at an individual level, those with high negative symptoms, particularly, those with anhedonia and/or avolition, show impairments of processing associated with transferring internalized reward value into learning and action execution (e.g., (Gold et al., 2012). These

prior behavioral findings suggest that motivational deficits in SCZ may reflect, at least in part, a deficiency of representing reward-related context information. However, although there are several behavioral studies suggesting the association between deficits in representing reward value with negative symptoms (Gold et al., 2012), it is not known whether patients with SCZ can use internally represented reward value to modulate cognitive control function at the neural level although there are some behavioral studies showing relatively intact reward-related facilitation effect on cognitive control function measured by the Wisconsin Card Sorting task in SCZ (Green, Satz, Ganzell, & Vaclav, 1992; Summerfelt et al., 1991). More importantly, there is no evidence as to whether individuals with SCZ can represent reward-related context information in the lateral PFC during cognitive control function. Therefore, the current study was designed to test specific questions as described below to fill the gap in current literature. In the next section I present my hypotheses that are relevant to each specific aims.

Presentation of Specific Aims and Hypotheses

Specific Aim 1: To examine the behavioral effect of motivational context on conflict processing in SCZ using a response conflict processing task (Padmala & Pessoa, 2011).

Hypothesis 1: I predicted that individuals with SCZ would show a deficiency in reward enhancement of cognitive control function in the presence of incentive-predicting information, as evidenced by reduced reward context effects compared to the HC and described in more detail below. On the other hand, I expected that individuals with SCZ would show normal reward-related responses to a reward cue itself, as shown by incentive effect at a similar level to the HC during reward-cue (cued by "*$20*") versus reward-context (cued by "*XX*") trials.

Specific Aim 2: To investigate neural mechanisms that lead to impaired reward context effect on cognitive control processing.

Hypothesis 2 (a): I predicted that individuals with SCZ would show reduced sustained neural activity in the DLPFC [Brodmann area (BA) 9/46] during reward versus baseline blocks compared to the HC group.

Hypothesis 2 (b): In contrast, I expected that individuals with SCZ would display intact transient neural activity in reward-related brain regions such as the ventral striatum in response to “$20” cues and in response to receipt of money.

Specific Aim 3: To examine the relationship between negative symptoms and both behavioral and neural indices of the reward context effect.

Hypothesis 3 (a): I predicted that individuals with SCZ having greater anhedonia and/or amotivation symptom severity would show a reduced reward context effect, although they might still show intact reward cue effect.

Hypothesis 3(b): I predicted that individuals with SCZ having greater anhedonia and/or amotivation symptom severity would show reduced transient trial-by-trial neural activity in the ventral striatum during “*$20*” vs. “*XX*” in reward conditions.

Hypothesis 3(c): I expected that individual differences in anhedonia and/or amotivation symptoms in SCZ would be negatively correlated with brain activations in the DLPFC during reward versus baseline conditions.

Methods

Participants and Recruitment Information. All participants were recruited through the Conte Center for the Neuroscience of Mental Disorders at Washington University in St. Louis to participate in return for payment ($25/h). In addition to this base payment, they were also given a maximum of $20 reward money depending on their behavioral performance on reward trials.

The inclusion criteria were: 1) age 18-50 years and 2) ability to give informed consent. Exclusion criteria were: 1) DSM-IV substance abuse or dependence within the past six months except nicotine; 2) DSM-IV major depression or dysthymia in the past year; 3) past head injury with neurological sequelae or loss of consciousness; 4) DSM-IV mental retardation, and 5) any contraindication to MRI including pregnancy, any metallic object in the body, and claustrophobia, etc. Participants' diagnoses were based on a Structured Clinical Interview for the *DSM-IV-TR* (First, Spitzer, Gibbon, & Williams, 2001) which was conducted by a Masters-level clinician. Using these criteria, 40 individuals with SCZ and 28 HC were recruited into the current study. Of these 68, four individuals with SCZ and one HC failed to pass our fMRI quality control measures and were not included for further analysis, as described in more detail below. Therefore, 36 individuals with SCZ and 27 HC were included for the main analyses. All individuals with SCZ were stable outpatients with *DSM-IV-TR* schizophrenia or schizoaffective disorder, taking stable antipsychotic medication doses for at least two weeks before participating in the current study. Of the 36 participants with SCZ, 25 (69.4%) were taking atypical antipsychotic medication, 3 (8.3%) were on a combination of both typical and atypical, and 4 (11.1%) were not taking any antipsychotic medication. All participants across groups were similar on sex, age, and parental education (see Table 1 for clinical and demographic characteristics of participants). On both the days of clinical assessment and on the day of scanning, participants received drug screening. If an individual tested positive for marijuana, cocaine, amphetamine, methamphetamine, or opiates, he or she was not allowed to participate in this study. Written informed consent was obtained from all participants, and all procedures were approved by the Washington University

Human Research Protection Office.

Clinical Rating Scales. Clinical symptoms including negative symptoms were rated using the Scales for the Assessment of Negative Symptoms (SANS; (Andreasen, 1983b)), the Scale for the Assessment of Positive Symptoms (SAPS; (Andreasen, 1983a)) by a psychologist or a trained master's level clinician. The positive and negative symptom domain scores were summarized using the following symptom domain scores (Andreasen, Arndt, Alliger, Miller, & Flaum, 1995): 1) positive symptoms- hallucinations and delusions and 2) negative symptom – alogia, anhedonia, avolition, affective flattening, and attentional impairment.

In addition, the Brief Negative Symptom Scale (BNSS; (Kirkpatrick et al., 2011) was also included to investigate the relationship between individual differences in anhedonia and/or avolition and neural responses during sustained context effect. This newly developed clinical measure which assesses 5 negative symptoms such as blunted affect, alogia, asociality, anhedonia, and avolition using 13 items, consistent with the recommendation of the 2005 National Institute of Mental Health (NIMH) and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Development Conference on Negative Symptoms (Kirkpatrick et al., 2006). It has been demonstrated to have good psychometric properties including inter-rater and test-retest reliability, convergent and divergent validity (Daniel, 2013). Importantly, the BNSS is designed to differentiate consummatory vs. anticipatory aspects of anhedonia by including two items asking about experience of pleasure during activities and one item about expected pleasure from future activities. This allows me to test two separate relationships between consummatory, "liking" pleasures vs. anticipatory, "wanting" pleasure and brain activity. That is, I can test the relation between individual differences in the severity of consummatory, "liking" pleasure and transient neural activity as a function of reward in ventral striatum. Also, at the same time, I can separately test the hypothesis that individual difference in the severity of anticipatory, "wanting" pleasure, as reviewed in the Introduction, would be negatively associated with sustained neural activity

during reward vs. baseline blocks in the DLPFC.

Individual-difference in Self-reports of Anhedonia. In addition to the clinical measures described above, all participants also completed self-reported measures, Chapman Social and Physical Anhedonia Scales (Chapman, Chapman, & Raulin, 1976) to examine individual differences in the severity of anhedonia/avolition symptoms. The Revised Physical Anhedonia Scale (Chapman & Chapman, 1978) consists of 61 items, which measure self-reported ability to experience pleasure from physical stimuli such as food and sex (e.g., "The beauty of sunsets is greatly overrated"). The Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman, & Mishlove, 1982) is a 40-item self-report scale to measure the ability of experiencing pleasure from non-physical stimuli such as talking and exchanging expressions of feelings in social interactions (e.g., "Getting together with old friends has been one of my greatest pleasures"). In correlation analysis using individual difference in negative symptoms, I converted scores on each subtest into a *z*-score (i.e., The Social and Physical Chapman Anhedonia), and then combined two z-scored scores into one composite score, as the mean and standard deviation for each subtest are different. In this way, the "standardized" score had an equal weight from the raw scores on each subtest.

Stimuli and Task Paradigm. A response conflict task originally developed by (Padmala & Pessoa, 2011) was modified for the use of fMRI scanner in current study. As presented in Figure 1, a mix of images-plus-words was used for stimuli. The images were either of a house or a building, and each image was overlaid with a word to create congruent, incongruent and neutral trials. For example, a congruent trial is one in which an image is presented with a matching word (e.g., a house picture with "*HOUSE",* building picture with "*BLDNG*"). However, an incongruent trial is one in which an image is presented with a conflicting (e.g., a house picture with "*BLDNG"*, a building picture with "*HOUSE").* Neutral trials are ones in which an image is presented with "*XXXXX*". Each participant performed six runs, which included two baseline and four reward runs. Each run contains six blocks, three of which were task blocks

and three of which were fixation blocks. Each fixation block lasted 30 seconds (see Figure 2 (a) for schematic presentation of a response conflict task).

Figure1:

Task Stimuli

House Congruent House Incongruent Building Neutral Building Incongruent

Note. A mix of either a house or building images and overlaid letters were used to create three different task trial types: congruent, neutral, and incongruent trials.

As briefly described above, participants first performed non-incentive baseline conditions with no knowledge of the potential monetary incentives to be earned on subsequent task blocks and then, performed four reward blocks. In both conditions, participants were asked to ignore the letter and pay attention to the picture by pressing “1” for a house or “2” for a building on a keyboard. Before they began each baseline and reward run, participants had two separate practice sessions in the scanner to ensure that they were familiar with what they were supposed to do in each baseline and reward task runs. Behavioral data were acquired while participants performed the response conflict task in the scanner. A subset of participants [SCZ: *n*=7, HC: *n*=10] completed a post-scan questionnaire asking about self-reported motivation and difficulty levels during task (see Table S1 for mean and SD in Supplementary Materials).

All BOLD scanning runs of a response conflict task were performed in a mixed block/ event-related design. Each run consisted of three blocks of 9 trials (27 trials per run), alternating with three fixation (resting state) blocks (30 seconds each, one after the first task block, middle, and end of each scanning block) in order to examine sustained effect lasted during each task block. The fMRI task paradigm consisted of two baseline runs and four reward runs with a total

of 162 trials, 54 per each trial-type (i.e., baseline, reward-cue, reward-context).. In both baseline and reward phases of the session, each run was separated by pauses for rest. During task blocks, the inter-trial interval of 2 to 6 seconds was temporarily jittered to ensure robust deconvolution of even-related fMRI responses.

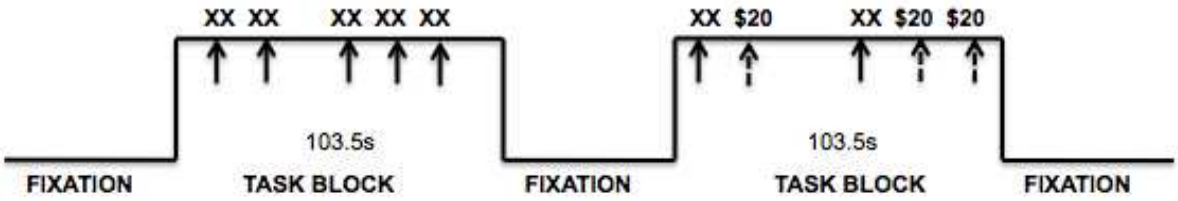
Figure 2 (b) shows an example of baseline blocks. Baseline sections consisted of two runs in which congruent, incongruent and neutral trials were intermixed with equal number of 18 trials per trial-type, resulting in the total 54 trials. Participants first performed baseline blocks in which each task block started with a start cue, "*TASK*" for 2 seconds and end with a cue, "*DONE*" for 2 seconds. After each start cue, "*TASK*"," there is a jitter, which varied between 0,2, and 4 seconds. In the baseline runs, each trial started with a cue, "*XX*" and participants was told that cues are irrelevant to their job of the task. This cue was presented for one second. Then, there was a jitter that varies between 2,4, and 6 seconds. Then, the target stimulus was presented for one second, followed by a delay of 0.5 seconds. Participants were instructed to press the index finger button to indicate that they saw a house image and the middle finger button to indicate that they saw a building image regardless of the overlaid word. After the target stimulus, visual feedback regarding the monetary points that they get on the trial as well as the cumulative points was presented for 1 second. Then, there was the second jitter or inter-trial interval (ITI) that varies between 2,4, and 6 seconds.

Following the two baseline runs, participants performed four additional reward runs where reward-cue ("*$20*") and reward-context ("*XX*") trials were intermixed with equal number of 54 trials each, resulting in the total number of 108 trials. Like the baseline sections, each reward-cue and reward-context trials were also intermixed with congruent, incongruent and neutral condition [reward-cue: congruent (20 trials), incongruent (16trials), neutral (18 trials); reward-context: congruent (16trials), incongruent (20trials), neutral (18trials)]. Figure 2(c) shows an example of reward blocks. In the four runs of reward trials, "*$20,*" a reward-cue indicated that a correct and fast response would be rewarded by getting 2000 points on the trial

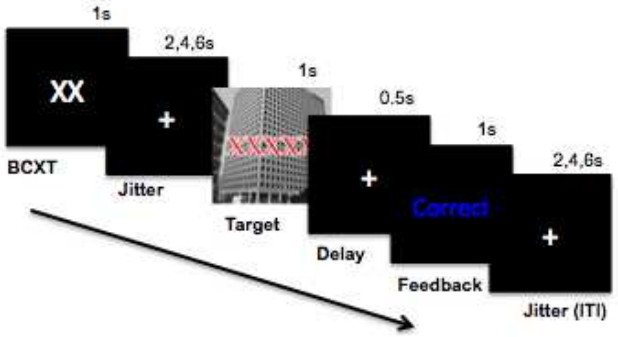
while “*XX*,” a reward-context cue indicated that there would be no reward (a zero point) on the trial. The structure of each run and participants’ job of the task were the same as the baseline runs. The RT threshold to determine “fast” response was set individually for each subject based on the median RT from the second baseline run.

Figure 2:

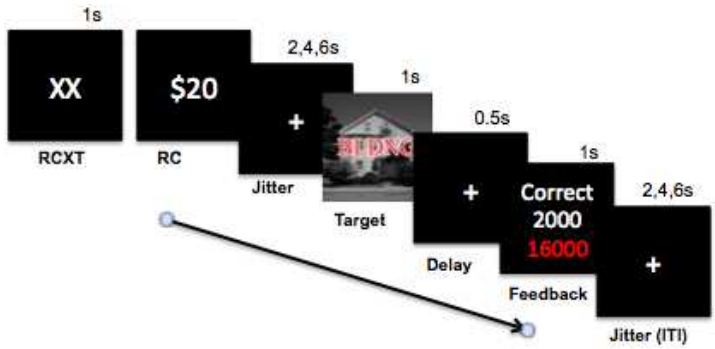
(a) Mixed State-item fMRI Design of the Response Conflict Task

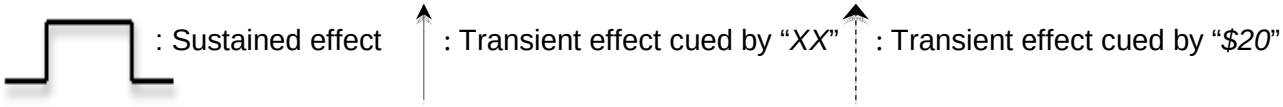


(b) Example of Baseline-Context Block



(c) Example of Reward Blocks





Note. BCXT: Baseline-Context, RC= Reward-Cue, RCXT= Reward-Context trials
(a): The mixed blocked and event-related experimental design used during a single fMRI run. Each functional run was separately blocked by fixation blocks to examine sustained effect lasted during entire task block (b): BCXT blocks: participants were presented with only baseline-context trials cued by "*XX*" without any knowledge about getting reward. Each trial evens repeated (c) reward blocks: reward-cue trials cued by "*$20*" and reward-context trials cued by "*XX*" were pseudo-randomly intermixed in equal proportions. In both (b) and (c) blocks, each block started with a start cue, "*TASK*" and ended with an end cue, "*DONE*." Nine event trials were presented per block. Here, (b) and (c) shows example of a trial in

each type of block.

fMRI Data Acquisition. All images were acquired on a 3T Siemens TM TRIO system with a 12-channel head coil. Both structural and functional images were acquired every scanning session. High-resolution MPRAGE T1 images (echo time (TE) = 2.98 ms, repetition time (TR) =2300ms, 160 slices, 1.0 x1.0 x 1.2 mm voxels) and T2 images (TE= 84ms, TR= 7000ms, 33 slices, 2.0 x 1.0 x 4.0 mm voxels) were acquired to be registered and transformed to a standardized atlas space (Koch et al., 2010; Talairach & Tournoux, 1988a), using a 12-dimensional affine transformation (Gradin et al., 2011; Woods, Cherry, & Mazziotta, 1992).a Functional images were collected in six runs of 214 frames each using an asymmetric spin-echo echo-planar sequence (TR = 2000ms, TE= 27ms, field of view = 256 mm, flip = 90,°33 slices). Functional images were acquired parallel to the anterior-posterior commissure plane with 4 mm^3 isotopic voxels. At the beginning of each blood oxygenation level-dependent (BOLD) scanning session, the first four images of each run were eliminated to allow for signal stabilization before preprocessing. Visual stimuli were presented using E-Prime software running on a Dell Inspiron laptop. Stimuli were projected to participants with an LCD projector onto a screen located behind the scanner. Participants were able to see the screen through an angled mirror positioned above the eyes. A fiber optic, light-sensitive keypress interfaced with the E-prime button box was used to record participants' behavioral performance.

General Data Analysis

All imaging data was analyzed using an in-house software (FIDL analysis package, www.nil.wustl.edu/~fidl/). The Statistical Package for the Social Sciences version 18 (SPSS Inc., Chicago, IL) was used for statistical analyses regarding demographic, clinical, behavioral variables and neural activity for group comparisons and post-hoc analyses.

fMRI Preprocessing. Structural and functional magnetic resonance imaging data preprocessing included the following typical steps: (1) correction for slice-dependent time shifts; (2) removal of the first four images of each run to allow for a steady-state BOLD signal; (3)

elimination of odd/even slice intensity differences due to interpolated acquisition; (4) realignment of the data acquired from each participant within and across runs to compensate for rigid body motion (Ojemann et al., 1997); (5) image intensity normalization to a whole-brain mode value of 1,000; (6) registration of the 3-D structural volume (T1) to the atlas template in the Talairach coordinate system (Talairach & Tournoux, 1988), using a 12-parameter affine transform and resampling to a 1-mm cubic representation (Buckner et al., 2004; Ojemann et al., 1997); (7) coregistration of the 3-D fMRI volume to the T2, and the T2 to the participant's structural image; (8) transformation of the fMRI data to a 3 x 3 x 3 mm voxel atlas space using a single affine 12-parameter transform; and (9) spatial smoothing using a 6-mm full-width at half-maximum Gaussian filter.

Movement Analysis. Measures of head movement within scan were assessed using the output of the rigid-body rotation and translation algorithm. The translations and rotations in the *x*, *y*, and *z* planes across frames and total root mean square (RMS) linear and angular precision measures were calculated for each run. BOLD runs in which a participant's standard deviation of RMS movement exceeded 20 were excluded from further analysis. Values for included runs were averaged for each subject, and analysis of variance (ANOVA) were performed for testing group differences. Using this criterion, 36 participants in SCZ and 27 in HC group provided usable functional imaging data. Groups did not differ significantly in terms of movement (RMS/frame [mean (standard deviation)] SCZ = 0.18 (0.11); HC = 0.15 (0.07)]; F (1, 62) = 1.85, p = .17).

General fMRI Data Analysis.

A voxel-wise general linear model (GLM) approach was used, which incorporated regressors for linear trend and baseline shifts. Using the mixed design, sustained and transient effects associated with reward enhancement on cognitive control can be simultaneously but independently coded within the same GLM, enabling dissociation of these two effects (Friston et al., 1995). The rationale of using this state-item approach is based upon the assumption that

event-related trial-by-trial effect should decay back to baseline during the ITI, whereas the state effects should remain constant during the task block (reviewed in (Petersen & Dubis, 2012).

Sustained context effects (i.e., one for the reward block and one for the baseline block) were modeled by box-car functions lasting the length of the task block using an assumption of a fixed-shape response of long duration (Fischl et al., 2002). The event-related transient effects were analyzed separately for each trial-type by estimating the values for eight time point regressors (starting at trial onset) within the hemodynamic response epoch, which was estimated to be 16 seconds (TR: 2 seconds, 8 scanning frames) using unassumed hemodynamic response shapes. More specifically, each trial is coded by a set of regressors for both the cue-type and target-related events as well as start ("*TASK*") and end ("*DONE*") cues. That is, regarding the event-related effects, 3 cue-type regressors are separately coded as follows; "*$20*," "*XX*" in reward, "*XX*" in baseline conditions separately, Also, regarding target-related events, 9 target-related trial types regressors (i.e., 3 condition types x 3 cue types) are separately coded.

Data Analysis

Behavioral Study (Specific Aim1):

To test my hypothesis about the behavioral data, repeated measures ANOVAs were conducted on correct trials for both reaction times (RT) and error data with within-subject factors of a *Reward* (BCXT, RC, RCXT) and a *Condition* (congruent, incongruent, and neutral trials) and a between-subject factor of a *Group* (HC, SCZ). Any significant interactions were followed by post-hoc contrasts to determine the source of the interaction. In analyses involving RT data, the reward context effect was estimated by subtracting the RT in RCXT trials cued by "*XX*" from the baseline trials cued by the same cue, "*XX*."

Neuroimaging Study (Specific Aim2):

To examine whether individuals with SCZ show reduced reward context effects in sustained activity, with the assumption of the hemodynamic response, I used a voxel-wise repeated measures ANOVA with a *Group* as a between-subject factor and a *Reward* (baseline, reward conditions) as a within-subject factor. I predicted a significant *Group* x *Reward* interaction, with individuals with SCZ showing less of an increase in sustained activity in regions such as the DLPFC in the incentive condition compared to the baseline condition.

To examine whether individuals with SCZ show intact cue-related reward effects, I conducted a voxel-wise repeated measures ANOVA using the transient cue-related estimates, with a *Group* as a between-subject factor, and a *Reward* ("*XX* " in BCXT, "*XX"* (RCXT), and "*$20"* (RC) in reward conditions) and *Time point* (the 8 time frame estimates) as within-subject factors. I predicted a significant *Reward* x *Time point* interaction, with an increase in cue-related activity in both ventral and dorsal striatum and DLPFC regions during *$20* vs. "*XX."* I predicted that a *Reward* x *Time point* interaction would be significant for both HC and individuals with SCZ. However, I did not predict a further interaction with a *Group* x *Reward* or *Group* x *Reward x Time point*.

In the analyses described above, I focused on regions showing interactions with time

point, given our use of unassumed GLMs in terms of transient cue-related activity. When appropriate, post hoc ANOVAs were performed within all significant regions identified by the ANOVAs described above. For these post hoc analyses, the mean percent signal change across each region was extracted for each of the eight estimated time point to visualize general pattern of activity. Among all time points frames, I focused on the average of time point 3 and 4 for the post-hoc analyses. Theses time points were chosen as they encompassed 5-8 seconds after stimulus onset, which would capture the initial peak in a stereotyped hemodynamic responses unconfounded by sustained activity. This was done for each applicable condition. Then, as briefly described above, I conducted post-hoc analyses using paired *t*-test to compare three *Reward* (e.g., BCXT, RCXT ("*XX*"), and RC ("*$20"*) by focusing on average of time point 3 and 4 to parse significance of cue-related effects.

In order to examine target and/or receipt-related effects, I also conducted a voxel-wise ANOVA on the target and/or feedback-related responses with *Reward* (BCXT, *RCXT*, *RC*) and *Condition* (incongruent, congruent, neutral) as within-subject factors and a *Group* (SCZ, HC) as a between-subject factor. I predicted that there would be main effects of *Reward* (receive *$20* money, receive no money cued by "*XX*") and a *Condition* (incongruent, congruent, neutral) and further interaction between a *Reward* and *Condition*, with both groups showing greater activation in the reward-related regions such as the ventral striatum for reward receipt (cued by "*$20*") on congruent trials. These ANOVAs were used in voxel-wise analyses either with *a priori* ROI masks or at the whole-brain level. To be specific, brain responses on incongruent trials were compared to those on neutral trials. The size of this difference in brain responses is called the "interference effect", which can be considered as an index of cognitive control. Also, brain responses on neutral trials were compared to those on congruent trials, referred to as "facilitation effect."

DLPFC and BG A Priori ROI Mask Analyses

Given previous works suggesting internal representation of abstract reward value during

cognitive control function in the DLPFC and striatum (Jimura et al., 2010; Locke & Braver, 2008), I started by constraining the analyses to *a priori* regions of interest (ROI) within the DLPFC and basal ganglia (BG). To be specific, I used masks of voxels within the DLPFC and BG including the ventral striatum and conducted voxel-by-voxel analyses restricted to these *a priori* ROIs. The anatomical DLPFC ROI mask regions were defined on an atlas-representative image using the boundaries described by Rajkowska and Goldman-Rakic (Rajkowska & Goldman-Rakic, 1995). The BG ROI mask regions including the ventral striatum were based on guidelines suggested by (Postuma & Dagher, 2006). All statistical activation maps from ROI were appropriately corrected for multiple comparisons using combined *p*-value and cluster thresholds determined using Monte Carlo simulation; an approach equivalent to that employed by the AlphaSim program in the AFNI software package. For DLPFC ROI mask regions, *z*-value of 2.05 and a contiguous 13 voxels for the DLPFC ROI mask were used. For the BG ROI mask region, *z* -value of 2.05 and a contiguous 14 voxels for the BG ROI mask region were used.

After the identification of group differences, for significant clusters, I extracted average BOLD responses values and imported them into SPSS for further post-hoc analyses to parse the source of significant effects. These analyses included independent and paired *t*-test as appropriate. I also conducted correlation analyses between the BOLD response in these significant regions during reward vs. baseline blocks and individual difference in negative symptoms scales (e.g., the SANS, the BNSS) using Pearson *r* correlation given *a priori* hypotheses regarding the role of the DLPFC and striatum during conflict processing in reward context.

Whole-Brain Group Analyses: Whole brain exploring analysis was performed to identify brain regions that revealed significant sustained or transient activity depending on reward context, as described above (see Supplementary Materials for all results from whole brain analyses). Whole-brain analyses were corrected for multiple comparisons using *p*-value/cluster size threshold of $p < .001$ and 13 contiguous voxels with *z* -values > 3.0. This correction was

determined by Monte Carlo simulations to provide a whole-brain false-positive rate of $p < .05$ (e.g., (Forman et al., 1995; Gaffrey, Barch, Singer, Shenoy, & Luby, 2013)).

When appropriate, using in-house peak finding scripts, the resulting significant maps in the whole-brain analyses were partitioned into ROI clusters where peaks of activity were considered separate regions if they were more than 15 mm apart from each other (e.g., (Michelon, Snyder, Buckner, McAvoy, & Zacks, 2003)). In addition, these ROIs were used to examine magnitude and time courses of the hemodynamic response for post-hoc contrasts to parse the source of significant effects.

Relation To Negative Symptoms (Specific Aim3):

1) The Correlation Between Negative Symptoms Severity and Two Behavioral Incentive Effects In SCZ. To test this, I correlated between clinical measures of negative symptoms severity scores in SCZ and mean RT decrement from non-incentive baseline to "*XX*" (RCXT) trials. Similarly, I also correlated between clinical measures of negative symptom severity scores in SCZ and mean RT decrement from "*XX*" (RCXT) to "*$20*" (RC) trials within reward conditions showing reward cue effect.

2) Correlation Between Negative Symptoms Severity and Sustained Brain Activity In the DLPFC During Reward vs. Baseline Blocks. I conducted voxel-wise Pearson correlations between self-reported avolition and/or anhedonia in SCZ and sustained activity in the DLPFC and other reward-related regions during reward versus baseline conditions.

