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Striatal Activity is Associated with Deficits of Cognitive Control and Aberrant Salience for Patients with Schizophrenia

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Table of Contents

List of Figures

List of Tables

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1. Introduction

Schizophrenia is a complex clinical disorder that has a devastating impact on those who suffer from it. The onset of the illness typically occurs in the early twenties, when individuals with the disorder develop symptoms such as disorganized thinking and hallucinations, so-called "positive symptoms". These symptoms can be managed by pharmacological intervention in some individuals. Other symptoms, like decreased speech production, decreased motivation, and a decreased interest in things, termed "negative symptoms", are more persistent and currently have few effective therapeutic interventions. Further, individuals with schizophrenia experience deficits of cognition in the domains of attention and cognitive control, for example, which further complicate the lives and treatment outcomes for individuals with this disorder. Despite decades of study, the specific pathophysiology of schizophrenia and all of its varied symptoms remain elusive. However, recent advances in fields such as neuroimaging and neurochemical imaging have allowed for prominent pathophysiological theories to be experimentally tested.

1.1. The Original Dopamine Hypothesis

The dopamine hypothesis, for example, is one of the longest held theories of schizophrenia origin and was developed after the discovery of antipsychotic drugs (see Howes & Kapur, 2009 for a review). These drugs were found to reduce dopamine concentrations in the brain by increasing the metabolism of dopamine or blocking its reuptake. The original dopamine hypothesis suggested that excess transmission at dopamine receptors led to psychotic symptoms, and blockade, by antipsychotic drugs, could resolve these symptoms. While this was a first step to understanding the mechanisms underlying the clinical expression of schizophrenia, this hypothesis did not directly address the relationship between dopamine transmission and

neurodevelopmental deficits, the role that genetics played, what brain region was associated with disorder, or what way this disruption influences positive and negative symptoms of schizophrenia. It also did not connect the relationship between cognitive deficits associated with the disorder and the proposed etiological mechanism.

1.2. The Revised Dopamine Hypothesis

The revised dopamine hypotheses, put forth by Davis et al. (1991), was motivated by new evidence from postmortem and metabolite findings, imaging data, and animal work. This evidence called into question the somewhat simple mechanism of illness posited by the original dopamine hypothesis – that schizophrenia resulted from excess dopamine – and added specificity to the original hypotheses by suggesting that schizophrenia resulted from prefrontal hypodopaminergia related to a hypoactive mesocortical dopamine system, and subcortical hyperdopaminergia related to a hyperactive mesolimbic dopamine system (Davis et al., 1991). At the time this hypothesis was driven by evidence suggesting that dopamine function could vary by brain region, by findings from PET studies showing reduced cerebral blood flow in the frontal cortex, and from animal studies that provided evidence linking prefrontal dopamine function to striatal dopamine tone. The revised dopamine hypothesis also linked symptom expression to cortical and subcortical dopamine dysregulation, suggesting that the positive symptoms of schizophrenia resulted from striatal hyperdopaminergia and negative symptoms were more associated with frontal hypodopaminergia, as the mesocortical system has been implicated in regulating both cognition and motivation (see Cools, 2008 for a review). Interestingly, the mechanisms that regulate dopamine tone in these regions are not unrelated. Abi-Dargham (2004) discussed mechanisms that regulate dopamine transmission, stating that disruptions in glutamatergic neurotransmission could have exaggerated excitatory effects on dopamine neurons in the ventral tegmental area (VTA) while understimulating dopamine

neurons in the mesocortical dopaminergic pathway leading to cortical hypodopaminergia. Understimulation of D1 neurons in the cortex may reduce its inhibitory effect on subcortical dopamine, thereby contributing to subcortical hyperdopaminergia.

1.2.1. The Revised Dopamine Hypothesis: Relationship to Cognitive Deficits

The revised dopamine hypothesis also provided a mechanism that could possibly explain the type of cognitive impairment displayed by individuals with schizophrenia. A substantial amount of evidence from neuropsychological studies of patients with PFC lesions studies and electrophysiology studies of primates, and later neuroimaging studies of humans, have shown that the frontal cortex plays an important role in cognitive domains like executive functioning and working memory (Goldman-Rakic, 1995). Patients with schizophrenia have shown deficits in these same domains, though deficits in individuals with schizophrenia broaden to other domains that include processing speed, learning, and episodic memory (Dickinson, Ragland, Gold, & Gur, 2008; Reichenberg & Harvey, 2007). One common denominator for many of these tasks may be the requirement of executive control, which is necessary to guide, coordinate, and update behavior flexibly. Given the importance of the PFC in cognitive control processes like updating information, protecting against irrelevant information, and shifting from one information set to another (Linden, 2007), understanding the nature of prefrontal dysfunction during cognition has clear relevance for understanding performance deficits associated with schizophrenia. A recent meta-analysis of imaging data of patients with schizophrenia performing working memory and cognitive control tasks generally found evidence for reduced prefrontal engagement (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009), which is consistent with the notion of hypofrontality. Another such meta-analysis did not find consistent evidence supporting hypofrontality of schizophrenia patients during working memory processing, nor did it find evidence supporting hyperfrontality (Van Snellenberg, Torres, & Thornton, 2006). Rather, this study found that prefrontal activation during working memory performance of

patients with schizophrenia varied across studies, demonstrating both increased activity and decreased activity compared to controls, and this activity was found to be moderated by the magnitude of performance differences between patients and controls (Van Snellenberg et al., 2006).

While the revised dopamine hypothesis was a step forward in conceptualizing schizophrenia etiology, it was not without its limitations. For example, many tenets of the hypothesis were based on animal research, as there was scant direct or indirect evidence in humans demonstrating low dopamine levels in the frontal cortex. Further, few studies at that time had demonstrated evidence of elevated dopaminergic striatal function in humans (recent studies, as discussed below, have provided some evidence for striatal dopamine dysregulation). However, it was influential for providing information about the locus of neural dysfunction and their relationship to symptom dysfunction.

1.3. The Second Revision of the Dopamine Hypothesis

Recently, a second revision of the dopamine hypothesis, proposed by Howes et al. (2009), shifted focus slightly from previous versions. It proposes, like previous theories, that striatal dopamine dysregulation is associated with psychosis in schizophrenia, but that a number of factors contribute to this dysregulation (for example, stress, drug use, genetics, fronto-temporal dysfunction, etc). Further, dopamine dysregulation associated with psychosis does not appear to be well explained by differences of dopamine transporters or D2 type dopamine receptors availability, given that differences between patients and controls are inconsistently found and are of small effect (Howes et al., 2012). Instead, this recent revision to the dopamine hypothesis suggests that the locus of striatal dopamine dysregulation lies with presynaptic dopaminergic control, which impacts baseline synaptic dopamine levels, dopamine release, and dopamine synthesis capacity. Positron emission tomography (PET) studies examining

differences in dopamine synthesis capacity typically use radiolabeled-*l*-dihydroxyphenylalanine (L-DOPA), which is converted to dopamine and stored in presynaptic vesicles for release (see 2006 for a review). A recent meta-analysis examining 618 patients with schizophrenia and 606 controls, taken from 44 studies, demonstrated a highly significant elevation in presynaptic dopamine functioning in patients with a large effect size (Cohen d=0.79; Howes et al., 2012). This pattern was true even when excluding studies with patients receiving antipsychotic medication. At least one study of patients with schizophrenia has localized the dopamine synthesis capacity abnormality to the associative striatum, particularly the precommissural dorsal caudate (Kegeles et al., 2010).

A number of studies over the past few years have provided robust support for the idea that presynaptic dopamine levels and dopamine release are associated specifically with psychotic symptoms and with antipsychotic use efficacy. For example, studies have found that dopamine synthesis capacity within the striatum is elevated for individuals who are at ultra-high risk for developing psychosis, that within the striatum increased synthesis capacity is localized to the associative striatum (Egerton et al., 2013; Howes et al., 2009), and capacity is positively correlated with the severity of prodromal symptomology but not with the severity of anxiety or depressive symptoms (Howes et al., 2009). There is evidence suggesting that dopamine synthesis capacity in the associative striatum may be able to predict the onset of psychosis, even amongst those individuals deemed to be at high risk for developing the disorder. Howes et al. (2011) assessed dopamine synthesis capacity of healthy participants and participants who were at ultra-high risk for psychosis, and then followed up with these participants 3 years later. Diagnostic interviews were done to determine who amongst the ultra-high risk group when on to develop a psychotic disorder. Subjects were then divided into three groups: healthy participants, those who were at high-risk for developing psychosis but did not transition, and those who were at high-risk for developing psychosis and did transition. The study found that participants who went on to transition to psychosis had significantly greater dopamine synthesis capacity within

the associative striatum than both the healthy and high-risk non-transition groups (Howes et al., 2011). Dopamine synthesis capacity may also be able to predict which patients with schizophrenia will respond to antipsychotic medication from those who will be treatment resistant (Demjaha, Murray, McGuire, Kapur, & Howes, 2012), such that patients to respond to medication have significantly greater dopamine synthesis capacity than patients who do not and well controls. While patients who are resistant to antipsychotic medication intervention may not show differences of dopamine synthesis capacity when compared with controls and patients who do respond to medication use, there is some early evidence to suggest that treatment resistant patients may have increased glutamate levels, particularly within the anterior cingulate (Demjaha et al., 2014)

The second revision of the dopamine hypothesis also de-emphasizes the role that the prefrontal cortex has on symptom expression, as the evidence supporting prefrontal hypodopaminergia is inconclusive. For example, dopamine transmission in the prefrontal cortex is mainly mediated by D1 receptors. While D1 dysfunction has been linked to cognitive dysfunction and negative symptoms in schizophrenia (Goldman-Rakic, Castner, Svensson, Siever, & Williams, 2004), studies examining the relationship between D1 receptor levels, schizophrenia symptoms, and cognition have either found no difference between patients and controls (Karlsson, Farde, Halldin, & Sedvall, 2002), decreased receptor density (Okubo et al., 1997), or increased D1 receptor density (Abi-Dargham et al., 2002; Berridge, 2007). Given these inconsistent results, the second revision focuses its attention on presynaptic dopamine as a mechanism leading to striatal dopaminergic dysregulation in schizophrenia.

1.3.1. Motivational Incentive Salience and Schizophrenia

The second revision of the dopamine hypothesis goes on to link its neurochemical hypothesis with the clinical phenomena of schizophrenia by considering the motivational incentive salience literature. The motivational salience hypothesis suggests that dopamine

mediates the conversion of an external stimulus from a neutral representation into one that is attractive or aversive (Berridge & Robinson, 1998). In addition to motivational salience there are other competing theories that describe the causal contribution mesolimbic dopamine activity has on reward and motivation, including theories of hedonia or 'liking' as well as learning and reward prediction theories (Berridge, 2007). Berridge (2007) reviewed these theories and the evidence to support them and suggested that, given the evidence, dopamine is not necessary for experiencing hedonia or for learning via prediction signals (Berridge, 2007). However, of the three theories dopamine was necessary to produce 'wanting' and dopamine activation was sufficient to assign incentive salience to external, neutral, stimuli (Berridge, 2007). While this argument suggests that, with regard to reward and motivation, dopamine may be more important for motivational incentive salience, it does not suggest that dopamine is unimportant for hedonics and learning. Rather, it suggests that the role of dopamine in the attribution of salience provides an interface where hedonics, reward prediction, and learning mechanisms allow for an organism to focus its efforts on what it determines to be valuable and facilitates motivational drives to action. The importance of dopamine for "wanting" or incentive salience is discussed in a review by Palmiter (2008), in which he examines the literature of genetically engineered mice that lack tyrosine hydroxylase (responsible for catalyzing the conversion of L-tyrosine to L-DOPA, precursor to dopamine) in all dopaminergic neurons. These mice, he observes, become hypoactive and aphagic (refusal to swallow), and starve by the time that they reach 4 weeks of age. Mice that are dopamine-depleted are not motivated to engage in goal-directed behaviors, but still have a preference for rewarding foods, like sucrose, and can still learn from conditioning. Restoring dopamine selectively in the dorsal striatum is sufficient to allow feeding, locomotion, and it appears to restore motivation to engage in goal-directed behaviors.

Under normal circumstances, dopamine mediates the acquisition of motivational salience assignment in response to a stimulus based on a person's experience or preference,

but it does *not* create this process *independent* of stimulus. In psychosis, however, the revised dopamine hypothesis suggests that dysregulated dopamine transmission leads to *stimulus-independent* release of dopamine, which then leads to aberrant salience assignment to external stimuli as well as internal representations (Kapur, 2003). As such, this hypothesis proposes that dysregulated dopamine release contributes directly to the formation of delusional symptoms via inappropriate attribution of salience to "neutral" events in the environment. More specifically, the psychotic experience is thought to evolve in stages, where initially an individual with schizophrenia may simply have a heightened "awareness", where previously irrelevant stimuli in the environment become relevant. Subsequently, these individuals may feel driven to act on and/or explain the newly relevant phenomenon (G. Roberts, 1992) at which point a top-down cognitive explanation is imposed. Over time, the delusional framework is created. With hallucinations a similar process may take place but with the initial aberrant salient experience being internal representations – internal thoughts, guilt, etc (Kapur, 2003). This recent revision to the dopamine hypothesis does describe how incentive salience models might explain negative symptoms, suggesting that dopamine dysregulation diminishes reward signals thereby producing symptoms like anergia and anhedonia in a similar way that dopamine depletion affects mice, but Kapur (2003) suggests that incentive models may be more appropriate for explaining positive symptoms.

1.3.2. Studies Examining Aberrant Incentive Salience and Schizophrenia

The formation and expression of aberrant salience assignment is thought to involve the dorsal and ventral striatum, which receives inputs dopaminergic inputs from the substantia nigra and VTA, respectively. As discussed above, glutamatergic projections from the PFC, amongst other regions, to the VTA also influence dopaminergic input to the ventral stratum. Few studies have examined the relationship between aberrant incentive salience, schizophrenia symptom expression, and brain functioning. Studies of healthy participants have shown that the ventral

striatum plays an important role in associative learning, where participants learn to associate relevance to a neutral stimulus after repeated paring with an unconditioned stimulus, using both appetitive and aversive stimuli (McClure & Lieberman, 2003; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). For patients with schizophrenia there is behavioral evidence suggesting they exhibit aberrant salience when performing a salience attribution test, which was particularly evident in patients with delusions (Roiser et al., 2009), and there is neuroimaging evidence that this aberrant salience assignment is associated with activity in the ventral striatum in both medicated (Jensen et al., 2008) and unmedicated (Esslinger et al., 2012) patient populations. Thus, there is evidence that 1) patients with schizophrenia, thought to have dysregulated dopaminergic activity, demonstrate aberrant salience assignment behaviorally; and 2) that this aberrant salience assignment is associated with activity in the ventral striatum. However, a number of studies suggest that the locus of the major dopamine abnormality of patients with schizophrenia compared to controls is in the dorsal striatum. What, then, is the relationship between dysregulated dopamine, aberrant salience, and dorsal striatal functioning? Moreover, is there are relationship between aberrant salience, dorsal striatal functioning, and other symptoms of schizophrenia like deficits of cognition?

1.4. Cognitive Control and Schizophrenia: Background

While patients with schizophrenia display cognitive deficits in a variety of domains, it may be the case that a common denominator for these deficits is impaired cognitive control. In fact, areas of relative cognitive strengths in schizophrenia are in tasks or domains that are not dependent on executive control. For example, meta-analytic studies have shown that effect size differences on tasks of simple attention are smaller than those of complex working memory tasks and executive functioning tasks (Dickinson et al., 2007; Reichenberg & Harvey, 2007). Further, a meta-analysis of a canonical task of executive control (the Wisconsin Card Sorting

Task; WCST) has shown that patients with schizophrenia are severely impaired (Dickinson, Ramsey, & Gold, 2007) and that their performance distinguishes them not only from controls, but other psychiatric groups as well (Johnson-Selfridge & Zalewski, 2001).

Cognitive control is thought to be a critical aspect of cognition as it allows for goal related information to be selected for maintenance and maintained, protected against interference, and updated when appropriate (Braver & Cohen, 2000; J. D. Cohen, Braver, & O'Reilly, 1996; Norman & Shallice, 2000; Oberauer, 2009; Randall & Munakata, 2000). This goal directed behavior might depend upon reward signals that have a neuromodulatory effect on neural processing in the prefrontal cortex (Braver & Cohen, 2000). Theoretical models of cognitive control dysfunction in schizophrenia (e.g. Braver, Barch, & Cohen, 1999) have suggested that disrupted dopaminergic signaling associated with schizophrenia interfere with a gating mechanism that facilitates the control of information during cognitive control. More specifically, Braver et al. (1999) suggest that dopamine activity signals the presence of goal relevant information, which allows this information to be updated or gated into active memory, and dysregulated dopamine signaling can disrupt the control of information gated into active memory as well as the protection of maintained information against irrelevant information. One problem with theories that propose updating of prefrontal information representations via direct mesocortical dopamine input is that this signal updates the PFC globally, which would make selective updating of prefrontal information representations difficult. Another indirect route by which dopaminergic signals may impact prefrontal control processing is through nondopaminergic inputs (e.g. basal ganglia-thalamocortical loops). One theory, originally proposed by Frank et al. (2001) addresses the global dopamine updating problem by suggesting that the basal ganglia, via guidance by dopaminergic inputs, may work to gate information in specific areas of the cortex during cognitive control.

1.4.1. Basal Ganglia Involvement in Cognitive Control

Frank et al. (2001) also proposes that cognitive control tasks, like working memory tasks, require rapid updating, maintenance, interference control, and a mechanism of gating. This model suggests that these processes are executed by an interaction between the basal ganglia and the frontal cortex, such that the frontal cortex uses continuously firing activation to maintain information over time and the basal ganglia fires only to trigger appropriate task related updating. Further, this model assumes that separate memory representations are possible and are represented via the striped micro-anatomy of the PFC (from Hazy, Frank, & O'Reilly, 2006). These stripes are characterized by small groups of interconnected neurons somewhat isolated from one another, which may protect them from interference from representations in nearby stripes. According to the model selective updating is accomplished via independent, updatable parallel loops known to exist in between the basal ganglia and the PFC (Middleton & Strick, 1994) that are selective to anatomical stripes in the PFC. By incorporating the stripe-based gating architecture this model attempts to address the global updating problem of other dopamine-based gating models.

The mechanisms that allow gating to occur in the Frank (2001) model are considered an evolutionary extension of the same mechanisms involved in the motor control system: the direct and indirect pathways (Hazy, Frank, & O'Reilly, 2007; Smith, Bevan, Shink, & Bolam, 1998). In the motor domain, learned action history shapes reward signaling to the basal ganglia, which then inhibits or disinhibits frontal motor representations to allow an action to occur and to inhibit unwanted actions. Neurons in the direct pathway, or the Go pathway, and the indirect pathway, or the NoGo pathway, originate in the caudate. The Go pathway is sensitive to D1 receptor stimulation and the NoGo pathway is sensitive to D2 receptor stimulation. When neurons in the Go pathway fire they inhibit the substantia nigra pars reticulate (SNr), which inhibits the thalamus, when then releases regions of the cortex from its tonic inhibition. When neurons in the NoGo pathway are tonically active, and inhibit the globus palladus, which disinhibits the SNr, and thus allows for tonic inhibition of the cortex via the thalamus. Increased activity of the Go

pathway is associated with facilitation of movement and increased activity of the NoGo pathway is associated with the inhibition of movement (Smith et al., 1998). Disorders of motor dysfunction, like Parkinson's, are the result of an imbalance of Go and NoGo pathway activity, where a depletion of dopamine in the striatum diminishes Go pathway activity and impairs movement initiation. Similarly, these pathways may inhibit and disinhibit regions of the frontal cortex responsible for representing target information necessary to mediate cognitive control demands. That is, Go pathway signals that are triggered by increases in dopamine in response to target stimuli and this Go activity facilitates information updating in the cortex. NoGo activity, on the other hand, is tonically active and facilitates the maintenance of information over time. Further, the model predicts that recurrent maintenance processes in the prefrontal cortex will demonstrate transient activity when a task irrelevant distractor is presented, but regions in the basal ganglia will not activate because the distractor fails to initiate an update signal (also see Gruber, Dayan, Gutkin, & Solla, 2006). *Thus, according to the model, during the execution of updating task relevant information one would expect to see "Go" activity in both the striatum and the frontal cortex, but during the presentation of task irrelevant distracters, a "NoGo" condition, one would not expect to see increased activity in the striatum but transient activity in the prefrontal cortex.*

Interestingly, few studies have explicitly examined the role of the striatum during updating task performance. Updating is thought to be an important part of executive functioning (Miyake et al., 2000; Oberauer, 2009) and can be described as the overwriting of active memory representations with new, task relevant information. It is a construct that has been shown to be separable from other cognitive constructs associated with executive functioning. For example, Miyake (2000) used a latent variable analysis and found that performance on updating tasks were dissociable from performance on tasks that required shifting between mental sets, or tasks that required the inhibition of proponent processes. Given the apparent construct validity for these updating tasks Collette et al. (2007) conducted a functional imaging study to identify

regions of the brain that activated similarly during updating processing. By adapting updating tasks from the Miyake (2000) study and using conjunction analysis they found a large cerebral network including the left frontopolar region and left middle frontal gyrus was common to the different updating tasks used in the study, although activation in some regions was more specific to the particular task used. They did not find basal ganglia involvement during updating task performance. However, because such a large number of cerebral areas were involved in updating they concluded that the unitary nature of the updating construct may be questionable. Alternatively, they note that in addition to updating the tasks that were used in the study required encoding, the maintenance of information, sequencing, and a response. As such, using an updating task that attempts to separate these processes may better capture brain activity associated with updating processing.

A study by Roth et al. (2006) used a visual updating task that was designed to separate maintenance activity from updating activity. They used a mixed-event blocked design and deconvolution analysis to estimate time courses, and also found that a distributed network of regions was associated with updating (greater activity during updating than during maintenance activity). Included within this network of regions was a region in the left lateral dorsal striatum. While this study provided some support for the involvement of the basal ganglia in updating, a number of other regions also showed similar patterns of activity (e.g. middle frontal gyrus) and there was no evidence to suggest that one region contributed differently to update processing than another.

Another study by McNab & Klingberg (2008) investigated the neural basis for accessing control to working memory storage. Their results were consistent with the idea that an individual's working memory capacity is determined by their ability to selectively filter irrelevant distracters, as they found that middle frontal gyrus and globus pallidus activity were significant predictors of working memory capacity, and globus pallidus activity was negatively correlated with distracter storage. That is, they suggest that globus pallidus activity actively filters

distracting information, thus freeing up working memory capacity. As globus pallidus activity decreases the number of distracting items stored increases. They suggest that the globus pallidus functions as a filter mechanism for working memory, however their results did not extend to the dorsal striatum.

To better examine the dynamic activations between the cortex and the basal ganglia during cognitive control, a study would need to utilize a single task that not only incorporates important component processes of cognitive control, but one that also isolates these elements from one another. Such a task was used in my prior work (Ceaser et al., in prep). In this previous study we used an event-related imaging design to isolate task events in time as well as a novel task of updating that separately examined updating, interference control (the protection of stored information against task irrelevant information), and simple maintenance. We found a dissociation between subcortical and cortical regions of the brain during updating and interference control, such that both cortical and subcortical regions displayed robust updating activity, but only cortical regions demonstrated increased activity when compared to a "do nothing" condition. The striatal regions that showed a main effect of condition (the conditions being update, interference control, and simple maintenance) and an interaction of condition by time (specifically, the time window encompassing the presentation of an update cue and a 7 second delay prior to the presentation of a probe) were almost entirely left lateral, and with the exception of one region in the caudate were all dorsal caudate or dorsal caudal putamen (dorsal were those with a $z \geq 2$ and caudal regions were those with a $y \geq 0$). This finding suggests while both cortical and subcortical regions are involved in updating processing, the patterns of activity in frontal cortex and striatum are dissociable, and are generally consistent with the pattern of effects one would predict from the Frank (2001) model.

1.5. Aberrant Salience and Cognitive Control: Proposed Study

While there is consistent evidence suggesting that the dorsal striatum is the locus of the

largest dopamine abnormality for patients with schizophrenia, evidence suggesting that this disruption of striatal functioning may lead to aberrant salience assignment, and some evidence suggesting the striatum may function as a cognitive gating mechanism that is likely dependent upon well regulated dopaminergic signaling, few studies if any have found a relationship between these findings. Thus, the question remains: Is there are relationship between aberrant salience, dorsal striatal functioning, and other symptoms of schizophrenia like deficits of cognition? Like other models describing the mechanisms of cognitive control impairment in schizophrenia (Braver & Cohen, 1999), the Frank model also predicts that dysregulated dopamine will disrupt the gating signal, in this case Go signal activity, and lead to impaired cognitive control. Dopamine dysfunction could cause the inappropriate updating of task irrelevant information (inappropriate Go signaling), or weaken maintenance signaling (disrupted NoGo signaling) for patients with schizophrenia. Both impairments could lead to increased distractor susceptibility for patients. If, given our previous work (Ceaser et al., in prep), the basal ganglia are selectively involved in updating we predict that patients, who have dysregulated striatal dopamine signaling, demonstrate increased activity compared to controls when presented with task irrelevant distractors. Further, it may also be the case that there is a relationship between aberrant salience assignment, thought to be associated with positive symptoms of schizophrenia like delusions and hallucinations, and disrupted cognitive control gating that leads to performance deficits during distractor resistance. In fact, evidence for this is provided by a recent study by Morris et al. (2012), who found that positive symptoms scores of schizophrenia were related to learned irrelevance, and that even within the patient group high positive symptom patients were significantly worse at ignoring irrelevant information than low positive symptom patients. One difficulty with linking impaired cognitive control to impaired subcortical DA function and aberrant salience in schizophrenia is that the majority of prior studies examining cognitive functioning in schizophrenia have not found a relationship to global measures of positive symptoms (Breier, Schreiber, Dyer, & Pickar, 1991; Nuechterlein et al.,

2011; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). However, few studies have specifically examined the relationship between specific subcomponents of cognitive control and the specific aspects of positive symptoms that the second revision of the dopamine hypothesis would predict to be related to abnormal (i.e. aberrant salience).

Using a novel task that is specifically designed to better isolate different aspects of cognitive control (e.g. updating, maintenance, and interference control), we will test whether or not patients demonstrate disrupted basal ganglia activity compared with controls during cognitive control performance, and determine whether or not these disruptions in brain activity are associated with particular aspects of behavioral performance as well as clinical symptoms of schizophrenia, specifically aberrant salience, delusions, and hallucinations.

1.6. Specific Aims

Specific Aim 1: Test the hypothesis that individuals with schizophrenia demonstrate dysregulated striatal activity during updating and interference control and that striatal activity predicts performance deficits. Using a novel task of cognitive control and functional magnetic imaging, I will scan both patients and controls to examine cortical and subcortical brain activity changes during task performance. Given evidence that patients with schizophrenia have dysregulated dopamine activity in the striatum I predict that individuals with schizophrenia will show: 1) reduced striatal signal during updating which will be associated with poorer updating performance; and 2) increased striatal activity during the presentation of irrelevant distractors, which will be associated with poorer distracter resistance.

Specific Aim 2: Test the hypothesis that in individuals with schizophrenia, increased striatal activity during distracter presentation will be positively associated with aberrant salience symptoms, delusions, and hallucinations of patients with schizophrenia. Using a variety of clinical tools to assess schizophrenia symptomology (including the Scale for the Assessment of Negative Symptoms, SANS; the Scale for the Assessment of Positive Symptoms,

SAPS; and the Aberrant Salience Inventory, ASI) I will examine the relationship between symptom scores and striatal activity during distracter presentation. Symptom scores of delusions and hallucinations will be obtained from the SAPS. The ASI will be used to assess overall aberrant symptom salience. I predict that increased striatal activity will be associated with increased symptom severity of delusions, hallucinations, and the index of aberrant salience from the ASI. Further, increased symptom severity will be associated with increased intrusion errors during distractor presentation.

2. Methods

Participants were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St. Louis. We recruited 56 participants (30 individuals with schizophrenia and 26 healthy controls). Of those participants, 4 were excluded from data analysis because of excessive head movement while in the scanner, 9 were excluded for not completing both phases of the study, and 1 healthy control was excluded because of aberrant behavioral performance (determined by mahalnobis distance, described below). This left us with 22 participants in the patient group and 20 participants in the healthy control group. Patients were diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002). These interviews were conducted by a master's-level clinician, who completed SCID-IV training and participated in regular diagnostic training sessions as part of the CCNMD. Controls were given a Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to determine the presence of a history of mental illness. Exclusion criteria for controls included a lifetime history of any psychiatric disorder and having a first-degree relative with a psychotic disorder. Participants in either group were excluded if they met criteria for substance abuse or dependence within the past 6 months, have a clinically unstable or severe medical disorder, a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous, had head trauma with loss of

consciousness, or met DSM-IV criteria for mental retardation. Patients were stable on antipsychotic medication doses for at least 2 weeks before participating in the study.

All participants were given the Vocabulary and Matrix reasoning subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) to assess both verbal and non-verbal intelligence. Socioeconomic status was assessed by asking participants two open-ended questions for each parent about what the parent currently does and what they did for a living most of their life. Parental education was assessed by asking participants open-ended questions about the highest level of education each parent attained. The answers were classified using a scale similar to the British Registrar General's social classification of occupations where occupations range from 0 (low occupational status) to 45 (high occupational status). Given that disease progression and cognitive disturbances associated with schizophrenia risk may impair educational attainment and achievement we focused on parental socioeconomic status and parental education as they may be a more appropriate way to assess developmental exposure to educational opportunities that could influence cognitive function (Resnick SM, 1992).

2.1. Clinical Rating Scales

We conducted assessments of the current level of clinical expression in both patients and controls. Clinical symptoms of patients were assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). These assessments were conducted by a master's-level clinician. All participants also completed the Chapman Psychosis Proneness Scales (L. J. Chapman, Edell, & Chapman, 1980), which included the Perceptual Aberration Scale, the Magical Ideation Scale, the Physical Anhedonia Scale, and the Social Anhedonia Scale.

We assessed aberrant salience specifically using the Aberrant Salience Inventory (ASI). The ASI was developed to asses the unusual or inappropriate assignment of salience,

significance, or importance to non-salient stimuli (Cicero, Kerns, & McCarthy, 2010). It consists of 29 items created to capture the phenomenological descriptions of the initial experience of psychosis in the literature (Kapur, 2003; Parnas, Handest, Saebye, & Jansson, 2003). Items for the ASI were generated by Cicero et al. (2010) based on the phenomenological descriptions of the initial experience of psychosis in the literature, descriptions of the prodromal phase of schizophrenia, and transcripts of interviews of people with schizophrenia. Cicero et al. (2010) found that the ASI was strongly, positively correlated with scales assessing psychotic-like experiences, including magical ideation and perceptual aberration, and other scales measuring psychosis-proneness. The ASI was also found to be positively correlated with social anhedonia, but the correlation was weaker than the correlation between ASI and other scales assessing psychoisis-proneness. The weaker relationship between ASI and anhedonia was predicted given previous work demonstrating a weaker relationship between psychosis-proneness and social anhedonia (Kwapil, 1998). Further, the ASI was found to be elevated in healthy individuals with elevated psychosis proneness as well as participants with a history of psychosis, even when comparing them with a psychiatric comparison group (Cicero et al., 2010). The utility of the ASI, compared to other scales measuring psychosis proneness, is in its specificity. While other scales, including magical ideation and perceptual aberration (CHAPMAN), the Structured Interview for Prodromal Syndromes (SIPS; Kwapil, 1998), and the Schizotypal Personality Questionnnaire (SPQ; Raine, 1991), contain items that are similar to aberrant salience there are other items that may tap into constructs that are related, but peripheral to the core construct of aberrant salience.

2.2. Task Design and Stimuli

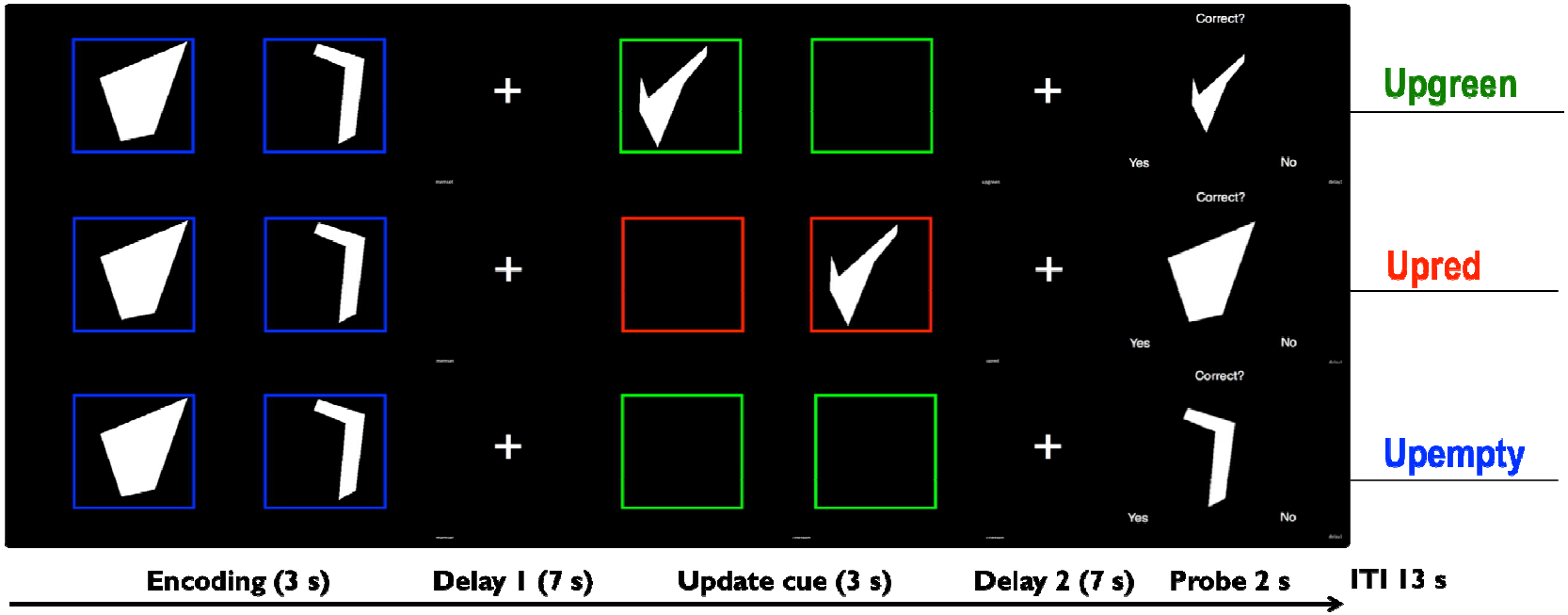
While in the scanner subjects completed a modified Sternberg-type delayed match-to-sample working memory task. The task contains a two-item working memory load consisting of two complex geometric shapes (Attneave & Arnoult, 1956) that were generated using a Matlab

algorithm (Collin & McMullen, 2002). These stimuli were chosen because they may be more difficult to encode than words or numbers, and thus we hoped to restrict encoding strategies used by subjects. By doing so we hoped that the level of difficulty for both patient and control groups would be more comparable, as individuals with schizophrenia and controls would be less likely to spontaneously engage in such verbal maintenance strategies. The shapes were white on a black background and each trial of the task consisted of three distinct, temporally isolated, periods: memory set presentation, update cue presentation, and probe presentation (see Figure 2.1). During the memory set participants were presented with two shapes, one after another, framed in a blue box. The shapes were presented for 1.5 seconds each. Participants were asked to memorize these shapes in the order that they were presented. After the second shape participants saw a fixation cross in the center of the screen that was presented for 7 seconds. Participants were instructed to focus on the cross while maintaining the previously presented items (Delay 1 in Figure 2.1). After the first delay participants were presented with the update cue items: 2 green or red boxes presented one after another for approximately 1.5 seconds each. If the boxes were green (an Upgreen trial, part A in Figure 2.1) and a shape appeared in one or both of the boxes, participants were asked to replace the original shape that appeared in that position (the first or second shape that was framed in blue during memory set presentation). During an Upgreen trial participants made either a partial (one shape, either in the first or second position) or a whole update of the original shapes presented during the memory set. If the boxes were red (a Upred trial; part B in Figure 2.1) participants were asked to ignore any new shapes that were presented and continue remembering the original shapes framed in blue. If, during the update cue, both boxes were empty (an Upempty trail; part C in Figure 2.1) participants were not required to do anything but maintain the original shapes of the memory set that were framed in blue. Boxes during Upempty trials could be either red or green. Because no new shape was presented participants were instructed that the color of the boxes was irrelevant.

At the presentation of the probe, participants were presented with one shape, the word

“Correct?” appeared at the top of the screen, and at the bottom the word “Yes” appeared on the right and the word “No” appeared on the left. Participants were asked to make a button press if the shape that was presented matched one of the two shapes that they were currently remembering. There were a total of 120 trials used in the task (52 Upgreen, 48 Upred, and 20 Upempty; Appendix Table F). A number of differing probe types were used in the task to capture a variety of errors that an individual could make during task performance. For example, during Upgreen trials the participant was probed with probed with the item they should have updated. This trial was called an “Update” trial. A correct response indicates that an appropriate update was made and that the new information was encoded into memory. There were a total of 20 Update trials. Another Upgreen probe we used was called a “Resist Maintenance” trial, and participants were probed with the shape in the original memory set that should have been replaced by the new item during the update cue. A correct rejection of this shape indicates that the subject rejected this item as one of the two correct shapes, but a response of “yes” to this items suggests that the participant incorrectly maintained this item in the target set. This type of trial is called a Resist Maintenance trial because participants must resist maintaining this shape when they were being asked to replace it during the update cue. There were a total of 20 Resist Maintenance trials. For trials where the participant was asked to ignore information (Upred), we probed participants with one shape from the original memory set. A correct response on this trial type suggests that the participant was able to maintain information even when presented with task relevant distracters during the update cue period. These trials are called “Resist Distracter” trials and there were 20 of these trials during the task. Another probe type that was used during Upred trials involved participants being probed with a shape that they were asked to ignore during the update cue. These trials are called “Resist Distracter Lure” trials and there were also

Figure 2. 1 Controlled Update Task Design



20 trials of this type in the task. A correct response during this trial type indicates that a participant correctly rejected a shape that did not match one of the to-be-remembered shapes. An incorrect response on this trial type suggests that the participant inappropriately encoded this shape into memory. Dysregulated salience assignment may lead to increased errors on this trial type, as task information designated as irrelevant may be inappropriately assigned some relevance. Finally, for Upempty trials participants were probed with an item from the original memory set. There were 14 of these trials and they are called “Maintenance” trials. A correct response indicates that the participant correctly maintained this information over the course of the trial. In addition to the probes used in the above mentioned trials participants were probed with shapes that were not presented previously. These trials are called “Novel Probe” trials (26 trials of this type) and were included to ensure that participants could reject probes that were obviously incorrect, and thus these trials gave us a measure of how well participants understood the task’s instructions.

2.3. fMRI Acquisition

Structural and blood-oxygen-level-dependent (BOLD) data was acquired with a 3T Tim TRIO scanner (Siemens, Malvern, Pennsylvania) at Washington University. Stimuli were projected behind the scanner, visible through a mirror above the eyes. Subjects completed 120 task trials over the course of 10 bold runs. The various trial types were, to the extent possible, evenly interspersed within the 10 runs. Twelve trials occurred in each run. Each trial lasted 35 seconds (Figure 2.1). Functional images were acquired using a gradient echo echo-planar sequence maximally sensitive to BOLD contrast (T2*) (repetition time [TR] = 2000 ms, echo time [TE] = 27 ms, field of view [FOV] = 256 mm, flip = 90°, voxel size = 4 mm3). Subjects completed a 7.38- minute BOLD run comprised of 210 volumes containing oblique axial images (35 slices per volume) which was acquired parallel to the anterior-posterior commissure. Structural images were acquired using a sagittal MP-RAGE 3D T1-weighted sequence (TR =

2400 ms, TE = 3.16 ms, flip = 8°; voxel size = 1 x 1 x 1 mm).

Preprocessing included: 1) Slice-time correction, 2) Removal of first 5 images from each run to reach steady state, 3) Elimination of odd/even slice intensity differences given interpolated acquisition, 4) Rigid body motion correction (Ojemann et al., 1997), 5) Intensity normalization to a whole-brain mode value of 1,000 without bias or gain field correction, 6) Registration using a 12-parameter affine transform of the structural image to a template image in the Talairach coordinate system (Talairach & Tournoux, 1988), 7) Co- registration of fMRI volumes to the structural image with 3 mm re-sampling (R. L. Buckner et al., 2004; Ojemann et al., 1997), and 8) Smoothing using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.4. Quality Control

We compared the two groups on movement indices and SNR to determine whether there were group differences in these factors that may be influencing group differences in fMRI results. If there were, we confirmed the results of analyses below using subsets of patients and controls matched for movement and SNR. We also used techniques discussed by Siegel et al. (2013) to remove from GLM estimation volumes in which head motion exceeded a threshold (0.5 mm of frame displacement). Participants who lost greater than 40% of the total number of frames, or more than 84 of the 210 frames, were excluded from further analysis.

3. Data Analysis

3.1. Demographics and Behavioral Data

We conducted a Mahalanobis distance analysis on the task variables to identify multivariate outlier values, or cases where an individual is responding differently compared to other participants across multiple dimensions. Mahalanobis distance was calculated separately for patients and control for accuracy (including trial types Maintenance, Resist Distracter, Resist Distracter Lure, Update, and Resist Maintenance trials). The probability of distance values were

computed separately for patient and control groups. Mahalanobis distance values were assessed using χ^2 (5, N = 43) = 11.07, $p < 0.05$), where values with a probability of less than 0.05 were determined to be outliers and were removed from further analyses.