3) Correlation Between Negative Symptoms Severity and Transient Cue-related Activity in the ventral striatum During "XX" versus "$20" Cued Trials within Reward Conditions.
I conducted voxel-wise Pearson correlations between self-reported avolition and/or anhedonia in SCZ and cue-related activity in the ventral striatum and DLPFC during "*XX*" versus "*$20*" cued trials within reward conditions.

Results

Participant Characteristics. Participants consisted of 27 HC with no personal or family history of psychosis and 36 individuals with SCZ. As presented in Table 1, the two groups were similar in terms of most demographic variables including age, sex, race, smoking status, or parental education except participant's education: the HC showed slightly higher educational level compared with individuals with SCZ In addition, the SCZ self reported significantly higher social and physical anhedonia relative to the HC (see Table 1 for clinical and demographic characteristics of participants).

Table 1:

Clinical and Demographic Characteristics of Participants

Variables	HC (N =27)	SCZ (N =36)	Group Comparison
	Mean (*SD*)	*Mean* (*SD*)	
Age (years)	35.56 (8.61)	38.96 (8.47)	F (1, 62) = 2.43, p =.12
Gender (% male)	55.6	69.4	χ^2 (1) = 1.28, p = .25
Race (% Caucasian)	29.6%	41.7	χ^2 (1) = 3.33, p = .18
Smoking status (%Smokers)	37.0%	68.8%	χ^2 (1) = 3.58, p= .06
Handedness (% right)	92.6%	80.6%	χ^2 (2) = 1.48, p= .47
Highest Parental Education (years)	14.11 (1.73)	13.80 (3.62)	F (1, 61) = .16, p = .68
Education (years)	14.51 (1.86)	13.13 (2.60)	F (1, 62) = 5.44, p= .02
Clinical Measures			
SAPS: Positive	-	4.83 (4.31)	
SANS: Negative	-	8.77 (3.33)	
BDI	2.14 (3.55)	8.47 (8.99)	t (61) = -3.44, p =.001
BNSS, consummatory	-	3.83 (2.83)	
BNSS, anticipatory	-	1.41 (1.42)	
BNSS, total	-	19.13 (11.16)	
Chapman Social Anhedonia	7.96 (6.03)	16.13 (7.93)	t (61) =-4.46, p =.00
Chapman Physical Anhedonia	9.81 (5.26)	17.52 (8.94)	t (61) =-3.98 p =.00
Antipsychotic Medications			
Typical antipsychotics (%)	-	11.1%	
Atypical antipsychotics (%)	-	69.4%	
Both typical and atypical antipsychotics (%)	-	8.3%	
Other Medications			
Antidepressant	-	44%	
Mood Stabilizer	-	16%	
Anticholinergic	-	25%	

Note. HC = healthy controls, BNSS= The Brief Negative Symptom Scale (Andreasen, 1983b), SCZ = schizophrenia, SAPS= The Scales for the Assessment of Positive Symptoms (Andreasen, 1983b), SANS = The Scales for the Assessment of Negative Symptoms (Andreasen, 1983b).

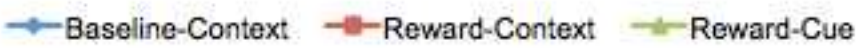
Behavioral Results

Reaction Times: I expected to replicate prior behavioral work (Mann et al., 2013) suggesting reduced reward context effect in SCZ, as evidenced by a smaller RT decrement from non-incentive baseline trials to RCXT trials both cued by "*XX*" compared to the RT decrement of the HC. On the other hand, I expected that individuals with SCZ would show an intact pattern of faster performance on "*$20*" trials in reward conditions rather than on "*XX*" trials within reward conditions, referred to as reward cue effect. To test this hypothesis, the median RT only for correct responses and error data were analyzed using a repeated measures ANOVAs with a *Reward* (BCXT (cued by "XX"), RCXT (cued by "*XX*"), RC (cued by "*$20*") and a *Condition* (neutral, congruent, incongruent trials) with within-subject factors and a *Group* (SCZ, HC) with a between-subject factor. It is assumed that RC trials refer to rewarded trials by getting additional reward money. In the current data set, approximately 72% of trials out of the total number of RC trials were rewarded (criteria: correct and RT below the median RT from the second baseline run for each individual).

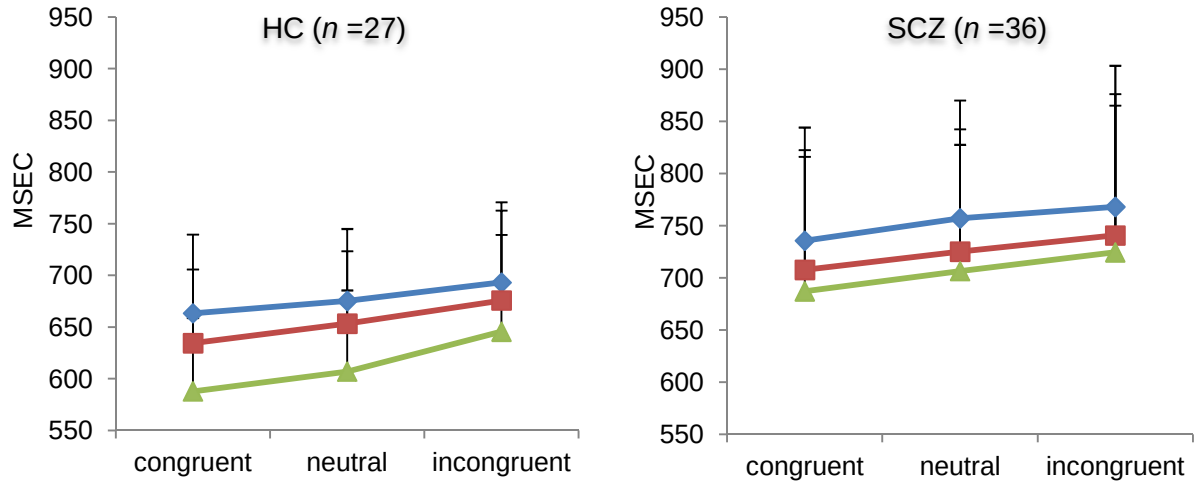
The repeated measure ANOVA indicated significant main effects of *Group* [F (1,61) = 10.38, p = .002, η^2_p= .14], *Reward* [F (2,122) = 34.12, p = .00, η^2_p= .35], and *Condition* [F (2,122) = 32.01, p = .00, η^2_p= .34]. The main effect of *Condition* indicated slower responses on incongruent trials compared to congruent trials [F (1,61)=51.93, p = .000, η^2_p= .46] and slower RTs on neutral trials compared with congruent trials [F (1,61)=18.66, p = .000, η^2_p= .23]. The main effect of *Reward* reflected faster performance on RCXT trials compared to BCXT conditions [F(1,61) = =12.93, p = .001, η^2_p= .17], RC compared to baseline conditions [F (1,61) = 60.98, p = .00, η^2_p= .50] as well as RC compared to RCXT conditions [F (1,61) =26.32, p = .000, η^2_p= .30].

Figure 3:

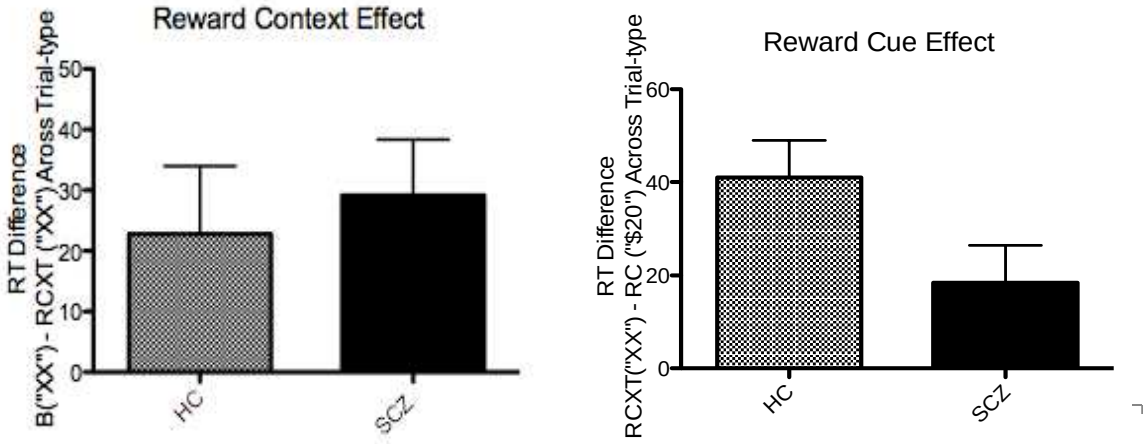
Behavioral Data



(a). Reaction Time Data



(b). Behavioral Indices of Reward Context and Cue Effects



Note. (a) Median reaction times for correct responses, (b) context and reward effects for reaction time data. Error bar represents SEM.
HC = healthy controls, SCZ = individuals with schizophrenia. The context effect was calculated by subtracting the mean of reaction times the reward-context condition from the mean of reaction time in baseline trials across all three conditions. The reward-cue effect was calculated by subtracting mean reaction time in reward-cue trials (cued by "*$20*") from mean of reaction time in reward-context trials (cued by "*XX*") across all three conditions.

As shown in Figure 3(a), the main effect of *Group* reflected overall slower RTs in SCZ compared with the HC. However, contrary to my prediction, I did not find a significant *Reward* by *Group* [F (2,122) = 1.49, p = .22, η^2_p= .02] interaction. There was also no significant *Condition* by *Group* [F (2,122) = .76, p = .46, η^2_p= .01] or *Reward* x *Condition* [F (4,244) = .91, p = .45, η^2_p= .01] or *Group* by *Reward* x *Condition* interactions [F (4,244) = .43, p = .78, η^2_p= .00].

Behavioral Indices of Reward Context and Cue Effects.

As noted above, contrary to my prediction, I did not see a significant *Reward* by *Group* interaction. To examine this effect in more detail, I conducted two follow-up analyses. First, I compared the magnitude of the reward context effect between individuals with SCZ and the HC. As described above, the reward context effect was computed by subtracting the RT in Reward-Context (RCXT) trials cued by "*XX*" from the baseline trials cued by the same cue, "*XX*" across all three trials-type. As shown in Figure 3 (b), individuals with SCZ (mean RT: 29.14) and HC (mean RT: 22.75) showed a similar reward context effect [F (1,62) = .19, p = .65, η^2_p= .27]. Secondly, I compared the magnitude of the reward cue effect between those with SCZ and the HC. Again, as mentioned above, the reward cue effect was estimated by subtracting the RT in RCXT trials cued by "*XX*" from the baseline trials cued by the same cue, "*XX*" across all three trials-type. Different from my expectation, as presented in Figure 3(b), I found that individuals with SCZ showed somewhat reduced reward cue effect (mean RT: 18.39) compared with the HC (mean RT: 41.01) at a trend level [F (1,62) = 3.81, p = .06].

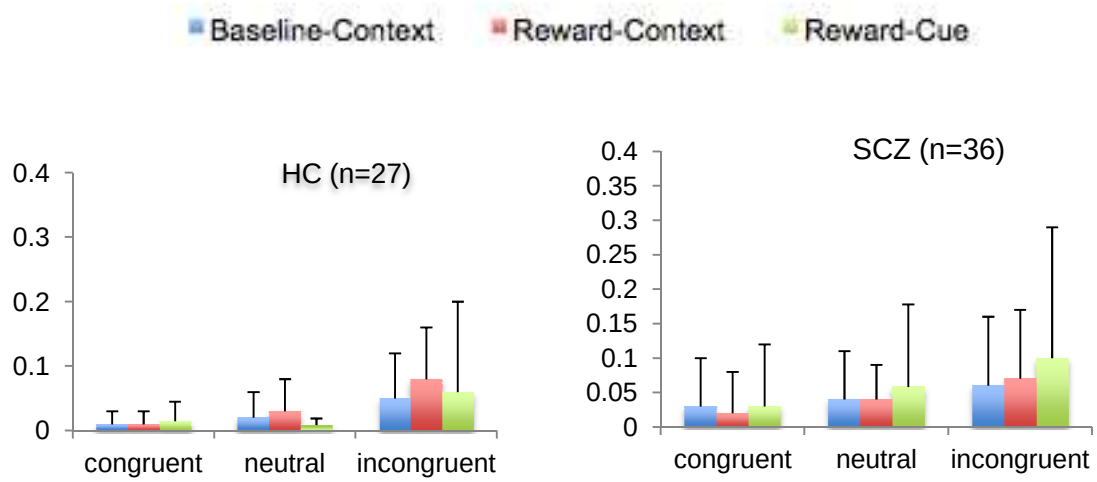
Psychometric Issues. It is commonly observed that SCZ have longer RTs and the standard deviation (*SD*) across the conditions for SCZ is typically larger than *SD* for HC (e.g., Mann et al., (2013)). This was true in the current data set [BCXT (Levene's Test= 5.14, p = .02, *SD*: 114.17 vs. 69.54), RCXT (Levene's Test= 11.19, p = .001, *SD*: 118.83 vs. 69.91), RC (Levene's Test =6.51, p = .01, *SD*: 124.59 vs. 75.34)]. Therefore, I cannot rule out the possibility that current behavioral findings are artificially influenced by the effects of longer RTs (Chapman

& Chapman, 1973). The most effective way to address this is to convert RT scores into *Z*-scores, which is consistent with previous work in SCZ (Mann et al., 2013) and (Faust, Balota, Spieler, & Ferraro, 1999)'s recommendation. Thus, I converted RT scores into *Z*-scores of the mean RT across all conditions as the measure of RT in each condition for each participant (Faust, 1999). By doing this approach, I could use *Z*-scores as a function of the magnitude of the SD. Then, I computed the same ANOVA described above. This ANOVA again indicated no significant two-way interaction between *Condition* and *Group* or *Reward* x *Condition* or *Group* by *Reward* x *Condition* interactions (all p = n.s.). Then, I also computed behavioral indices of reward context and cue effects described above. Again, the non-significant group differences in the reward context effect [F (1,62) = .19, p = .65] and reduced reward cue effect in SCZ relative to HC [F (1,62) = 3.81, p = .05] remained even when accounting for overall longer RTs in the SCZ.

Accuracy: As shown in Figure 3 (c), the analogous ANOVA on error data indicated only a significant main effect of *Condition* [F (2,122) = 16.98, p = .00, η^2_p= .21], reflecting more errors on incongruent trials compared to congruent trials [F (1,61) = 27.92, p = .000, η^2_p= .31] and neutral trials compared to congruent trials at a trend level [F (1,61) = 3.48, p = .06, η^2_p= .05]. There were no significant main effects of *Reward* [F (2,122) = .94, p = .39, η^2_p= .01] or *Group* [F (1,61) = 1.89, p = .17, η^2_p = .03]. In addition, there were no significant interactions of *Reward and Group* [F (2,122) = 1.84, p = .16, η^2_p = .02], *Condition and Group* [F (2,122) = .28, p = .75, η^2_p = .005], *Reward* and *Condition* [F (4,244) = .82, p = .51, η^2_p = .01] as well as *Reward* x *Group* x *Condition* interaction [F (4,244) = .38, p = .81, η^2_p= .00] (see Figure 3 (c)). Given that there was no significant main effect of *Group* on error data, further analyses as described below were focused on using RT data.

Figure 3 (c):

Error Data



Neuroimaging Results (Specific Aim2)

1) Sustained Components of Motivated Cognitive Control Function

To examine whether individuals with SCZ would show reduced reward context effects in sustained activity at a neural level, I conducted a voxel-wise repeated measures ANOVA with *Group* as a between-subject factor and *Reward* (baseline, reward conditions) as a within-subject factor in both whole brain and ROI analyses. I predicted a significant a *Group* x *Reward* interaction, with individuals with SCZ showing a less of an increase in sustained activity in regions (i.e., the DLPFC) during reward blocks compared to the baseline blocks relative to the HC.

Effects of Reward in the *A Priori* ROIs: Given *a priori* regions of interest in the DLPFC and BG implicated in reward processing, the voxel-wise ANOVA as described above was restricted to the DLPFC and BG *a priori* ROI regions by separately applying each DLPFC and BG mask regions to the results of the voxel-wise ANOVA. As presented in Table 2 and Figure 4 (a), DLPFC ROI analyses revealed a significant main effect of *Reward* in the bilateral DLPFC regions. Post-hoc paired *t*-tests to compare neural activity during reward vs. baseline blocks

across groups indicated that sustained activity in reward blocks were greater relative to baseline blocks across groups [right DLPFC (*x*: 42, *y*: 16, *z*: 29), paired *t*-test (62)= 4.30, *p* =.000; left DLPFC (*x*: -42, *y*: 10, *z*: 30), paired *t*-test(62)= 3.54, *p* =.001]. However, no regions displayed a main effect of *Reward* in the BG mask regions.

Effects of Group in the *A Priori* ROIs: A significant main effect of *Group* was identified in the DLPFC and BG ROI analyses. As presented in Table 2 and Figure 4 (b), HC group showed greater sustained activity relative to individuals with SCZ in the lateral globus pallidus. On the other hand, in the middle frontal gyrus and putamen, individuals with SCZ showed overall greater sustained activity than the HC group at a group level [right DLPFC (*x*: 41, *y*: 19, *z*: 27) and Putamen (*x*: 14, *y*: 10, *z*: -3)].

Interaction of Reward and Group in the *A Priori* ROIs: As presented in Table 2, I also found a *Group* x *Reward* interaction in the Putamen (*x*:22, *y*: 10, *z*: 3) from BG ROI analysis. However, no region displayed the interaction effect from the DLPFC analysis. As shown in the bottom panel of Figure 4 (c), post-hoc paired *t*-test to compare sustained activity during reward vs. baseline blocks for each group revealed that the HC group showed an increased of sustained activity as a function of reward context in the Putamen (*x*:22, *y*: 10, *z*: 3) from the BG analysis [paired *t*-test(26) =4.10, *p* =.000]. However in the same region, individuals with SCZ did not show significant differences in sustained activity as a function of reward context (paired *t*-test (35)= -.70, *p* =.48) different from the HC.

Table 2:

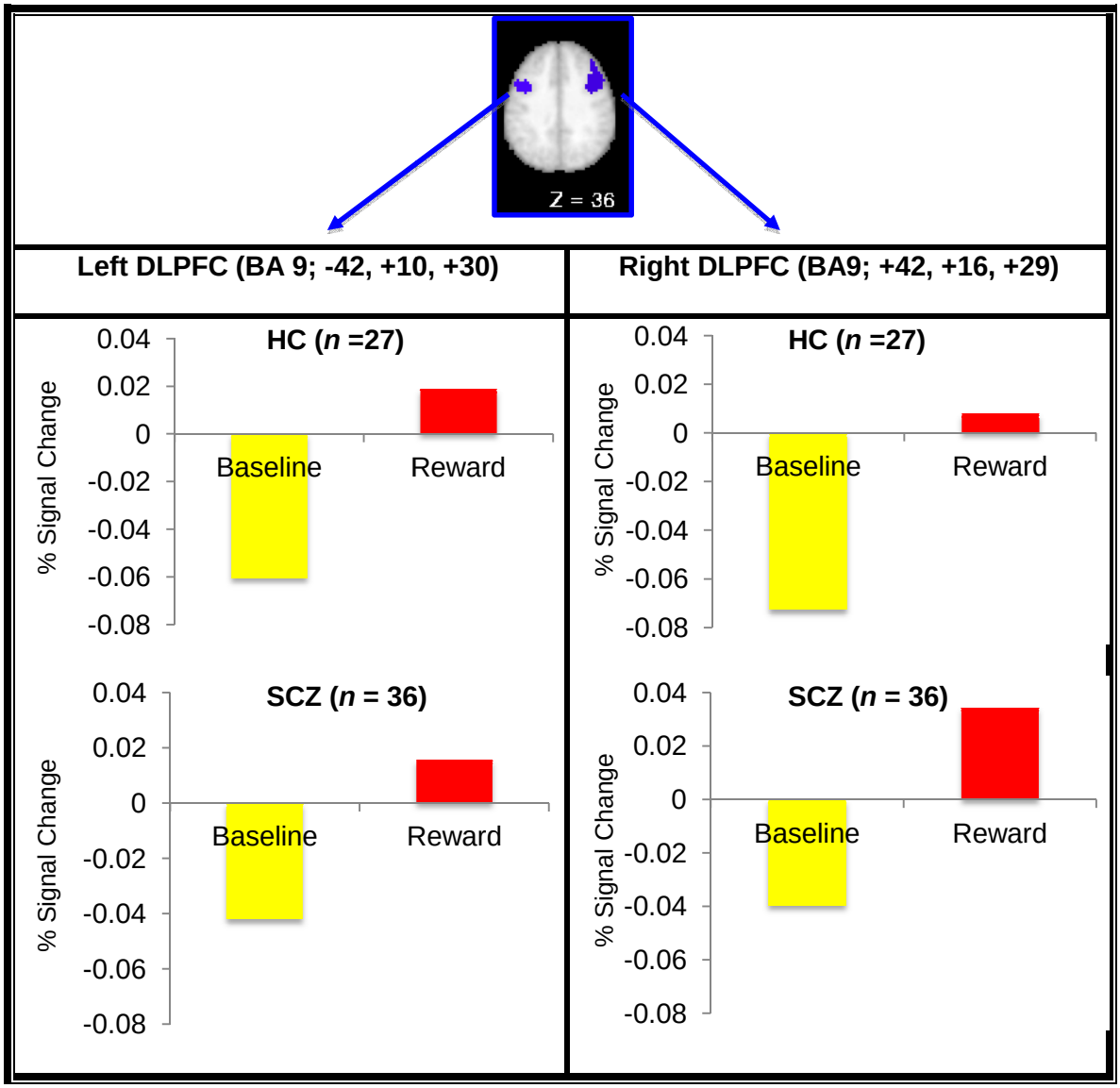
Sustained Context-dependent Activity: Main effect of Reward, Group and Reward x Group Interaction Effect

Effect	Analysis	BA	Region of Activation	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]
					x	*y*	*z*		
Reward	DLPFC ROI	9	Middle Frontal Gyrus	267	42	16	29	3.97	R > B
		9	Middle Frontal Gyrus	81	-42	10	30	3.34	R > B
Group	DLPFC ROI	9	Middle Frontal Gyrus	44	41	19	27	2.61	SCZ > HC
	BG ROI		Putamen	25	14	10	-3	2.82	SCZ > HC
			Lateral Globus Pallidus	24	-22	-6	-2	2.99	HC > SCZ
			Lateral Globus Pallidus	15	23	-8	2	2.78	HC > SCZ
Reward x Group	BG ROI		Dorsal Striatum	24	22	10	3	2.66	SCZ: B > R HC: R > B

Note. B= baseline, BG =basal ganglia, DLPFC =dorsolateral prefrontal cortex, HC = healthy controls, R= Reward, ROI = region of interest, SCZ = individuals with schizophrenia, WB = whole brain analysis.
Z values represent mean activation across the region. [a] Post-hoc paired *t*-tests or independent *t*--tests were conducted (all $p < .05$). See text for detailed post-hoc analyses.

Figure 4 (a):

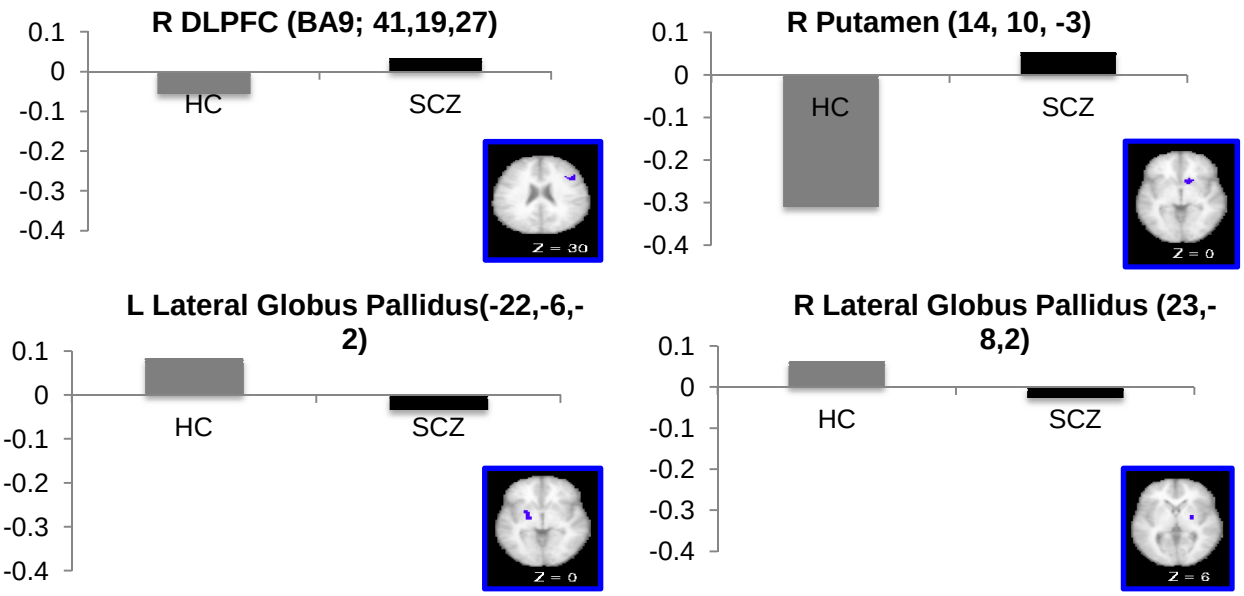
Bilateral DLPFC Regions Displaying Main Effect of Reward in *A Priori* ROI Analyses



Note. DLPFC = dorsolateral prefrontal cortex, HC= Healthy Controls, ROI = region of interest, SCZ = individuals with schizophrenia. This figure represents the results of repeated measures ANOVAs from the DLPFC ROI analysis. *Reward* (reward, baseline blocks) is a within-subjects factor and *Group* is a between-subjects factor. Post-hoc paired t-tests were conducted to compare sustained activity during reward vs. baseline blocks across groups on each region ($p < .05$). DLPFC ROI analyses were appropriately corrected for multiple comparisons using combined *p*-value and cluster thresholds (*z* -value: > 2.05, 13 contiguous voxels)

Figure 4 (b):

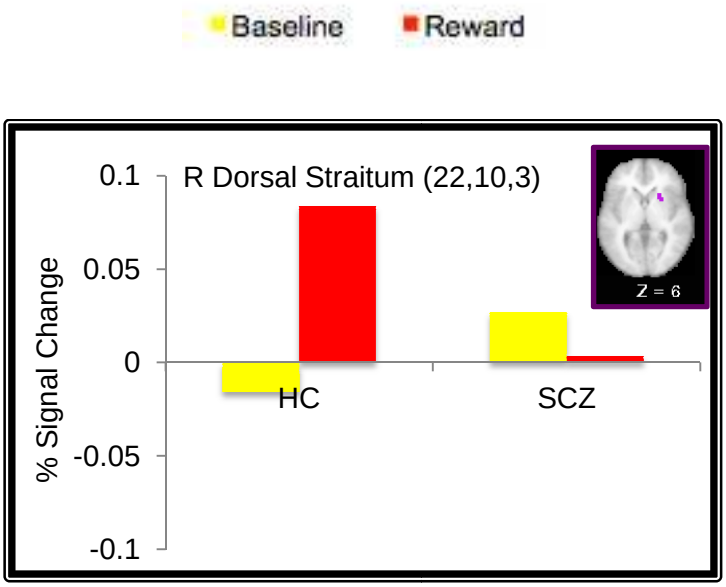
Regions Displaying a Main Effect of Group from the DLPFC and BG ROI Analyses



Note. BG= Basal Ganglia, DLPFC= Dorsolateral Prefrontal Cortex, HC= Healthy Controls, R= Right, SCZ= Schizophrenia, L= Left

Figure 4 (c):

Regions Displaying Reward x Group Interaction in the BG Mask Analyses



Note. BG = Basal Ganglia, R = right, ROI = Region of Interest

Sustained Component of Motivational Cognitive Control: Results Summary

Consistent with prior work in healthy individuals (e.g., (Jimura et al., 2010; Padmala & Pessoa, 2011), the current study found that the bilateral DLPFC showed increased sustained activity during reward compared to baseline blocks across groups. These results validate the use of response conflict processing paradigm used in current study, which was designed to measure changes in neural activity as a function of reward context. Contrary to my prediction, a *Reward* x *Group* interaction effect was not identified in the DLPFC but in the dorsal striatum where individuals with SCZ showed reduced sustained activity during reward vs. baseline contexts different from the HC.