Chi-squared tests were used for categorical variables (gender, ethnicity) to determine if these distributions differed between groups. We conducted t-tests on age, education level, parental education, symptom scores, and measures of IQ (standard scores of verbal and non-verbal IQ) to determine if these variables differed between diagnostic groups. Independent Mann-Whitney U tests were done for variables that failed to demonstrate variance equality.

With regard to task data, because we were primarily interested the Update and Resist Distracter Lure trials, we conduced at repeated measures ANOVA, with trial type (2 levels; Update and Resist Distracter Lure trials) as the within subject factor and diagnosis (2 levels; patients and controls) as the between subject factor. We were particularly interested in these trials because behavioral accuracy is critically dependent on intact gating functioning. Planned contrasts were done when appropriate to determine whether patient performance significantly differed from controls. A secondary repeated measures ANOVA was done that included the remaining task trials, with trial type (6 levels; Maintenance, Resist Distracter, Resist Maintenance, and the 3 novel probe trial types) as the within subject factor and diagnosis (2 levels; patients and controls) as the between subject factor.

3.2. fMRI Data Analysis

3.2.1. Types of GLMS

We analyzed the fMRI task data in two ways, creating two sets of GLMs. The first set of GLMs focused on the 3 events that occurred during the update cue of the trial. We refer to this as the "*Condition*" analysis. For the Condition analysis all trial types were collapsed into three events, ignoring the different probe types that could occur within a condition: 1) the update condition (Upgreen) in which participants were required to make a update of information, 2) the

interference control condition (Upred) in which participants were required to ignore distracters, and 3) the maintenance condition (Upempty) in which participants were not presented any shape stimuli, and were simply required to maintain the items from the memory set. Analyses at the level of Condition could reveal differences between groups when tasked with making an update, ignoring distracters, or simply maintain information. A second way we analyzed the fMRI task data was to take into account the different probe types within each task condition (i.e. breaking the Upred condition into Resist Distracter, Resist Distracter Lure, and Resist Distracter Novel Probe trial types). Breaking conditions up allowed us to examine brain activity associated with specific errors of interference control, inappropriate updating errors for example (Resist Distracter Lure trials), as apposed to a more general error of interference control (i.e. Upred Condition trials). We refer to this as the "*trial type*" analysis. For each of these sets of GLMs, we estimated task-related activity in each voxel for each subject without assuming a hemodynamic response function (HRF) response (Ollinger, Corbetta, & Shulman, 2001). Fifteen frames of each trial were estimated for correct and incorrect trials of separately, and the resulting beta estimates of event-related responses at each trial time point were entered into second-level analyses that treated subjects as a random factor.

3.2.2. Analysis Approach: Independently Defined ROIs versus Anatomical Mask

One approach we used to examine the effects of task Condition was to use ROIs identified in a previous study of healthy controls using the same task paradigm to assess the brain activity as a function of task condition (Ceaser et al., in prep). The results of this study revealed patterns of brain activity in response to task conditions that differed between cortical and subcortical brain regions. Using these independently defined ROIs allows us to enhance statistical power to detect effects by restricting our analysis to only voxels within the previously defined regions, but also to attempt to replicate our previous findings and to determine whether activity in these regions went on to interact with diagnosis. These regions will be referred to as

the *independently defined ROIs* in the results section. We considered a region to be significant for this analyses if $p<.05$.

We were also specifically interested in whether regions in the prefrontal cortex and basal ganglia, specifically the dorsal striatum, demonstrated condition effects. Thus, as a second approach we used anatomical masks of the basal ganglia (Wang et al., 2008) and the prefrontal cortex (Rajkowska & Goldman-Rakic, 1995), and examined voxel-wise analyses of brain activity within these masks. These ROIs were combined into a single mask (see Appendix A for a multislice image of the combined masks) and we used a small volume type I error correction, implemented via the Analysis of Functional Neuroimages AlphaSim, of $Z > 2.32$, $k = 20$ voxels for this combined ROI mask. This analysis could produce regions that show main effects of condition and time, and a 2-way interaction of condition by time.

3.2.3. Replication of Prior Results in Healthy Individuals

To determine whether we could replicate findings from our previous study in the Independently defined ROIs, we examined only the healthy participants in the current study and conducted a repeated measures ANOVA at the region level with condition (3 levels; Upgreen, Upred, and Upempty) and time (5 levels) as factors. The 5 TRs we used for this analysis corresponded to the 5 TR following the presentation of the update cue (frames 8-12, accounting for hemodynamic lag). Only correct trials were examined in this analysis. If an ROI demonstrated either a significant effect of condition or an interaction of condition and time, we then conducted follow-up analyses to determine the source of theses effect, with each analyses comparing one condition to another. Separate ANOVAs were done for conditions Upgreen versus Upempty and Upred versus Upempty.

Following the ROI analysis using previously defined regions, next conducted voxel-wise analyses within our anatomical masks using only the controls to see if our previous results would replicate. Specifically, we conducted voxel-wise repeated measures ANOVA with

condition (3 levels; Upgreen, Upred, and Upempty) and time (15 levels) as factors. We included all 15 frames of the trial in the analysis to capture regions that show effects of interest, but at *any time* during the course of the trial. We then tested whether or not condition effects occurred when we would expect them to during the update component of the trials. For any region demonstrating an effect of condition or an interaction of condition and time, we followed up with an analysis that focused on 5 frames that occurred after the presentation of the update cues and prior to the response of the probe (frames 8-12, accounting for hemodynamic lag). Specifically, we conduced a second repeated measures ANOVA at the region level with condition (3 levels) and time (5 levels) as factors. We examined the source of any such effect in the manner described above, by comparing Upgreen versus Upempty and Upred versus Upempty separately.

Specific Aim 1: Test the hypothesis that individuals with schizophrenia demonstrate dysregulated striatal activity during updating and interference control and that striatal activity predicts performance deficits.

3.3. Condition Analysis

With regard to our first aim, we first examined whether the striatal activity of patients displayed different responses to task Condition, updating (Upgreen), interference control (Upred) and maintenance (Upempty) demands, when compared with controls. For the independently defined ROIs, we conducted a repeated measures ANOVA at the region level with condition (3 levels; Upgreen, Upred, and Upempty), diagnosis (2 levels; patients and controls), and time (5 levels; frames 8-12) as factors, using only the data from correct trials. Because we were only interested in regions that interacted with at least condition and diagnosis, we only explored the effects of regions that showed a significant 2-way interaction of condition by diagnosis, or a significant 3-way interaction of condition by time by diagnosis.

We then conducted voxel-wise analyses within our *a priori* anatomical masks. This analysis involved a repeated measures ANOVA with diagnosis (2 levels), update cue (3 levels), and time (15 frames) as factors, treating subjects as a random factor. Given that we were specifically interested in regions that interacted with both diagnosis and condition, regions that demonstrated either a significant 2-way interaction of diagnosis by condition or a 3-way interaction of diagnosis by time by condition were used for further analyses. We also examined effects of condition and diagnosis at the whole brain level to uncover brain regions that demonstrate interactions of interest that were not within either or ROIs or our anatomical masks. We set a whole-brain multiple comparison correction of $p < 0.05$ using a $Z > 3$ and a cluster sized of at least 21 contiguous voxels (McAvoy, Ollinger, & Buckner, 2001; Ollinger et al., 2001). Given that we were primarily interested in effects occurring within our regions of interest we have chosen to place results from our whole brain analysis in the Supplemental material section. Of note, we recognize that should we find results in regions in our a priori mask and not regions outside the mask, we cannot claim specificity to regions inside the mask given the differential levels of significance required. However, we felt that this was the best balance between providing sufficient power to test a priori hypotheses and being open to unpredicted effects.

We included all 15 frames in the analyses in the previous step to capture regions that show effects of interest, but at *any time* during the course of the trial. Once these regions were identified, we then tested whether condition effects in these regions occurred in response to the update events, using a repeated measures ANOVA with diagnosis (2 levels), update cue (3 levels), and time (5 levels; frames 8-12) as factors, treating subjects as a random factor. Only correct trials were used for this analysis. For regions demonstrating significant interactions of interest, we explored the interaction in the manner described above examining Upgreen versus Upempty and Upred versus Upempty for both diagnostic groups separately.

3.4. Trial type Accuracy Analysis

The second part of Aim 1 involved examining the relationship between brain activity and behavioral performance. We predicted that patients with schizophrenia would demonstrate dysregulated striatal activity when compared to controls, and this dysregulation would result in *decreased* activity during incorrect trials relative to correct trials when patients are tasked with making an information update. In addition, given our predicted relationship between interference control, striatal activity, and aberrant salience, we predicted with when patients are tasked with ignoring distractors they would demonstrate *increased* activity during incorrect trials relative to correct trials. To test these predictions, we examined activity during the update cue phase for specific probe types used in the task (i.e. Update and Resist Distracter Lure) as a function of trial accuracy, as opposed to examining the broad update cue conditions (i.e. Upgreen, Upred, and Upempty) as a function of accuracy.

The benefit of examining individual trial types is that we can test predictions about specific types of errors. For the Update trial type, an error indicates that the participant rejected an item that was presented during a green update cue, suggested that this item was not appropriately incorporated into the participant's active memory set. Looking at this specific type of error is more informative than looking at any type of error a participant could make during the Upgreen condition, as these could involve failing to identify an item that should have been updated, or incorrectly identifying the to-be-replaced item or incorrectly identifying the novel probe as correct. In the case of Resist Distracter Lure trials, a correct response indicates that participants correctly rejected a response probe that was previously presented as a distracter. If a participant makes an error on this trial type, it indicates that the participant incorrectly accepted the response probe that was previously presented as a distracter, suggesting that they made an inappropriate update. Errors made for the Upred condition, on the other hand, could be

the result of an incorrect acceptance of a distracter, but it could also result from participants forgetting the original memory set item, or incorrectly identifying a novel probe as correct.

To test these hypotheses, we conducted two repeated measures ANOVA (one examining Resist Distracter Lure performance and one examining Update performance), with accuracy diagnosis as the between subject factor (2 levels, patients and controls) and both accuracy (2 levels, correct and incorrect) and timepoint (15 frames) as within subject factors. For any significant regions, we conducted a second repeated measures ANOVA for each trial type of interest with diagnosis (2 levels), accuracy (2 levels), and time (5 levels; frames 8-12) as factors, to determine whether the effects reflected group differences during the update component of the trial. We focused our analyses on regions that demonstrated either an interaction of diagnosis by accuracy, or the 3-way interaction of diagnosis by time by accuracy.

Specific Aim 2: Test the hypothesis that in individuals with schizophrenia, increased striatal activity during distracter presentation will be positively associated with aberrant salience symptoms, delusions, and hallucinations of patients with schizophrenia.

3.5. Relationship between Symptoms and Brain Activity Analysis

The symptom analysis focused on Magical Ideation, Perceptional Aberration, Social Anhedonia, and Physical Anhedonia from the Chapman scales, as well as the total score from the ASI. We first sought to replicate the relationships between ASI and other measures of psychosis proneness and anhedonia observed previously (Cicero et al., 2010), where strong positive correlations between ASI scores, Magical Ideation, and perceptual aberration were found. We included measures of anhedonia (Social and Physical) with the expectation that there would be little or no correlation between measures of anhedonia and measures of psychosis proneness. By including measures of anhedonia we could assess whether the relationships between cognition, brain functioning, and symptoms were specific to individual symptom domain

(e.g. psychosis proneness) or if they generalized to multiple symptom domains (e.g. psychosis proneness and anhedonia).

To examine the relationship between brain activity and symptom expression we first restricted our analysis to regions from the Trial Type Accuracy Analysis that demonstrated sensitivity to differences in accuracy during Resist Distracter Lure and Update trials during the time period following the presentation of the update cue (frames 8-12). We then extracted the average magnitude of activity from the 5 time points of interest for these regions and ran Pearson's correlation analyses between the average of these time points and symptom scores. We predicted that patients would display a significant positive correlation between brain activity, specifically dorsal striatal activity, associated with the update cue during Distracter Resistance Lure trials and ASI, but only when incorrect responses were made to the probe. We did not predict a correlation between brain activity associated with Distracter Resistance Lure trials and ASI when patients made correct responses to the probe, given that ASI and interference control errors are proposed to result from striatal dysregulation and correct trials are not thought to result from such dysregulation. That is, striatal activity during incorrect Distracter Lure trials may represent instances where dysregulation was sufficient enough to produce false alarms, whereas activity during correct trials was not have sufficient to produce false alarms. Further, as noted above, we did predict to find significant correlations between ASI and psychosis proneness scales (i.e. Magical Ideation and Perceptual Aberration). Thus, if dorsal striatal activity is positively associated with aberrant salience, we would also expect to see a positive correlation between striatal activity and psychosis proneness scales for patients, but not a strong correlation between striatal activity and measures of anhedonia.

4. Results

4.1. Demographics

Demographic data for each group is shown in Table 4.1. We did not observe differences in gender between groups (χ^2 (1) = 1.43, p = 0.23). We conducted T-tests examining differences of age, subject education, parental education, and measures of IQ between diagnostic groups. We did not find group differences in parental education (t(36) = -1.19, p = 0.34) or subject education (t(35) = -0.99, p = 0.9). However, we did find a significant difference of age (t(40) = 2.49, p = 0.02) between groups, such that the patient group was slightly older than the control group (see Table 4.1). We also found a marginal difference in ethnic composition of our groups (χ^2 (3) = 8.1, p = 0.057, φ = 0.42). Given these differences in age and ethnicity we used these variables as covariates during all planned follow up analyses that explored effects that interacted with diagnosis from the voxel-wise analyses.

4.2. Clinical and Cognitive Measures

While controls had numerically higher scores on measures of verbal and non-verbal IQ, these differences were not statistically significant (verbal IQ trended towards significance (t(40) = -1.85, p = 0.07)). We observed significant differences between the groups on most symptom measures, including all Chapman scales (Magical Ideation, Perceptual Aberration, Social Anhedonia, and Physical Anhedonia; Table 4.1).[1] Interestingly, patients and control scores on

4.3. Task Performance

[1] Nonparametric tests were used to compare Perceptual Aberration, Physical Anhedonia, and Magical Ideation between groups as these variables failed to demonstrate variance homogeneity.

Table 4. 1 Demographics, Task Data, and Symptom Scores for Patients and Controls

	SCZ (N=22)	Controls (N=20)	Sig.	ES (*d*)
Demographics				
Age	40.41 (8.4)	33.65 (9.19)	**0.02**	0.77
Gender	75% Male	55% Male	0.23	
Race	11 AA, 10 Cau	14 AA, 2 Asian, 2 Cau, 1 Other	**0.06**	0.42
Subject Education (Years)	15.0 (3.51)	15.1 (2.59)	0.9	
Parental Education (Years)	13.54 (4.74)	14.7 (3.1)	0.34	
Neuropsychological Testing/Questionnaires				
IQ (WAIS III - Vocab)	91.36 (17.33)	100.5 (14.32)	0.07	
IQ (WAIS III - Matrix)	103.86 (14.55)	105.5 (12.24)	0.7	
Aberrant Salience Inventory (ASI)	13.59 (8.29)	9.05 (6.88)	0.06	0.6
Chapman - Perceptual Aberration*	7.59 (9.23)	2.25 (2.48)	**0.03**	0.79
Chapman - Magical Ideation*	11.18 (7.27)	5.10 (4.41)	**0.001**	1.01
Chapman - Social Anhedonia	19.64 (9.04)	9.35 (6.02)	**0.001**	1.34
Chapman - Physical Anhedonia*	24.41 (12.68)	10.7 (6.37)	**0.001**	1.37
Experimental Task				
Resist Distracter	0.63 (0.23)	0.69 (0.19)	0.34	
Resist Distracter Lure*	0.52 (0.26)	0.74 (0.19)	**0.006**	0.97
Maintenance*	0.67 (0.22)	0.7 (0.16)	0.46	
Update	0.72 (0.17)	0.82 (0.13)	**0.03**	0.66
Resist Maintenance*	0.49 (0.29)	0.69 (0.16)	**0.02**	0.85
Resist Distracter Novel Probe	0.60 (0.30)	0.81 (0.25)	**0.02**	0.76
Maintenance Novel Probe*	0.64 (0.31)	0.81 (0.21)	**0.04**	0.64
Update Novel Probe*	0.61 (0.32)	0.84 (0.18)	**0.02**	0.88

Demographics, cognitive scores, symptom scores, and task data for both patients and controls. P-values of differences between groups are listed under the heading “Sig.” Significant p-values are printed in red text. Effect sizes (Cohen’s d) for significant between group differences are listed under the heading “ES (d)”. Variables with an asterisk failed tests of equal variances between groups. The p-values for these variables were generated using nonparametric tests.

our measure of aberrant salience (ASI) did not significantly differ from one another, although the difference between groups trended towards significance ($t(40) = 1.92$, $p = 0.06$, $d = 0.6$). Task performance for the two diagnostic groups can be seen in Figure 4.1. We also examined our behavioral data using d' (the results can be found in Appendix E). Overall, controls performed better than patients during the task. Our repeated measures ANOVA of trial type (2 levels, Update and Resist Distracter Lure) and diagnosis (2 levels, patients and controls) revealed a main effect of diagnosis ($F(1,38) = 20.23$, $p < 0.001$), but no main effect of trial type ($F(1,38) = 1.76$, $p = 0.19$), and no interaction of trial type and diagnosis ($F(1,38) = 2.7$, $p = 0.11$) when using the sphericity correction. Follow up t-tests revealed that performance for both the Update trial type ($t(38) = -2.47$, $p = 0.02$) and the Resist Distracter Lure trial type ($t(38) = -3.35$, $p = 0.002$) differed between patients and controls, such that patients performed significantly worse on both trial types. Given that we found significant differences of novel probe performance between diagnostic groups (suggesting a global cognitive deficit rather than one specific to distracter resistance, for example) we conducted separate multiple regression analyses to test whether diagnostic group could significantly predict Resist Distracter Lure and Update performance. We found that diagnostic group trended towards significantly predicting Resist Distracter Lure performance when controlling for novel probe performance ($B = 0.1$, $t(41) = 1.88$, $p = 0.07$). We did not find that diagnostic group predicted Update accuracy when controlling for Update Novel Probe performance, trend or otherwise ($B = 0.08$, $t(41) = 1.33$, $p = 0.19$). A repeated measures ANOVA on the remaining trial types revealed a significant main effect of diagnosis ($F(1,38) = 14$, $p = 0.001$), a trend towards a main effect of trial type ($F(2.5,38) = 2.25$, $p = 0.1$), and a significant interaction of diagnosis by trial type ($F(2.5,38) = 3.11$, $p = 0.04$) when using the sphericity correction. Follow up t-tests revealed significant differences between diagnostic groups for all trial types, with the exception of Resist Distracter and Maintenance trial types (see Table 4.1). For all trial types that demonstrated significant differences between diagnostic groups, patients performed worse that controls.

4.4. Replication of Prior fMRI Results in Healthy Individuals

4.4.1. Independently Defined ROI Results

Examination of brain activity in healthy controls within the independently defined ROIs demonstrated either an effect of condition or an interaction of condition by time (Table 4.2) in all seven regions. This included bilateral middle frontal gyrus (MFG), left lateral inferior frontal gyrus (IFG), right lateral precentral gyrus, left lateral putamen, and right lateral caudate body (Table 4.2). Previously we found that these regions demonstrated either effects of condition or interactions of condition and time, suggesting these regions were sensitive to task condition. In the prior study when examining the pattern of activity in these regions in response to the presentation of the update cue, we found that all regions demonstrated significant differences between Upgreen and Upempty conditions, suggesting that activity in both cortical and subcortical regions demonstrated robust activity to updating demands when compared with activity during simple maintenance. Only cortical regions, however, demonstrated either significant or trend level differences between Upred and Upempty, suggesting striatal activity selectively activated to updating demands when compared with distracter presentation and simple maintenance. In the current study, as predicted, Upgreen activity for all cortical regions was significantly greater than Upempty activity (with the exception of one region in the precentral gyrus, although it trended towards significance). Only one cortical region demonstrated a predicted significant difference between Upred and Upempty (IFG, -39, 4, 30; Table 4.2 and Figure 4.2A), such that Upred activity was greater than Upempty activity. This finding is a replication of our previous study, suggesting that activity in the IFG is sensitive to both updating and distracter presentation task demands. Other regions, previously found to sensitive to both task demands (i.e. right lateral precentral gyrus and left lateral MFG) did not demonstrate the same condition sensitivity in the current sample, suggesting that condition sensitivity may be localized to the IFG. Of the striatal regions, the region in the left putamen

Figure 4. 1 Task Accuracy for Diagnostic Groups

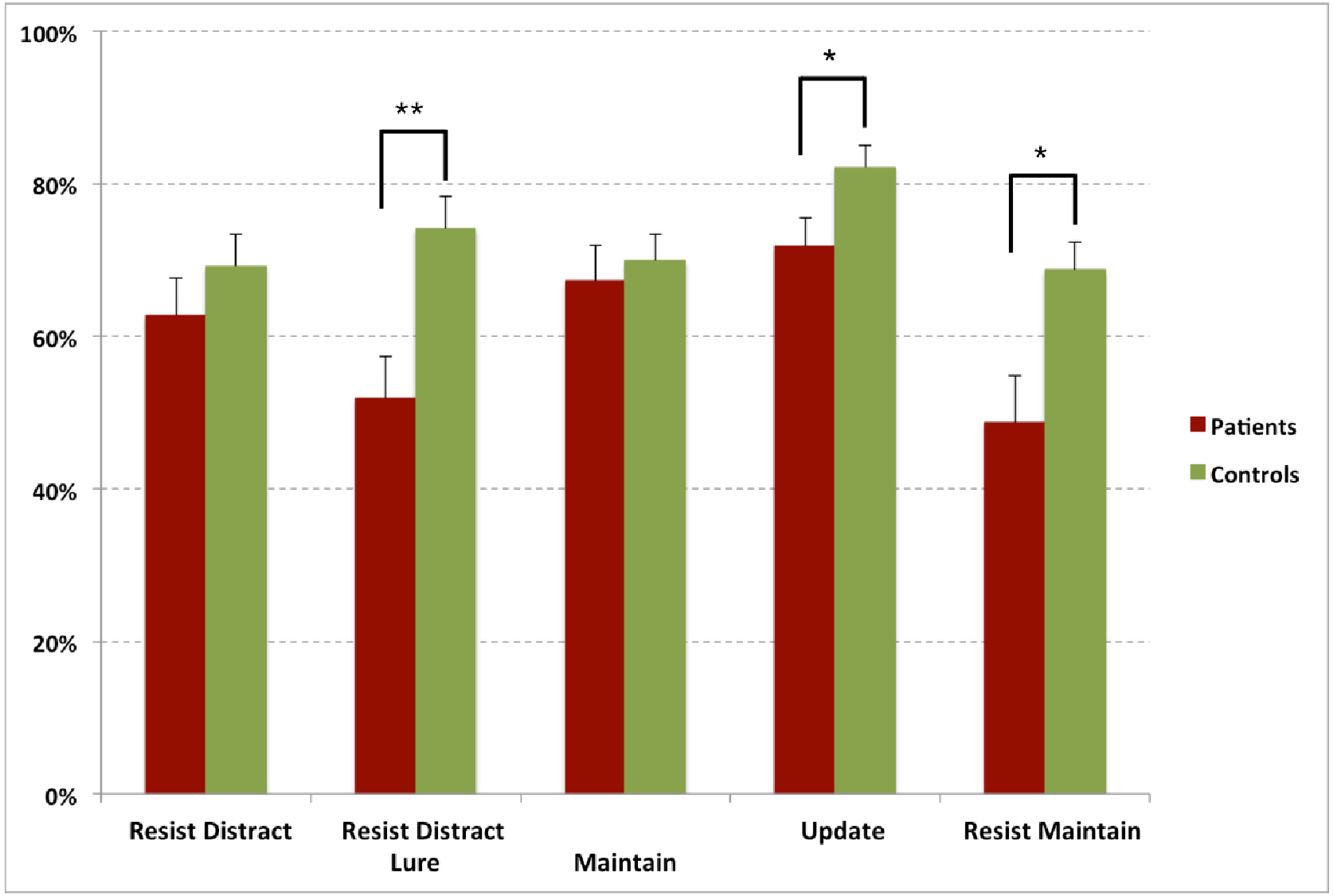


Table 4. 2 Regions from the Previous Data Set and Their Condition Effect in Healthy Controls from the Current Data Set

X	Y	Z	Size	Hemisphere	Region	BA	Effect at frames 8-12			Direction	
							Analysis of Current Study	*F*	*p*	*Upgreen vs. Upempty*	*Upred vs. Upempty*
Controls, Independently Defined Regions											
Condition Effect in Previous Study											
-43	22	30	27	Left	MFG	9	Cond	6.83	0.003	G > E**	no diff
-39	4	30	25	Left	IFG	9	Cond	12.89	<0.0001	G > E**	R > E*
41	5	33	20	Right	Precentral Gyrus	9	Cond X Time	3.42	0.03	no diff	no diff
Condition X Time in Previous Study											
-18	-3	13	155	Left	Putamen		Cond	4.72	0.02	G > E*	no diff
13	-10	19	46	Right	Caudate Body		Cond X Time	4.37	0.01	no diff	no diff
-42	17	29	211	Left	MFG	9	Cond	8.84	0.001	G > E**	no diff
42	13	32	79	Right	MFG	9	Cond X Time	3.54	0.02	G > E**	no diff

Independently defined ROIs are listed in the table under the heading “Controls, Independently Defined Regions” and are organized based on whether they demonstrated an effect of condition or interaction of condition and time in the previous study. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. Listed under this heading is what analysis the independently defined ROIs demonstrated the effect as well as the corresponding F and p values of that effect. In the table, under the heading Direction, the pattern and significance of that effect is listed. MFG = Middle Frontal Gyrus and IFG=Inferior Frontal Gyrus. G = Upgreen trials, E = Upempty trials, and R = Upred trials. *p<0.05 and **p<0.01. “no diff” signifies no statistically significant difference.

demonstrated significantly greater Upgreen versus Upempty activity, but there was no difference between Upred and Upempty (-18, -3, 13; Table 4.2 and Figure 4.2C). Thus, we again found that regions within the caudate and putamen demonstrated condition sensitivity to Upgreen relative to Upempty and not Upred relative to Upempty. This is consistent with theproposed role of the striatum as an information gate, striatal activity activates when the gate is open but not when distracters a presented. Further, while a region in the right lateral caudate demonstrated a significant interaction of condition and time, neither Upgreen nor Upred activity significantly differed from Upempty activity. When examining the time course of this region Upempty activity was, unexpectedly, intermediate to that of Upgreen and Upred, which may explain why neither condition differed from Upempty. When we examined whether Upred and Upgreen significantly differed within this caudate region we found that they did such that Upgreen was significantly greater than Upred ($F(1,19) = 4.85$, $p = 0.02$).

4.4.2. Anatomical Mask of Basal Ganglia and Prefrontal Cortex

We next conducted voxel-wise analyses in our anatomical *a priori* regions of interest using only the data from the healthy controls. Regions demonstrating an effect of condition or an interaction of condition by time from healthy control subjects can be found in Table 4.3. One region demonstrated a main effect of condition (left MFG, -43, 29, 27), with follow-up analysis indicating a highly significant effect of condition during frames 8-12 ($F(2,19) = 18.92$, $p < 0.001$; Figure 4.3A), such that Upgreen was significantly greater than Upempty but there was no difference between Upred and Upempty. There were 5 regions that demonstrated significant interactions of condition and time when examining all 15 timepoints, including 3 regions in the MFG, bilaterally. Only 2 of them (-42, 24, 23 and 42, 21, 29) demonstrated significant effects of

Figure 4. 2 Brain Activity of Healthy Controls and Patients Within Regions Defined in a Previous Data Set

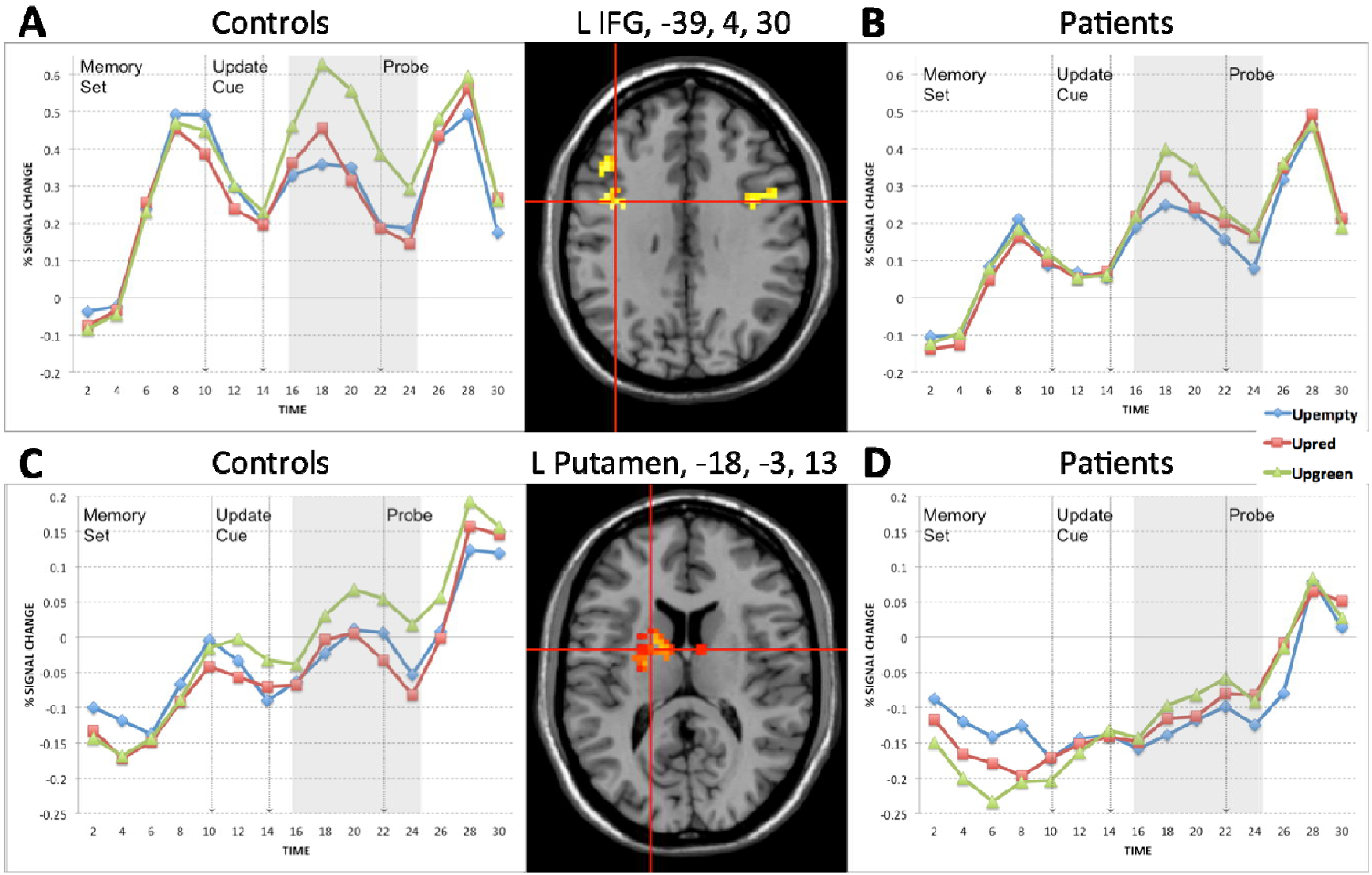
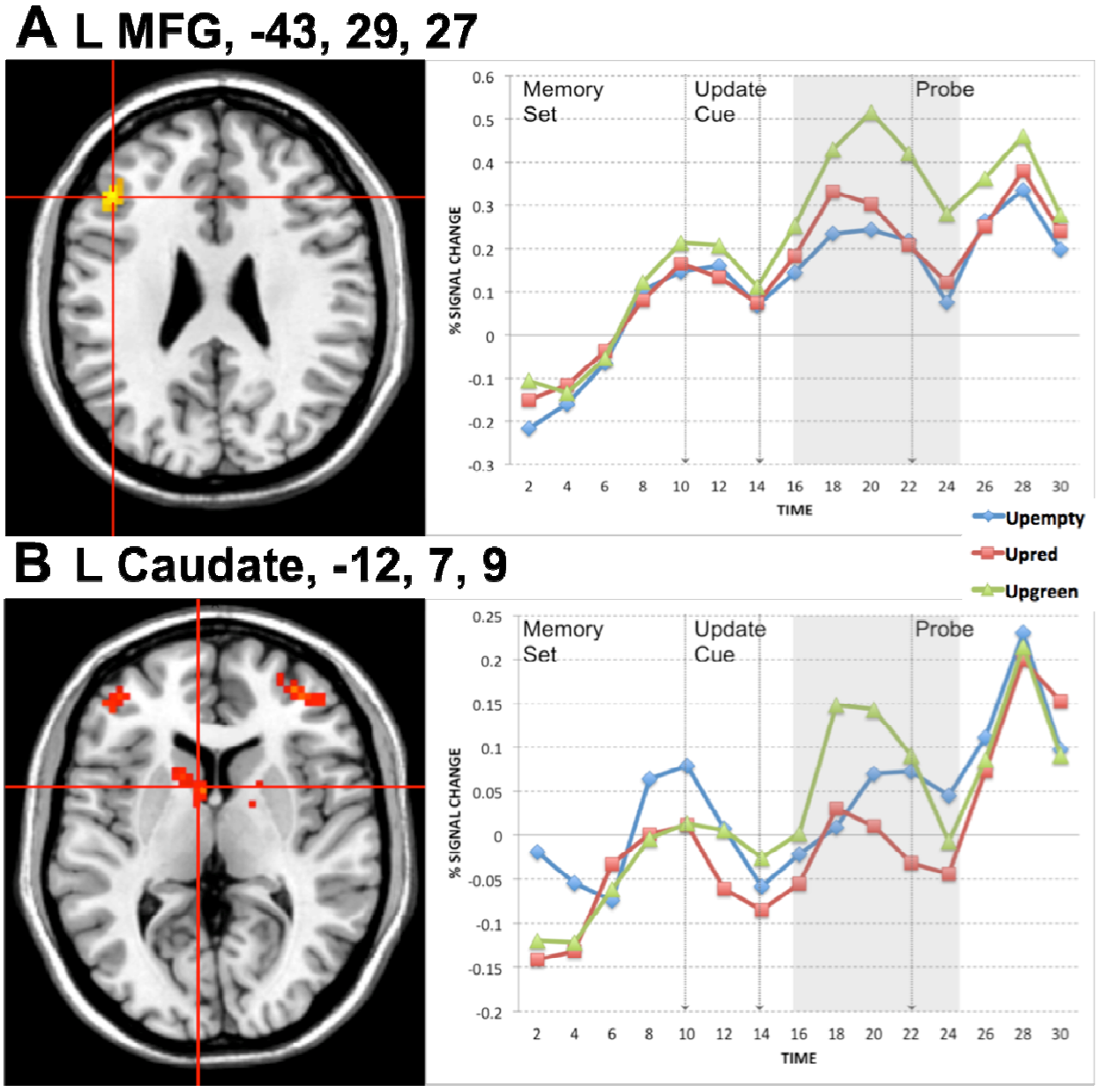


Table 4. 3 Regions from the Current Data Set of Healthy Controls that Demonstrated Effects of Condition

X	Y	Z	Size	Hemisphere	Region	BA	Effect at frames 8-12			Direction	
							Analysis	*F*	*p*	*Upgreen vs. Upempty*	*Upred vs. Upempty*
Regions Identified in Current Data Set in Healthy Controls											
Condition											
-43	29	27	32	Left	MFG	9	Cond	18.92	<0.0001	G > E**	no diff
Condition X Time											
-12	7	9	36	Left	Caudate Body		Cond X Time	2.99	0.004	G > E**	E > R*
20	-1	9	21	Right	Putamen		Cond X Time	0.56	0.81		
37	51	3	47	Right	MFG	10	Cond X Time	1.11	0.41		
-42	24	24	285	Left	MFG	46	Cond X Time	3.02	0.04	G > E*	no diff
42	21	29	262	Right	MFG	9	Cond	8.4	0.001	G > E**	no diff

Regions within our anatomical masks from healthy control in the current data set that demonstrated Condition effects are listed in the table under the heading “Regions Identified in the Current Data Set in Healthy Controls”, and are organized on the left side under headings like “Diagnosis” or “Condition X Time” based on whether they demonstrated these effects when examining all 15 time frames of the trial. Listed under the heading “Effect at frames 8-12” is in what analysis the independently defined ROIs demonstrated an effect as well as the corresponding F and p values of that effect. In the table, under the heading Direction, the pattern and significance of that effect is listed. MFG = Middle Frontal Gyrus. G = Upgreen trials, E = Upempty trials, and R = Upred trials. *p<0.05 and **p<0.01. “no diff” signifies no statistically significant difference.

Figure 4. 3 Regions of Healthy Controls from the Current Data Set that Demonstrated Effects of Condition



condition or condition by time in response to the update cue (Table 4.3). For both of these regions, Upgreen activity was significantly greater than Upempty, but neither showed differences between Upred and Upempty activity. While there were two regions in the dorsal striatum that demonstrated interactions of condition and time when examining all 15 frames of the trial, only a region in the caudate (-12, 7, 9) continued to demonstrated a significant interaction of condition and time in analyses restricted to the time periods associated with the update cue ($F(2,19) = 2.99$, $p = 0.004$; Table 4.3). For this region Upgreen activity was significantly greater than Upempty activity, and there was a significant difference between Upred and Upempty, such that, unexpectedly, Upempty activity was significantly greater than Upred activity (Figure 4.3B). Thus, a number of the regions identified in a previous study demonstrated predicted differences between Upgreen and the comparison condition, Upempty, such that Upgreen activity was greater than Upempty. Only one region in the IFG demonstrated a predicted difference between Upred and Upempty.

Specific Aim 1: Test the hypothesis that individuals with schizophrenia demonstrate dysregulated striatal activity during updating and interference control and that striatal activity predicts performance deficits.

4.5. Condition Results

4.5.1. Independently Defined ROIs

We started by examining whether activity in the independently defined ROIs differed as a function of diagnostic group. Results from this analysis can be found in Table 4.4. We found that activity within 2 regions demonstrated a significant interaction of diagnosis and condition, including a region in the left IFG (-39, 4, 30) and a region in the left MFG (-42, 17, 29). For the IFG, activity during the Upgreen condition was significantly greater than activity during Upempty for both patients and controls (Figure 4.2A and 4.2B). Controls demonstrated significantly greater Upred than Upempty activity (there was a trend towards greater Upred versus Upempty

Table 4. 4 Regions from a Previous Data Set and Their Diagnosis by Condition Effects for Patients and Controls from the Current Data Set

X	Y	Z	Size	Hemi	Region	BA	Diagnosis Interaction			Direction (Patients)		Direction (Controls)	
							Analysis	*F*	*p*	*Upgreen vs. Upempty*	*Upred vs. Upempty*	*Upgreen vs. Upempty*	*Upred vs. Upempty*
Condition													
-43	22	30	27	Left	MFG	9	Dx X Cond	2.55	0.09				
-39	4	30	25	Left	IFG	9	Dx X Cond	3.76	0.03	G > E**	no diff	G > E**	R > E*
41	5	33	20	Right	Precentral Gyrus	9	Dx X Cond	0.56	0.57				
Condition X Time													
-18	-3	13	155	Left	Putamen		Dx X Cond	1.51	0.28				
13	-10	19	46	Right	Caudate Body		3-way	2.08	0.03	no diff	no diff	no diff	no diff
-42	17	29	211	Left	MFG	9	Dx X Cond	3.54	0.02	no diff	R > E*	G > E**	no diff
42	13	32	79	Right	MFG	9	Dx X Cond	2.54	0.09				

Statistics for independently defined regions that demonstrated diagnosis by Condition effects. We only conducted follow up analyses for the update cue period on regions that demonstrated a significant effect of condition or a significant interaction of condition and time. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. The direction of Upgreen and Upred versus Upempty effects for controls found in the previous analysis (Table 4.2) are listed to the right of the direction of effects for patients to ease comparison between the two groups within this table. G = Upgreen trials, E = Upempty trials, and R = Upred trials. *p<0.05 and **p<0.01. “no diff” signifies no statistically significant difference.

for patients, $p = 0.095$). When we compared Upgreen activity for the IFG (-39, 4, 30) between groups we found a trend towards significantly greater for controls than it was for patients ($F(1,41) = 3.13$, $p = 0.09$), but no difference between groups for Upred activity ($F(1,41) = 0.18$, $p = 0.67$).The other region that demonstrated a diagnosis by condition interaction was a region in the left MFG. In this region controls demonstrated significantly greater Upgreen than Upempty activity and this difference trended towards significance for patients ($p = 0.07$). Interestingly, within this region, patients, but not controls showed greater Upred than Upempty activity. When we compared Upgreen activity for the MFG (-42, 17, 29) between groups we found that activity was significantly greater for controls than it was for patients ($F(1,41) = 4.52$, $p = 0.04$), but no difference between groups for Upred activity ($F(1,41) = 0.52$, $p = 0.47$).