2) Transient Components of Motivated Cognitive Control Function

Transient Cue-related Neural Activity As a Function of Reward: To examine whether individuals with SCZ showed intact cue-related reward effects, a voxel-wise repeated measures ANOVA using the cue-related estimates, with *Group* as a between-subject factor, and *Reward* (Baseline-Context (BC: "*XX*"), and Reward-Cue (RC: "$20") and Reward-Context (RCXT: "*XX*") in reward conditions) and *Time point* (the 8 time frame estimates) as within-subject factors. I predicted a significant *Reward* x *Time point* interaction, with an increase during RC (cued by "*$20*") vs. RCXT (cued by "*XX*") in cue-related activity in the ventral striatum. In addition, I predicted that the *Reward* x *Time point* interaction during "*$20"* vs. "*XX"* would be significant for both HC and individuals with SCZ. However, I did not predict a further interaction with a *Reward* x *Group* x *Time point* as I predicted intact reward-related transient activity in SCZ.

Effects of Reward In the *A Priori* ROIs: Regions in the bilateral DLPFC, Putamen and caudate body from the DLPFC and BG ROI analyses displayed significant interactions between *Reward* (RC, RCXT, BCXT trials) and time point (see Table 3 for exact coordinates for each region). As predicted, post-hoc paired *t*-tests on each region displaying the interactions of *Reward* and time point at the average of time point 3-4 revealed a pattern of greater trial-by-trial activity on RC trials relative to RCXT and baseline trials, although some regions showed deactivation on either or both RCXT and baseline trials (see Figure 5 for example time courses).

Effects of Group In the *A Priori* ROIs: No region displayed a significant *Group* effect within the DLPFC and BG masks.

Interactions of Reward and Group In the *A Priori* ROIs: Regions in the Putamen and lateral globus pallidus displayed a significant *Reward x Group* interaction in the BG ROI analyses (see Table 4 for exact coordinates for each region). No region displayed a *Reward* x *Group* interaction in the DLPFC mask. To identify the source of the significant effect from the BG analyses, post-hoc paired *t*-tests were performed on each region displaying the interactions of *Reward* (RC, RCXT, BCXT) for each group. As shown in Figure 6, in both putamen and

lateral globus pallidus, HC showed increased trial-by-trial activity on RC trials relative to RCXT and BCXT trials. However, individuals with SCZ did not show any significant differences in terms of trial-by-trial activity as a function of reward.

Table 3:

Transient Reward x Time Point in DLPFC and BG ROIs Analyses

Analysis	BA	Region of Activation	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]
				x	*y*	*z*		
Basal Ganglia		Putamen	30	-19	3	-1	3.24	RC >**BCXT**$^{+}$ =RCXT
		Medial Globus Pallidus	16	-14	-8	0	3.33	RC > RCXT= **BCXT**
		Caudate Body	85	12	-3	14	3.81	RC> **RCXT**= **BCXT**
		Caudate Body	30	-14	-10	19	3.22	RC > **RCXT** =BCXT
DLPFC	9	Middle Frontal Gyrus	253	-38	20	29	4.27	RC > **RCXT** =BCXT
	9	Middle Frontal Gyrus	385	37	23	29	4.49	RC > **RCXT** =BCXT

Note. BCXT= Bseline-Context trials, deact= deactivation, DLPFC = dorsolateral prefrontal cortex, RC = Reward-Cue trials, RCXT = Reward-Context trials,. Time window for post-hoc analyses= average of time point 3 and 4 (see Data Analysis). **Bold** indicates deactivated regions.

[a]Post-hoc paired *t*-tests were conducted to examine the relationship between neural activity on reward trials and other cue-type activity on each region (p <0.05). ^{+}p-value was 0.05.

Table 4:

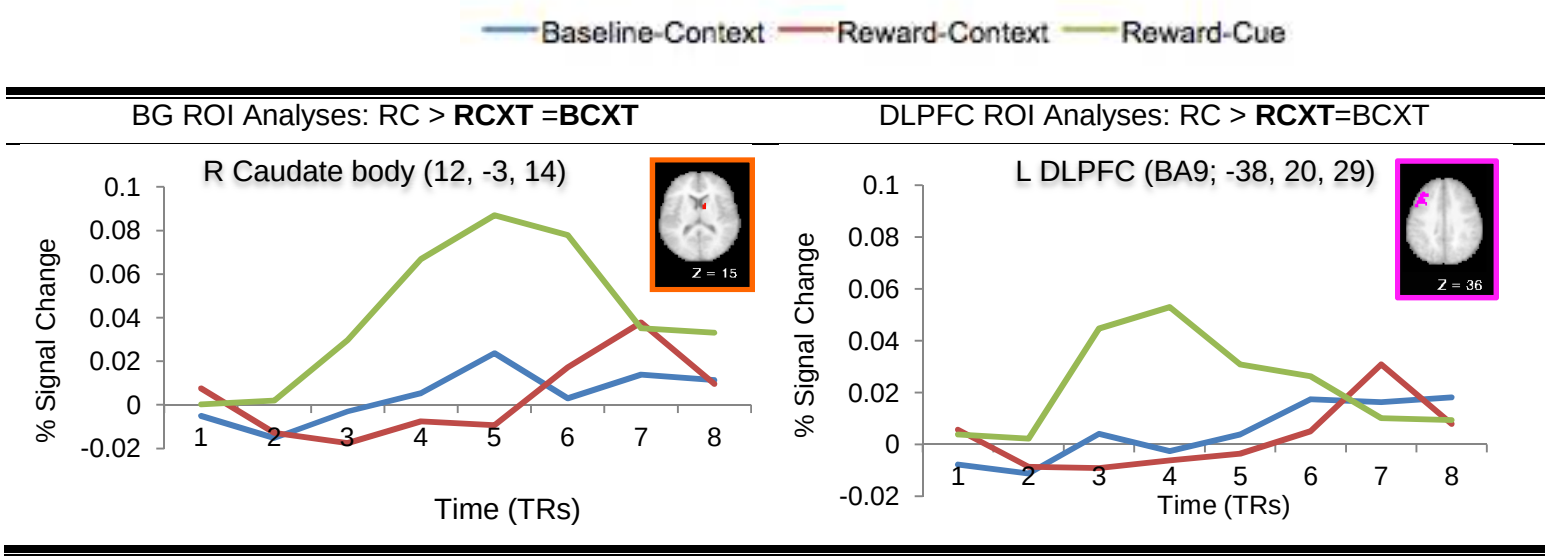
Transient Reward x Group x Time Point Interaction in the BG ROI regions

Region of Activation	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]	
		x	*y*	*z*		HC	SCZ
Putamen	37	21	3	0	3.13	RC > **RCXT**=**B**	RC =B =RCXT
Lateral Globus Pallidus	22	-23	-13	2	2.82	RC > RCXT=**B**	RC =B=RCXT

Note. BA = Broadman Area, B= baseline, RC = Reward-Cue, RCXT=Reward-Context, ROI = Region of interest, HC = Healthy controls,
SCZ = Schizophrenia, WB = Whole brain analysis.
[a] Post-doc *t*-tests to identify the source of significant effects were performed at the average of time point 3-4 (see the text for more detail).
Bold letters indicate cue-type trials on which regions showed deactivations.

Figure 5:

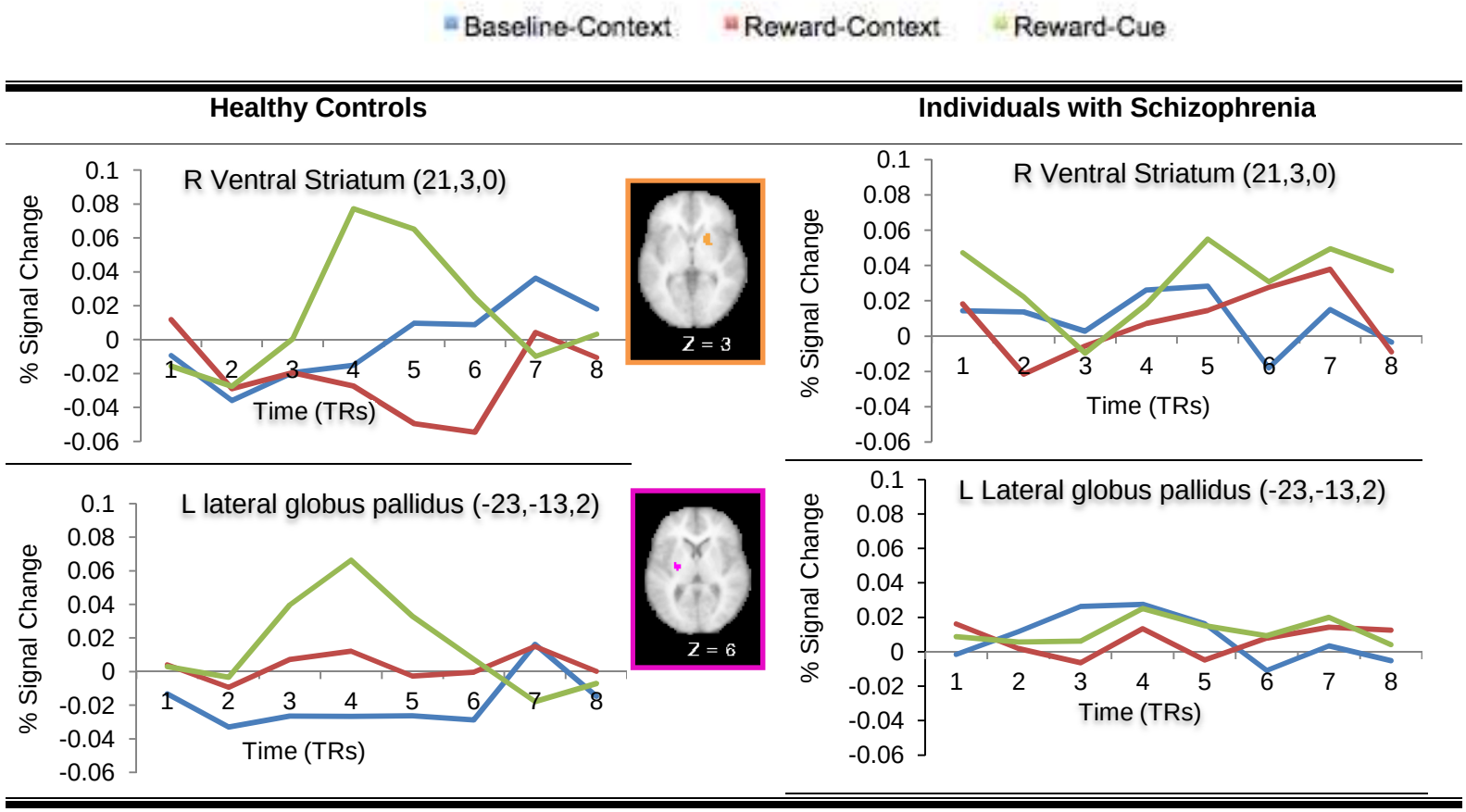
Example Time Courses From BG and DLPFC ROIs Showing a Significant Interaction Between Reward x Time Point



Note. BCXT= Baseline-Context, BG = basal ganglia, deact= deactivation, DLPFC= dorsolateral prefrontal cortex, RCXT= Reward-Context, RC = Reward-Cue, ROI = Region of Interest**. Bold** indicates deactivated regions. Post-hoc paired *t*-tests were conducted to determine the relationship between transient neural activity on reward-cue trials and other cue-type trials on each region at the average of time point 3-4 ($p < .05$).

Figure 6:

Example Time Courses for Each Cue-type From BG ROIs Showing a Significant Interaction Between Reward x Group x Time Point



Note. BG= Basal Ganglia, R= Right, L= Left

2-2) Transient Target-related Neural Activity: In addition to neural activity relating to transient trial-by-trial activity, I also examined target/receipt-related effects from the voxel-wise ANOVA on the target/feedback responses with 3 *Reward* (BCXT, RC, RCXT), 3 *Condition* (incongruent, congruent, neutral), and Time point (8 time points) as within-subject factors and a *Group* (SCZ, HC) as a between-subject factor. Again, to understand the source of any interaction with time point, I focused on averaged time point 3-4 as described above. I predicted that there would be main effects of reward *Reward* (receive $20 money, receive no money cued by "*XX*") and a *Condition* (incongruent, congruent, neutral) and further interaction between a *Reward* and *Condition*, with both groups showing reduced conflict-related processing in the reward-related regions such as the ventral striatum for reward receipt (RC: cued by "*$20*") on incongruent trials. These ANOVAs were used in both voxel-wise whole-brain and ROI analyses. All voxelwise statistical tests were corrected for multiple comparisons and the correction factor was determined by Monte Carlo AlphaSim simulations to provide a whole-brain false-positive rate of $p < 0.05$ (Langdon, Corner, McLaren, Coltheart, & Ward, 2006).

Interactions of Reward and Group in the *A Priori* ROIs: In the ANOVA restricted to *a priori* regions of interest using the DLPFC and BG masks, *Reward* (BCXT, RCXT, RC) x *Time point X Group* interactions were identified in several regions in the bilateral DLPFC, Putamen and medial globus pallidus (see Table 5 for coordinates for each region). In the putamen and medial globus pallidus, HC did not show a different degree of target-related activity as a function of reward, while individuals with SCZ showed greater target-related activity on BCXT ("*XX*") than that on RCXT at a trend level (p =.05). In the right DLPFC (BA9; x:25, y:37,z: 29), HC showed reduced target-related activity during RC/RCXT vs. BCXT while individuals with SCZ showed no different activity as a function of reward in the same right DLPFC (see Figure 7 for time courses).

Table 5:

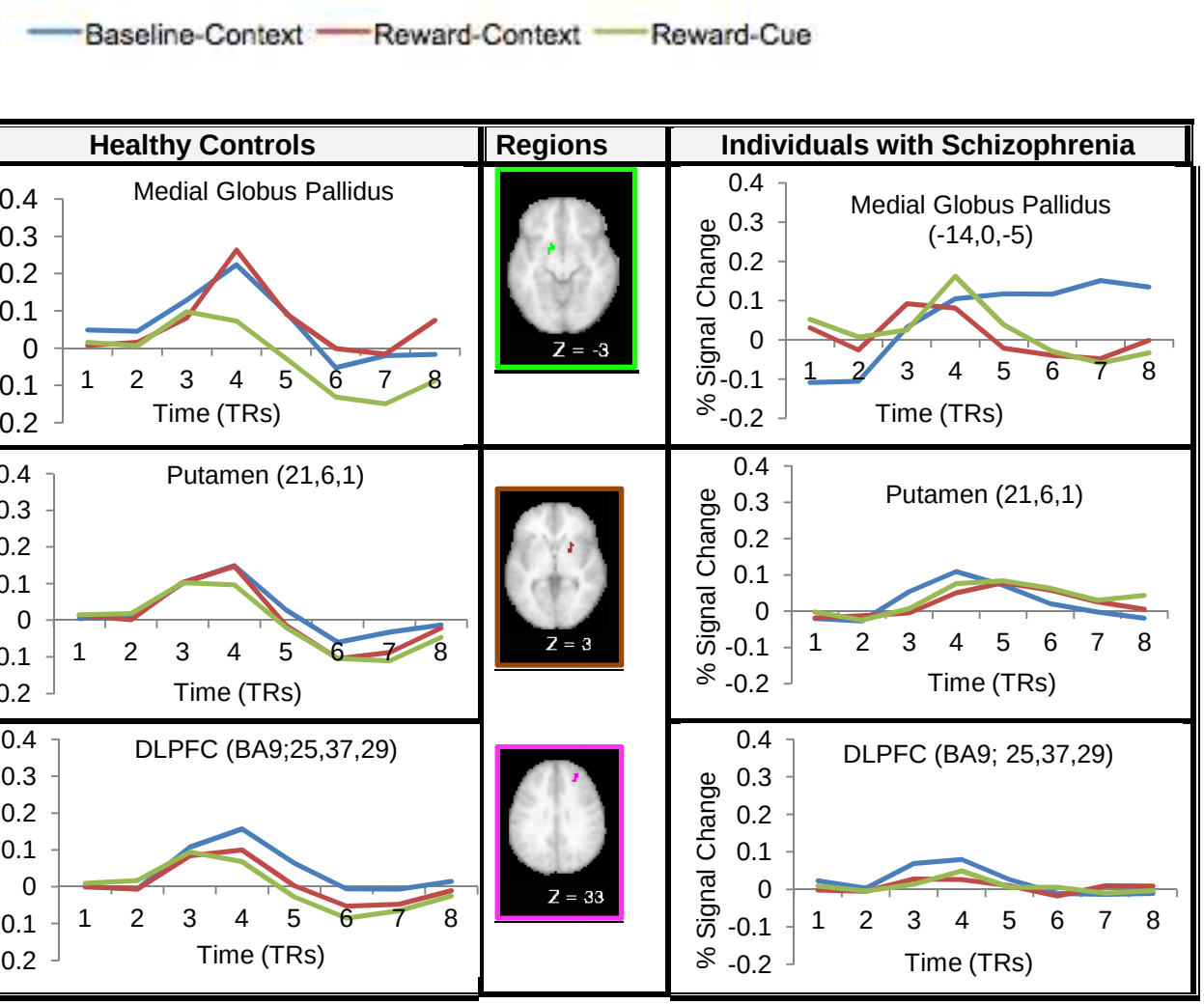
Reward x Group Interaction in the Target-related Activity

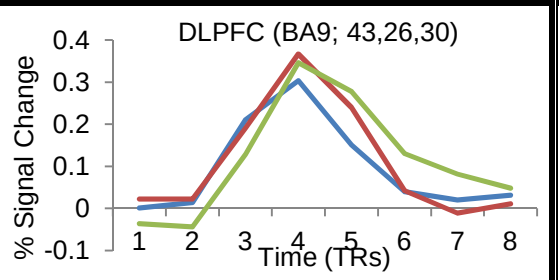
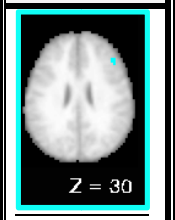
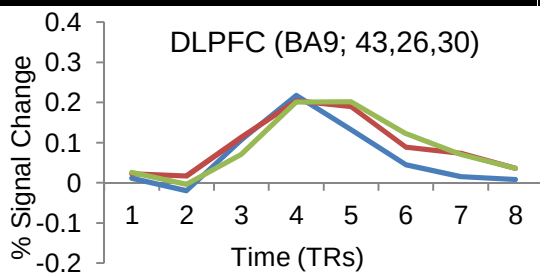
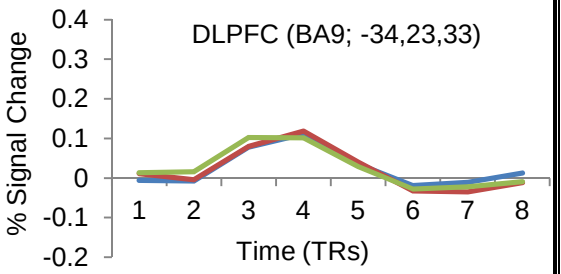
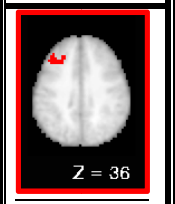
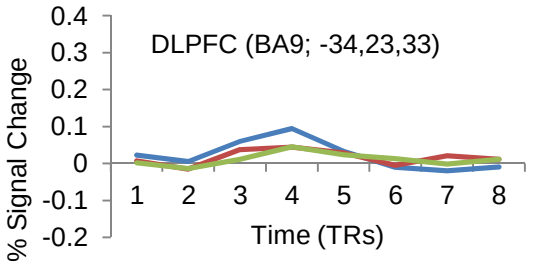
Analysis	BA	Region of Activation	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]			
				x	*y*	*z*		HC		SCZ	
Basal Ganglia								RCXT=RC=BCXT		RCXT=RC=BCXT	
		Medial Globus Pallidus	25	-14	0	-5	3.31	TP3	TP4	TP3	TP4
								RCXT=RC=BCXT	RCXT >RC=BCXT	RCXT= RC=BCXT	
		Putamen	15	21	6	1	2.64	RCXT=RC=BCXT		BCXT >RCXT^{+}= RC	
DLPFC	9	Superior Frontal Gyrus	16	25	37	29	2.62	B >RCXT^{+}=RC		RCXT=RC=BCXT	
	9	Middle Frontal Gyrus	51	-34	23	33	3.09	RCXT=RC=BCXT		BCXT> RC=RCXT	
								RCXT=RC=BCXT		RCXT=RC=BCXT	
	9	Middle Frontal Gyrus	20	43	26	30	2.54	TP3	TP4	TP3	TP4
								BCXT>RC^{++}=RCXT	RCXT=RC=BCXT	RCXT=RC=BCXT	

Note. BCXT=Baseline-Context, RC = Reward-Context, RCXT=Reward-Context, TP = Time Point. $^{+}$ p = .05, $^{++}$ p =0.08. [a] Post-doc three paired t-tests (RC-baseline, RC-RCXT, RCXT-baseline) at the average of time point 3-4 for each group were conducted (p < .05).
Yellow indicates region where neural activities on RC-RCXT, RC-BCXT and RCXT-BCXT at the average of time point 3-4 did not differ. In this case, another paired *t*-tests at each time point 3 and 4 for each group were separately conducted to identify the source of significant effect

Figure 7:

Time Courses for Regions Displaying a Reward x Group Interaction in the Target-related DLPFC and BG ROIs Analyses



Healthy Controls	Regions	Individuals with SCZ
		
		

Interactions of Reward and Condition In the *A Priori* ROIs: In the ANOVA restricted to *a priori* region of interest using the DLPFC and BG mask regions, I found *Reward* (BCXT, RCXT, RC) x *Condition* (congruent, incongruent, neutral) *x Time point* interactions in the left DLPFC and the Putamen as presented in Table 6. To examine target-related activity, I focused on examining the difference in neural activity between incongruent and neutral conditions. The size of this difference in brain responses is called the "interference effect". Furthermore, I also examined whether the magnitude of facilitation effect (neutral-congruent) was different as a function of reward-related cue-types (i.e., RC vs. RCXT). Due to the enhancing reward effect on cognitive control, it is expected that facilitation effect would be greater on RC or RCXT compared to that on BCXT across groups, especially in the DLPFC.

Post-hoc paired *t*-tests using the interference effect (incongruent-neutral) were conducted to determine the relationship between reward and other cue-type activity. As presented in Figure 8 (a), conflict-related brain responses in the DLPFC (incongruent-neutral) were significantly reduced on RC trials (cued by "XX", zero money) compared to RCXT (cued by "$20") or baseline trials across two groups (see Figure S4 for full time courses for this effect). However, neural activity on incongruent and neutral trials at the average of time point 3-4 in the Putamen did not differ as a function of reward cue-type. When I did another follow-up paired t-tests at each time point 3 and 4, the interference effect (incongruent-neutral) at time point 4 on RCXT trials was greater compared to that on BCXT (see Table 6 for paired t-tests for each time point 3 and 4). Another set of paired *t*-tests using the facilitation effect (neutral-congruent) was conducted to determine the relationship between reward and other cue-type activity. As presented in Figure 8 (b), facilitation effect on RCXT at the average time point3-4 in the left DLPFC was greater on BCXT or RC (p= .04).

Interactions of Condition and Group In the *A Priori* ROIs: As shown in Table 6, several regions in the left inferior frontal gyrus and the right Putamen from the DLPFC and BG *a priori* ROI analyses displayed a *Condition* (congruent, incongruent, neutral trials) x *Group* (SCZ, HC)

interaction. As can be seen in Figure 9, in these regions, HC showed greater neural activity on incongruent relative to congruent and neutral trials while individuals with SCZ showed no significantly different activity as a function of condition type in the same regions.

Interactions of Reward, Condition, and Group In the *A Priori* ROIs: Only the right DLPFC (*x*: 30, *y*:28, *z*:32) displayed a *Reward* x *Condition* x *Group* x *Time point* interaction. To test whether the presence of rewards affect cognitive control related activity in the DLPFC, I focused on examining whether or not conflict-related brain activity (incongruent-neutral) was reduced on RC ("*$20"*) compared to RCXT trials ("*XX*") (see Figure 10 (a) for the magnitude of interference effect between the two groups). Repeated measures ANOVAs on the interference effect (incongruent-neutral) were conducted with *Reward* (RC, RCXT) as within-subject factor and Group (SCZ, HC) as between-subject factor. No main effect of *Reward* [$F(1, 61) = 2.16$, $p = .14$, $\eta^2_p = .03$], *Group* [$F(1, 61) = .25$, $p = .61$, $\eta^2_p = .004$], *Reward x Group* [$F(1, 61) = 1.01$, $p = .31$, $\eta^2_p = .01$] were identified. Further, analogous repeated ANOVAs described above on interference effect were conducted at each time point 3 and 4. Again, there were no main effect of *Reward*, *Group* and *Reward x Group* (all $p > .05$).

To identify the source of this four-way interaction, I conducted an analogous ANOVA on the magnitude of "facilitation" effect between neutral and congruent trials at the average of time point 3-4 with *Reward* (RC, RCXT) as within-subject factor and Group (SCZ, HC) as between-subject factor. This ANOVA revealed no main effect of *Reward* (RC, RCXT) $F(1, 61) = 1.79$, $p = .18$ $\eta^2_p = .03$ and *Group* $F(1, 61) = .002$, $p = .96$, $\eta^2_p = .000$] but significant *Reward x Group* interaction [$F(1, 61) = 4.94$, $p = .03$, $\eta^2_p = .07$]. Follow-up paired t-tests on the facilitation effect for HC revealed that the facilitation effect did not differ as a function of reward cue-type [RC-RCXT: paired *t*-test ($t(26) = .70$, $p = .48$] while for the SCZ, the facilitation effect (neutral-congruent) on RCXT was greater than RC [RC-RCXT: paired *t*-test ($t(35) = -2.45$, $p = .02$)]. That is, this four-way interaction effect in the right DLPFC was driven by a greater magnitude of the facilitation effect during RCXT vs. RC trials in SCZ. Figure 11 shows time course of the right DLPFC

displaying a Reward x Condition x Group x Time point.

Table 6:

Transient Target-related Activity in The DLPFC and BG *A Priori* ROIs Analyses

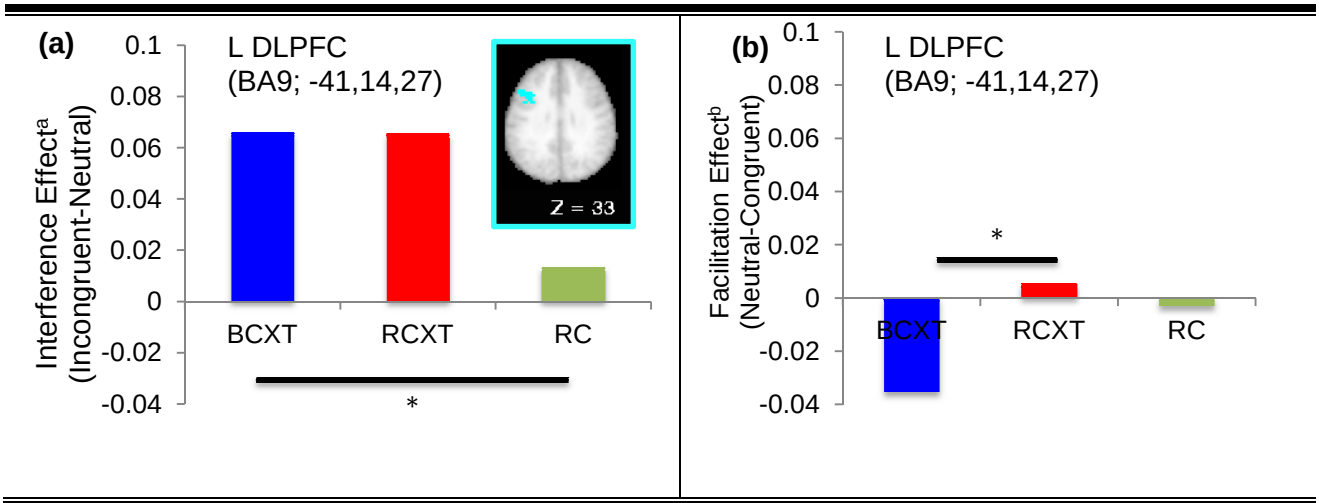
Analysis	Region of Activation	BA	Cluster size (voxels)	Talairach Coordinates *x*	*y*	*z*	*Z*	Activation Pattern During Time Point 3-4[a]	
Interaction of Reward and Condition								**Interference Effect[b]**	**Facilitation Effect[c]**
DLPFC ROI	Middle Frontal Gyrus	9	68	-41	14	27	3.11	RC > BCXT=RCXT	RCXT >BCXT=RC
BG ROI	Putamen		23	25	-12	6	3.13	RCXT=**BCXT**=RC[c]	RCXT >BCXT^{+++}=RC
								TP 3	TP4
								RCXT=BCXT=RC	RCXT>BCXT***=RC
Interaction of Condition and Group[d]								HC	SCZ
DLPFC ROI	Inferior Frontal Gyrus	9	36	49	14	23	3.44	I > N =C	I = C > N
	Inferior Frontal Gyrus	9	27	-34	7	28	3.07	I > N =C	I > C^{++}=N
BG ROI	Putamen		137	-16	1	10	3.83	I > N =C	I = N = C
	Lateral Globus Pallidus		19	-27	-20	0	2.91	I > N =C	I = N = C
	Lateral Globus Pallidus		24	14	-4	4	3.54	I > C =N	I = N = C
	Caudate Body		16	15	-11	20	2.68	I > C =N	I = N = C
								TP3	TP4	TP3	TP4
	Ventral Striatum		29	17	11	0	3.04	I=N =C	I> N^{++}=C	**I=N=C**	I=N=C

Note. BCXT= Baseline-Context, BG= basal ganglia, C= congruent, DLPFC= dorsolateral prefrontal cortex, HC = healthy controls, I= incongruent, N = neutral, RC = Reward-Cue, RCXT= Reward-Context ,SCZ = schizophrenia, TP= time point. **Bold** letters indicate cue-type on which neural activity was deactivated. *** p=.000, $^{++}$ p=0.08, $^{+++}$ p=0.09. [a] Post-hoc paired t-tests at the average of time point 3-4 were conducted to identify the source of the interaction effects displayed above. [b] To identify the source of *Reward* x *condition* x time point, interference effect using difference of neural activity between incongruent and neutral trials at the average of time point 3-4 for each cue-type (e.g., RC, RCXT, BCXT). Then, post-hoc three paired t-tests (RC-BCXT, RC-RCXT, RCXT-BCXT) were performed to determine the relationship of conflict effect among three cue-types. [c] Facilitation effect using difference of neural activity between neutral and congruent trials at the average of time point 3-4 for each cue-type. Then, post-hoc three paired t-tests (RC-BCXT, RC-RCXT, RCXT-BCXT) were performed to determine the relationship of facilitation effect among three cue-type. [d] To identify the source of *condition x group* x time point interaction, post-hoc three paired t-tests (incongruent-neutral, congruent-neutral, incongruent-congruent) for each group. Yellow indicates regions where RCXT=BCXT=RC at the average of time point 3-4. To identify the source

of significant effect, another set of three paired *t*-tests (RC-BCXT, RC-RCXT, RCXT-baseline) at each time point 3 and 4 were separately conducted.

Figure 8:

Regions Displaying a Reward x Condition x Time Point in Target-related DLPFC *A Priori* Mask Analyses



Note. BG= Basal Ganglia, DLPFC = Dorsolateral Prefrontal cortex, L = left, RC = Reward-Cue, RCXT= Reward-Context, ROI = Region of interest. * $p < .05$

[a] Interference effect was estimated by difference in neural activity on between incongruent and neutral trials. [b] Facilitation effect was estimated by difference in neural activity on between neutral and congruent trials.

Figure 9:

Example of Time Courses For Regions Displaying a Condition x Group x Time Point Interaction in the Target-related DLPFC and BG ROIs Analyses

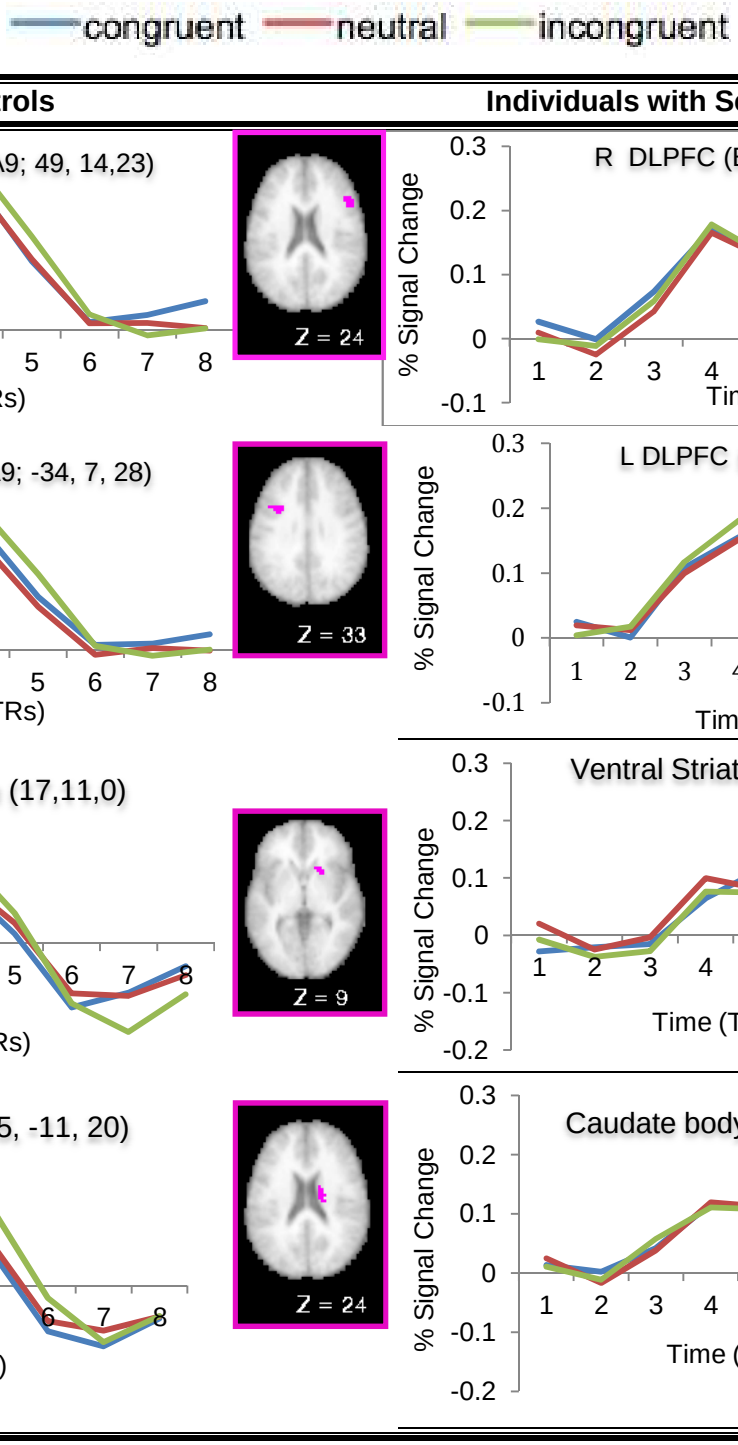
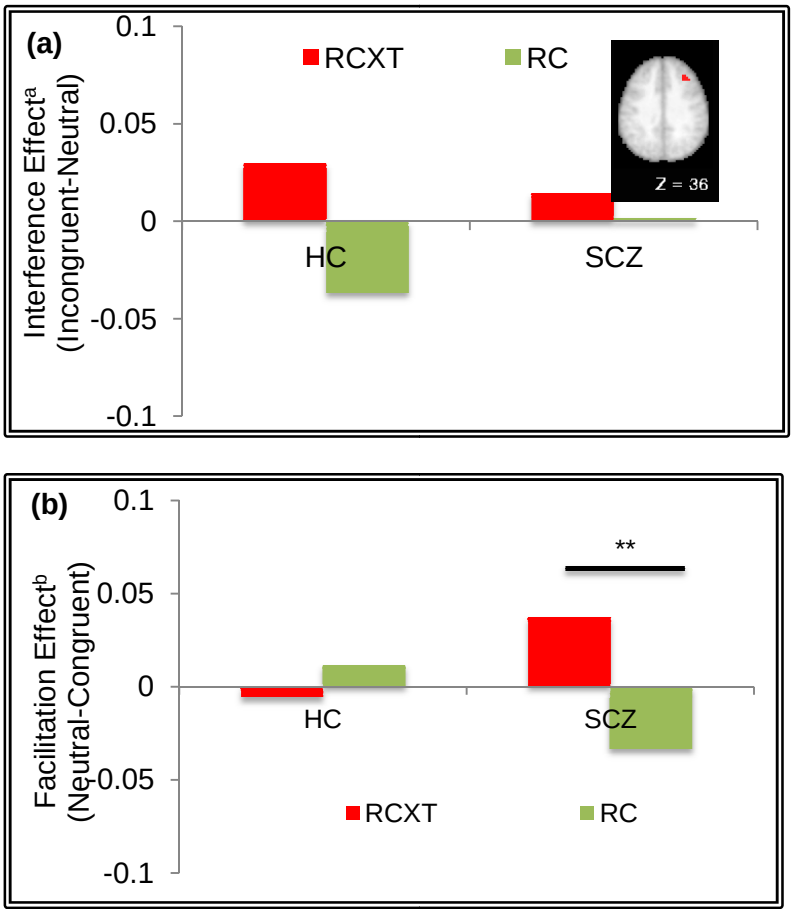


Figure 10:

Interference and Facilitation Effects during Reward-Cue vs. Reward-Context in the Target-related DLPFC ROI Analyses

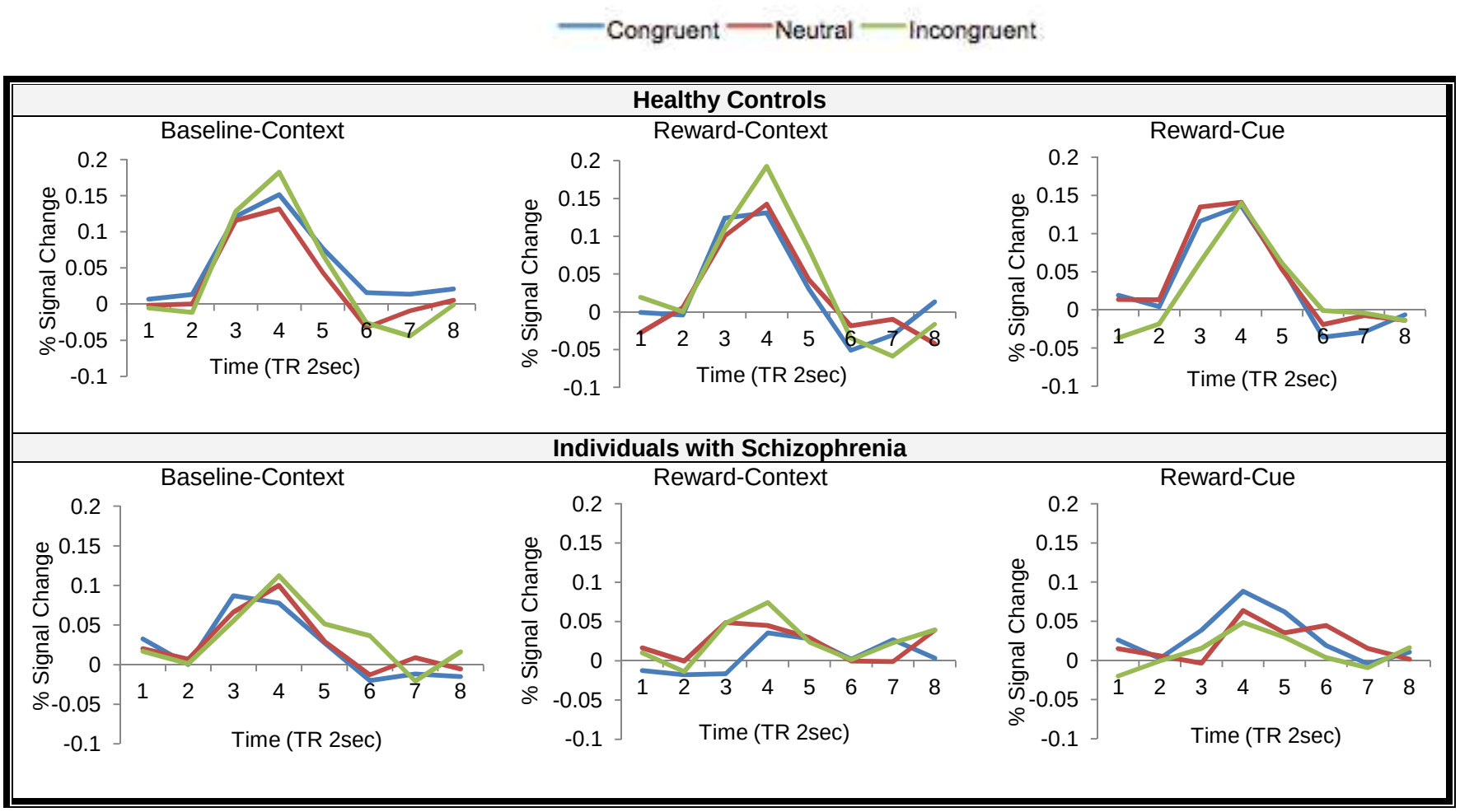


Note. ** p = .02

DLPFC= dorsolateral prefrontal cortex, HC= Healthy controls, RC =Reward-Cue, RCXT=Reward-Context, ROI = Region of interest, SCZ=Schizophrenia. [a] At the average of time point 3 and 4, for both groups, the magnitude of interference effects on RC was not significantly different compared to that on RCXT. See more detail in the text. [a] At the average of time point 3-4, SCZ group showed greater facilitation effect on RCXT relative to RC while the HC showed no different magnitude of facilitation effect.

Figure 11:

Time courses for the Right DLPFC Region Displaying a Reward x Condition x Group Interaction in the Target Related Activity



Transient Component of Motivational Cognitive Control: Results Summary

During the reward-related cue phase, consistent with prior work in healthy individuals, regions in the DLPFC showed increased transient trial-by-trial activity as a function of reward as well as in a sustained fashion as described in the section above. However, different from my prediction, I found a *Reward* x *Group* interaction effect in the ventral striatum, with individuals with SCZ showing reduced transient activity as a function of reward-predicting cue compared with the HC at a group level.

During the subsequent target and/or reward receipt-related phase, right DLPFC displayed *Reward* x *Condition* x *Group* x *Time point* interaction. Post-hoc tests by focusing on inference effect (incongruent-neutral trials) during RCXT vs. RC trials revealed that for both groups, the magnitude of the interference effect did not differ depending on the presence of rewards. However, another set of post-hoc analyses on the facilitation effect (neutral-congruent) revealed that this four-way interaction was driven by greater magnitude of facilitation effect on RCXT compared to that on RC trials in SCZ while the HC did not display significantly different degree of interference effect on RC vs. RCXT. One plausible interpretation about these results is that regardless of the presence of rewards (i.e., $20), the knowledge about potential reward itself, which is hypothesized to be integrated with task-relevant information, might have led to greater facilitation effect on RCXT relative to RC. Relating to this, it is worth pointing out that there was anecdotal report from the SCZ saying that they felt more pressure to perform better and more distracted to respond this task after RC was presented compared to when they performed after RCXT cue was presented. Although only a small subset of participants completed post-scan questionnaire asking about task difficulty (HC: n=10, SCZ: n=7), both groups reportedly felt somewhat higher level of difficulty during reward vs. baseline contexts (see Supplementary Materials for post-scan analyses) ($p < .05$).

Behavior-Brain Relationships

The Relationships Between Sustained Activity in the DLPFC and Behavioral Indices of Reward Context and Cue Effects.

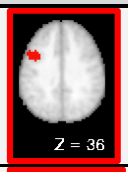
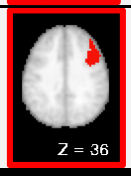
Another set of Pearson correlation analyses was conducted between behavioral indices of context effect and increased sustained activity during reward vs. baseline blocks in the bilateral DLPFC region displaying a main effect of *Reward* in the DLPFC *a priori* ROI mask analyses as presented in Table 7. There were no significant associations between sustained activity and behavioral indices of context effect (all $p > 0.10$). The correlation analysis with regions from the whole brain analysis is presented in Supplementary Materials.

The Relationship Between Transient Activity and Behavioral Indices of Reward Context and Cue effects.

To examine the relationship between transient brain activity and behavior in SCZ, I conducted voxel-wise Pearson correlation analyses using behavioral indices of context and cue effects as described above and transient neural activity from regions displaying a ROI effect of *Reward (*see Table 8A) *and* ROI interaction effect of *Reward* and *Group* (see Table 8B)

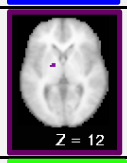
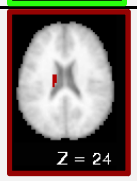
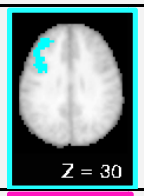
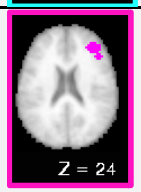
Table 7:

Relationship between Behavioral Context Effects and Sustained Brain Activity in SCZ

Sustained activity during Reward vs. baseline		Behavioral Context Effect
(B) L DLPFC (BA9: -42, 10,30)		-.007(.96)
(C) R DLPFC (BA9: 42, 16,29)		.08 (.63)

Note. L= left, R= right, DLPFC= dorsolateral prefrontal cortex.This table represents Pearson correlation *r* and *p*-value in parentheses. (A): Region displaying *Reward (reward, baseline blocks)* x *Group* interaction at a whole brain level,(B) and (C): Regions displaying a main effect of *Reward (reward, baseline blocks*) in ROI DLPFC mask analyses.

Table 8A:
Relationships between Behavioral Reward Effects and Transient Brain Activity Displaying *A Priori* ROI Reward Effect in SCZ

Regions		Behavioral Context[1]	Behavioral Cue[2]
Putamen (-19,3,1)		-.16 (.34)	-.21(.20)
Medial Globus Pallidus (-14,-8,0)		-.006(.97)	.007(.96)
Caudate Body (12,-3,14)		-.009(.95)	-.06(.70)
Caudate Body (-14,-10,19)		.07(.68)	-.03(.82)
DLPFC (-38,20,29)		.14(.39)	.20(.22)
DLPFC (37,23,29)		-.08(.62)	.03(.86)

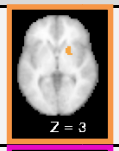
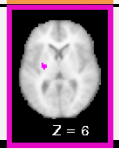
Note. DLPFC= Dorsolateral Prefrontal Cortex. This table represents Pearson correlation *r* and *p*-value in parentheses.

[1] The relation between behavioral context effect and neural activity during RCXT vs. baseline in each ROI region displaying a Reward x Time point at the average of 3 and 4 was examined using Pearson correlation analysis in SCZ (*n* =36)

[2] The relation between behavioral reward cue effect and neural activity during RC vs. RCXT in each ROI region displaying a Reward x Time point at the average of 3 and 4 was examined using a Pearson correlation analysis in SCZ (*n* =36)

Table 8B:

Relationships between Behavioral Reward Effects and Transient Brain Activity in *A Priori* ROI Regions Displaying Reward and Group Interaction Effect in SCZ

Region		Behavioral Context[1]	Behavioral Cue[2]
Ventral Striatum (21, 3, 0)		-.01 (.99)	-.18 (.31)
Lateral Globus Pallidus (-23, 13,2)		-.15 (.37)	-.29 (.09)

Note. RC =Reward-Cue, RCXT= Reward-Context. This table represents Pearson correlation *r* and *p*-value in parentheses.

[1] The relation between behavioral context effect and neural activity during RCXT vs. baseline in each ROI region displaying a Reward x Group x Time point at the average of 3 and 4 was examined using a Pearson correlation analysis in SCZ (*n*=36)

[2] The relation between behavioral reward cue effect and neural activity during RC vs. RCXT in each ROI region displaying a Reward x Group x Time point at the average of 3 and 4 was examined using a Pearson correlation analysis in SCZ (*n*=36)

Different from my prediction, for SCZ, Pearson correlation analyses revealed no significant correlation between transient context-related neural activity during reward-context vs. BCXT trials in the lateral globus pallidus and ventral striatum from a *Reward* x *Group* x time point interaction and behavioral indices of context effect on RT data (*all p* > 0.05). Also, the same pattern of non-significant correlation was observed in regions displaying ROI effect of Reward.

The Relationship Between Negative Symptoms and Both Behavioral and Neural Indices of Reward Context Effects Results (Specific Aim 3)

Behavior-Symptom Relationships

3-3) Behavior-Negative Symptom Relationship (see Table 9): Based on previous evidence about relationships between self-reported negative symptoms and reward-related neural

responses (Waltz et al., 2009), I expected to find a negative correlation between self-reported avolition and/or anhedonia and behavioral reward context effect in SCZ showing the greater negative symptom severity, the more decreased reward context effect. In contrast, I expected to find no significant correlation between negative symptom severity and reward cue effect in SCZ. However, different from prediction, I did not find association between negative symptom and behavioral indices of reward context and cue effects on RT data. There were no significant correlations between any individual difference in negative symptoms scales including the SANS, BNSS, and Chapman anhedonia scales and behavioral indices of reward and context effect for SCZ (all p >0.05).

Table 9:

Relationships between Behavioral Reward Effects and Individual Difference in Symptoms of SCZ

Symptom Measures	Behavioral Context Effect	Behavioral Cue Effect
BNSS: Total scores	-.01(.99)	.07(.70)
BNSS: consummatory[a]	-.03 (.84)	.13 (.46)
BNSS: Anticiaptory[a]	-.10 (.56)	.29 (.09)
Chapman Social Anhedonia	-.13 (.47)	.20 (.25)
Chapman Physical Anhedonia	-.20 (.25)	-.08 (.67)
SAPS: Total	.24 (.16)	.01 (.98)
SANS: Total	-.06 (.74)	.10 (.55)

Note. BNSS = Brief Negative Symptom Scale, SANS= Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.
[a]Each subtest of the BNSS was z-scored. Each value represents Pearson correlation coefficient, r and p-value in parentheses

Brain-Symptom Relationships

3-4) Sustained Brain Activity and Negative Symptom Relationships: Based on previous evidence about relationships between self-reported negative symptoms and reward-related neural responses (e.g., (Waltz et al., 2009), I expected to find negative correlation between symptoms severity and neural activity in the DLPFC during reward-context vs. baseline conditions, with patients having most severe negative symptoms showing the least increase in sustained activity in the DLPFC during reward as compared to baseline blocks.

At a group level, individuals with SCZ showed similar pattern of increased sustained activity during reward vs. baseline blocks in the bilateral DLPFC from the ROI analyses like the HC group as described above. To address the relationships between individual difference in negative symptoms and sustained activity in the same DLPFC for SCZ, I conducted Pearson correlation analyses using sustained activity in the bilateral DLPFC regions displaying a main effect of *Reward* in Figure 12. As predicted, at an individual level, patients with greater negative symptoms scores as measured by total score of the SANS tended to show a less of an increase in the sustained activity in the right DLPFC (r = -.39, p = .01) and the left DLPFC (r = -.37, p =.02). Further, I attempted to ascertain that these correlations are not just due to outliers, which may artificially inflate a correlation. Therefore, I used two commonly used procedures by examining the Cooks' Distance metric (cutoff > 1) and leverage values (cutoff > 0.5) (e.g., Spengler et al., 2010; Strigo et al., 2014;). In the left DLPFC, after excluding a potential outlier (maximum value of Cook's Distance: 1.4), the correlation failed to reach significance (r = -.17, p = .31) (see Figure 12A).

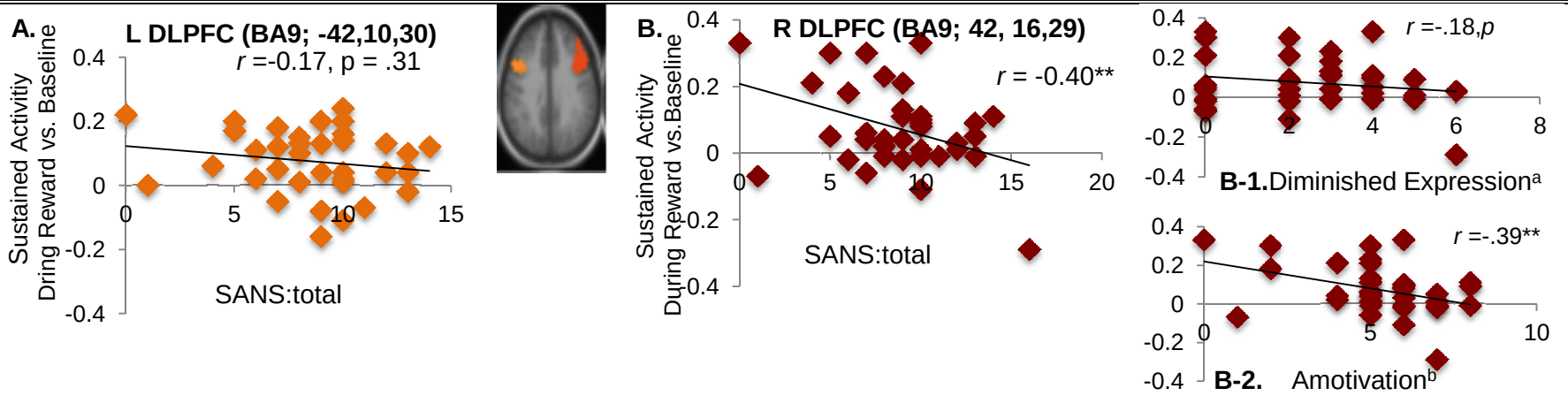
In terms of correlation between increased sustained activity during reward vs. baseline blocks in the right DLPFC and the total score of the SANS, none of the data points showed a value greater than 0.7 (Cook's Distance) and 0.2 (leverage value) and most data points had values smaller than 1.0 (Cook & Weisberg, 1982). This significant association between increased sustained activity during reward vs. baseline blocks in the right DLPFC and the

severity of SANS is presented in Figure 12 (B).