A region in the right caudate body (13, -10, 19) demonstrated a 3-way interaction of diagnosis by time by condition (Table 4.4). However, when comparing Upgreen versus Upempty and Upred versus Upempty during the frames following the update cue, neither diagnostic group demonstrated a significant difference between conditions. As mentioned above, examining the time course for this region revealed an unexpected increase of Upempty activity, such that it activity was intermediate to Upgreen and Upred for controls. This was not also the case for patients. Generally, putamen activity for patients was numerically lower than controls and did not appear to respond to trial events (i.e. the memory set and update cue) that way that control putamen activity did. The elevated Upempty activity and Upgreen activity for controls may explain why we observed a significant interaction of diagnosis by condition for this region whilst failing to observe differences between the comparison condition and Upgreen/Upred. However, when we compared caudate activity between diagnostic groups during Upgreen and Upred conditions we found that while controls had numerically higher Upgreen and Upred activity, these differences were not significant ($F(1,41) = 2.19$, $p = 0.15$ and $F(1,41) = 1.26$, $p = 0.27$, respectively).

Table 4. 5 Regions from the Current Data Set that Demonstrated Diagnosis by Condition Effects Within our Anatomical Masks

X	Y	Z	Size	Hemisphere	Region	BA
Diagnosis						
-23	-10	4	149	Left	Globus Pallidus	
24	-11	5	126	Right	Globus Pallidus	
24	-11	5	126	Right	Globus Pallidus	
16	-1	19	34	Right	Caudate Body	
16	-1	19	34	Right	Caudate Body	
-40	38	7	282	Left	IFG	46
29	53	2	57	Right	MFG	10
-36	20	23	33	Left	MFG	9
40	9	30	65	Right	IFG	9
30	30	28	30	Right	MFG	9
-40	8	33	31	Left	Precentral Gyrus	9
Condition						
-42	4	31	22	Left	IFG	9
Condition X Time						
-19	0	8	243	Left	Putamen	
17	3	10	152	Right	Putamen	
36	52	5	40	Right	MFG	10
-41	23	25	390	Left	MFG	46
42	20	29	265	Right	MFG	9
-28	34	33	21	Left	SFG	9
Diagnosis X Time						
-24	-4	2	53	Left	Putamen	
-16	-5	20	24	Left	Caudate Body	
15	-6	21	35	Right	Caudate Body	
-39	5	31	39	Left	IFG	9

28	31	-5	37	Right	IFG	47
-39	43	6	190	Left	MFG	46
-39	34	25	44	Left	MFG	46
46	22	26	63	Right	MFG	46
35	6	32	22	Right	Precentral Gyrus	9

Regions within our anatomical masks from the current data set that demonstrated diagnosis by Condition effects within our anatomical masks. They are organized on the left side under headings like “Diagnosis” or “Condition X Time” based on whether they demonstrated these effects when examining all 15 time frames of the trial. We only conducted follow up analyses for the update cue period on regions that demonstrated a significant interaction of condition and diagnosis. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. G = Upgreen trials, E = Upempty trials, and R = Upred trials. *p<0.05 and **p<0.01. “no diff” signifies no statistically significant difference.

4.5.2. Anatomical Mask of Basal Ganglia and Prefrontal Cortex

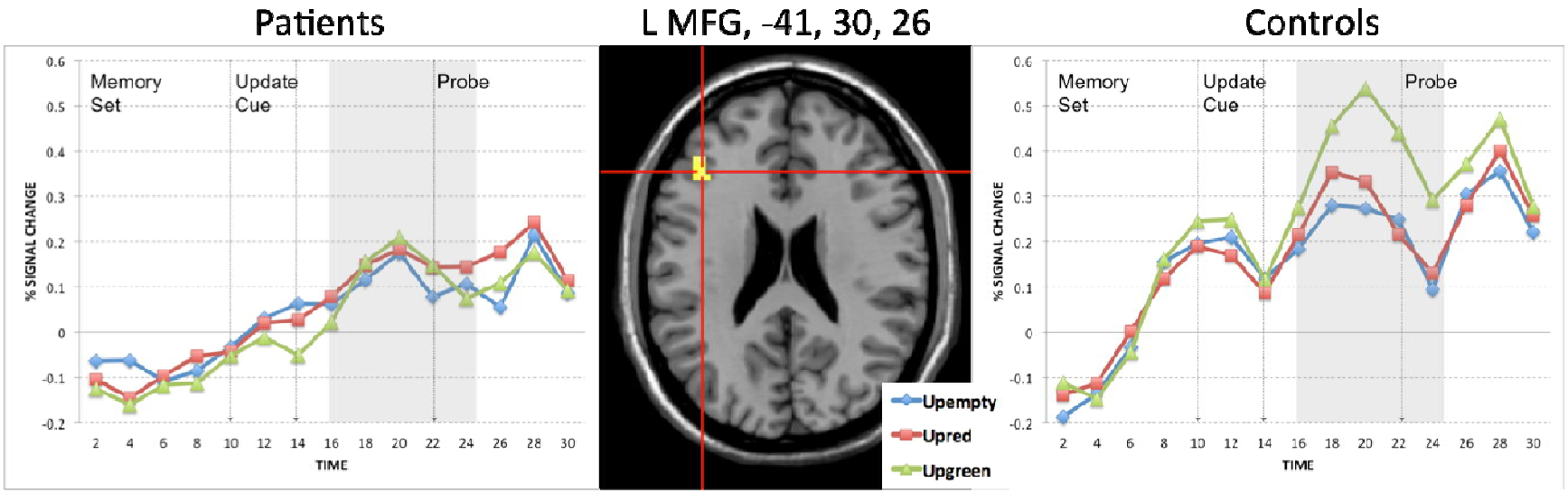
Regions from our *a priori* anatomical mask analysis that demonstrated either a main effects of task condition, time, and diagnosis, or interactions are listed in Table 4.5. We focused our analysis on regions that demonstrated either an interaction of diagnosis by condition or Diagnosis by time by condition. Results from the whole brain analysis can be found in Appendix B. Only one region demonstrated a condition X diagnosis interaction: left lateral MFG (-41, 30, 26; not in Table 4.5), an interaction that held when examining only the 5 frames following the update cue ($F(2,41) = 6.4$, $p = 0.004$). The pattern of activity within this region was that only controls demonstrated significant greater activity during Upgreen versus Upempty (Table 4.5, Figure 4.4), with no significant difference between Upred and Upempty. When we compared differences of Upgreen and Upred activity within this region between groups we found that controls has significantly greater activity during Upgreen relative to patients ($F(1,41) = 4.53$, $p = 0.04$) but there was no difference between Upred activity ($F(1,41) = 0.7$, $p = 0.41$).

4.6. Trial type Accuracy Results

4.6.1. Anatomical Mask of Basal Ganglia and Prefrontal Cortex

We conducted a repeated measures ANOVA for each trial type with accuracy (correct and incorrect trials) and time (all 15 time points of the trial) as a within subjects factors, and diagnostic group (patients and controls) as the between subjects factor, separately for Update and Resist Distractor Lures. We did not examine trial type effects within the independently defined regions because those regions were defined by examining Condition effects (e.g. Upgreen). We could not examine the effect of trial type accuracy in the previous sample due to lack of behavioral variability (many participants from the previous study made few errors, if any). Further, these independently defined regions were identified examining differences between conditions during only correct trials. Thus, it was unclear whether they would demonstrate effects of accuracy. Given that we were primarily interested in regions that interacted with

Figure 4. 4 Frontal Region from the Current Data Set that Demonstrated a Diagnosis by Condition Interaction



diagnosis we focused our analyses on regions that demonstrated either an interaction of diagnosis by accuracy or diagnosis by time by accuracy. Regions that demonstrated relevant effects from our whole brain analysis can be seen in the Appendix C and D.

We first focused on the Resist Distracter Lure trial type (Table 4.6). During this trial type participants are presented with a distracter during the update cue, which they are instructed to ignore. During the probe, however, they are presented with the item they were instructed to ignore. Correct trials indicate a correct rejection of the probe and incorrect trials suggest they inappropriately encoded the distracter. Two regions demonstrated and interaction of accuracy and diagnosis, including the right lateral putamen (23, 0, 4) and right lateral MFG (40, 13, 30) when examining all 15 frames of the trial. When examining whether these regions demonstrated this effect following the presentation of the update cue (in this case, the presentation of a distracter) we found that both regions still demonstrated a significant interaction of diagnosis and accuracy (Table 4.6). For patients, activity during incorrect trials (where, at the probe, the identified the distracter presented during the update cue as a correct response) was significantly greater than trials when they correctly rejected the distracter at the probe. This was true for both the putamen (Figure 4.5A) and the MFG (Figure 4.5C). Controls, however, did not show this pattern. If anything, for controls *correct trial* activity within a region in the putamen trended towards being significantly *greater* than incorrect trial activity following the update cue (Figure 4.5B), which is the opposite of the pattern observed for patients in this region. The same was true of controls for activity in the MFG, where correct trial activity was numerically greater than incorrect trial activity (Figure 4.5D).

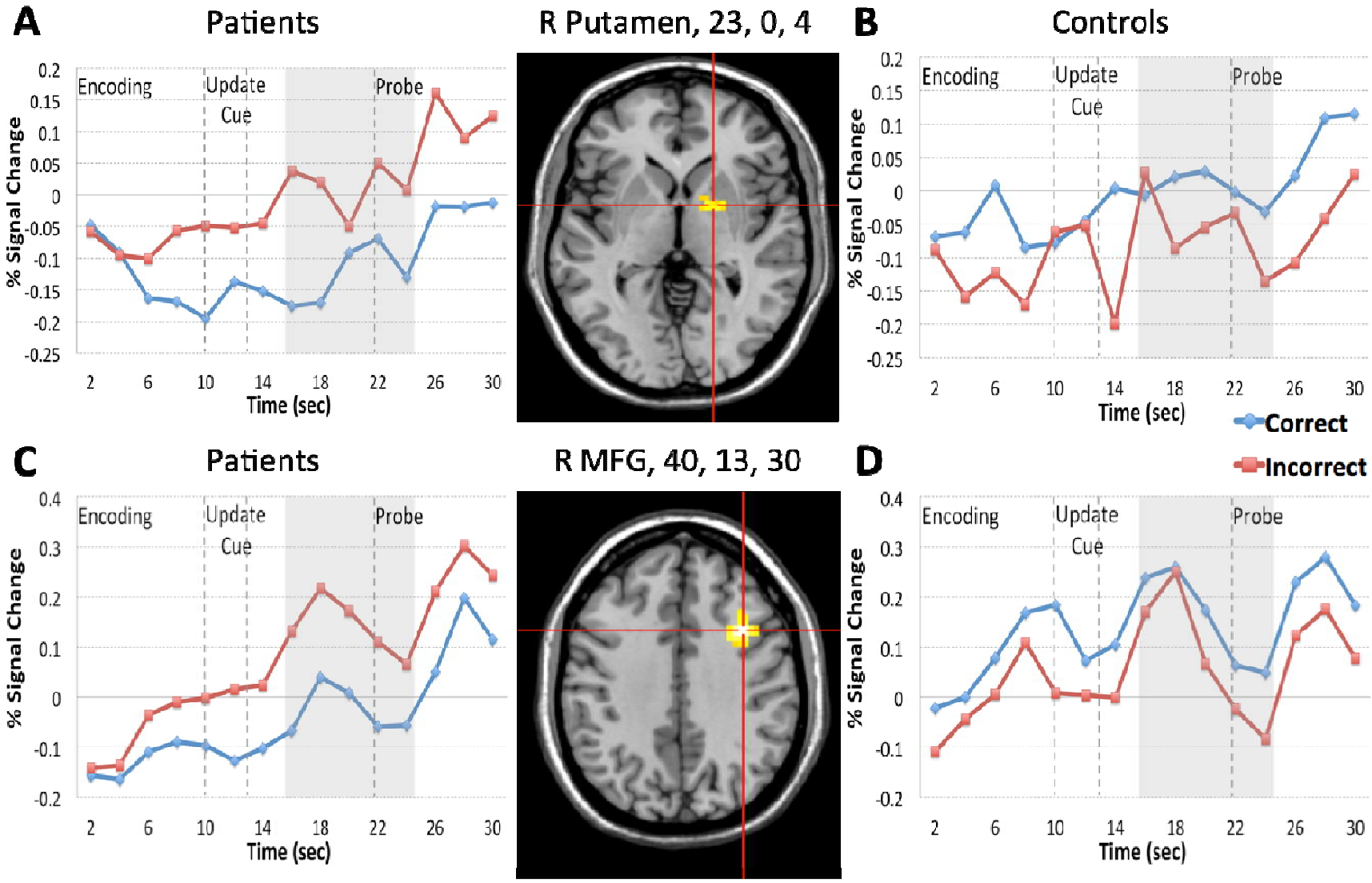
Next we examined the Update trial type. Here participants are presented with a new shape during the update cue and are signaled to remember the new shape in place of one of the original items in the memory set. At the probe they are presented with one of the update items presented at the update cue, to which they would respond “yes”. Correct responses

Table 4. 6 Regions Demonstrating an Effect of Diagnosis by Resist Distracter Lure Trial Type Accuracy within our Anatomical Masks

X	Y	Z	Size	Hemi	Region	BA	Effect at frames 8-12			Correct vs. Incorrect	
							Analysis	*F*	*p*	*Patients*	*Controls*
Diagnosis											
-25	-18	-1	44	Left	Putamen						
-39	35	2	45	Left	IFG	46					
23	51	6	21	Right	SFG	10					
-33	48	13	22	Left	MFG	10					
-33	7	33	25	Left	Precentral Gyrus	9					
Accuracy											
25	55	3	21	Right	SFG	10					
Accuracy X Time											
23	-14	7	35	Right	Putamen						
Diagnosis X Accuracy											
23	0	4	44	Right	Putamen		Dx X Acc	10.41	0.003	cor < incor**	cor > incor**
40	13	30	70	Right	MFG	9	Dx X Acc	14.7	<0.0001	cor < incor**	no diff

Regions from the current data set that demonstrated diagnosis by Resist Update Lure accuracy. They are organized on the left side under headings like “Diagnosis” or “Accuracy” based on whether they demonstrated these effects when examining all 15 time frames of the trial. We only conducted follow up analyses for the update cue period on regions that demonstrated a significant interaction of accuracy and diagnosis. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. “cor” = correct trials and “incor” = incorrect trials. *p<0.05 and **p<0.01. “no diff” signifies no statistically significant difference.

Figure 4. 5 Regions Demonstrating a Diagnosis by Resist Distracter Lure Trial Type Accuracy Interaction



suggest that information was appropriately remembered, and incorrect responses suggest that participants did not update the item as instructed. We again focused our analyses on regions that interacted with at least both diagnosis and accuracy.

When examining all 15 time frames there were 2 regions that demonstrated an interaction of diagnosis and accuracy (bilateral globus pallidus, -21, -7, 0 and 25, -17, 0) and 2 regions that demonstrated a 3-way interaction of diagnosis by time by accuracy (bilateral IFG, including 40, 43, 1 and -42, 8, 31). When examining whether these regions continued to interact with diagnosis and accuracy in analyses restricted to the frames following the presentation of the update cue (frames 8-12) we found that two regions from bilateral globus pallidus and one region in the IFG demonstrated significant interactions of diagnosis by accuracy (Table 4.7). For patients, activity in both regions of the globus pallidus significantly differed when comparing correct and incorrect Update activity following the presentation of the update cue, such that correct activity was greater than incorrect activity (Figure 4.6A and 4.6C). For controls, correct and incorrect activity in these regions also significantly differed from one another, however incorrect trial activity in both regions was greater than correct trial activity. The pattern for controls when comparing correct Update trial activity to incorrect Update trial activity was the opposite of the pattern of correct versus incorrect Update trial activity for patients (Figure 4.6B and 4.6D). We did not expect to find that healthy controls demonstrate and opposite pattern of effects relative to patients when looking at correct and incorrect trial performance. One possible explanation for this may be related to differences in the proportion of correct and incorrect trials available for analysis between groups. Controls made significantly fewer errors on both Resist Distracter Lure and Update trials, which could results in more variable averaged time courses for incorrect trials. This interpretation makes some sense, particularly when visually inspecting the time course of putamen activity for controls during incorrect Resist Distract Lure trials (Figure 4.5 B).

Another region, right lateral IFG, also demonstrated a significant effect of diagnosis by accuracy following the presentation of the update cue, but when comparing correct and incorrect Update trial activity within diagnostic groups neither group demonstrated a difference (Table 4.7). We examined the time course of activity for this region to determine where the effect was coming from. While numerically the pattern of activity in this region was the same for patients and controls as what we observed in the globus pallidus (greater correct than incorrect trial activity following the presentation of the update cue for patients and the opposite pattern for controls), the differences did not reach significance. There did appear to be differences earlier during the trial (around the onset of the memory set) for both patients and controls that may have driven the initial interaction of diagnosis by time by accuracy when we examined all 15 time frames.

For our first aim we found evidence to suggest that patients with schizophrenia demonstrated deficits of updating and interference control and that, at least for interference control, there was a trend to suggest that this deficit of behavioral performance for patients was not due to a general deficit of distracter resistance. That while both cortical and subcortical activity for controls generally demonstrated condition sensitivity, for patients condition sensitivity was reduced, particularly within the striatum. We also found that evidence to support our hypothesis that dysregulated striatal activity was associated with interference control performance deficits for patients, given that striatal activity during incorrect trials was greater than correct trial activity. However, contrary to our predictions, we found that for patients a region in the cortex also demonstrated greater incorrect relative to correct interference control trial activity. Further, controls demonstrated the opposite pattern of activity relative to patients when comparing correct and incorrect trial activity, which was not expected.

<u>Specific Aim 2:</u> Test the hypothesis that in individuals with schizophrenia, increased striatal activity during distracter presentation will be positively associated with aberrant salience symptoms, delusions, and hallucinations.

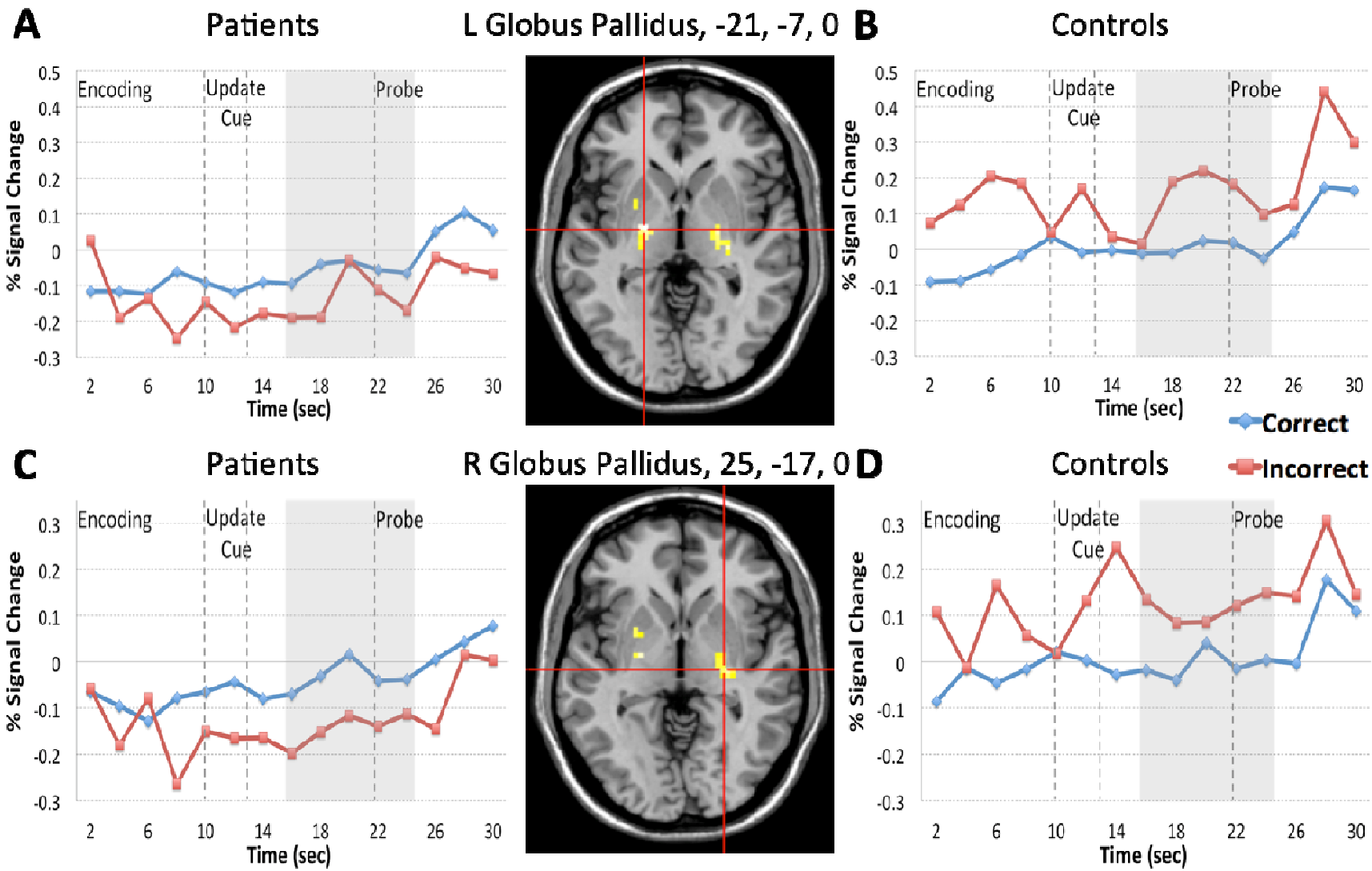
Table 4. 7 Regions Demonstrating an Effect of Diagnosis by Update Trial Type Accuracy within our Anatomical Masks

X	Y	Z	Size	Hemisphere	Region	BA	Effect at frames 8-12			Correct vs. Incorrect	
							Analysis	*F*	*p*	*Patients*	*Controls*
Diagnosis											
24	-9	4	222	Right	Putamen						
14	3	15	92	Right	Caudate Body						
-22	-8	5	251	Left	Globus Pallidus						
-40	38	7	211	Left	IFG	46					
30	30	-5	40	Right	IFG	47					
23	52	3	23	Right	SFG	10					
39	18	28	133	Right	MFG	9					
-39	8	34	42	Left	Precentral Gyrus	9					
Accuracy											
-36	8	29	34	Left	IFG	9					
44	8	32	38	Right	MFG	9					
Accuracy X Time											
11	-1	14	27	Right	Caudate Body						
35	34	-5	28	Right	MFG	47					
37	28	29	87	Right	MFG	9					
-44	11	29	64	Left	IFG	9					
Diagnosis X Time											
44	40	-2	49	Right	Sub-Gyral	10					
-40	44	3	180	Left	IFG	10					
42	18	30	91	Right	MFG	9					
Diagnosis X Accuracy											
-21	-7	0	34	Left	Globus Pallidus		Dx X Acc	9.49	0.004	cor > incor*	cor < incor**
25	-17	0	34	Right	Globus Pallidus		Dx X Acc	13.99	0.001	cor > incor**	no diff

Diagnosis X Time X Accuracy											
40	43	1	41	Right	IFG	10	Dx X Acc	4.53	0.04	no diff	no diff
-42	8	31	24	Left	IFG	9	Dx X Acc	0.01	0.92		

Regions from the current data set that demonstrated diagnosis by Update accuracy. They are organized on the left side under headings like “Diagnosis” or “Accuracy” based on whether they demonstrated these effects when examining all 15 time frames of the trial. We only conducted follow up analyses for the update cue period on regions that demonstrated a significant interaction of accuracy and diagnosis. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. “cor” = correct trials and “incor” = incorrect trials. *p<0.05 and **p<0.01. “no diff” signifies no statistically significant difference.