Accumulating evidence from factor analysis of analytic studies of negative symptom scales studies suggests that the SANS includes two independent factors: (1) diminished expression, which consists of affect flattening and alogia, and (2) amotivation, which consists of anhedonia, avolition, and asociality (e.g., (Blanchard & Cohen, 2006; Strauss et al., 2012). To further investigate what factor mainly led to the significant association with sustained activity in the right DLPFC described above, I conducted two separate correlation analyses using individual difference in diminished expression and amotivation subscales of the SANS, respectively (see Figure 12B-1 and 2). As presented in Figure 12B-2, the significant association between the total SANS and sustained activity in the right DLPFC is driven by the association between individual difference in amotivation and sustained activity during reward context in the right DLPFC (r = -0.39, p= 0.01). These results show that patients having greater negative symptoms, in particular, amotivation symptoms tended to show a less of an increase in sustained activity during reward vs. baseline blocks in the right DLPFC.

Figure 12:

Relationships Between Sustained Activity in the DLPFC and the Severity of Negative Symptoms in SCZ



Note. Orange and dark red region represents left and right dorsolateral prefrontal cortex, respectively. Threshold of *z*=2.05 and 13 voxels within ROI DLPFC mask

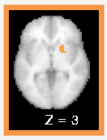
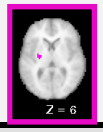
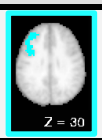
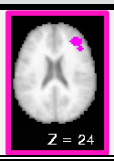
A. Non-significant correlation in the left DLPFC between sustained activity during reward vs. baseline blocks and the severity of negative symptom scores after excluding an outlier (See text for more detail). **B.** Significant correlation in the right DLPFC between sustained activity during reward vs. baseline blocks and the severity of negative symptom scores, which was mainly driven by the association between "motivation" subscales of the SANS and sustained activity during reward context in the same right DLPFC (B-2). **B-1**.[a] The sum of affective flattening and alogia subscales of the SANS, **B-2**. [b] the sum of anhedonia, avolition, asociality subscales of the SANS

** $p < 0.02$, DLPFC= dorsolateral prefrontalcortex, L = left, R= right, SANS = The Scales for the Assessment of Negative Symptoms (N.C. Andreasen, 1983b)

3-5) Transient Brain Activity and Negative Symptom Relationships: Another set of Pearson correlation analyses were also conducted to examine the relationship between transient cue-related reward context and/or cue effects and individual difference in amotivated symptom for each group in the ventral striatum and lateral globus pallidus regions displaying *Reward x Group x Time point* interactions as well as in the DLPFC region displaying *Reward x Time point* interactions. As presented in Table 10, in terms of transient neural activity, neural reward effect during RC vs. RCXT trials in the left DLPFC (-38, 20, 29) significantly correlated with individual difference in the BNSS (total scores) in SCZ (see Figure 13 for scatter plot of correlations)

Table 10:

Correlations Between Transient Activity and Individual Difference in Amotivated Symptoms in Schizophrenia

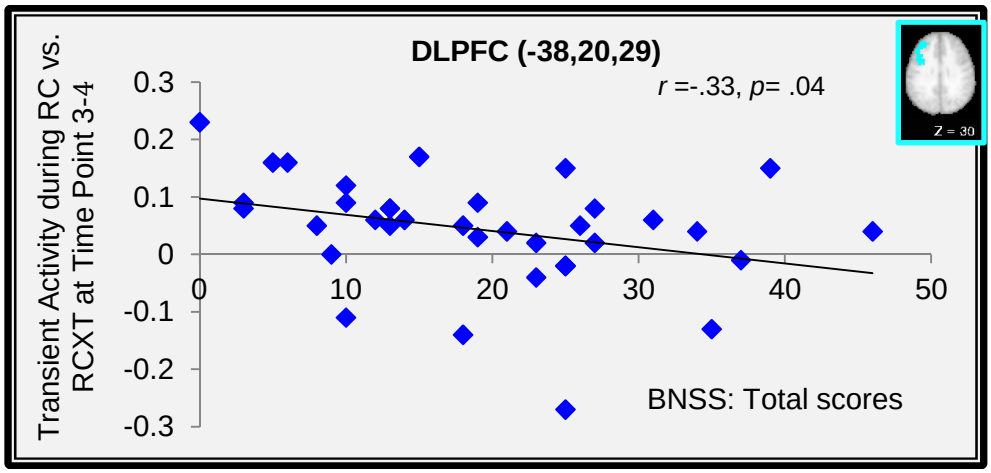
Ventral Striatum (21, 3, 0)	SAPS	SANS	BNSS	Chapman Anhedonia[a]	
Neural Context Effect[b]	-.15(.40)	.16 (.34)	.13(.45)	.19(.27)	
Neural Reward Effect[c]	.07(.67)	-.18(.29)	-.08(.64)	-.14(.41)	
Lateral Globus Pallidus (-23,13,2)	SAPS	SANS	BNSS	Chapman Anhedonia[a]	
Neural Reward Effect	.08(.66)	-.17(.32)	.20(.24)	-.18(.30)	
Neural Context Effect	-.26(.12)	.28(.10)	.28(.10)	.21(.23)	
DLPFC (-38,20,29)	SAPS	SANS	BNSS	Chapman Anhedonia[a]	
Neural Reward Effect	-.17 (.30)	-.25 (.13)	-.33(.04)	.005 (.97)	
Neural Context Effect	.04 (.79)	.20 (.23)	.24 (.15)	.08 (.63)	
DLPFC (37, 23, 29)	SAPS	SANS	BNSS	Chapman Anhedonia[a]	
Neural Reward Effect	-.11 (.49)	-.21 (.20)	-.17(.30)	.01 (.91)	
Neural Context Effect	-.14 (.39)	.02 (.87)	-.004(.98)	.10 (.54)	

Note. This table represents Pearson correlation *r* and *p*-value in parentheses in SCZ (*n* =36). Yellow indicates significant association. SAPS= The Scales for the Assessment of Positive Symptoms (N.C. Andreasen, 1983b), SANS = The Scales for the Assessment of Negative Symptoms (N.C. Andreasen, 1983b). BNSS =The Brief Negative Symptom Scale (N.C. Andreasen, 1983b). [a] As described in the Methods section, each subtest of the Chapman scale, Social and Physical anhedonia scores were z-

scored and then combined into one composite score. [b] Neural context effect was estimated by contrast of transient activity during RCXT vs. BCXT trials. [c] Neural cue effect was estimated by the contrast of transient activity during RC vs. RCXT trials.

Figure 13:

Relationship between Transient Neural Activity and Individual Difference in Negative Symptoms



Note. BNSS: Brief Negative Symptom Scale, DLPFC = Dorsolateral Prefrontal Cortex.

3-6) Comparisons of the magnitude of two Correlation Coefficients

Of note, two significant correlations between individual difference measures and brain activity were observed in the DLPFC mask from the same sample (SCZ: *n*=36). Due to the role of the DLPFC in representing and sustaining reward value during cognitive control, it is expected that the magnitude of correlation between sustained activity in the DLPFC and individual difference scores would be greater than that of correlation between transient activity in the DLPFC mask regions and individual difference scores. To test this, I examined the relationship of the two Pearson correlation coefficients in the DLPFC *a priori* mask regions as described above (see Figure 12 and Table 10 for each correlation). However, different from the expectation, Fisher's *r* to *Z* transformations indicated that the magnitude of two correlations (i.e., sustained versus transient) did not differ significantly [$Z = 0.28$, two-tailed $p = 0.77$) (Steiger, 1980).

Furthermore, to test whether the regions showing both sustained and transient effects in

the right DLPFC mask regions included overlapping voxels, I created a overlap map of the two right DLPFC regions (x:42, y:16,z: 29) and transient cue-related effects (x:37,y:23,z:29). I found no overlapping voxels. The region displaying sustained context-dependent effect was located more in the lateral portion of the DLPFC (x:42, y:16,z: 29) relative to the other DLPFC region (midlateral PFC: x:37,y:23,z:29). These results might suggest that right lateral DLPFC is more involved in *sustaining* reward-related contextual information, which is hypothesized to be integrated with task-relevant goal information during cognitive processes. To support this, emerging evidence from both primates and human neuroimaging work shows that right-lateralized portion of the DLPFC (e.g., (x:41,y:21, z:28)) is involved in encoding and sustaining information about reward-related contexts in motivationally salient situations (e.g., (Jimura, Locke, & Braver, 2010; Watanabe & Sakagami, 2007)

Relation to Negative Symptoms: Results Summary

As predicted, individuals with SCZ having greater negative symptoms, in particular, amotivation symptoms, showed less of an increase in sustained activity during reward compared to baseline blocks in the DLPFC. With regard to transient cue-related activity, more severe negative symptoms scores (i.e., the BNSS) at an individual level were significantly associated with transient cue-related activity in the DLPFC during RC (cued by "*$20*") vs. RCXT (cued by "*XX*", zero money), but not in the ventral striatum. Taken together, the current individual difference analyses could suggest the interpretation that the representation and maintenance of reward value during cognitive control, which is hypothesized to be supported by the bilateral DLPFC, might be related to patients' negative symptom.

Overall Results Summary:

In the sections above I reported three main analyses: 1) Behavioral data during a response conflict task (reward context and cue effects); 2) fMRI data during the response conflict task, and 3) The relations to negative symptoms of SCZ.

Behavioral Results: The behavioral results revealed two main patterns in SCZ: Intact reward context effect but trend-level reduced cue effect in SCZ. Contrary to our prior behavioral findings (Mann et al., 2013), current data showed that like the HC, individuals with SCZ also showed faster performance even on RCXT ("*XX*", zero money) than BCXT ("*XX*" in baseline blocks). On the other hand, individuals with SCZ showed marginally significant reduced reward cue effect relative to the HC, as evidenced by less reduction in RT from RCXT ("*XX*") to RC ("$20") within reward blocks. Regarding the HC group, I found a general enhancement of reward on cognitive performance as evidenced by faster performance on RCXT or RC relative to BCXT trials (i.e., main effect of reward, but no reward x condition interaction). These behavioral results are not consistent with (Padmala & Pessoa, 2011) showing that interference effect was reduced with rewards (i.e., reward x condition interaction effect).

fMRI Data During Response Conflict Processing: Different from our prediction, but in parallel of the behavioral findings, the neuroimaging data suggested that both groups showed increased sustained activity during reward vs. baseline blocks supported in the bilateral DLPFC. Additionally, contrary to the HC, individuals with SCZ failed to show an increase in both transient neural activity as a function of reward-predicting cues in the DA-related subcortical regions (i.e., ventral striatum) and the sustained activity as a function of reward contexts (i.e., dorsal putamen).

Consistent with prior neuroimaging work in healthy individuals suggesting the engagement of the DLPFC in reward processing (e.g., Jimura et al., 2010), we found that that interference effect (incongruent-neutral) was reduced on RC ("$20") relative to BC or RCXT

across groups. Interestingly, *Reward* x *Condition* x *Group* x *Time point* interaction in target-related activity was observed in the right DLPFC; the group of individuals with SCZ showed greater degree facilitation (neutral-congruent) even on RCXT trials relative to that on RC trials. It is possible that any knowledge about potential rewards itself (i.e. reward-related information) may have resulted in greater facilitation effect in the SCZ.

Relationships to Negative Symptoms in SCZ: I found an association between sustained and transient brain activity in the DLPFC and individual difference in negative symptoms in SCZ. The right DLPFC (BA9: +42, +16, +29) region displayed a significant association between individual differences in negative symptoms severity as measured by clinical ratings of the SANS and increased sustained neural activity during reward vs. baseline blocks. Of note, as described above, this region is the same region showing the similar pattern of greater sustained activity during reward vs. baseline blocks for both groups at a group level. Also, transient cue-related activity in the DLPFC during RC vs. RCXT was significantly associated with individual differences in total scores from the BNSS. These results suggest that patients' negative symptom may reflect a deficiency of representing and sustaining reward value during cognitive processes, which is hypothesized to be supported by the DLPFC. Given the heterogeneity of this illness, these current results pronounce the importance of individual level analysis in SCZ, which may contribute to our better understanding about specific nature of symptomatology in SCZ.

Discussion

The present study examined the effect of reward (i.e., monetary incentives) on cognitive control at both behavioral and neural levels by using a mixed state-item fMRI design. Importantly, by examining the relationship between individual difference in negative symptoms (i.e., amotivation) in SCZ and neural activity, this study elucidated specific aspects of motivated cognitive control function (i.e., sustained context-dependent vs. transient trial-by-trial reward-related activity) relating to negative symptoms of the illness. Thus, the present findings can be divided into five broad categories: 1) Behavioral reward context and cue effects; 2) Sustained context-dependent activity; 3) Transient trial-by-trial cue-related activity; 4) Transient target-related activity, 5) Relation to negative symptoms in SCZ. Lastly, I will discuss these findings together focusing on new insights underlying neural mechanism of *a*motivation in SCZ based on current data set.

1.Behavioral Reward Context and Cue effects.

Given that the response conflict processing task is a validated task showing the enhancing effect of monetary incentives on inhibitory control in healthy individuals (Padmala & Pessoa, 2011), we adopted the task and modified it for the use of mixed state-item fMRI design. To be specific, Padmala and colleagues found a significant *Reward* (reward cued by “$20”, no-reward cued by “$00”) x *Condition* (or *Congruent* called in their work; congruent, incongruent, neutral) interaction as well as a main effect of *Reward*. However, the current study did not find a significant *Reward* x *Condition* interaction effect. Rather, there was only a significant main effect of *Reward* (baseline, RCXT, RC), suggestive of general effect of monetary incentives on enhancing speed of performance across groups.

It is possible that one explanation for the weak or non-significant -*Reward* by *Condition* behavioral effects in present study is that the participants found the task someone easier than in the (Padmala & Pessoa, 2011) study. In terms of accuracy, overall performance in current study (accuracy in the HC: 0.92~0.99) was somewhat better compared to that in Padmala and

colleagues (approximate range of accuracy: 0.86~0.97). As presented in Supplementary Table 1, self-reported task difficulty measured in post-scan questionnaire also indicated that a subset of participants (*n*=17) felt that this task was very easy. Thus, the comparison of accuracy data between two studies seems to be suggestive that the weak or non-significant *Reward* by *Condition* interaction effect may be due to relatively different difficulty level given individual sample in independent studies. It is required to use more challenging conflict processing paradigm, which should be designed to be sensitive to different levels of difficulty depending on the sample recruited in the future studies.

One of the primary aims of this study was to replicate our prior behavioral findings using the same response conflict processing task paradigm. Our prior research (Mann et al., 2013) had suggested a reduced reward context effect in SCZ at a behavioral level, but an intact reward cue effect. In contrast, in present study, individuals with SCZ showed an intact reward context effect, but some evidence for a reduced incentive cue effect. The discrepancy between two studies may be due to methodological differences and heterogeneity of the illness between the studies. The clear difference in current study from (Mann et al., 2013) is that present study used a modification of the response conflict task for the use of mixed state-item fMRI design. Thus, current study included jittering period ranging from 2 to 6 seconds between the presentation of cue and target phase while our prior behavioral study did not include such jittering period; target phase was followed right after the presentation of each cue. Thus, it is possible that due to such jittering period after cue presentation, participants had some time to prepare for upcoming stimuli, which in turn may have resulted in relatively intact pattern of reward context effect for the SCZ in current study.

Of note, in current study, individuals with SCZ showed considerable individual variations relative to HC. In terms of RT data, as described above, Levene's Test showed that the *SD* in SCZ was significantly larger than the SD in HC, suggesting greater individual variation in SCZ relative to HC. These findings support the importance of examining analyses of individual

differences as a function of symptoms in schizophrenia, as compared to only group analyses. Of note, individuals with SCZ included in current study had slightly higher level of negative symptoms (total SANS: 8.77) compared to those in our prior study (total SANS: 7.78). Thus, the heterogeneity of symptoms and considerable variations of behavioral performance in SCZ (e.g., (Goldstein, Beers, & Shemansky, 1996; Manoach, 2003) may contribute to discrepancy across behavioral studies depending on compositions of the sample recruited in independent studies. Thus, I also examined behavioral performance in relationship to individual differences in negative symptoms. I will discuss current findings relating to individual difference in negative symptoms, in particular, amotivation in the next section below.

In summary, I predicted a specific pattern of behavioral deficits, that is, reduced reward context effects in SCZ, consistent with prior work (Mann et al., 2013). Contrary to my prediction, I found no diagnostic group difference in terms of behavioral reward context effect. However, the lack of diagnostic group differences in one sense provides an opportunity to examine neural findings in a situation not confounded by different behavioral performance between SCZ and HC groups. Within this context, I will discuss neuroimaging data in the next section below.

2. Sustained Context-dependent Component of Motivated Cognitive Control

The early line of investigations into the effect of reward on cognitive control in healthy populations tended to focus on examining transient trial-by-trial reward-related cue effects on cognitive control, as described in the Introduction. However, updating reward value in a transient manner may not be sufficient to maximize reward outcomes. Accumulating evidence converges to suggest that keeping goals active in a sustained manner via proactive control in the DLPFC facilitates preparatory processing and in turn, leads to enhanced cognitive performance (e.g., (Chiew & Braver, 2013; Jimura et al., 2010; Locke & Braver, 2008). Importantly, different from Padmala and Pessoa (2011), the mixed state-item fMRI design used in current study enabled to me to examine both sustained context-dependent and transient cue-related components of motivated cognitive control; (Padmala & Pessoa, 2011) included only

reward conditions in which reward-cue (*$20*) and no-reward cue (*$00*) were used.

As described in the Introduction above, given the hypothesis that patients' core *non-emotional* context processing deficits are due to a disturbance in DLPFC function (e.g., (Barch et al., 2001), I hypothesized that individuals with SCZ would show reduced sustained activity during reward context in the DLPFC compared with HC. However, contrary to my prediction, but paralleling present behavioral findings, individuals with SCZ showed an intact pattern of greater sustained activity in the bilateral DLPFC during reward vs. baseline contexts, as did the HC. Interestingly, a *Reward* x *Group* interaction effect was identified in the subcortical regions (i.e., dorsal striatum) where patients showed blunted sustained activity during reward contexts.

Consistent with prior neuroimaging work in healthy individuals suggesting the role of the right lateral PFC on reward processing (e.g., (Jimura et al., 2010; Locke & Braver, 2008), the DLPFC displayed greater sustained activity during reward versus baseline blocks in both HC and individuals with SCZ. In the whole brain analyses presented in the supplement, we did find that the individuals with schizophrenia showed a significant reduction in sustained activity in the orbital frontal cortex (OFC), but not the DLPFC. This was not a finding that I predicted *a priori*. However, accumulated evidence from non-human primates (reviewed in (Schultz, Tremblay, & Hollerman, 1998) and healthy neuroimaging studies (reviewed in (Hollerman, Tremblay, & Schultz, 2000; McClure, York, & Montague, 2004) points to the fact that several cortical regions including the OFC and DLPFC and subcortical neural structures (e.g., the BG) play a distinct role during reward processing depending on each phase of reward processing. To be specific, the OFC is implicated in computing the nature of reward value, serving to hold the information in working memory, which in turn facilitates goal-directed responses (Wallis, 2007). The DLPFC system is considered to integrate reward value obtained from other projections from the OFC and other PFC regions and making plan to obtain valued outcomes.

Our findings showing reduced sustained activity in the OFC during reward context in SCZ may indicate that patient's are impaired in computing and maintaining mental

representations of reward value necessary to regulate upcoming behavior. A number of previous studies in SCZ have suggested that these functions are impaired and associated with altered OFC function and altered reinforcement learning (Kring & Barch, 2014; Strauss, Waltz, & Gold, 2014). Prior research using reinforcement learning paradigms has consistently suggested that individuals with SCZ may have impairments in reward value computation due to abnormal function of the OFC and BG systems, as evidenced by their difficulty making rapid behavioral adjustment according to explicit feedback. For example, in (Gold et al., 2012)'s behavioral work using a probabilistic reinforcement learning paradigm, individuals with SCZ showed their difficulty in choosing a stimulus previously associated with a higher reward value (i.e., monetary incentives), which reflect patients' deficiency to use explicit representation of feedback to make trial-by-trial behavioral adjustment when choosing a response (Waltz, Frank et al., 2011; Waltz & Gold, 2007). In particular, individuals with SCZ with higher negative symptoms tended to show a less tendency to learn from monetary gains relative to learning loss-avoidance. At a neural level, these behavioral reinforcement learning deficits in SCZ are thought to be associated with abnormal responses in the OFC and BG systems (e.g., (Waltz & Gold, 2007; Waltz et al., 2013), reviewed in (Strauss et al., 2014). However, these ideas are speculative, especially given that we did not find a behavioral difference in reward context effects.

The BG *a priori* ROI analysis revealed blunted sustained activity during reward vs. baseline contexts in SCZ relative to HC in the dorsal striatum. The basal ganglia complex is another major component of the neural circuitry that is involved in reward processing (reviewed in (Delgado, 2007). The striatum is known to be a major input structure of the BG, which is considered to represent a neural circuit responsible for mediating goal-directed behavior by receiving synaptic input from cortical and subcortical afferents (Kimura et al., 2003; Samejima et al., 2005). Specifically, the dorsal striatum, which consists of the caudate nucleus and the putamen, receives extensive projections from the DLPFC as well as other frontal regions.

The dorsal striatum is thought to be one of motivation-sensitive regions of which neural

activity is modulated by reward context (Delgado, Locke, Stenger, & Fiez, 2003; Delgado, Stenger, & Fiez, 2004). Specifically, neural activity in the dorsal striatum is thought to be affected by both magnitude of rewards and valence of stimulus (reward versus punishment) (e.g.,(Nieuwenhuis et al., 2005). For example, (Katsyri, Hari, Ravaja, & Nummenmaa, 2013) found that wins (monetary gain) versus losses evoked significantly greater transient trial-by-trial activity in the dorsal striatum in healthy individuals. In a similar vein, current study extended this line of work by showing that the HC group showed increased sustained activity in the dorsal striatum during reward compared to baseline context. In contrast, individuals with SCZ showed blunted sustained activity in the same region during reward context. Taken together, these results suggest abnormal function of the OFC and dorsal striatum system, potentially reflecting altered maintenance reward value during cognitive control in SCZ. However, again, we did not see evidence in the current study for behavioral differences at the group level in the reward context effect. It is possible that these would be more apparent in a more challenging task, but that is a speculation that awaits empirical testing.

3. Transient Reward-Cue-related Activity

Reward processing is not a unitary concept. Rather, it consists of several dissociable constructs including reward prediction, reward receipt, and feedback phases of reward processing. Contrary to the traditional notion that motivational impairments in SCZ may come from their inability to experience pleasure (e.g., Meehl (1989)), an increasing number of behavioral and neuroimaging studies converge to suggest that amotivation in SCZ may come from a specific phase of DA-driven reward processing (e.g., dysfunctional reward anticipation, reinforcement learning deficits). For example, regardless of medication status, several studies found less ventral striatal activation during the presentation of reward-predicting cues in SCZ relative to HC (e.g., (Esslinger et al., 2012; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006). In contrast, there is neural evidence showing that individuals with SCZ displayed intact pattern of increased transient activity at the receipt of reward, particularly with no cognitive

demand (e.g., action selection, action execution) (e.g., (Dowd & Barch, 2012). Importantly, patients' severe negative symptom severity has been relatively consistently found to be associated with blunted VS activity during reward-predicting cues (e.g. (Dowd & Barch, 2012). Consistent with this line of reasoning, in the current study, individuals with SCZ showed blunted VS activity during reward-predicting cues while HC showed increased neural activity as a function of reward in the VS.

Consistent with prior neuroimaging work in healthy adults, the present study closely replicated the pattern of increased transient neural activity as a function of reward in the bilateral DLPFC and subcortical brain regions including the putamen and caudate body across groups. However, a *Reward* x *Group* interaction effect was identified in several subcortical regions. HC showed increased transient activity during RC ("*$20*") versus RCXT ("*XX*" in reward blocks) or baseline ("*XX*") in the VS and lateral globus pallidus. In contrast, individuals with SCZ showed blunted neural activity regardless of reward-predicting cues in the same subcortical regions.

The VS is a part of a OFC-limbic circuit subserving emotional and reward-related processing and thought to be involved in processing both primary (e.g., pleasant sensory outcomes: taste, smell, sights) and secondary rewards (i.e., monetary incentives) (Aharon et al., 2001; Haber & Knutson, 2010; Knutson, Fong, Bennett, Adams, & Hommer, 2003; Rolls et al., 2003). The current findings of reduced VS and globus pallidus activity is consistent with previous work showing blunted VS activity during reward anticipation in SCZ regardless of antipsychotic medication status. For example, a number of neuroimaging studies using a variant of a monetary incentive delay task found less ventral striatal activation during the presentation of reward-predicting cues in unmedicated individuals with SCZ (Esslinger et al., 2012; Ghuman et al., 2013; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wustenberg, et al., 2006; Schlagenhauf et al., 2009) as well as in those with typical antipsychotic mediations (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Kirsch et al., 2007; Schlagenhauf et al., 2008). These patterns of abnormal neural activity during reward

anticipation is consistent with prior studies showing abnormal striatal activity during reward anticipation (e.g., (Esslinger et al., 2012; Ghuman, van den Honert, & Martin, 2013; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006), but is in contrast to relatively intact patterns of striatal activity in response to the receipt of reward in many in previous studies (e.g., (Dowd & Barch, 2012); see (Kring & Barch, 2014; Strauss et al., 2014) for recent literature review). Thus, activity during reward anticipation may represent a specific biological target relating to patients' amotivation.

4. Transient Target-related Activity

In the past several decades, there is a surge of research interests regarding how cognitive control interacts with motivation in the field of basic cognitive neuroscience (e.g., (Chiew & Braver, 2014; Locke & Braver, 2008; Padmala & Pessoa, 2011). A rich literature from both behavioral and neuroimaging work in healthy individuals points to the findings that task-relevant goal representation is enhanced in motivationally salient situations via top-down control (e.g., (Sescousse, Li, & Dreher, 2014; Watanabe, Kodama, & Hikosaka, 1997; Watanabe & Sakagami, 2007) as confirmed by several meta-analytic reports (e.g.,(Liu, Hairston, Schrier, & Fan, 2011; Sescousse, Caldu, Segura, & Dreher, 2013). This effect is called "motivated cognitive control" (e.g., (Mann et al., 2013), as described in the Introduction. Importantly, the enhanced task-relevant goal representation in reward contexts is thought to facilitate cognitive processing especially when demands on cognitive control are high (e.g., conflict-related responses on incongruent trials) (e.g., (Padmala & Pessoa, 2011).

Conflict processing presumably engendered by incongruent trials requires a higher demand on cognitive control function to inhibit task-irrelevant stimuli to generate task-relevant response (reviewed in Carter & van Veen, 2007). During the target phase, consistent with previous literature about cognitive control in healthy populations (e.g.,(Padmala & Pessoa, 2011), we closely replicated prior findings by showing that several cortical and subcortical brain

regions thought to be involved in cognitive control function (i.e., inferior frontal gyrus, cingulate gyrus, precuneus) showed greater activity on incongruent trials than congruent or neutral trials across groups from a whole brain analysis.