Figure 4. 6 Regions Demonstrating a Diagnosis by Update Trial Type Accuracy Interaction



4.8. Relationship between Symptoms and Brain Activity Results

For our second aim we sought to examine the relationship between brain activity, specifically striatal activity, and aberrant salience for patients with schizophrenia. We first assessed the relationship between ASI scores and measures of psychosis proneness and anhedonia from the chapman scales. For patients (Table 4.8, burgundy text) we found that ASI scores were, as expected, positively correlated with perceptual aberration magical ideation. However, contrary to expectation, ASI scores were also positively correlated with measures of physical anhedonia and social anhedonia. For controls, we found that ASI was only significantly correlated with magical ideation (Table 4.8, green text). All correlations between ASI and measures from the Chapman scales were positive for controls.

With regard to the relationship between brain activity of patients during correct and incorrect Resist Distracter Lure trials, we conducted a correlational analysis examining the relationship between brain activity of regions demonstrating an effect of accuracy by diagnosis (putamen and MFG, see above) during Distracter Lure trials and symptom expression scores. Because we predicted that the susceptibility to distracter presentation would be associated with aberrant salience, we examined brain activity during both correct and incorrect trials.

For patients (burgundy text), aberrant salience did not significantly correlate with putamen activity in response to the update cue when patients made correct responses. Correct trial putamen activity of patients significantly positively correlated with only one other measure of psychosis proneness – magical ideation. Incorrect trial activity in the putamen of patients following the presentation of the update cue did positively correlate with aberrant salience (Table 4.8 and Figure 4.7), and this correlation was significant. Incorrect trial activity in the putamen of patients also demonstrated a significant positive correlation with magical ideation. We tested whether the correlation between ASI and putamen activity for correct versus incorrect trials differed for patients (Meng, Rosenthal, & Rubin, 1992), and we found a trend towards

Table 4. 8 Correlations Between Correct and Incorrect Resist Distracter Lure Trial Type Brain Activity and Aberrant Salience, Psychosis Proneness, and Anhedonia Measures

	ASI	PR	PA	SA	MI	Putamen (correct)	Putamen (incorrect)	MFG (correct)	MFG (incorrect)
ASI		0.20	0.11	0.38	0.72**	-0.38	-0.32	0.20	-0.24
PR	0.69**		0.26	0.67**	0.51*	-0.34	-0.49*	-0.35	-0.71**
PA	0.48*	0.49*		0.74**	0.09	0.03	-0.24	-0.43	-0.59**
SA	0.54**	0.7**	0.63**		0.39	-0.22	-0.6**	-0.39	-0.76**
MI	0.73**	0.87**	0.56**	0.77**		-0.47*	-0.41	0.21	-0.44
Putamen (correct)	0.19	0.40	0.19	0.33	0.45*		0.53*	-0.27	0.25
Putamen (incorrect)	0.56**	0.34	0.32	0.23	0.43*	0.33		-0.11	0.6**
MFG (correct)	-0.33	-0.33	-0.38	-0.27	-0.34	0.22	-0.32		0.44
MFG (incorrect)	0.37	0.26	-0.16	0.11	0.22	0.03	0.22	0.34	

Correlations between Resist Distracter Lure, correct and incorrect, trial brain activity and clinical symptom measures. Patient correlations are printed in burgundy and controls correlations are printed in green. ASI = aberrant salience inventory. PR = perceptual aberration. PA = physical anhedonia. SA = social anhedonia. MI = magical ideation. *p<0.05 (2-tailed) and **p<0.01 (2-tailed).

significance (z=-1.56, p = 0.06). Correct activity in the MFG negatively correlated with ASI scores, but this correlation did not reach significance. The direction of the correlation between correct MFG activity and other measures of psychosis proneness, including perceptual aberration and magical ideation, was also negative but these correlations also did not reach significance. We were interested in determining whether the correlation between incorrect trial activity and ASI differed between he putamen and MFG, and found that the correlations did not significantly differ (z=0.8, p = 0.21).

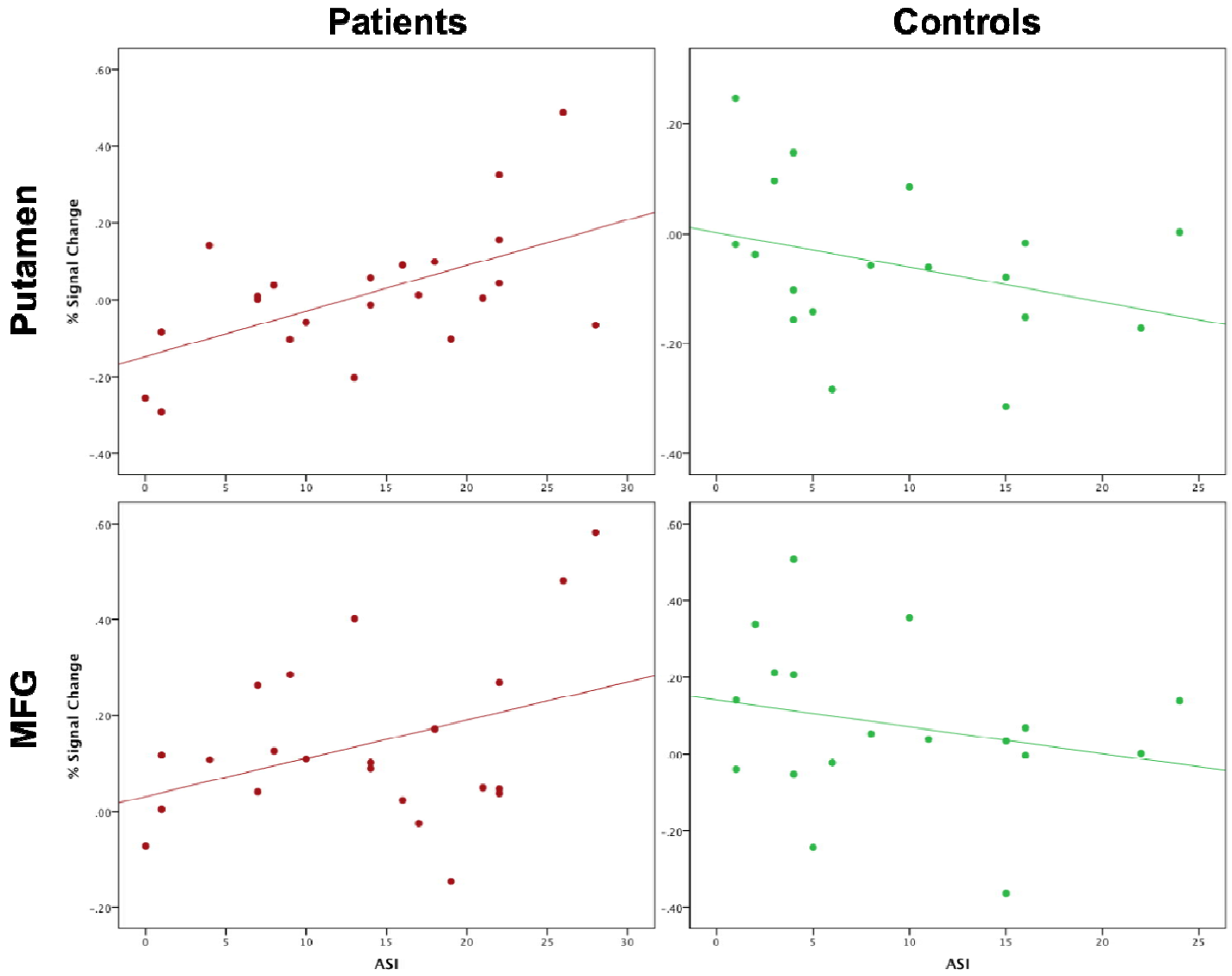
For controls (Table 4.8, green text), we found no correlation between ASI scores and either correct or incorrect activity for the putamen and MFG (Table 4.8). Incorrect Resist Distracter Lure activity in the putamen was negatively correlated with perceptual aberration and social anhedonia, but did not significantly correlate with any other measure of psychosis proneness or anhedonia. We found that, when comparing the correlation between putamen activity and social anhedonia, correlations for correct trial and incorrect trial activity significantly differed from one another (z=-1.83, p = 0.03). However, we did not find that the correlation between correct trial putamen activity and perceptual aberration differed from the correlation between incorrect trial putamen activity and perceptual aberration (z=-0.72, p = 0.24), nor did the correlation between correct trial putamen activity and magical ideation differ from the correlation between incorrect trial putamen activity and magical ideation (z=-0.29, p = 0.39). For the MFG, while correct activity did not significantly correlate with any measure of psychosis proneness or anhedonia, incorrect trial activity demonstrated significant negative correlations with perceptual aberration, physical anhedonia, and social anhedonia. The correlation between MFG activity and perceptual aberration significantly differed between correct and incorrect trials (z=-1.8, p = 0.04) as did the correlation between MFG activity and social anhedonia when comparing correct and incorrect trial activity (z=-1.98, p = 0.02), but correlations between MFG activity and physical anhedonia did not differ when comparing correct and incorrect trials (z=-

0.77, p = 0.2). Incorrect trial activity in the MFG for controls was not significantly correlated with ASI (Figure 4.7) or magical ideation, although the direction of the correlations for these variables was also negative. Finally, we examined whether the significant correlation between ASI and incorrect trial putamen activity significantly differed between patients and controls. We found that, indeed, it did (z=2.89, p = 0.004).

Next we examined the relationship between aberrant salience and brain activity in regions from the trial type analysis (see above) that demonstrated a significant interaction of diagnosis and Update accuracy. We found that two regions, bilateral globus pallidus (Table 4.7), during the Update trial demonstrated a significant interaction of diagnosis by accuracy in response to the update cue. For both of these regions patients demonstrated a significant positive correlation between ASI scores and brain activity, but only during correct trials (Table 4.9 and Figure 4.8). The correlation between ASI and incorrect trial activity significantly differed from the correlation between ASI and correct trial activity for both left (Z= 2.26, p = 0.01) and right (Z = 2.84, p = 0.002) lateral globus pallidus. Left lateral globus pallidus activity also significantly correlated with magical ideation in the same direction, but not with perceptual aberration or the anhedonia measures. Right lateral globus pallidus activity, however, demonstrated significant positive correlations with all other measures of psychosis proneness and anhedonia.

For controls, we observed a significant negative correlation between ASI and right lateral globus pallidus activity during incorrect Update trials. Activity in this region did not significantly correlate with other measures of psychosis proneness or anhedonia. When we compared the correlation between ASI and right lateral globus pallidus activity during incorrect and correct trials we found that no difference between correlations (z=-1.14, p = 0.13). While correct trial activity in bilateral globus pallidus did not significantly correlate with ASI, we did observe significant negative correlations with magical ideation (Table 4.9) bilaterally. Neither correlation

Figure 4. 7 Scatter Plots Depicting the Relationship Between ASI and Brain Activity During Correct Resist Distracter Lure Trials



between left and right globus pallidus correct trial activity and magical ideation significantly differed from respective incorrect trial correlations between brain activity and magical ideation.

For our second aim we predicted that increased activity during striatal activity during distracter presentation would be positively associated with positive symptoms expression, particularly with ASI. We found that while correct trial activity of the putamen or MFG did not significantly correlate with symptom expression incorrect trial activity did, but only for the putamen and not the MFG. Further, this was true for patients but not controls. This finding was consistent with the predicted relationship between interference control deficits for patients, striatal dysregulation, and symptom expression. We also found that for patients increased globus pallidus activity during correct Update trials was associated with ASI, which is consistent with the idea that greater activity in the basal ganglia is associated with aberrant salience. While we would predict that regions within the globus pallidus demonstrate increased activity other regions (regions within the external capsule) would not. Given its size, it is difficult to say where the regions demonstrating effects of interest in our study fall within the globus pallidus.

5. Discussion

This study first sought to test whether individuals with schizophrenia have dysregulated striatal activity when processing cognitive control demands, whether this dysregulation is associated with performance deficits, and whether striatal activity is associated with aberrant salience symptoms. The current study was motivated by previous work that proposed a role for the dorsal striatum as a mechanism of gating during cognitive control (Hazy et al., 2006; Miller, 2013), the putative dependence of this mechanism on dopamine signaling, and evidence of dysregulated dopamine signaling in the associative striatum for patients with schizophrenia (Howes et al., 2012; Kegeles et al., 2010). Thus, we first predicted that the brain activity of patients, particularly in the dorsal striatum, would differ from controls during updating and

interference control performance. Using a novel task that separately examined updating, interference control, and simple maintenance, we found evidence suggesting that both prefrontal and striatal activity differed between patients and controls during the execution of task demands. Overall, patients demonstrated a decreased magnitude of prefrontal activity in response to updating demands when compared with controls, and, unlike controls, patients did not show differences in activation between updating and interference control relative to simple maintenance in the striatum. We found some evidence for altered caudate activity during task processing, though the pattern was not as clear as that for prefrontal cortex. When examining differences of brain activity between diagnostic groups during correct and incorrect updating and predicted that dysregulated striatal activity would be associated with aberrant symptom expression for patients. We found that, indeed, striatal activity was associated with aberrant salience symptom expression for patients but not controls and the correlation between striatal activity and aberrant salience significantly differed between diagnostic groups. Interestingly, although both prefrontal cortical activity and striatal activity of patients with schizophrenia demonstrated similar patterns of activity in response to cognitive control demands, only striatal activity was significantly correlated with aberrant salience symptom expression. Each of these findings will be discussed in more detail below. However, first we will discuss the results of our replication analyses in just the healthy controls.

5.1. Replication of Prior fMRI Results in Healthy Individuals:

5.1.1. Independently Defined ROI

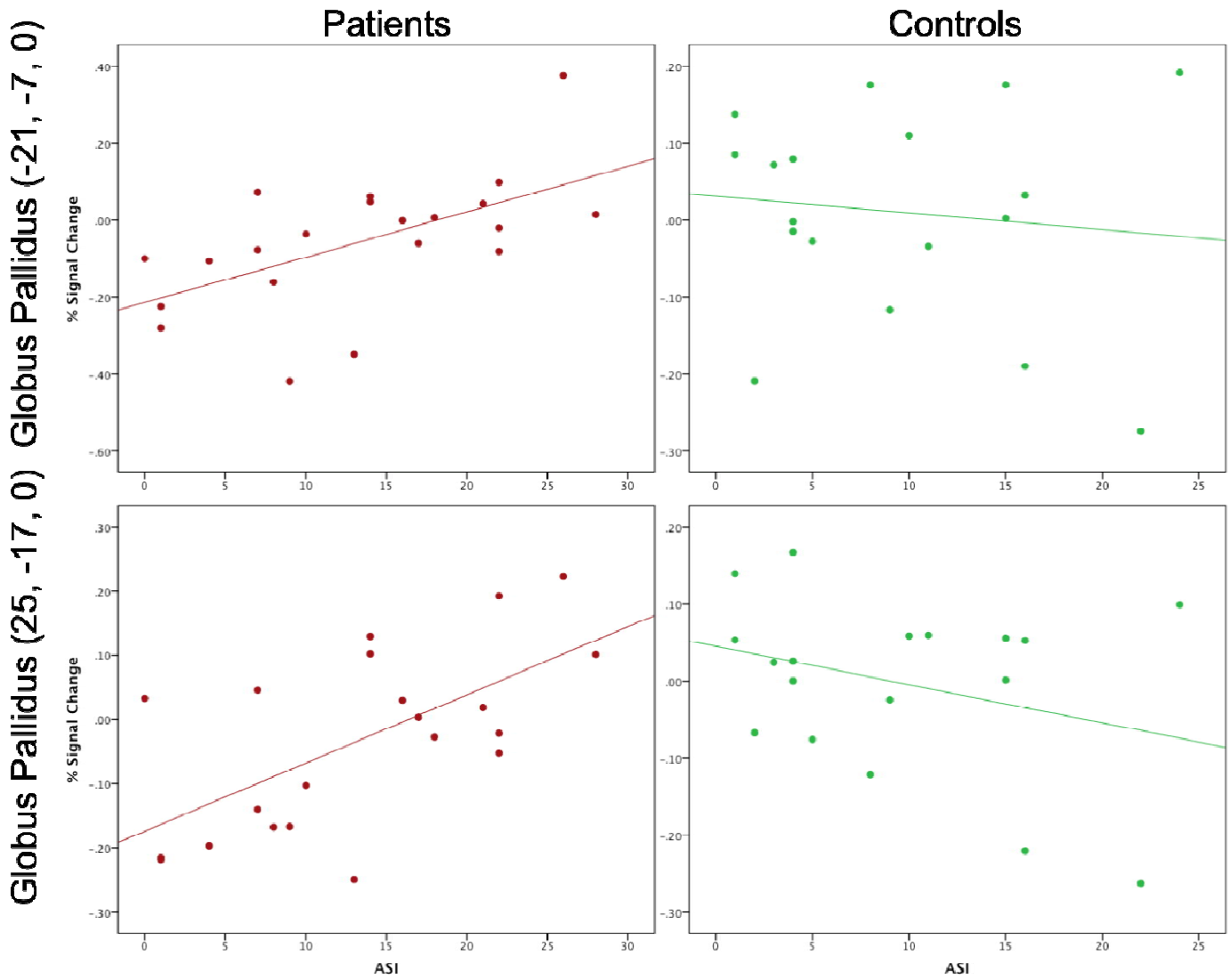
Previously we found that cortical activity increased during both information updating events and distracter presentation compared to a basic maintenance condition, but that activity within the dorsal striatum selectively activated to information updating and not interference control (Ceaser et al., in prep). Further, we found that during the presentation of the update cue, only brain activity within an anatomical mask of the basal ganglia, and not the prefrontal or

Table 4. 9 Correlations Between Correct and Incorrect Update Trial Type Brain Activity and Aberant Salience, Psychosis Proneness, and Anhedonia Measures

	ASI	PR	PA	SA	MI	L Globus Pallidus (correct)	L Globus Pallidus (incorrect)	R Globus Pallidus (correct)	R Globus Pallidus (incorrect)
ASI		0.20	0.11	0.38	0.72**	-0.11	-0.24	-0.31	-0.59*
PR	0.69**		0.26	0.67**	0.51*	-0.05	0.16	-0.31	0.26
PA	0.48*	0.49*		0.74**	0.09	0.11	0.32	-0.03	0.30
SA	0.54**	0.7**	0.63**		0.39	0.03	0.22	-0.22	0.21
MI	0.73**	0.87**	0.56**	0.77**		-0.48*	-0.43	-0.59*	-0.38
L Globus Pallidus (correct)	0.58**	0.37	0.37	0.31	0.51*		0.65**	0.65**	0.17
L Globus Pallidus (incorrect)	0.15	0.21	0.24	0.17	0.29	0.58**		0.52*	0.42
R Globus Pallidus (correct)	0.64**	0.54*	0.52*	0.6**	0.65**	0.86**	0.41		0.27
R Globus Pallidus (incorrect)	-0.16	0.12	0.21	0.10	-0.06	0.08	0.51*	0.11	

Correlations between Update, correct and incorrect, trial brain activity and clinical symptom measures. Patient correlations are printed in burgundy and controls correlations are printed in green. ASI = aberrant salience inventory. PR = perceptual aberration. PA = physical anhedonia. SA = social anhedonia. MI = magical ideation. *p<0.05 and **p<0.01.