More importantly, we were interested in determining whether the presence of rewards moderated these conflict-related differences in brain activity. Prior work has suggested the role of the DLPFC in representing and integrating reward value to modulate cognitive control presumably through enhanced representation of reward value (e.g., (Ballard et al., 2011; Engelmann et al., 2009; Locke & Braver, 2008). Thus, it was expected that individuals with SCZ would show impaired DLPFC-driven cognitive control function during reward contexts compared with the HC. Relating to this, *Reward x Condition x Group x Time poin*t interaction was identified in the right DLPFC (x:30, y: 28, z: 32) where for both groups, the magnitude of interference effect (incongruent-neutral trials) did not differ as a function of rewards. Rather, the four-way interaction was driven by different degrees of the facilitation effect only in SCZ; the SCZ showed greater magnitude of facilitation effect (neutral-congruent trials) on RCXT than that on RC trials. This is not a finding that I expected *a priori*. It might be that regardless of the presence of rewards, general knowledge about potential rewards itself in motivationally salient situations may have greater impact to the SCZ, which may have resulted in greater facilitation effect on the RCXT than that on RC trials.

The DLPFC is a core component of a brain network that supports cognitive control function to regulate goal-directed behavior (e.g., (Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). There is a very robust literature suggesting that individuals with SCZ have deficits in the active maintenance of *non-emotional* context information in working memory, which may be necessary to regulate upcoming responses towards goal-oriented behavior, as referred to as context processing (Cohen & Servan-Schreiber, 1992) and see (Lee & Park, 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009) for a meta-analytic summarizing evidence). More recently, it has been increasingly

considered that motivational contexts (i.e., reward conditions) as well as reward-related external cues may enhance cognitive performances presumably via enhanced maintenance of reward information in the DLPFC (e.g., (Jimura et al., 2010). In current study, group analyses revealed that different from my expectations, the SCZ showed an intact pattern of greater sustained context-dependent and transient cue-related DLPFC activity as a function of motivational factors like the HC. In this context, I will discuss what components of neural activity (i.e., sustained context-dependent vs. transient cue-related DLPFC activity) are more closely related to patient's negative symptoms at an individual level in the next section below.

Behavior-Brain Relationships:

In present study, I attempted to elucidate specific behavioral indices of reward processing and the corresponding neural responses. I predicted that behavioral indices of reward context and cue effects would be associated with the corresponding BOLD signal changes in the DLPFC and BG. Contrary to my predictions, there was no statistically significant correlations between behavioral indices of reward context and/or cue effects and corresponding neural responses in the DLPFC and BG ROIs regions. This may be due to a ceiling effect given consistently high performance across condition-type. As noted above, many participants felt this task was relatively easy for them (see self-reported post-scan questionnaire results in Supplementary Materials) and average accuracy rate was approximately 97% and 95% for HC and SCZ, respectively. Thus, there is a possibility that relatively high accuracy rates could have masked true correlation between behavior and brain activity.

5.Relation to Negative Symptoms in SCZ

In addition to examining reward-related cue activity in SCZ, another critical component of the present investigation was to examine specific neural mechanisms closely relating to amotivation (i.e., anhedonia and/or avolition) in SCZ. I did not find any significant relationships between individual differences in self-report or clinical ratings of negative symptoms or anhedonia (i.e., the SANS, the BNSS) and either behavioral index of the reward context or cue

effects. The non-significant relationships between individual differences in self-report or clinical ratings of negative symptoms or anhedonia and either behavioral index of the reward context or cue effects are consistent with prior work (Mann et al. (2013). Considering the relatively reasonable sample of participants for SCZ (*n*=36), it is unlikely that non-relationship to negative symptoms is due to low power. I had also predicted that individual difference in anhedonia and/or amotivation in SCZ would be negatively associated with sustained activity in the DLPFC during reward vs. baseline conditions. Consistent with my hypothesis about sustained activation, patients with greater amotivation showed reduced sustained activity during reward vs. baseline blocks in the right DLPFC. Of note, the right DLPFC is the same brain region in which patients with SCZ showed similar pattern to HC of greater sustained activity during reward vs. baseline contexts at a group level. It should be noted that individual differences in diminished expression subscales of the SANS were not found to be significantly associated with sustained activity during reward blocks in the same DLPFC. Although this finding should be considered provisional and requires further study, motivational impairments in SCZ may reflect their inefficiency of representing and *sustaining* reward value during their cognitive control function potentially due to abnormal DLPFC-medicated context processing.

In terms of the association between transient cue-related activity and negative symptoms in SCZ, given prior work showing a negative association between individual difference in anhedonia and transient cue-related activity in the ventral striatum (e.g.,(Dowd & Barch, 2012), I predicted that individuals with SCZ having greater anhedonia and/or amotivation would show a less of transient cue-related activity in the ventral striatum during RC ("*$20*") vs. RCXT ("*XX*") within reward blocks. Different from my prediction, I did not find any significant correlation between specific aspects of anhedonia as measured by the BNSS and neural activity in the ventral striatum. However, transient cue-related activity during RC vs. RCXT in the DLPFC showed a significant association with individual differences in BNSS total scores.

Considering converging evidence suggesting dissociable neurobiological mechanism of

“anticipatory” and “consummatory,” “liking” aspects of anhedonia (amotivation) (reviewed in (Kring & Barch, 2014; Strauss et al., 2014), I attempted to examine neural mechanism relating to specific aspects of anhedonia by using several individual difference measures (i.e., the BNSS. and sustained activity during reward contexts in the DLPFC. However, I did not find any significant correlation between specific aspects of anhedonia as measured by the BNSS and sustained activity during reward contexts in the DLPFC. It may be due to limited number of items in the BNSS for each “anticipatory” (one item) and “consummatory” (two items) aspects of negative symptoms in SCZ. Additionally, the BNSS is a relatively new, and thus less well-validated clinical scale (based on the 2005 NIMH recommendation) relative to the SANS and PNSS. Thus, it may be required to increase statistical power by adding enough number of items for each “anticipatory” and “consummatory” aspects of negative symptoms.

6. Overall Limitations and Future Directions

Despite crucial findings relating to amotivation in SCZ, as with any study, the present study has several limitations. The primary limitation was that most patients with SCZ recruited in this study were taking dopamine receptor blocking antipsychotic medications, which may influence reward-related neural responses (McCabe, Huber, Harmer, & Cowen, 2011). Antipsychotic medications have been shown to affect reward-related neural responses in healthy adults (Abler, Erk, & Walter, 2007; Mathews et al., 2012) and patients with SCZ (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Nielsen et al., 2012). Thus, I cannot exclude a possibility that current results may have been affected by antipsychotic medications. However, to my knowledge, there is no empirical study reporting significant correlations between estimation of antipsychotic drug dose and any negative symptom ratings and/or neural responses to reward-predicting cues [e.g., (Dowd & Barch, 2012; Gold et al., 2012; Mann et al., 2013; Waltz et al., 2010). Despite a potential impact of antipsychotic medication on reward processing, importantly, it is highly unlikely that current findings are purely related to antipsychotic action, as motivational deficits as evidenced by abnormality of reward-related

neural responses have been observed even in unmedicated patients with first-episode SCZ (Esslinger et al., 2012; Schlagenhauf et al., 2009)) and individuals at prodromal phase o f the illness (Piskulic et al., 2012; Yung & McGorry, 1996).

Another limitation is that I cannot exclude a possibility that reward context effect might be driven by arousal differences across blocks. Relating to this, there is a debate regarding the reward specific versus salience debate of the striatum. For example, it is proposed that the striatum is involved in coding stimulus saliency as well as reward processing ((Zink, Pagnoni, Martin, Dhamala, & Berns, 2003; Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004). However, there is still evidence that the striatum is not merely mediating stimulus salience as evidenced by a deactivation in the ventral striatum in response to the omission of an unexpected reward (Knutson et al., 2001; S. M. McClure, Berns, & Montague, 2003; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Pagnoni, Zink, Montague, & Berns, 2002). To support this, empirical data suggests that when participants were asked to complete subjective arousal ratings using a Likert-type scale after the presentation of reward-relating cues in the scanner, individuals with SCZ showed similar patterns of arousal as the HC did; both groups rated themselves as more anxious after loss cues than after either gain cues or neutral cues (Waltz et al., (2010)).

Future Directions:

Based on several limitations pointed out above, I would like to suggest several things to be addressed in future research. First of all, as described in the Introduction, an increasing amount of neurobiological evidence converges to suggest that the anticipatory and consummatory phases of reward processing are distinctive. In current task paradigm, we could not disentangle reward outcome-related responses from target-related responses. To address this, is would be necessary to use a paradigm that temporally dissociates the response phase from the feedback phase. Further, in order to elucidate specific neural mechanism that is closely related to each distinctive aspects of amotivation symptom (i.e., anticipatory versus

consummatory of amotivation), it is necessary to develop and use clinical measures of negative symptoms, aiming to differentiate anticipatory versus consummatory aspects of amotivation with better psychometric properties. In present study, I attempted to address this issue by including a clinical rating scale, the BNSS and several self-report measures of anhedonia symptoms (i.e., the Chapman Social and Physical Anhedonia Scales). However, I could not find significant association between neural responses during anticipatory phase and individual difference in anticipatory subscale of the BNSS, which only includes one item about expected pleasure from future activities. Thus, it is crucial to increase discriminating power of the BNSS by increasing more items for distinctive consummatory versus anticipatory subscales of amotivation.

In the context of increased interests towards elucidating the neural mechanism underlying amotivation in SCZ in recent years, and necessity of developing better negative symptom measures (reviewed in (Kring & Barch, 2014), the Clinical Assessment Interview for Negative Symptoms (CAINS; (Kring, Gur, Blanchard, Horan, & Reise, 2013) has recently finalized its development and psychometric validation (Horan, Kring, Gur, Reise, & Blanchard, 2011). The CAINS is a newly developed clinical rating scale designed to assess negative symptoms across multiple domains, which contains one tapping emotion expression (four items) and the other measuring motivation and expected pleasure (nine items) (Kring et al., 2013). Thus, the CAINS is a promising clinical rating tool that can be used in future study aiming to differentiate specific mechanisms associated with “anticipatory” versus “consummatory” aspects of negative symptoms in SCZ.

In present study, I conducted hypothesis-driven *a priori* Region-of-Interest Analyses by focusing on the role of the DLPFC and striatum during reward processing in SCZ. Although current study provided neural evidence suggesting the relevance of individual difference in amotivation with neural activity in the DLPFC during reward contexts in SCZ, functional connectivity abnormality within reward network of brain regions would provide another piece of crucial evidence that would contribute to completing a “big picture” about neural mechanisms

underlying amotivation in SCZ. Relating to this, a very rich literature in reward processing shows the involvement of a brain network of cortical-subcortical regions in healthy individuals, with quantitative evidence from meta-analytic studies (e.g., (Engelmann et al., 2009; Liu et al., 2011; Sescousse et al., 2013)). To be specific, both non-human primate and healthy human imaging work points to the findings that both several regions in the DLPFC and OFC, and striatum are at the center of reward-related brain network (e.g.,(Balleine, Delgado, & Hikosaka, 2007; Delgado, 2007; Jimura et al., 2010; Wallis & Miller, 2003). More importantly, neuroanatomical evidence shows that most of cortex including the DLPFC projects to the striatum (e.g., (Rosenbloom, Schmahmann, & Price, 2012). That is, the dorsal striatum receives major projections from the DLPFC while the ventral striatum receives extensive projections from the ventral PFC including the OFC (reviewed in (Delgado, 2007; Gottfried, 2011). Therefore, future studies examining functional connections of the DLPFC and striatum during reward processing might elucidate different pattern of reward-related neural responses between diagnostic groups. Along with functional and structural connections of the frontostriatal regions, it is speculated that individuals with SCZ may show a breakdown in connectivity of the DLPFC with striatum (e.g., (Anticevic, Repovs, Krystal, & Barch, 2012; Quan et al., 2013)) presumably due to their inefficiency of top-down control. For example, it is possible that the DLPFC-striatum connectivity during RCXT versus baseline might be reduced in SCZ relative to HC considering both structural and functional neuroimaging evidence suggesting the abnormal connectivity of the DLPFC and other subcortical regions (i.e., the striatum) in SCZ

7. General Conclusions

This study was designed to examine the effect of reward using monetary incentives on cognitive control in SCZ at both behavioral and neural levels. By examining reward context and cue effects at both behavioral and neural levels, this study attempted to elucidate specific neural mechanism underlying amotivation in SCZ. At a behavioral level, individuals with SCZ showed

intact pattern of reward context effect like the HC, while they showed somewhat reduced reward cue effects relative to HC. At a neural level, in terms of sustained context-dependent component of motivated cognitive control, individuals with SCZ showed an intact pattern of greater sustained activity during reward context in the bilateral DLPFC like the HC. However, individual difference analyses revealed that patients having greater amotivation displayed more reduced *sustained* context-dependent as well as *transient* trial-by-trial cue-related activity in the DLPFC as a function of rewards. Taken together, although these findings should be interpreted with caution and replicated in further study, current study provided neural evidence suggesting patients' DLPFC function during reward processing is closely related to amotivation in SCZ at an individual difference level.

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Supplementary Materials

Post-Scan Questionnaire of Analysis

Self-reported Motivation: A Repeated-measures of ANOVA on self-reported motivation was conducted to make sure that motivational states were manipulated by monetary incentives. There was a significant main effect of *Motivation* [F (2,30) = 4.78, p= .01, η^2_p= .24]. Neither main effect of *Group* [F (1,15) = .68, p = .42, η^2_p= .04] nor *Motivation* (RCXT, RC, B) x *Group* interaction [F (2,30) = .04, p = .95, η^2_p= .003] was identified. Three post-doc paired t-tests (RC-baseline, RCXT-Baseline, RC-RCXT) were conducted to follow up a main effect of *Motivation*. Both groups reported higher motivation on RC ("$20") than baseline ("XX") [paired t-test (16)=2.74, p=0.01] and on RC ("$20") relative to RCXT ("XX") within reward blocks [paired t-test (16)=2.63, p= .018]. However, there was no difference in self-reported motivation between RCXT and baseline [paired t-test (16)= 0.23, p= .87].

Self-reported Task Difficulty: another repeated-measures ANOVA on difficulty was conducted. There was a significant main effect of *difficulty* [F (1,15) = 5.38, p= .03, η^2_p= .26]. Neither main effect of *Group* [F (1,15) = .008, p = .92, η^2_p= .001] nor *Difficulty* (reward, baseline blocks) x *Group* interaction [F (1,15) = 2.25, p = .15, η^2_p= .13] was identified. Post-hoc paired t-test on difficulty between reward and baseline blocks indicates that both groups felt somewhat higher level of difficulty on reward than baseline blocks [paired t-test (16)=2.52, p= .02].

Supplementary Table 1:

Post-Scan Questionnaire of Analysis

Task Blocks	HC (n=10)	SCZ (n=7)
Baseline Blocks		
How motivated were you on this	5.50 (1.43)	5.00 (1.00)
How difficult was this task, in general?	2.0 (1.69)	2.71 (1.70)
Reward Blocks		
How motivated were you on “XX” trials?	5.50 (1.58)	5.14 (0.89)
How motivated were you on “$20” trials?	6.20 (0.91)	5.85 (0.69)
How difficult was this task, in general?	4.0 (2.40)	3.14 (1.57)

Note. Higher value represents higher level of motivation and difficulty ranging from 1 (very unmotivated, very easy) to 7 (very motivated, very difficult).

Whole Brain Analyses:

Sustained Context-dependent Component of Motivated Cognitive Control

Whole-Brain Effects of Reward: The voxel-wise ANOVA as described above was conducted at a whole brain level to examine exploratory effects. A significant main effect of *Reward* (reward, baseline blocks) was identified in a number of regions in the middle and inferior frontal gyrus and parietal lobe including the precuneus (see Table S2 for exact coordinates of each region and the pattern). To follow up, I conducted paired *t*-tests to compare sustained activity during reward vs. baseline blocks on each region showing a main effect of *Reward* across groups. As shown in Figure S1, most regions showed greater sustained activity during reward than baseline blocks.

Whole-Brain Effects of Group: No region displayed a main effect of *Group* at a whole brain level.

Whole-Brain Interaction of Reward and Group: A significant *Group* x *Reward* interaction was also found in the right OFC (*x*:32, *y*: 33, *z*: -5) and right claustrum (*x*:22, *y*: 27, *z*: 2) in the whole-brain analysis (see Table S3 for exact coordinates of each region and the pattern shown in each region). To further identify the source of *Reward x Group interactions* effects, I conducted post-hoc paired *t*-tests to compare sustained activity during reward vs. baseline blocks for each group. As presented in Figure S2 below, the HC showed greater activity during reward vs. baseline blocks in all regions displaying a *Reward x Group* interaction [the right OFC (*x*: 32, *y*: 33, *z*: -5), paired *t*-test (26)=3.52, *p* =.002); the right claustrum (*x*:22, *y*: 27, *z*: 2), paired *t*-test (26)= 3.51, *p* =.002]. In contrast, individuals with SCZ failed to show an increase of sustained activity as a function of reward context: a group of SCZ showed greater activity in baseline relative to reward blocks in the right OFC [(*x*:32, *y*: 33, *z*: -5): paired *t* –test (35)= -2.57, *p* = .01] and the right claustrum at a trend level [(*x*:22, *y*: 27, *z*: 2), paired *t* -test (35)= -2.02, *p* =.05].

Supplementary Table 2:

Activated and Deactivated Regions Displaying a Main Effect of Reward in a WB Analysis

Region of Activation	BA	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]
			x	*y*	*z*		
Activation							
Precentral Gyrus	9	147	42	4	34	4.42	R > B
Middle Frontal Gyrus	8	20	38	28	43	3.89	R >B
Middle Frontal Gyrus	9	67	48	25	31	4.64	R >B
Inferior Frontal Gyrus	9	19	-46	5	32	3.95	R >B
Middle Temporal Gyrus	22	80	52	-41	5	4.49	R > B
Declive		87	-11	-77	-20	5.35	R > B
Pyramis		120	-25	-63	-30	5.12	R > B
Superior Parietal Lobule	7	151	30	-61	53	4.88	R > B
Precuneus	7	111	-20	-64	44	4.41	R > B
Inferior Semi-Lunar Lobule		62	-12	-76	-35	5.02	R > B
Inferior Parietal Lobule	40	151	43	-49	46	4.30	R > B
Inferior Parietal Lobule	40	102	-35	-55	45	4.50	R > B
Precuneus	7	131	15	-65	41	4.48	R > B
Pyramis		62	14	-75	-30	4.74	R > B
Inferior Parietal Lobule	40	21	-51	-45	48	4.015	R >B
Culmen		22	-34	-49	-30	4.65	R >B
Cerebellar Tonsil		21	3	-54	-34	3.77	R >B
Deactivation							
Superior Temporal Gyrus	40	74	49	-48	20	4.46	B > R
Fusiform Gyrus	37	126	-41	-61	-13	5.32	B > R
Fusiform Gyrus	37	40	-41	-46	-17	4.70	B > R
Fusiform Gyrus	19	125	-30	-72	-14	5.46	B > R
Middle Temporal Gyrus	39	26	45	-59	9	3.88	B > R

Region of Activation	BA	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]
			x	*y*	*z*		
Inferior Occipital Gyrus	19	44	40	-74	-2	4.04	B > R
Cuneus	19	113	-27	-74	27	4.88	B > R
Fusiform Gyrus	37	86	45	-54	-9	4.62	B > R
Middle Occipital Gyrus	19	67	35	-80	18	4.36	B > R
Middle Occipital Gyrus	19	34	-25	-87	14	4.36	B > R
Precuneus	19	158	28	-73	33	4.55	B > R
Declive		119	31	-66	-14	5.02	B > R
Culmen		94	-27	-54	-16	5.02	B > R
Culmen		74	32	-48	-17	4.85	B > R

Note. B= baseline, R= reward, R = right, L = left, HC = healthy controls, SCZ = individuals with schizophrenia, WB= Whole brain, *Z* values represent mean activation across the region.
[a] post-doc paired *t*-tests between reward and baseline blocks across groups were performed.

Supplementary Table 3:

Sustained Context-dependent Activity: Reward x Group Interaction Effect

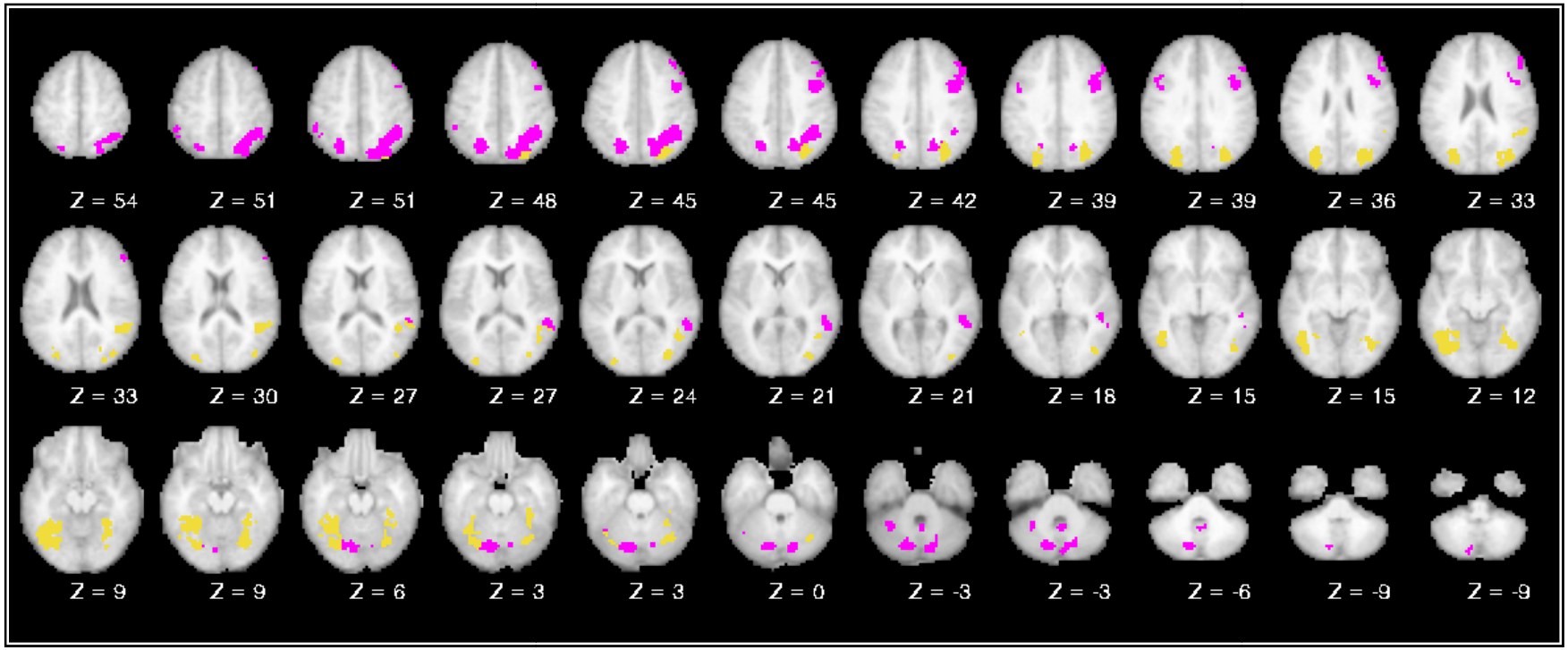
Effect	BA	Region of Activation	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]
				x	*y*	*z*		
Reward x Group	47	Orbitofrontal Cortex	13	32	33	-5	4.10	SCZ: B > R HC: R > B
		Claustrum	20	22	27	2	3.58	SCZ: B > R HC: R > B

Note. B= baseline, BG =basal ganglia, DLPFC =dorsolateral prefrontal cortex, HC = healthy controls, R= Reward, ROI = region of interest, SCZ = individuals with schizophrenia, WB = whole brain analysis. *Z* values represent mean activation across the region.

[a] Post-hoc paired *t*-tests or independent *t*--tests were conducted (all $p < .05$). See text for detailed post-hoc analyses.

Supplementary Figure 1:

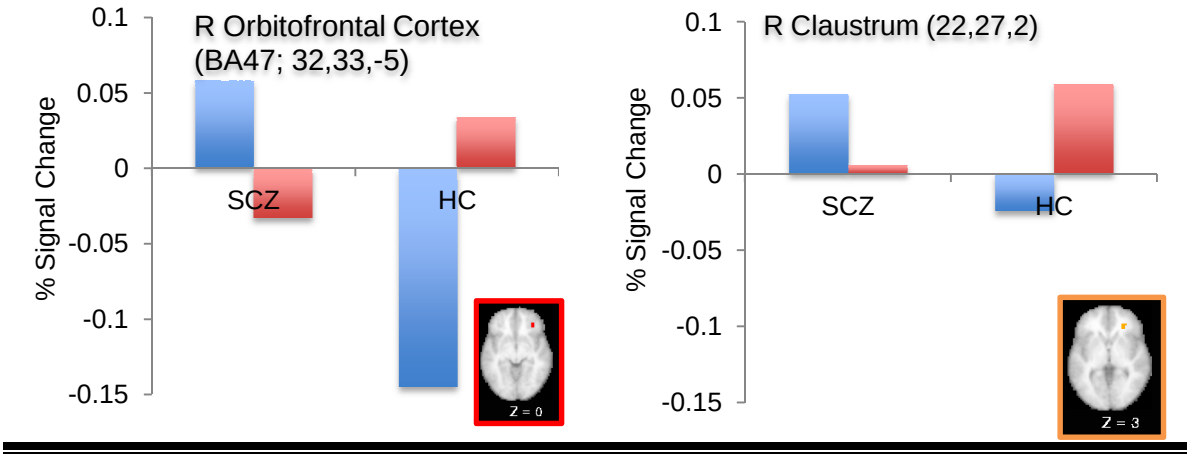
Regions Displaying a Main Effect of *Reward* At a Whole Brain Level



Note. This figure represents regions displaying a main effect of *Reward*. As described in the text, post-hoc paired *t*-tests (reward -baseline blocks) were performed on each region across groups ($p < .05$) to compare sustained activity depending on each task block. Pink indicates activated regions with the pattern of greater sustained activity during reward relative to baseline blocks. Yellow represents deactivated regions with the pattern of greater deactivation during baseline than reward blocks across groups. See TableS1 for the exact cooridinates for each region in Supplementary Material

Supplementary Figure 2:

Regions Displaying Whole Brain Reward x Group Interaction Effect



Note. HC = Healthy controls, R = Right, SCZ = Schizophrenia

Transient Trial-by-Trial Component of Motivated Cognitive Control

Whole-Brain Cue-related Effects of Reward: First of all, a voxel-wise ANOVA at a whole brain level as described above was performed to examine exploring effects. I found a significant main effect of transient *Reward* x *Time point* in a number of regions in the DLPFC, cingulate, lingual gyrus and parietal regions including precuneus as presented in Table S4 (see Table S5 for exact coordinates for deactivated regions and the example time courses for Figure S3 in Supplementary Materials). To understand the source of the interaction effect, post-hoc three paired *t*-tests (i.e., RC-BCXT, RCXT-BCXT, RC-RCXT) were conducted in order to determine the relationship between reward and other types of trials such as RCXT and BCXT trials. As described in the Data analysis above, post-hoc analysis regarding any interaction effect with time point focused on the average of time point 3 and 4. Figure S4 shows the example time courses for regions displaying reward-related cue-type effect. Most regions including the middle frontal gyrus as well as in the cuneus and precuneus showed greater transient activity on RC trials than RCXT or BCXT trials from a whole brain level.

Supplementary Table 4:

Regions Displaying a Reward x Time Point Interaction at a WB Level (z > 3.0, 13 voxels)

Region of Activation[a]	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*
			x	*y*	*z*	
Regions where RC> RCXT=BCXT						
Middle Frontal Gyrus	9	155	44	7	38	5.26
Middle Frontal Gyrus	6	68	44	-1	52	4.84
Middle Frontal Gyrus	10	35	-30	49	12	4.01
Precentral Gyrus	9	80	44	23	35	4.86
Superior Frontal Gyrus	6	29	40	15	52	4.76
Inferior Frontal Gyrus	9	57	-36	5	27	4.37
Superior Temporal Gyrus	40	98	50	-52	20	4.72
Middle Temporal Gyrus	22	23	52	-37	-1	4.87
Middle Occipital Gyrus,	18	296	31	-80	-8	7.03
Middle Occipital Gyrus	19	186	-39	-78	0	5.41
Lingual Gyrus	17	287	16	-88	4	6.52
Cuneus	17	195	-10	-88	6	5.15
Cuneus	19	162	30	-82	22	4.68
Cuneus	31	176	-22	-81	24	4.54
Superior Parietal Lobule	7	319	-27	-62	43	6.13
Superior Parietal Lobule	40	75	42	-52	57	4.80
Parietal lobe, Precuneus	7	380	27	-62	41	5.79
Angular Gyrus	40	132	48	-55	36	5.33
Pyramis		71	-38	-73	-32	4.88
Culmen		163	-35	-56	-22	6.36
Culmen		71	30	-41	-21	5.76
Culmen		42	-28	-32	-20	5.29
Regions where RC =BCXT > RCXT						
Middle Temporal Gyrus	37	84	41	-64	8	5.09
Fusiform Gyrus	37	37	48	-52	-8	4.34
Middle Occipital Gyrus	19	117	38	-81	7	5.04
Occipital Lobe	19	179	-22	-76	-11	5.31
Lingual Gyrus	19	72	-30	-61	2	4.71
Regions where RC > BCXT > RCXT						
Declive		166	29	-56	-13	6.65

Note. BCXT= Baseline-Context, BA = Broadman Area, RC= Reward-Cue, RCXT= Reward-Context, WB=Whole brain.

[a] Post hoc paired *t*-tests were performed on each region displaying significant cue-type x time point interaction as described in the text. The mean activation at the average of time point 3 and 4 for reward-cue, reward-context, baseline-context trials were used in three *t*-tests (Reward-Cue-Baseline-context, Reward-Context-Baseline-Context, Reward-cue – Reward-Context trials) to determine the relationship between reward and other cue-type activity.

Supplementary Table 5:

Activated and Deactivated Regions Displaying a Reward x Time Point Interaction from a Whole Brain Level

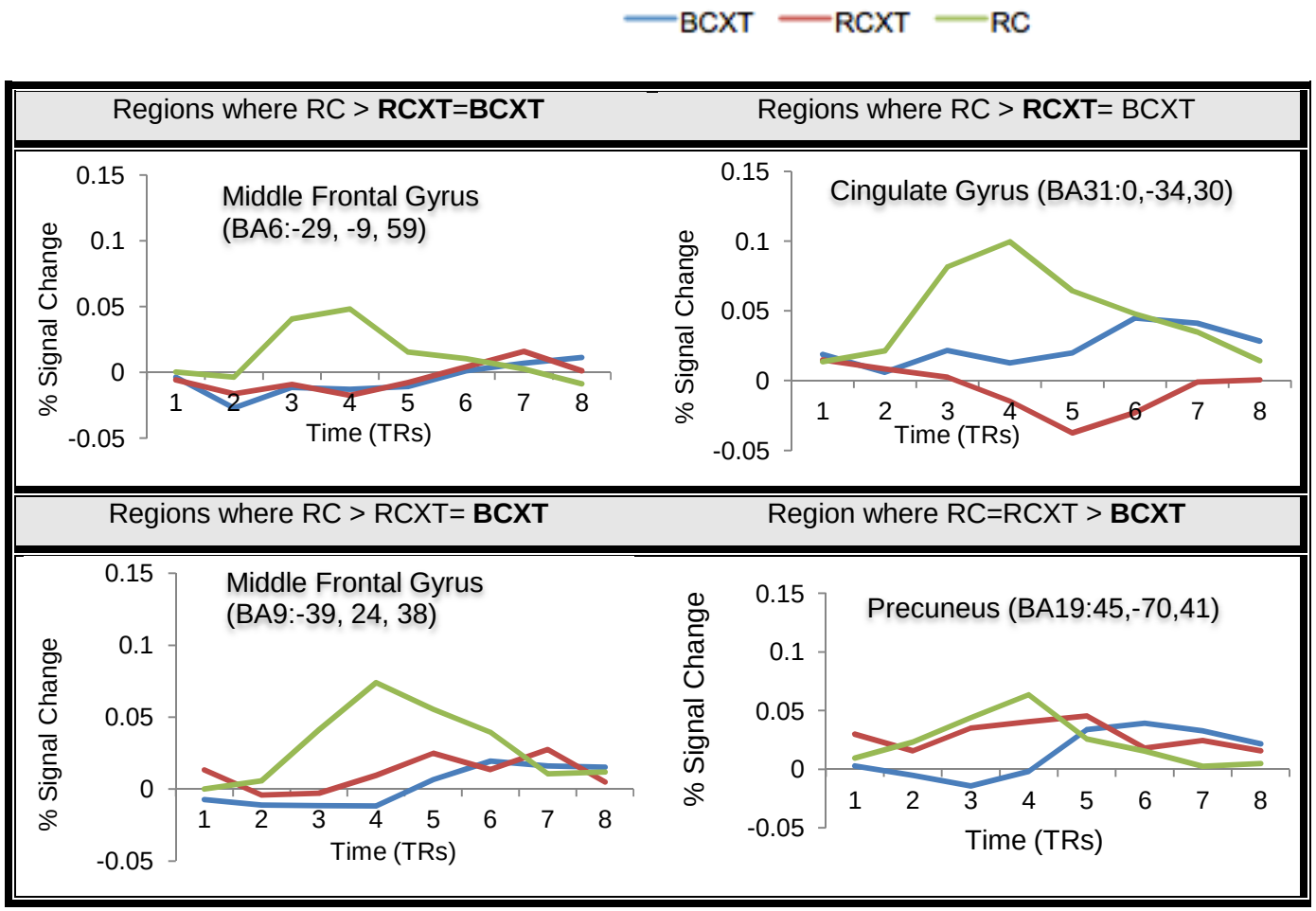
Regions	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*
			x	*y*	*z*	
Regions where RC > ***RCXT***=***BCXT***						
Middle Frontal Gyrus	6	217	-29	-9	59	5.34
Middle Frontal Gyrus	6	168	24	-6	60	5.21
Middle Frontal Gyrus	6	61	-20	7	60	4.84
Middle Frontal Gyrus	10	84	37	37	24	4.35
Middle Frontal Gyrus	9	15	-33	40	29	3.76
Precentral Gyrus	4	29	30	-24	66	4.79
Superior Frontal Gyrus	6	179	-2	5	51	4.54
Superior Frontal Gyrus	8	66	3	22	50	4.22
Superior Frontal Gyrus	10	53	29	46	14	4.50
Inferior Frontal Gyrus	13	19	-34	12	-15	4.13
Cingulate Gyrus	32	23	8	21	34	3.75
Posterior Cingulate	31	60	20	-60	21	4.31
Superior Temporal Gyrus	22	13	48	13	-4	4.10
Lingual Gyrus	18	107	5	-65	5	5.01
Lingual Gyrus	19	47	16	-54	-1	4.23
Cuneus	18	151	-2	-76	16	4.31
Lingual Gyrus	18	107	-16	-70	6	4.68
Cuneus	19	125	10	-85	27	3.85
Inferior Frontal Gyrus	13	19	-34	12	-15	4.13
Cingulate Gyrus	32	23	8	21	34	3.75
Cingulate Gyrus	24	45	17	-4	40	4.13
Superior Temporal Gyrus	22	28	-52	10	1	4.89
Posterior Cingulate	31	60	20	-60	21	4.31
Superior Temporal Gyrus	22	13	48	13	-4	4.10
Lingual Gyrus	18	107	5	-65	5	5.01
Lingual Gyrus	19	47	16	-54	-1	4.23
Inferior Parietal Lobule	40	364	-45	-40	51	4.97
Postcentral Gyrus	3	70	46	-21	50	5.37
Precuneus	7	280	-1	-75	43	5.83
Precuneus	7	165	-4	-57	48	4.90
Precuneus	7	28	3	-40	44	3.95
Thalamus		22	-15	-28	-2	4.65

Regions	BA[1]	Cluster size (voxels)	Talairach Coordinates			*z*
			x	*y*	*z*	
Caudate Body		53	13	-10	20	4.45
Lateral Posterior Nucleus		36	-15	-20	18	3.39
Insula	13	24	31	15	17	3.78
*Regions where RC > **RCXT**= BCXT*						
Middle Frontal Gyrus	6	63	-45	1	39	4.48
Lingual Gyrus	18	178	-1	-78	-1	5.19
Cingulate Gyrus	31	175	0	-34	30	6.31
Posterior Cingulate	30	112	21	-70	7	4.57
Precuneus	7	138	-15	-66	32	4.61
Posterior lobe, Tuber		58	47	-59	-25	4.85
*Regions where RC > RCXT= **BCXT***						
Precentral Gyrus	9	42	-39	24	38	4.32
Middle Frontal Gyrus	11	24	-29	39	-3	4.83
Temporal lobe, Sub-Gyral	37	43	-48	-42	-4	5.20
Inferior Parietal Lobule	40	52	-51	-55	36	4.55
Thalamus		13	18	-29	-2	4.52
Posterior Cingulate	29	20	5	-44	11	4.34
Thalamus		21	7	-24	14	4.70
*Regions where RC=RCXT > **BCXT***						
Precuneus	19	90	45	-70	41	4.15

Note. BCXT= Baseline-Context, RCXT= Reward-Context, RC= Reward-Cue
Relating to Table3, these regions were identified from a cue-type (BCXT, RCXT, RC) x time point interaction at a whole-brain level ($z > 3.0$, 13 continuous voxels). Here these regions include at least one or all deactivated regions depending on cue-type activity. **Bold** indicates deactivated regions.
Post hoc paired *t*-tests were performed on each region displaying significant cue-type x time point interaction.The mean activation at time point 3 and 4 for reward, no-reward, baseline trials were used in three t-tests (reward-baseline, reward-no-reward, no-reward-baseline trials) to determinie ine the relationship between reward and other cue-type activity

Supplementary Figure 3:

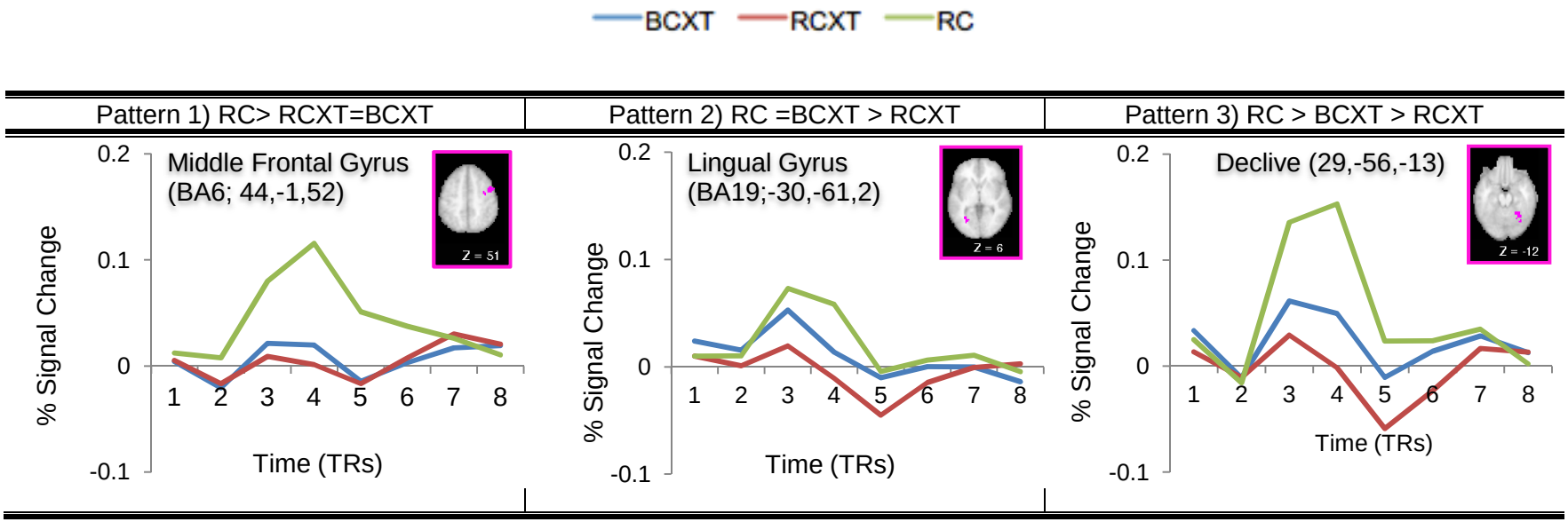
Example Time courses for ROI (de)activated Regions Displaying a Reward x Time point Interaction from WB Analyses



Note. BCXT=Baseline-Context, RC =Reward-Cue, RCXT= Reward-Context, WB= Whole brain. **Bold** indicates deactivated region

Supplementary Figure 4

Example Time Courses From Regions Showing a Significant Interaction Between Reward x Time Point From WB Analyses



Note. BCXT= Baseline-Context, RCXT= Reward-Context, RC = Reward-Cue trials, WB= Whole Brain
Post-hoc paired *t*-tests were conducted to examine the relationship between neural activity on reward trials and other cue-type activity on each region during time point 3-4 ($p < .05$). Lines indicate the average time courses for each cue-type

Whole-Brain Effects of Group: Whole brain analysis again revealed a main effect of *Group* x *Time point* in the frontal and superior parietal lobes (see Table S6 for exact coordinates in each region and Figure S5 for example time courses below). Among regions displaying *Group* effect, I did not include several regions in the temporal, postcentral, cinglulate gyrus, and cuneus showing uninterpretable time courses for further analyses. Again, post-hoc independent *t*-tests focused on the average of time point 3-4 as described in the Data Analysis above. As shown in Table S6, regions in the precentral, superior temporal, lingual gyrus and superior parietal lobule displayed greater transient activity in HC group compared with individuals with SCZ. The cuneus displayed greater activity in those with SCZ relative to the HC.

Whole-Brain Interaction of Reward and Group: Regions in the medial, superial PFC, the temporal, occipital and parietal lobe displayed significant interactions between *Group* and *Reward* within time window (the 8 time frames, TR:2 seconds). As presented in Table S7 and Figure S6 for the example time courses, several regions in the middle occipital gyrus, postcentral, and temporal gyrus displayed a significant *Reward x Group* interaction. In most regions, the HC group showed greater transient activity on RC (cued by "$20") trials relative to RCXT (cued by "XX") and/or baseline (cued by "XX") trials. On the other hand, individuals with SCZ showed a less of an increase in trial-by-trial activity on RC trials relative to baseline and/or RCXT trials. For example, the medial frontal gyrus displayed greater activity on RC trials than baseline in the HC group while individuals with SCZ failed to show an increase in their transient activity on RC trials than baseline trials in the same region.

Supplementary Table 6:

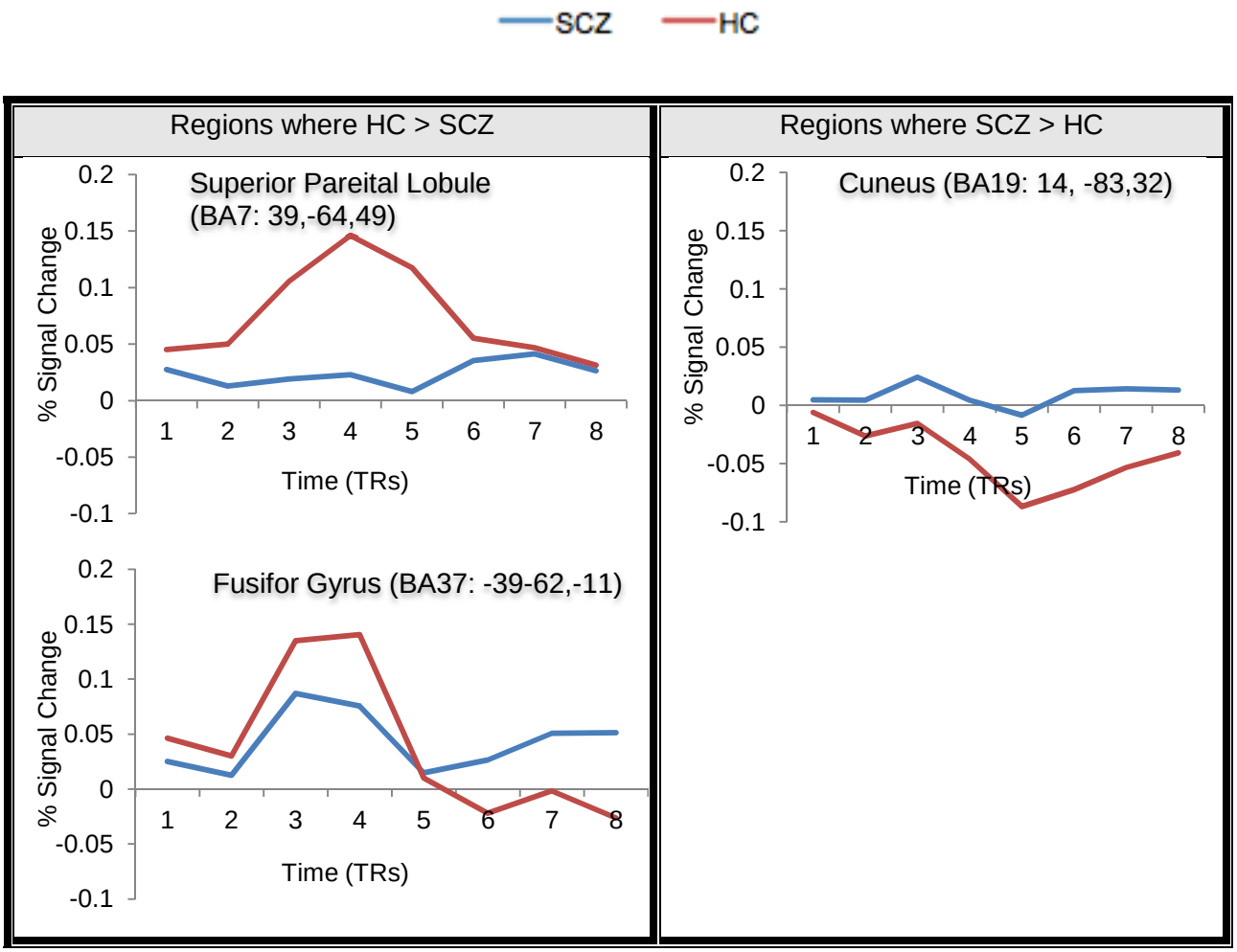
Transient Group x Time Point Interaction at a Whole Brain Level

Region of Activation	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]
			x	*y*	*z*		
Regions where HC > SCZ							
Superior Parietal Lobule	7	16	39	-64	49	3.73	HC > SCZ
Precentral Gyrus	4	31	34	-21	51	3.99	HC > **SCZ**$^{+}$
Fusiform Gyrus	37	21	-39	-62	-11	3.77	HC > SCZ^{++}
Superior Temporal Gyrus	39	39	54	-54	21	4.59	HC > SCZ^{++}
Lingual Gyrus	18	13	19	-87	-10	3.49	HC > SCZ^{+}
Regions where SCZ > HC							
Cuneus	19	15	14	-83	32	3.64	SCZ > **HC**

Note. HC = Healthy controls, SCZ = schizophrenia.
[a] Post-hoc independent sample *t*-tests were conducted to compare neural activity between the two groups during time point 3-4 across three cue-types (baseline, no-reward, reward) ($p < 0.05$). Yellow indicates regions where *p*-value < 0.10: $^{+}p = 0.05$, $^{++}p = 0.08$. **Bold** indicates deactivated regions

Supplementary Figure 5:

Example Time courses for Regions Displaying a Group x Time Point Interaction from WB Analyses



Note. SCZ = Schizophrenia, HC = Healthy controls, WB = Whole brain

Supplementary Table 7:

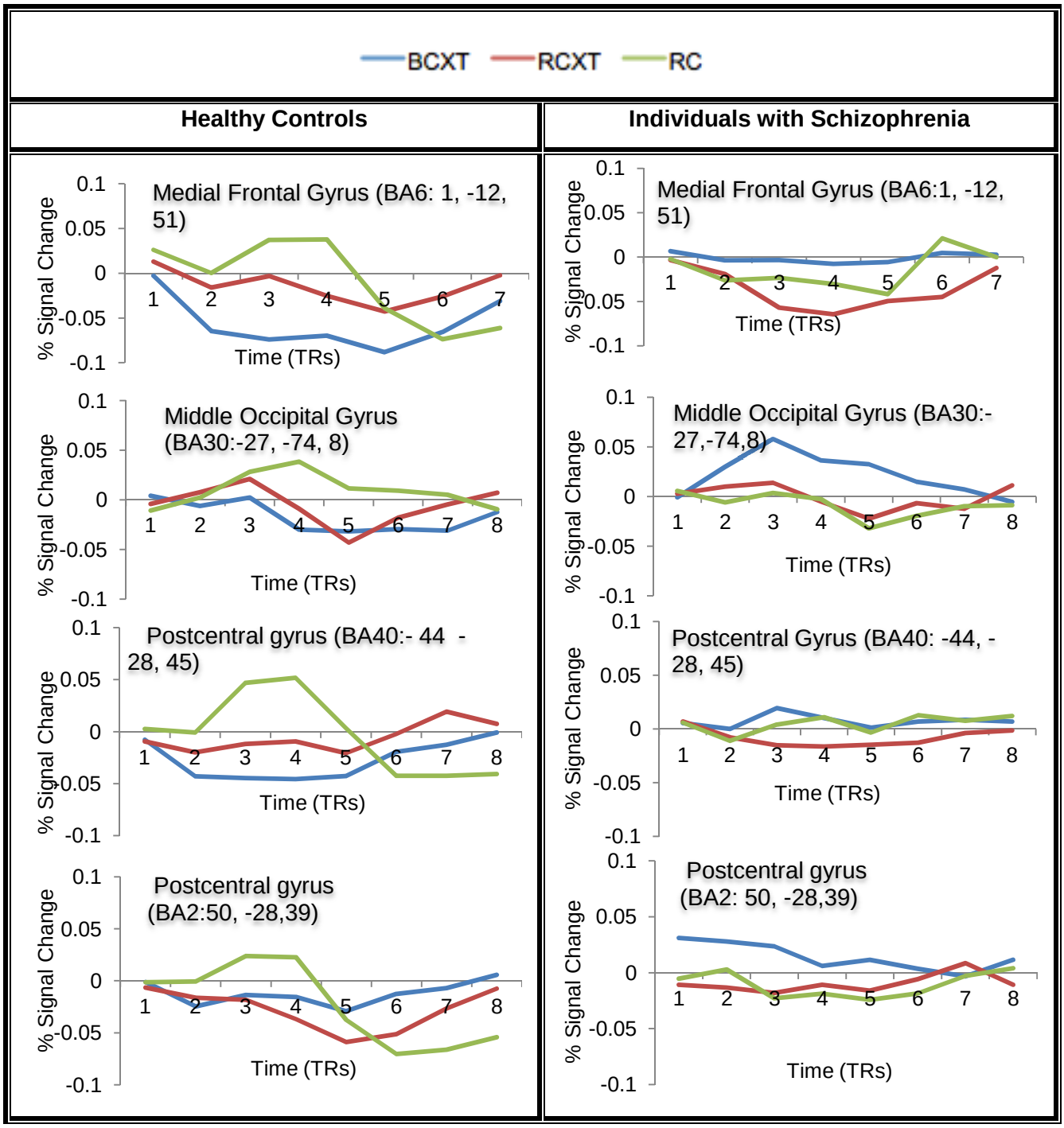
Transient Reward x Group x Time Point Interaction

Analysis	Region of Activation	BA	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Pattern[a]	
				x	*y*	*z*		HC	SCZ
WB	***Regions where RC > B=RCXT or RCXT=B in HC***								
	Medial Frontal Gyrus	6	20	1	-12	51	3.44	RC > **BCXT**=**RCXT**	**RC** =**BCXT**> **RCXT**$^{+}$
	Middle Occipital Gyrus	19	15	-34	-75	-10	3.71	RC > RCXT^{++}=BCXT	RC >**BCXT** $^{+++}$= RCXT
	Middle Occipital Gyrus	30	20	-27	-74	8	4.27	RC > RCXT^{+}= **BCXT**	BCXT >RC =RCXT
	Fusiform Gyrus	37	64	45	-53	-10	5.17	RC> RCXT=B	BCXT>RC^{+++}=RCXT
	Postcentral Gyrus	40	139	-44	-28	45	4.85	RC > **BCXT**= **RCXT**	RC =BCXT> **RCXT**$^{+}$
	Postcentral Gyrus	2	15	50	-28	39	3.85	RC > **RCXT**=**BCXT**	BCXT> **RC**$^{++}$ =**RCXT**
	Postcentral Gyrus	3	20	48	-17	43	3.96	RC > **BCXT**$^{+}$=**RCXT**	BCXT > **RCXT=RC**
	Lingual Gyrus	18	25	4	-92	-10	4.44	RC >RCXT^{++} =BCXT	RC= RCXT>**BCXT**$^{++++}$
WB	***Regions where RC=RCXT >B in HC***								
	Superior Temporal Gyrus	41	15	-51	-21	4	3.99	RC=**RCXT** > **BCXT**	**RC** =BCXT=RCXT

Note. BA = Broadman Area, B= baseline, RC = Reward-Cue, RCXT=Reward-Context, ROI = Region of interest, HC = Healthy controls, SCZ = Schizophrenia, WB = Whole brain analysis.
[a] Post-doc *t*-tests to identify the source of significant effects were performed at the average of time point 3-4 (see the text for more detail).
Bold letters indicate cue-type trials on which regions showed deactivations. Yellow indicates region where *p*-value < 0.10: ^{+}p = 0.05, ^{++}p = 0.06, $^{+++}p=0.07$.

Supplementary Figure 6:

Example Time courses for Regions Displaying Reward x Group x Time point Interaction from a WB Analyses



Transient Target-related Neural Activity

Whole-Brain Effects of Condition: The voxel-wise ANOVA revealed a *Condition* x *Time point*, as well as a *Condition* x Group x *Time point* effect across groups. As presented in Table S8, several regions in the middle, inferior frontal gyrus, occipital gyrus, and precuneus showed greater activity on incongruent trials than congruent or neutral trials across groups at a whole brain level (see Figure S7 for the time courses in each region).

Whole-Brain Interactions of Condition and Group: As presented in Table S9 and S10, in most regions in the middle, superior, and inferior frontal gyrus and the occipital lobe, the HC showed greater activity in incongruent than congruent or neutral conditions while individuals with SCZ showed no significant differences as a function of condition type in the same regions except one region in the inferior frontal gyrus (*x*:53, *y*:20, *z*:4): those with SCZ also showed similar pattern of greater activity on incongruent trials relative to congruent and neutral trials like the HC. However, many regions in the inferior parietal lobule, precuneus and superior parietal lobule did not display significant differences depending on condition type for both groups (see Figure S8 for the time courses).