Figure 4. 8 Scatter Plots Depicting the Relationship Between ASI and Brain Activity During Incorrect Update Trials



parietal cortices, could significantly predicted whether an individual made a correct or incorrect response at the probe. These results provided some support for the idea that the basal ganglia may function as a mechanism of information gating during cognitive control, and were consistent with previous studies examining subcortical contributions to cognitive control. For example, a lesion study of stroke patients found that lesions of the left lateral putamen and surrounding white matter resulted in deficits of distracter resistance (Baier et al., 2010), suggesting that the basal ganglia may play an important role in gating relevant information. Similarly, McNab et al. (McNab & Klingberg, 2008) found that the globus pallidus demonstrated selective associations with filtering unnecessary storage activity, suggesting that increases of globus pallidus activity may serve to filter our distracters from entering working memory storage. Other studies have shown that the dorsal striatum is involved in selective updating (Murty et al., 2011; Roth et al., 2006) and working memory manipulation (Lewis, Dove, Robbins, Barker, & Owen, 2004) when compared with other cognitive control processes. A study of dopamine depletion in the caudate of marmoset monkeys demonstrated the importance of dopamine when executing these cognitive processes, as the monkeys demonstrated selective deficits of a delayed response task but preserved attentional set-shifting (Collins, Wilkinson, Everitt, Robbins, & Roberts, 2000), although dopamine depletion influencing updating may not be the only explanation of these results.

Using the regions from our previous study we examined whether healthy controls from our current data set demonstrated the same pattern of condition effects. We again found that healthy control participants demonstrated greater prefrontal and striatal activity during updating than simple maintenance conditions. We also found some evidence that prefrontal activity in these independently defined regions demonstrated some transient activity to distracter presentation, consistent with our previous findings, though not all of the prefrontal regions demonstrated this effect. We did not find a significant response to distracter presentation within any of the striatal regions. These findings are partially consistent with the findings from our

previous study, and suggest that while both the cortex and striatum process updating demands, the striatum may selectively activate and the PFC, particularly the IFG, may demonstrate more general condition sensitivity. For one of the independently defined striatal regions (right lateral caudate) we found maintenance activity that was intermediate to interference control and update activity. This was unexpected, given that participants were not presented with any shapes during the maintenance condition and maintenance activity that was greater than interference control activity was not something we found during our previous study. Because we used maintenance trials as our comparison condition increased activity during this condition may explain why we did not find differences between maintenance and updating or interference control. This finding is discussed in more detail below.

5.1.2. Anatomical Mask of Basal Ganglia and Prefrontal Cortex

In this analysis we identified regions that demonstrated condition effects (instead of examining condition effects only within regions defined in the prior study) and found multiple regions within the left and right MFG demonstrated condition effects in response to the presentation of the update cue, as did one region in the left caudate. The pattern for regions within the MFG was that updating activity was significantly greater than maintenance, with no difference between interference control and maintenance. While interference control activity in this region was numerically higher than maintenance activity (Figure 4.3A) following presentation of the update cue, the fact that we did not find a significant difference between these conditions is not consistent with our previous work. It may be the case, however, that we generally lacked the power reliably to detect this subtle difference between the transient cortical response to distracter presentation and activity during the maintenance condition, even though our control sample in this data set is larger than the previous data set. That is, we found the same relative patterns of activity that we did in our previous study but given the difference between interference control and maintenance activity is small although the difference exists the

significance of this difference may vary across smaller samples. The region in the caudate also demonstrated greater updating than maintenance activity, but greater maintenance activity when compared with interference control activity. One explanation for this increase of activity during maintenance trails compared to interference trials within the striatum is that it may reflect a salient cue orientation signal (Redgrave, Gurney, & Reynolds, 2008), as discussed next.

We used maintenance as a comparison condition because, unlike updating and interference control conditions, no shapes are presented during the update cue period. We assumed that there should be little to no change in striatal activity during this period given that striatal neuron projecting to the direct pathway would not activate in the absence of stimulus presentation and striatal neurons projecting to the indirect pathway are tonically active, and would not demonstrate a change of activation. After reviewing plots of time courses during the three different update cue conditions we see that this is not the case, and for many regions there is in fact mild to moderate increases of brain activity during the update cue period of maintenance trials. While no shapes were presented during this time empty boxes that are either red or green in color are presented and this presentation may be sufficient to elicit an increase of striatal activity, particularly in the caudate given that the boxes are salient and behaviorally relevant. A study by Zink et al. (2003) examined in humans the possibility that the striatum may function to process salient events regardless of reward value, rather than coding rewards and reward-related stimuli. They examined striatal response to nonrewarding salient stimuli using fMRI while manipulating the behavioral relevance of stimuli by manipulating salience by manipulating the frequency of distracter occurrence (such that high frequency resulted in less salience) and the behavioral relevance of the distracter (distracters that required a response and those that did not). They found that activity in both the nucleus accumbens and caudate increased in response to high salience nonrewarding stimuli, but activity in the caudate only did so when the stimuli was behaviorally relevant. Thus, increased caudate activity we observed during maintenance may reflect the salient, behaviorally relevant, properties of the

green and red boxes presented during maintenance trials. Further, increased maintenance activity compared with interference control activity may also reflect the increased salience of "no-shape" maintenance trials when compared with "ignore-shape" distracter trials, given that the majority of trials used in the task presented either one or two shapes and thus maintenance trials were less frequent.

Specific Aim 1: Test the hypothesis that individuals with schizophrenia demonstrate dysregulated striatal activity during updating and interference control and that striatal activity predicts performance deficits.

5.2. Condition Discussion

To address our first aim we examined brain activity during updating, distracter presentation, and simple maintenance in both our independently defined ROIs and in an anatomical mask of the prefrontal cortex and the striatum. Given that patients with schizophrenia may have dysregulated striatal activity and that activity in the striatum may be associated with information gating, we predicted that patients would demonstrated an attenuated striatal response in response to updating demands and an attenuated response to task conditions cortically. We first examined diagnostic differences at the condition level to identify broad difference in responses to updating, distracter presentation, and simple maintenance in regions that were defined using a previous data set of healthy controls. Three regions demonstrated significant interactions of condition and diagnosis – two in the dorsolateral prefrontal cortex (DLPFC) and one region in the caudate. Patients demonstrated greater DLPFC activity for updating compared to maintenance activity and even significantly greater DLPFC activity during interference control when compared with maintenance. Within the caudate there were no differences between conditions for patients and a plot of the time course revealed poor separation between conditions following the update cue. Controls also demonstrated significantly greater update and interference control DLPFC activity when compared with

maintenance and no difference between conditions in the caudate, however a plot of the time course for controls revealed that there was separation between conditions but maintenance activity in the caudate that was intermediate to update and interference control activity. We did find that update and interference control activity for controls in the caudate significantly differed when we compared them directly. When comparing neural response to task demands between diagnostic groups we found that updating activity within the IFG and MFG for controls was significantly greater than updating activity within these regions for patients, but that there was no difference between groups when examining interference control activity within these regions and no differences between groups when examining caudate activity. So, while updating activity in the DLPFC for patients was significantly greater than comparison conditions, updating activity was still significantly lower than for controls. In the anatomical mask analysis, we found only one region in the MFG (BA 9) that demonstrated an interaction of condition and diagnosis. In this region, controls demonstrated significantly greater updating activity when compared with maintenance (an numerically greater interference control activity compared with maintenance), whereas patients did not demonstrate significant differences between task conditions. When comparing the neural response to task demands between diagnosis groups we found no differences, although control activity to updating and interference control was numerically greater.

These results provide some support for the hypothesis that patients would demonstrate dysregulated striatal activity during cognitive control demands, as evidenced by poor discrimination during 3 different task conditions. Interestingly, this was true when examining correct trials and this lack of discrimination was truer for the striatum than it was for regions within the DLPFC when examining our independently defined regions (Table 4.4), although activity for patients in one region of the DLPFC (MFG; -41, 30, 26; Figure 4.4) also demonstrated poor discrimination between conditions. Importantly, however, we also saw evidence for altered activity in the DLPFC. Of the DLPFC regions that demonstrated an

interaction of diagnosis by condition we also observed that the response to updating demands for patients within a region was numerically lower than controls. It is interesting that the regions demonstrating tasks effects within our anatomical masks correspond to segments of the striatum striatal that have anatomical and functional connectivity with the DLPFC. For example, Draganski et al. (2008) examined cortico-striatal connectivity using probabilistic tractography and a novel method of creating voxel-based connectivity profiles to represent projections from a source to multiple target regions, called voxel connectivity profiles, on magnetic resonance diffusion imaging data of 30 healthy subjects. The aim of the study was to compare basal ganglia and thalamic connectivity of humans with anatomical patterns demonstrated in nonhuman primates, and to provide evidence of pathways between spatially segregated regions of the basal ganglia/thalamus and cortical regions. Amongst other findings, they found that rostral and caudal regions within the caudate and putamen demonstrated strong connectivity with the DLPFC and orbital frontal cortex (OFC). These findings were supported by Barnes et al. (2010), who used a combination of resting state functional connectivity MRI and graph theoretic analyses to parcellate subcortical structures of individual subjects and found that the locations of significant cortical-basal ganglia functional connectivity was consistent with connectivity of basal ganglia segments described above. While there is good evidence for both anatomical and functional connectivity between segmented cortico-striatal loops, the nature of the relationship during cognitive control has yet to be fully elucidated. A critical question for future research is to what degree does altered activity in the striatum and the DLPFC reflect an abnormal functional loop, and whether some of the variance in DLPFC disruption in schizophrenia might actually reflect dysregulated striatal function.

One way that cortico-striatal loops may impact cognitive control is through information gating, which may be accomplished through dense dopaminergic innervation of the striatum that transiently strengthen inputs to the frontal cortex, and by extending models of disinhibitory gating from the motor literature. As described in the introduction section, this gating mechanism

has been described computationally by Frank et al. (2001) and, more recently, by Hazy et al. (Hazy et al., 2007). In this model, dopamine based reinforcement-learning provides appropriate learning signals that train direct pathway medium spiny neurons (MSNs) in the dorsal striatum when to fire, inhibiting the substantia nigra, which then releases the thalamus from tonic inhibition. Thalamic disinhibition enables, but does not cause, excitation of a segregated cortico-striatal loop and thus an information update, the same way that disinhibition via the basal ganglia sets a pattern of motor readiness in premotor networks rather than generating a command for muscular contraction (Chevalier & Deniau, 1990). Striatal spiny neurons in the indirect pathway are in competition with neurons in the direct pathway as they promote greater inhibition of thalamic neurons. In the prefrontal cortex, robust maintenance occurs through a combination of recurrent excitatory connectivity and bistability, which is toggled to and from a maintenance state via input from the basal ganglia. Hazy et al. (2007) also suggests that actively maintained representations in the prefrontal cortex may demonstrate top-down biasing of processing in relevant brain areas (e.g. posterior cortex, hippocampus, and basal ganglia), which may occur only when output-generating laminae within frontal cortical columns reach a threshold via basal ganglia-thalamic input signals (Hazy et al., 2007). Similarly, others suggests that dopamine and basal ganglia output may function to stabilize the information gate during distraction by enhancing task relevant memories in the cortex (Gruber et al., 2006) or that output from the basal ganglia gradually trains or builds up representations in the prefrontal cortex, and that without this input cortical representations are not as robust or distinct (Miller, 2013).

Based on the relationship between the prefrontal cortex and the basal ganglia described in the models discussed above, certain predictions could be made about how these regions will behave during specific task conditions. For example, during information updating one can expect that MSNs in the direct pathway will activate more strongly than MSNs in the indirect pathway, resulting in inhibition of the substantia nigra, disinhibition of the thalamus, and

activation of the prefrontal cortex region within that cortico-striatal loop. During interference control, however, without appropriate dopaminergic input, MSNs in the indirect pathway will continue their tonic inhibition of the substantia nigra, which leads to inhibition of the thalamus and cortical regions within that segregated loop. The prefrontal cortex will activate in response to a distracter, but without basal ganglia-thalamic input signals this activation will not reach threshold. Thus, if dopamine signaling in the striatum were disrupted, as is the case with psychosis, one may expect that striatal output would be affected, perhaps though increased competition between direct and indirect MSNs resulting in weaker activation in response to updating demands, and with weaker basal ganglia-thalamic output to the cortex the cortical threshold would be more difficult to meet. Our finding that within the striatum patients demonstrated poor discrimination between conditions and appear to have an attenuated cortical response to updating demands are consistent with these predictions.

The models also imply that increases of brain activity in dorsal striatal and prefrontal regions should be associated with an update occurring, regardless of whether the update should have happened, because the “gate” opens anytime information is admitted to working memory stores. Further, a failure to update should be associated with decreased striatal and prefrontal activity because the “gate” failed to open. If a participant were to inappropriately update a distracter, for example, we would expect to see similar patterns of prefrontal and striatal activity that we would see during an appropriate update. We explored this idea in our analysis of trial type accuracy.

5.3. Trial type Accuracy Discussion

Given differences of behavioral accuracy between diagnostic groups during the Update and the Resist Distracter Lure trial types we examined whether brain activity during correct and incorrect trials differed within prefrontal and striatal regions, and across diagnostic groups. The Resist Distracter Lure trial is interesting because at the response probe participants are presented with items they should have ignored earlier during update cue. If participants indicate

that this items is correct it suggests that they inappropriately updated or attended to this item instead of ignoring it as instructed. This inappropriate update should be reflected in changes of brain activation during the update cue. Further, this analysis is interesting because it examines differences of brain activity between correct and incorrect Resist Distracter Lure trials that occur during time frames associated with the update cue, even though distinguishing feature between correct and incorrect trials is the response to the probe that occurs later. As predicted we found increased activity for incorrect trials compared with correct trials within a right DLPFC region and within the right putamen, but for patients not controls. For controls, activity within the DLPFC demonstrated no difference between correct and incorrect trials, and greater correct trial activity than incorrect trial activity within the putamen – the opposite pattern of patients with schizophrenia. This finding supports the idea that for patients, activity occurring in response to the update cue, even when instructed to ignore these items, meaningfully contributes to later behavioral accuracy at the probe. Not only did we find that there were differences in activity for correct trials and incorrect trials, suggesting that striatal activity was not simply a byproduct of arousal due to stimulus orientation, but we found greater activity during incorrect trials. This finding fits the prediction one would make based on the computational models of gating (e.g. Frank et al., 2001) described above, where increases of striatal and prefrontal activity are associated with gating information into working memory, and suggests that this processing will lead to a someone identifying an incorrect item as correctly matching a memory representation.

We also examined whether cortical and subcortical brain activity differed between diagnostic groups during correct and incorrect Update trials. Correct responses during Update trials indicate that the participant correctly identified the “to-be-remembered” shape at the probe and incorrect trials indicate that the participant rejected the shape, suggesting they did not update or encode new information as instructed. Again, although correct and incorrect trials are defined by the response made at the probe, we examined activity that was associated with the presentation of the “to-be-remembered” items. Behaviorally, we found that patients and control

performance significantly differed for this trial type, although the effect was smaller for the Update (Cohen's d = 0.66) versus the Resist Distracter Lure trial type (Cohen's d = 0.97). With regard to brain activity, we found that bilateral globus pallidus activity for patients was significantly *greater* for correct than incorrect trials.

In Hazy et al. (2007) model described above, the globus pallidus is associated with the indirect pathway and receives inhibitory input from striatal MSNs. This inhibition activates the globus pallidus, causing disinhibition of substantia nigra pars reticulata (which is tonically inhibited by the globus pallidus), and this disinhibition of the substantia nigra competes with inhibitory input from striatal MSNs associated with the direct pathway. Thus, increases of activation of the globus pallidus should disinhibit the substantia nigra, making it *less* likely that the cortex will be released from thalamic inhibition and *less* likely that an update will occur. Our finding of greater activity on correct versus incorrect trials in the globus pallidus in patients is not consistent with the predictions of the Hazy model, depending on where in particular the regions of the globus pallidus lie. However, this result might be consistent with the findings of McNab et al. (2008). They found that increases of globus pallidus activity, which preceded the presentation of distracters, was associated with increasing working memory storage. They suggested that the globus pallidus might function as an information filter that increases activity in response to relevant task information and decreases activity in response to irrelevant information. In this context it makes some sense that increases of activity within the globus pallidus are associated with correct trials of information updating as task relevant information is being filtered in and lower activity is associated with errors, but again we only found this pattern of effects for patients and not controls. Of the two globus pallidus regions that demonstrated a significant interaction of diagnosis and accuracy for Update trials, controls only demonstrated a difference between correct and incorrect trial activity within the left lateral globus pallidus, such that correct trial activity was significantly less than incorrect trial activity (Figure 4.6B) – the opposite pattern that patients displayed.

The findings from our trial type accuracy analyses provide some support our hypotheses from Aim 1, such that for patients striatal activity distinguished between correct and incorrect trials suggesting that increases of striatal activity during distracter presentation are associated with deficits of interference control. However, we did not find that striatal activity selectively distinguishes between correct and incorrect Resist Distracter Lure trials as a region in the DLPFC also demonstrated significant differences between correct and incorrect trial activity for patients. Further, we found evidence that for patients the globus pallidus significantly distinguished between correct and incorrect Update trial activity for patients, although the pattern of the effect again differed between diagnostic groups and was, perhaps, not consistent with the predictions of the Hazy model.

Unfortunately, with our current design it is difficult to disentangle the causal contributions of prefrontal and striatal regions have on behavioral outcomes, given the relationship between basal ganglia output and prefrontal function described above. For example, it is possible that basal ganglia output precedes prefrontal activation and increases of activity represent information updating whereas prefrontal activity represents storage and maintenance related activity of the updated item. It is also possible that prefrontal activity during distracter presentation may occur first and increases of striatal activity result from downstream effects of cortical activity, perhaps through glutamatergic afferents from the cortex to spiny neurons in the striatum (Rosell & Giménez-Amaya, 1999). Further, we did not find the same pattern of activity during correct and incorrect Resist Distracter Lure trials for controls. If this cortico-striatal mechanism is indeed a mechanism of gating we should expect to see the same pattern of results regardless of diagnostic status. That is, if controls inappropriately update information it should be reflected in a neural response of the striatum and the prefrontal cortex. The fact that we failed to find differences between correct and incorrect trials for controls or the patterns we did find were the opposite of patients with schizophrenia might suggest that the activity we observed for patients reflects something might be specific to disease state and not directly

related gating. However, when examining brain activity in regions that showed interactions of accuracy and time for the Resist Distracter Lure and Update trials (e.g. right putamen, Table 4.6 and right caudate, MFG and left IFG, Table 4.7) to explore the pattern of brain activity between groups as a function of accuracy, we found that for a region in the putamen that demonstrated an accuracy by time interaction both patients and controls demonstrated numerically greater incorrect Resist Distracter Lure trial activity than correct trial activity. Further, the activity for both patients and controls in regions that demonstrated an effect of Update accuracy by time did not appear to differ when comparing correct and incorrect trials to one another. Thus, we found some evidence that to suggest that patient and control activity during correct and incorrect Resist Distracter Lure and Update trials is more comparable, but further work is need to determine if the counterintuitive finding that patients and controls demonstrate opposite patterns of brain activity during task performance.

It may also be the case that errors made by controls were related to processing deficits that had little to do with the inappropriate processing of distracters during the update cue, and were related to other factors that made them error prone (e.g. inattention at the probe). If this were the case the neural signature that would distinguish correct from incorrect trials may not have occurred in either prefrontal or striatal regions, and may have occurred at some other point during the trial than the update cue response period. Another possibility is that we simply lacked a sufficient number of error trials for controls to detect reliable differences of brain activity between correct and incorrect trials, given that patients' behavioral performance was significantly worse than controls for both Resist Distracter Lure and Update trial types. While it is difficult to make conclusive statements about the trial type accuracy results from our control sample, it was clear that patients demonstrated increased susceptibility to distracters, with a large effect size, and poorer updating behaviorally, and that these performance deficits were associated with striatal and prefrontal activity during update cue presentation.