Supplementary Table 8:

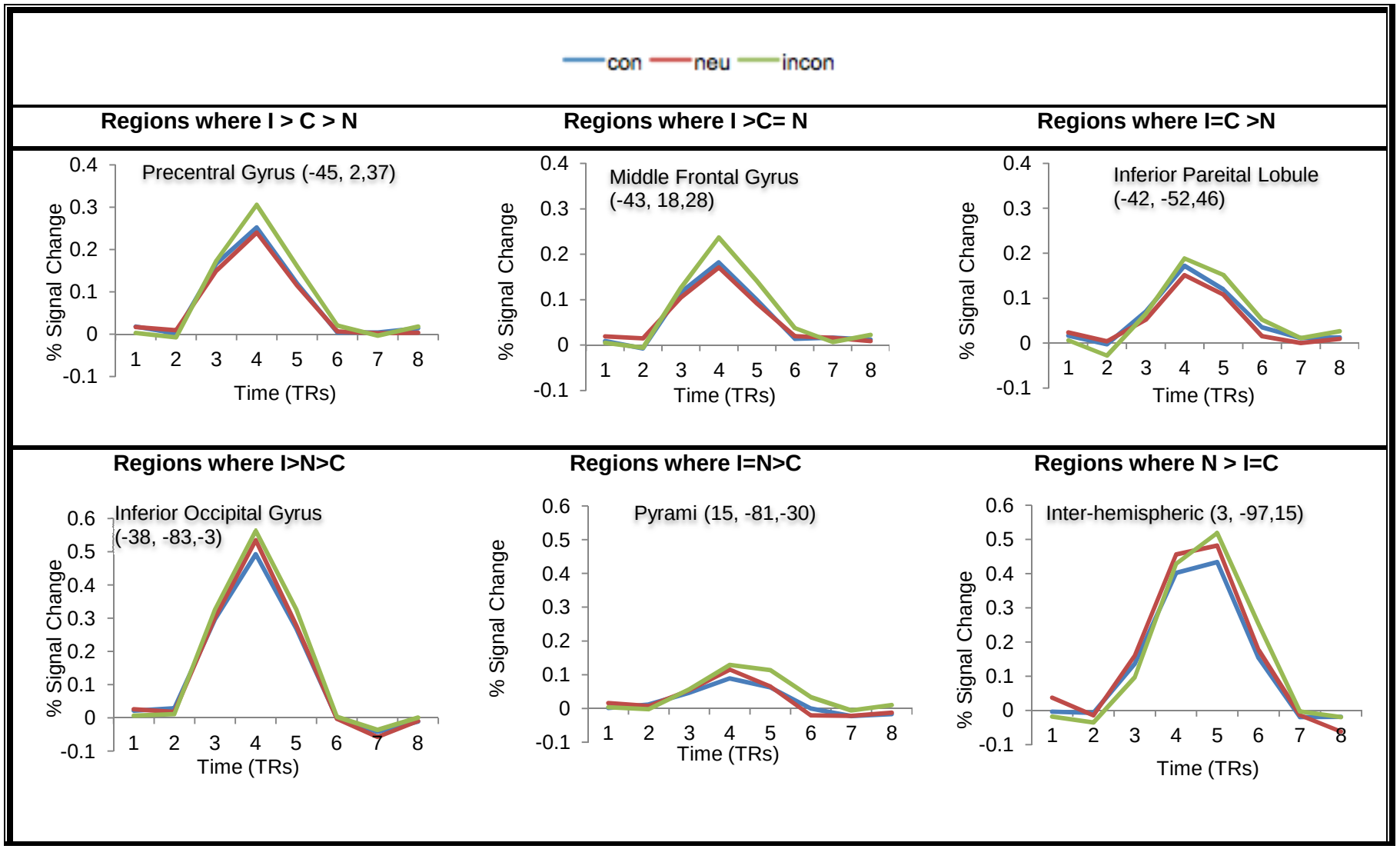
Transient Target-related Interactions of Condition and Time Point at a Whole Brain Level

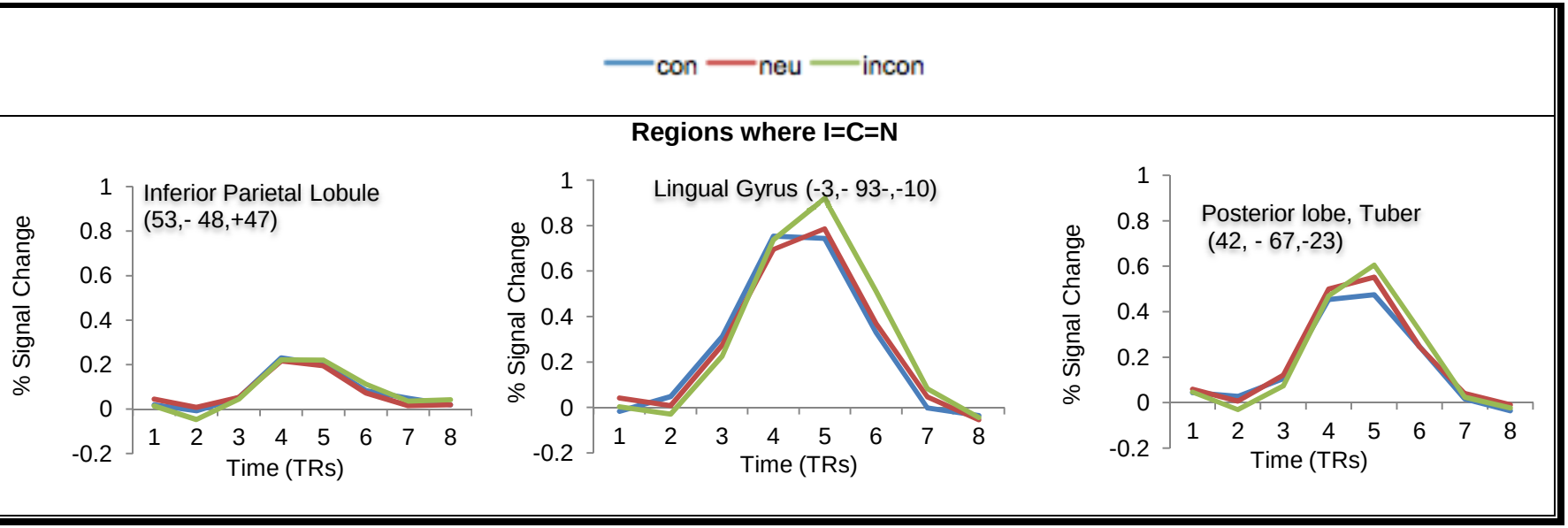
Region of Activation	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Patterns[a]		
			x	*y*	*z*				
Regions where I > C > N									
Precentral Gyrus	6	260	-45	2	37	6.26	I > C > N		
Regions where I > C = N									
Middle Frontal Gyrus	9	201	-43	18	28	6.19	I > C = N		
Medial Frontal Gyrus	8	223	-1	19	47	4.90	I > C = N		
Inferior Frontal Gyrus	47	30	45	20	-1	5.01	I > C = N		
Inferior Frontal Gyrus	46	39	-47	28	14	4.68	I > C = N		
Inferior Frontal Gyrus	47	48	-48	18	0	5.28	I > C = N		
Middle Occipital Gyrus,	19	38	-40	-68	-10	4.49	I > C = N		
Cingulate Gyrus	31	62	-2	-38	27	4.79	I> C^{+}=N		
Posterior Cingulate	30	41	0	-60	10	4.88	I > C = N		
Precuneus	19	147	-28	-69	36	4.57	I > C = N		
Medial Geniculum Body		30	-18	-25	-1	4.73	I > C = N		
Regions where I=C >N									
Middle Temporal Gyrus	21	20	-51	-30	-5	4.12	I = C > N		
Inferior Parietal Lobule	40	154	-42	-52	46	5.53	I = C > N		
Regions where I>N>C or I=N>C or N > I=C									
Inferior Occipital Gyrus	18	8	-38	-83	-3	3.80	I > N >C^{++}		
Posterior Lobe, Pyramis		19	15	-81	-30	4.63	I=N>C^{+++}		
Cuneus	19	19	30	-77	29	3.99	I=N> C^{++}		
Cuneus	18	19	3	-97	15	4.92	N > I = C		
Regions where I=C=N [b]							TP3-4	TP5	TP6
Precuneus	7	76	1	-77	45	4.59	I=C=N	I> N^{+}>C	I>C=N
Inferior Parietal Lobule	40	33	53	-48	47	4.41	I=C=N	I=C=N	I>C^{+++}=N
Lingual Gyrus	18	22	-3	-93	-10	4.58	I=C=N	I>C=N	I>C=N
Posterior Lobe, Tuber		13	42	-67	-23	3.96	I=C=N	I=N>C	I>C=N

Note. C= congruent, N= neutral, I =incongruent. Yellow indicates where *p*-value was <0.10: $^{+}$ *p*=0.05, $^{++}$ *p*=0.06, $^{+++}$*p*=0.09. [a] As described in the text, post-hoc three *t*-tests (incongruent-neutral, congruent-neutral, incongruent-neutral) at the average of time point 3-4 across cue-type ($p < 0.05$) were performed on each region displaying condition effect. [b] For regions showing no significant activity among types of conditions at the average of time point 3-4, additional post-hoc *t*-tests at later time point 5 and 6 were computed to identify exact source of significance effect

Supplementary Figure 7:

Example Time courses for Regions Displaying Condition x Time point Interaction from WB Analysis





Note. C = Congruent, I = Incongruent, N= Neutral trials

Supplementary Table 9:

Transient Target-related Activity: Condition x Group x Time Point At a Whole Brain Level

Region of Activation	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Patterns During Time Point 3-4	
			x	*y*	*z*		HC	SCZ
Frontal Lobe								
Precentral Gyrus	6	26	51	-1	42	4.38	I >C=N	I=C=N
Precentral Gyrus	6	42	-50	-2	45	4.29	I >C=N	I=C>N
Precentral Gyrus	6	62	-36	-9	49	4.68	I >C=N	I=C>N
Medial Frontal Gyrus	6	92	3	-2	55	4.37	I >C=N	I=N>C
Paracentral Lobule	31	59	1	-24	48	4.43	I >C=N	I=N>C
Superior Frontal Gyrus	6	20	-1	17	61	4.04	I >C=N	I=C=N
Inferior Frontal Gyrus	44	36	-48	5	16	4.07	I >C=N	I=C=N
Medial Frontal Gyrus	8	21	4	19	45	3.98	I>C=N	I=C=N
Inferior Frontal Gyrus	44	41	54	6	14	4.36	I >C=N	I=C=N
Inferior Frontal Gyrus	45	19	53	20	4	4.06	I >C=N	I=C>N
Middle Frontal Gyrus	6	62	37	-1	51	4.94	I >N^{++} =C	I =C=N
Limbic Lobe								
Anterior Cingulate[a]	32	49	7	48	-1	4.44	I =C=N	**I =C=N**
Temporal Lobe								
Sub-Gyral, white matter		101	-45	-41	4	5.31	I>C=N	C>$\mathbf{N^{++}}$=I
Middle Temporal Gyrus	22	51	50	-43	3	4.73	I>C=N	I =C=N
Middle Temporal Gyrus	37	158	-45	-63	11	5.53	I>C=N	I =C=N
Middle Temporal Gyrus	21	20	-52	-4	-11	4.67	I>C=N	**I =C=N**
Middle Temporal Gyrus	22	20	-66	-36	4	4.46	I>C=N	**I=C>**$\mathbf{N^{++}}$
Precuneus	7	37	28	-66	26	4.37	I=N>C	I =C=N
Middle Temporal Gyrus[a]	39	62	-30	-66	20	4.89	I =C=N	**I =C=N**
Sub-Gyral, white matter[a]		32	36	-51	5	4.16	I =C=N	I =**C**=N
Occipital Lobe								
Cuneus	18	151	15	-75	17	4.93	I>C =N	I =C=N
Cuneus	17	79	-9	-96	2	4.96	I>C=N	I =C=N
Inferior Temporal Gyrus	37	84	-41	-63	-4	5.01	I>C=N	I =C=N
Lingual Gyrus	18	37	4	-84	00	4.04	I>C=N	I =C=N
Cuneus	18	133	-18	-75	17	4.83	I>C=N	I =C=N
Inferior Occipital Gyrus	18	46	-33	-86	-4	4.93	I=N>C	I =C=N
Middle Occipital Gyrus	18	61	-26	-91	12	4.52	I=N>C	I =C=N
Middle Occipital Gyrus	18	29	12	-94	15	4.37	I=N>C	I =C=N
Middle Occipital Gyrus	37	40	45	-67	4	4.39	I=N>C	I =C=N
Inferior Occipital Gyrus	18	17	32	-80	-5	4.25	I=N>C	I =C=N
Middle Occipital Gyrus	19	35	30	-87	17	4.62	I=N>C	N>I=C
Cuneus	19	113	9	-84	30	4.66	I=N>C^{++}	I =C=N
Cuneus	30	26	9	-60	7	4.16	I=N^{+}>C	I =C=N

Regions of Activation	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*	Activation Patterns	
			x	*y*	*z*		HC	SCZ
Cuneus	18	115	-12	-89	18	4.72	I=N> C^{+}	I =C=N
Parietal Lobe								
Inferior Parietal Lobule	40	108	-41	-28	42	4.85	I> C=N	I =C=N
Inferior Parietal Lobule	40	38	-60	-37	40	4.82	I =C > N	I =C=N
Supramarginal Gyrus	40	40	-58	-48	27	4.83	I> C=N	I>N^{++} =C
Postcentral Gyrus	4	45	41	-18	43	4.47	I >C^{+++}=N	I =C=N
Postcentral Gyrus	5	63	-29	-39	64	4.84	I >C^{++}=N	I =C=N
Declive		44	-21	-59	-16	4.08	I >C^{+++}=N	I =C=N
Precuneus	19	160	-19	-81	34	4.78	I =N>C^{++++}	I =C=N
Precuneus	7	96	18	-78	44	5.00	I =N > C	I =C=N
Superior Parietal Lobule	7	173	26	-61	48	5.18	I=N>C^{++}	I =C=N
Precuneus	7	71	7	-51	44	4.20	I =C=N	I =C=N
Precuneus	31	38	16	-49	30	4.40	I =C=N	**I** =**C**=**N**
Precuneus	7	141	-15	-56	55	5.15	I =C=N	I =C=N
Superior Parietal Lobule	7	60	8	-65	56	4.52	I =C=N	I =C=N
Postcentral Gyrus	3	154	31	-34	58	4.91	I =C=N	I =C=N
Insula	13	16	-40	-44	25	4.23	I =C=N	I =C=N
Angular Gyrus	39	18	-27	-55	32	4.07	I =C=N	I =C=N
Postcentral Gyrus	2	75	52	-28	38	4.87	I =C=N	I =C=N
Postcentral Gyrus	40	26	-53	-26	17	4.41	I =C=N	I =C=N
Inferior Parietal Lobule	40	58	40	-46	39	4.41	I =C=N	I =C=N
Postcentral Gyrus	2	20	-45	-27	57	3.93	I =C=N	I =C=N
Declive		20	-7	-84	-19	4.32	I =C=N	I =C=N
Pyramis		10	-17	-71	-27	3.67	I =C=N	I =C=N
Uvula		17	-29	-83	-25	4.43	I =C=N	I =C=N
Cerebellum								
Culmen		57	-32	-55	-26	4.74	I >C^{++} =N	I =C=N
Claustrum		20	26	18	-4	4.44	I >C^{+} =N	I =C=N
Culmen		18	-6	-57	2	4.38	I =N>C^{+++}	I =C=N

Note. C = congruent, HC= healthy controls, N= neutral, I = incongruent, SCZ= schizophrenia.
Post-hoc paired t-tests were performed at the average of time point 3-4 (see Methods). [a i]ndicates regions where individuals with SCZ showed uninterpretable timecourses. Yellow dicates regions where p-value was <0.10:^{+}p= 0.05, ^{++}p =0.06, ^{+++}p =0.07, ^{++++}p =0.08. **Bold** letters indicate condition in which neural activity was deactivated. Blue indicates regions where I=C=N at the average of time point 3 and 4. Additional follow-up paired *t*-tests at each time point 3,4,5,6 were conducted to identify the source of interactions. The results were presented in Supplementary Materials (see TableS10).

Supplementary Table 10:

Regions Displaying Condition x Group Interaction at Early or Later Time Point

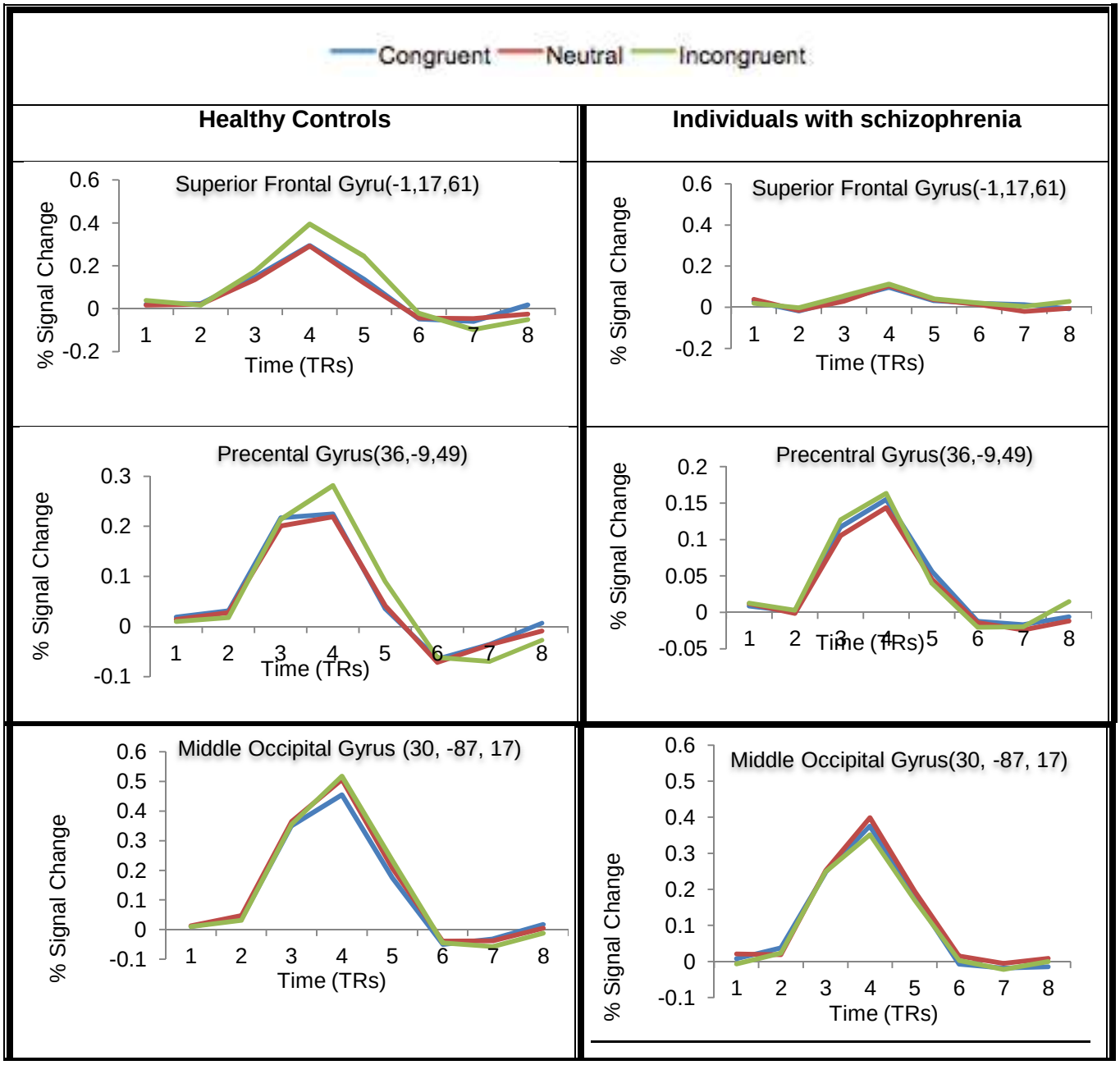
Regions of Activation	BA[1]	Cluster size (voxels)	Talairach Coordinates			*Z*	Post-Hoc *t*-tests			
Regions where I=C=N at the average of TP3-4[a]			*x*	*y*	*z*		HC		SCZ	
							TP3	TP4	TP3	TP4
Postcentral Gyrus	2	75	52	-28	38	4.87	I=C=N	I=C=N	I=C=N	N>I=C
Postcentral Gyrus	40	26	-53	-26	17	4.41	I=C=N	I=N>C	I=C=**N**	C=N>I^{+++}
Inferior Parietal Lobule	40	58	40	-46	39	4.41	I=C=N	I=C=N	I=C=N	N=C>I^{++++}
Postcentral Gyrus	2	20	-45	-27	57	3.93	I=C=N	I>C=N	I=C=N	I=C=N
Pyramis		10	-17	-71	-27	3.67	I=C=N	I>C=N	I>C^{+++}=N	N>I=C
Regions where I=C=N at the average of TP3-4[b]							TP5	TP6	TP5	TP6
Precuneus	7	71	7	-51	44	4.20	I>N=C	**I=C=N**	I=C=N	**I=C=N**
Precuneus	31	38	16	-49	30	4.40	I>**C**=N	**I>C**$^{+}$**=N**	**I**>C^{+}=N	**I**>C=**N**
Precuneus	7	141	-15	-56	55	5.15	I>C=N	**I=C=N**	I=C=N	**I=C=N**
Superior Parietal Lobule	7	60	8	-65	56	4.52	I=N>C	I=N>C	I=C=N	I=C=N
Postcentral Gyrus	3	154	31	-34	58	4.91	I>**C=N**	**I=C=N**	C=N>I	**I=C=N**
Insula	13	16	-40	-44	25	4.23	**I>C=N**	**I=C=N**	**I=C**=N	**I=C=N**
Angular Gyrus	39	18	-27	-55	32	4.07	I>C=N	I>C**=N**	I=C=N	I=C=N
Declive		20	-7	-84	-19	4.32	I>C=N^{++}	I>C=N	C=I>N^{++++}	I>C^{+++}=N
Uvula		17	-29	-83	-25	4.43	I>C=N	I>C=N	C>I=N	I=C=N

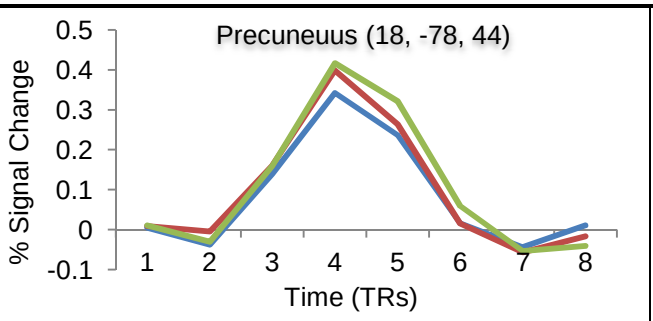
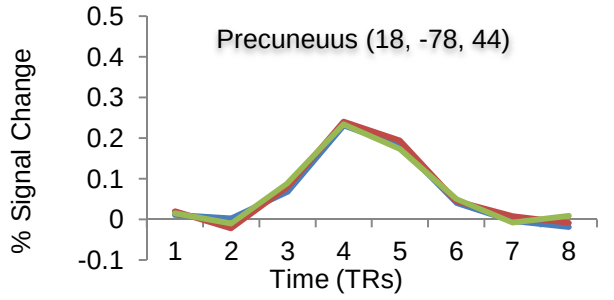
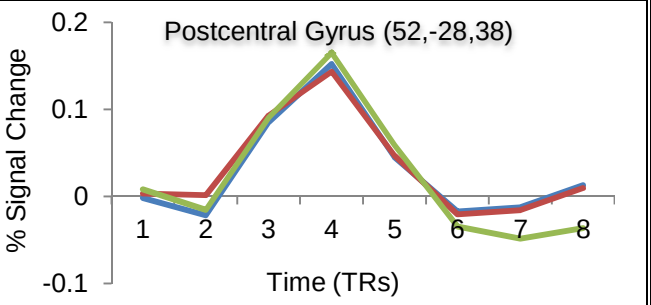
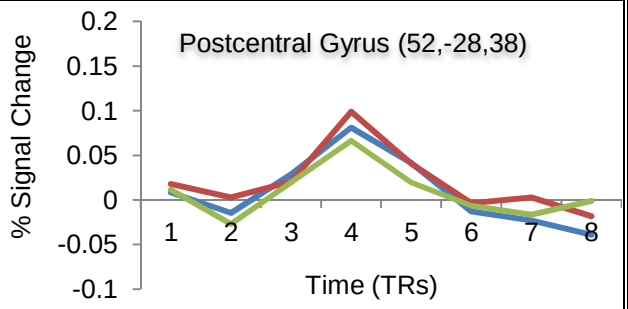
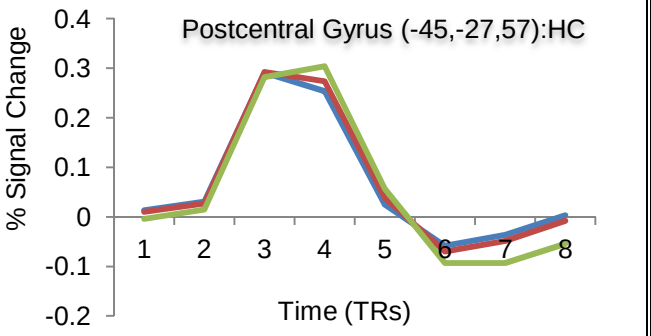
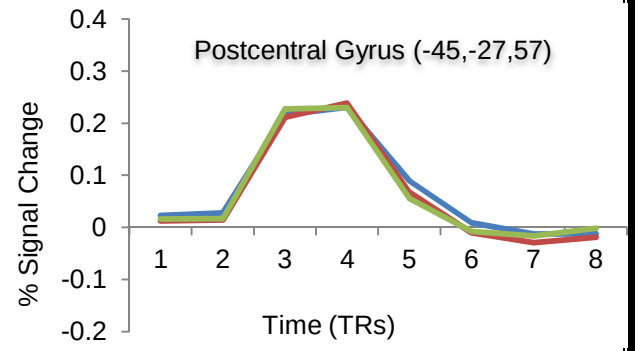
Note. BA=Broadman Area, C= congruent, I= incongruent, N=neutral,TP = Time Point. Yellow indicates regions where $p < 0.10$; $^{+}p = 0.05$, $p=$ $^{++}0.07$, $^{+++}p = 0.08$, $^{++++}p = 0.09$. **Bold** indicates deactivated regions. This table represents regions displaying no different activity as a function of condition-type at the average of time point 3-4 from Table S9. In this case, to identify the exact source of condition x group x time point interaction, first, post-doc-t-test at each time point 3,4,5,6 were conducted for each group, separately.

[a] indicates regions where the source of interaction effects were found either or both at time point 3 and 4. [b] indicates regions where the source of interaction effects were found either or both at time point 5 and 6.

Supplementary Figure 8:

Example Time courses for Regions Displaying a Condition x Group x Time point Interaction from WB Analyses



Healthy Controls	Individuals with schizophrenia
	
	
	

Behavior-Brain Relationships

The Relationship Between Sustained Activity in the DLPFC and Behavioral Indices of Reward Context and Cue Effects.

I correlated increased sustained activity during reward vs. baseline blocks in the OFC (BA47: 32, 33,-5) displaying a *Reward* x *Group* interaction from a whole brain analysis. There were no significant associations between sustained activity and behavioral indices of context effect (r = -0.02, p =.89).

Brain-Symptom Relationships

Sustained Brain Activity and Negative Symptom Relation

I also correlated between negative symptom scores and sustained activity in the OFC region (x: 32, y: 33, z: -5) displaying *Reward* x *Group* interaction. Again, there was no significant association between sustained activity in the OFC and symptom (r = -.15, p =.35) in the whole brain analysis.