<u>Specific Aim 2:</u> Test the hypothesis that in individuals with schizophrenia, increased striatal activity during distracter presentation will be positively associated with aberrant salience symptoms, delusions, and hallucinations of patients with schizophrenia.

5.4. Relationship between Symptoms and Brain Activity Discussion

Our second aim was to identify a relationship between behavioral deficits of cognitive control, brain activity associated with these deficits, and symptom expression. More specifically, we predicted that striatal activity of patients would demonstrate a relationship between cognitive control deficits and aberrant salience symptom expression given the possibility that mechanisms of cognitive control may also be involved in regulating salience assignment.

The results of our Trial Type Accuracy analysis revealed that, for Resist Distracter Lure trials, patients demonstrated increased activity both in the striatum and DLPFC when an inappropriate update may have occurred. We examined whether this activity was associated with aberrant salience, other measures of psychosis proneness, and anhedonia. We found that only striatal activity during incorrect trials correlated significantly with aberrant salience, such that individuals with higher striatal activity during incorrect trials had higher aberrant salience scores. Further, we found that within the same striatal region, the correlation between aberrant salience and incorrect trial activity was stronger than the correlation between aberrant salience and incorrect trial activity, suggesting some specificity, although the effect was only at trend level. When examining the relationship between striatal activity and other psychosis proneness scores we found that both correct and incorrect trial activity in the striatum similarly correlated with another psychosis proneness measure (magical ideation; $r = 0.45$ and $r = 0.43$, respectively) and not, importantly, with measures of anhedonia. We included measures of anhedonia to contrast the relationship between brain activity and symptoms associated with positive symptoms and symptoms associated with negative symptoms. We predicted that if brain activity associated with cognitive control gating should be more strongly associated with positive symptoms than

negative symptoms given that altered salience assignment is primarily an explanation of psychotic symptoms associated with schizophrenia as discussed by Kapur (2003). Thus, while patient striatal activity during Resist Distracter Lure trials was more broadly correlated with positive symptoms, aberrant salience was selectively associated with errors associated with deficits of interference control. Within the DLPFC, we found no significant correlation between any of the symptom measurements for patients and brain activity. For controls, we found no significant correlation between aberrant salience and brain activity. There was a relationship between activity in the striatum and DLPFC and positive symptoms and anhedonia in controls, but in an opposite direction than that found for patients.

Results from the Update trial type analysis for patients revealed somewhat similar results, such that increases of globus pallidus activity during correct trial only were significantly correlated with aberrant salience and other measures of psychosis proneness and anhedonia. So again, we find that for patients greater basal ganglia activity is associated with greater symptom expression of aberrant salience, but also greater expression of psychosis proneness and anhedonia, although left lateral globus pallidus was selectively correlated with psychosis proneness and not anhedonia. For controls, we found negative correlations between correct and incorrect Update trial globus pallidus activity and aberrant salience, psychosis proneness, and anhedonia. Again, this was the opposite pattern that we observed for patients.

The reversed direction of correlations between brain activity and symptom scores in patients versus controls was unexpected, but perhaps not too surprising given patients and controls demonstrated the opposite pattern of brain activity during correct and incorrect Resist Distracter Lure and Update trials. However, that explanation does not fully account for why, at and individual level, symptom expression increases for controls as brain activity decreases. It is possible that differences in the degree to which patients and controls express symptoms may have impacted our results. For example, all measures from the Chapman scales demonstrated significant differences between patients and controls, which may make one wonder if symptom

expression for controls was at floor levels with little variation across individuals. It is important to point out that there was only a trend level difference of aberrant salience symptoms between patients and controls, suggesting variation of symptom expression was somewhat comparable between patients and controls. One benefit of the ASI is that it was determined to be a valid measure of aberrant salience for both clinical and nonclinical samples (Cicero et al., 2010). Thus, ASI symptoms expressed some range across individuals, but do these symptoms correlate with other measures of psychosis proneness and anhedonia in the way we would expect them to? We found that within the control sample aberrant salience was highly correlated with psychosis proneness but not anhedonia, providing evidence of discriminant validity within our nonclinical sample. So, while symptom expression for controls in this sample is lower than patients we have some evidence suggesting symptom expression within our control sample demonstrates some variability and behaves as expected. Even so, the correlations between brain activity during task performance and aberrant salience for controls were almost uniformly negative, like they were for other measures of psychosis proneness and anhedonia.

One potential interpretation of these findings is that they perhaps run contrary to the idea that psychotic experience exists as a part of a continuum (described previously by Linscott & van Os, 2010), or that psychotic experiences and odd thinking exist to a lesser degree in nonclinical sample and are produced by some of the same mechanisms that produce these symptoms in clinical samples. For example, we found that psychotic symptoms that presumably have the same underlying mechanism correlated differently with striatal activity between patients and controls. Others that have examined the relationship between brain activity and psychosis proneness of healthy individuals, to detect regions associated with psychotic symptom expression within nonclinical samples, have found mixed results. For example, Ettinger et al. (2013) examined psychosis proneness and neural activation during a procedural learning task, thought to be sensitive to sensitive to dopamine fluctuation, and found positive correlations between psychosis proneness and, amongst other regions, the caudate, putamen,

and frontal regions. However, these findings were not consistent with previous work of theirs examining the relationship between psychosis proneness and fronto-striatal-thalamic brain activity during involuntary or voluntary inhibition (from Ettinger et al., 2013), where they found negative relationships between brain activity and psychosis proneness. They suggest that this may be explained by differential influences of dopamine on tasks involving inhibition and tasks involving procedural learning. Further, Corlett et al. (2012) examined the relationship between brain activity during prediction error and psychosis proneness for a sample of healthy volunteers and found negative correlations between symptom expression and brain activity in the dorsal striatum and DLPFC, however they do not interpret the direction of this finding. Further work is needed to clarify some of the causal neural mechanisms of psychotic symptom expression within nonclinical samples and the degree to which similar relationships are found in clinical and non-clinical samples

Regarding the relationship between aberrant salience and brain activity for individuals with schizophrenia, our findings of a relationship between aberrant salience and dorsal striatal activity are somewhat distinct from previous studies. For example, Roiser et al. (2009) examined whether patients with schizophrenia demonstrated deficits of motivational incentive salience, or learning stimulus-reinforcement associations where neutral stimuli acquire relevance through primary reinforcement and subsequently influence behavior. They used a novel task, the Salience Attribution Task (Schmidt & Roiser, 2009), that required participants to make speeded responses to earn money in the presence of conditioned stimuli, and found that while some patients demonstrated adaptive motivational salience acquisition patients with greater delusional symptoms demonstrated aberrant salience acquisition. However, they found that aberrant salience was correlated only with negative symptoms. Using the same task they examined the neural basis of adaptive motivational salience acquisition in healthy controls and found that higher cue relevance was associated with increased activity within the ventral tegmental area and its dopaminergic projections, including the thalamus, ventral striatum, and

prefrontal cortex – regions previously implicated in motivational salience – and positive correlations between brain activity and adaptive reward learning (Roiser, Stephan, Ouden, Friston, & Joyce, 2010). This same group examined whether patients at high-risk for developing psychosis demonstrated aberrant incentive salience as well as altered dopamine synthesis capacity and brain activity relative to controls during salience acquisition. While they found no group differences between aberrant reward prediction and no difference between dopamine synthesis capacity, they did find aberrant salience acquisition behaviorally for the high-risk group that differed relative to controls and a positive correlation between ventral striatal responses and inappropriate salience assignment (Roiser, Howes, Chaddock, Joyce, & McGuire, 2013).

Taken together, these findings provide some evidence demonstrating that aberrant incentive salience is associated with psychosis and psychosis risk, and that as expected salience acquisition is associated with brain regions previously identified to be associated with this type of learning, including the ventral striatum. However, they acknowledge the conundrum that despite the relationship between the ventral striatum and motivational incentive salience acquisition, in schizophrenia the largest dopamine abnormality, thought to underlie deficits of salience acquisition, occurs in the dorsal rather than the ventral striatum (Howes et al., 2012). For patients the relationship between the dorsal striatum function, increased presynaptic dopamine storage and release with the dorsal striatum, aberrant salience and cognitive deficits associated with the disorder have been unclear. As such, the current study is the first to identify a relationship between dorsal striatal activity, cognitive control deficits associated with schizophrenia, and clinical symptom expression of psychotic symptoms.

5.5. Limitations

Limitations of the study include the relatively modest sample size. These results should be replicated in a larger, independent sample to support these findings. Upon reviewing the time

course of activity during the Condition and Trial Type analysis we observed that patients seemed to have lower activity than controls in response to the presentation of the memory set (e.g. Figure 4.4). It is possible that behavioral deficits we observed were the results of goal representation deficits associated with schizophrenia (reviewed in Barch & Ceaser, 2012). Failing to adequately encode the memory set would significantly impair the ability of participants to respond appropriately to update cues and make correct responses when probed. The impact of goal representation deficits, while not a focus of this current study, is something that warrants further exploration given that it may be a common mechanism of cognitive dysfunction for schizophrenia. We should note, however, that we did not find significant differences between patients and controls behaviorally on measures of simple maintenance and maintenance when presented with distracters. That is, when tasked to simply maintain information over time patients and controls had comparable maintenance performance, even when presented with distracting information in the interim. Thus, there is evidence that patients are able to maintain information over time but their performance decreases as task demands become more complex (i.e. making an information update, ignoring distracters, etc).

Further, aberrant salience theories of symptom expression are based on findings of increased dopamine synthesis capacity within the associative striatum for patients with schizophrenia and thus altered striatal dopamine signaling. Altered dopamine signaling was not something that was measured in this study, and thus it is not clear to what extent our findings related to this dysfunction for patients with schizophrenia. Further work is needed to determine if, for example, aberrant salience symptoms correspond to changes of dopamine fluctuation or if it is associated with increased striatal activity for patients during distraction. The relationship between brain activity, dopamine signaling, and psychosis proneness is also something that warrants further study, as it is not clear whether subclinical symptoms expressed by non-psychotic individuals result from the same mechanism that brings about these symptoms for psychotic individuals. Or, perhaps a better question is what mechanisms are sufficient to bring

about subclinical symptom expression assuming that multiple mechanisms contribute to symptom expression? It was difficult to interpret the results of our control sample given this ambiguity, but what was clear was that patients and controls demonstrated different patterns of brain activity in response to the same task conditions and for individual subjects there were different patterns of relationships between brain activity and symptom expressions for patients and controls.

This study also lacked a psychiatric control group. We found differences between patients and controls and we believe that these differences reflect disease pathology that is specific to psychosis and schizophrenia. However, it may also be the case that these differences we observed are present when comparing individuals with schizoaffective, bi-polar disorder, or a mood disorder. Thus, future work would need to test whether the differences between patients and controls observed in this study are specific to schizophrenia, generalize to symptoms of psychosis more broadly, or are also present when comparing healthy individuals with individuals who have diagnosable mental illness that do not involve psychosis. It is important to note that aberrant salience and the mechanisms that are thought to underlie aberrant salience symptoms are not specific to schizophrenia. As discussed in Howes et al., (2009), about 8% of the population report psychotic experiences, and dopamine dysfunction has been observed in family members of those individuals with schizophrenia, individuals with schizoptypy, and those at high risk for developing psychosis. So, while our patient population consists of individuals diagnosed with schizophrenia we believe that, because the underlying mechanism of aberrant salience is the same, the striatal dysregulation and association with aberrant salience symptoms will be present in other individuals experiencing, or at risk for experiencing, psychotic symptoms. However, the question of whether differences we observed between diagnostic groups is present when comparing psychotic and non-psychotic patient groups. With regard to aberrant salience symptoms, to some degree this question was addressed by Cicero et al. (2010). They examined aberrant salience scores of individuals with psychosis who were inpatients at a

forensic state hospital with a psychiatric comparison group who were also inpatients at said hospital. The psychiatric comparison group was composed of a variety of patients with nonpsychotic diagnoses, including bipolar I, II, and NOS, mood disorder NOS, personality disorders, posttraumatic stress disorder. These individuals were taking psychotropic medication, including mood stabilizers, antidepressants, as well as antipsychotics. They found significant differences between the psychosis group and the non-psychosis group such that the psychosis group had higher ASI scores than the non-psychosis group, suggesting that when controlling for illness acuity and possibly even antipsychotic medication use aberrant salience is greater for individuals with a history of psychosis.

Finally, it is possible that antipsychotic use by our patient participants may have influenced their results. Patient participants in this study were required to be stable on their medication for at least 2 weeks prior to study participation. We did not assess what medications patients were prescribed due to complexities with gathering this information that could result in, at best, inaccurate or, at worst, misleading information about medication use and its effect on our results. For example, there are differences between what medications a patient has been prescribed, what medications a patient remembers being prescribed, what medications patients are actually taking, and the extent of dopamine blockade occurring in the brain of patients – the latter point being what we are ultimately interested in measuring. Thus, the relationship between self-report measures of medications use and dopamine blockade are unclear. This is not to say, however, that the influence medication use has had on our results is irrelevant. As discussed above, increased presynaptic dopamine and subsequent dopamine release is thought to underlie symptoms of aberrant salience. There is evidence demonstrating a relationship between treatment response to medication and increased presynaptic dopamine synthesis capacity (Demjaha et al., 2012), so it may be the case that because our patients were stable on their medications the amount of dopamine release resulting from increased presynaptic dopamine concentrations was reduced due to antipsychotic blockade. That is, antipsychotic medication

use by our patient participants may have reduced aberrant salience symptoms and thus attenuated the relationship between symptom expression and brain activity we observed. However, without a direct measure of dopamine fluctuation it is difficult to say with, any certainty, what effect medication use by patients has had on our results.

5.6. Conclusions

To our knowledge, this is the first study to find a relationship between dorsal striatal activity, cognitive control, and aberrant incentive salience, described by Kapur (2003), in patients with schizophrenia. We found evidence consistent with the hypothesis that the basal ganglia, particularly the associative striatum, may meaningfully contribute to the processing of cognitive control demands via information gating. Further, while we found evidence that both the striatum and DLPFC demonstrated altered activity during task demands, we found that for patients with schizophrenia striatal activity was selectively associated with the expression of aberrant salience symptoms, symptoms that are thought to result from dysregulated dopamine signaling. These findings provide potential treatment targets that could improve symptoms and functional outcome of patients with schizophrenia. For example, cognitive remediation that improves the regulation of information gating, a core component of executive control, an important predictor of functional outcome of severe mental illnesses (Berk et al., 2013; Martinez-Aran et al., 2002; 2007), should also impact aberrant salience symptom expression. Our future work will focus on further exploring the relationship between deficits of cognition associated with psychosis and brain functioning with the aim of developing more effective treatments for individuals with schizophrenia that will ultimately improve their quality of life.

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7. Figure Captions

Figure 2.1: **Controlled Update Task Design**. Trials representing the 3 update cue events (Upgreen, Upred, and Upempty). For each trial participants are first shown two shapes, the first one for 1.5 seconds and then a second for 1.5 seconds. They are instructed to remember these shapes in the order that they were presented. After a 7 second delay (Delay 1), 1 of 3 update cue conditions occurs. During the Upgreen condition participants are shown either 1 or 2 new shapes (one after another) framed in green and are tasked with replacing 1 or both of the corresponding memory set items. During the Upred condition particpants are shown 1 or 2 new shapes framed in red and are instructed to ignore these shapes and to continue remembering the items from the memory set. During the Upempty condition participants are shown empty boxes that are either red or green. They are told that if no new shape is presented during the update cue they are to simply continue remembering the items from the memory set. Each box during the update cue is presented for 1.5 seconds. A second delay (Delay 2) follows the update cue, after which the probe is presented for 2 seconds. During the probe participants are presented a shape and asked if it matches one of the shapes that they are currently remembering. They respond by pressing a “yes” button or a “no” button. Probe types vary for each update cue condition. During Upgreen, for example, participants can be probed with a shape presented during the update cue that they should have remembered (Update trial type), to which they should respond “yes”. Or, during an Upred trial participants can be probed with an item presented during the update condition that they should have ignored (Resist Distracter Lure trial type), to which they should respond “no”.

Figure 4.1: **Task Accuracy for Diagnostic Groups.** Task accuracy for patients (burgundy) and controls (green). While generally patients performed numerically worse than controls on all trial

types, these differences were only significant for the Resist Distracter Lure, Update trial types, and Resist Maintenance trials. *p<0.05 and **p<0.01.

Figure 4.2: **Brain Activity of Healthy Controls and Patients Within Regions Defined in a Previous Data Set.** The figures above list the full trial time course of brain activity of healthy controls and patients from the current data set within regions defined in a previous data set. Green lines represent Upgreen activity, red lines represent Upred activity, and blue lines represent Upempty activity. “Memory Set” in the figure denotes the period during which the memory set items are presented. “Update Cue” in the figure and the two arrow lines represent the onset (10 seconds) and offset (13 seconds) of the update cue event. The gray box (16-24 seconds) represents the time frame used in our follow up update cue analyses (corresponding to frames 8-12), which is shifted from the offset of the update cue to account for hemodynamic lag. “Probe” in the figure and the arrow line at the 22 second time point indicate the onset of the probe. We plotted the time course of brain activity for patients and controls for two representative regions, left lateral inferior frontal gyrus (IFG) and left lateral putamen, that demonstrated significant effects of condition for healthy controls went on to significantly interact with diagnosis. The regions that time courses were taken from appear in the cross hairs of the brain figure. Controls are listed in the first column (Figure 4.2A and 3C) and patients are listed in the second column (Figure 4.2B and 3D). These regions were selected because they represent a region in the frontal cortex and the striatum that demonstrated condition effects for controls. For controls we observed significant differences between Upgreen and Upempty during frames 8-12 (16-24 seconds) for the IFG (-39, 4, 30) and putamen (-18, -3, 13). We also observed a significant difference between Upred and Upempty for the region in the IFG, but not the putamen region for controls. The region in the IFG went on to interact with diagnosis. Patients demonstrated a significant difference between Upgreen and Upempty during frames 8-12 (16-24 seconds) for the IFG (-39, 4, 30) and a trend towards difference between Upred and

Upempty ($F(1,21) = 3.06$, $p = 0.095$). For putamen activity of patients, we observed no differences between either Upgreen and Upempty or Upred and Upempty.

Figure 4.3: **Regions of Healthy Controls from the Current Data Set that Demonstrated Effects of Condition.** Time courses for representative regions from the frontal cortex and striatum derived from our current sample of controls that demonstrated condition effects following the update cue. Green lines represent Upgreen activity, red lines represent Upred activity, and blue lines represent Upempty activity. We found that both regions demonstrated significant differences between Upgreen and Upempty, but only the caudate demonstrated differences between Upred and Upempty. However, we found the unexpected pattern that Upempty activity was greater than Upred activity.

Figure 4.4: **Frontal Region from the Current Data Set that Demonstrated A Diagnosis by Condition Interaction.** The time courses for a region in the middle frontal gyrus that demonstrated an interaction of diagnosis and condition during frames 8-12 (gray box in the figure). Green lines represent Upgreen activity, red lines represent Upred activity, and blue lines represent Upempty activity. Again, we found that control participants demonstrated significantly greater Upgreen versus Upempty activity in this region, and Upred activity was intermediate to Upgreen and Upred (the difference between Upred and Upempty, however, was not significant). Patients, however, did not demonstrate a difference between the three condition types.

Figure 4.5: **Regions Demonstrating a Diagnosis by Resist Distracter Lure Trial Type Accuracy interaction.** We plotted the 2 regions (putamen, 23, 0, 4 and MFG, 40, 13, 30) that demonstrated diagnosis by Resist Distracter Lure accuracy following the presentation of the update cue. Red lines in the figure represent incorrect trial activity and blue lines represent correct trial activity. During Resist Distracter Lure participants are probed with an item they were instructed to ignore. If participants respond “no” they are correctly rejecting this item. However, if participants respond “yes” it suggests that they inappropriately updated this item when it was presented. “Memory Set” in the figure denotes the period during which the memory set items

are presented. “Update Cue” in the figure and the two arrow lines represent the onset (10 seconds) and offset (13 seconds) of the update cue event. The gray box (16-24 seconds) represents the time frame used in our follow up update cue analyses (corresponding to frames 8-12), which is shifted from the offset of the update cue to account for hemodynamic lag. “Probe” in the figure and the arrow line at the 22 second time point indicate the onset of the probe. For both the putamen (top row of the figure) and MFG (bottom row of the figure) we found that for patients incorrect trial activity was significantly greater than correct trial activity for frames 8-12 (16-24 seconds during the trial), consistent with the idea that increases of brain activity in these regions are associated with information updating. For controls we found the opposite pattern, such that incorrect trial activity was significantly less than correct trial activity for the putamen, and numerically, but not significantly, less than correct trial activity in the MFG.

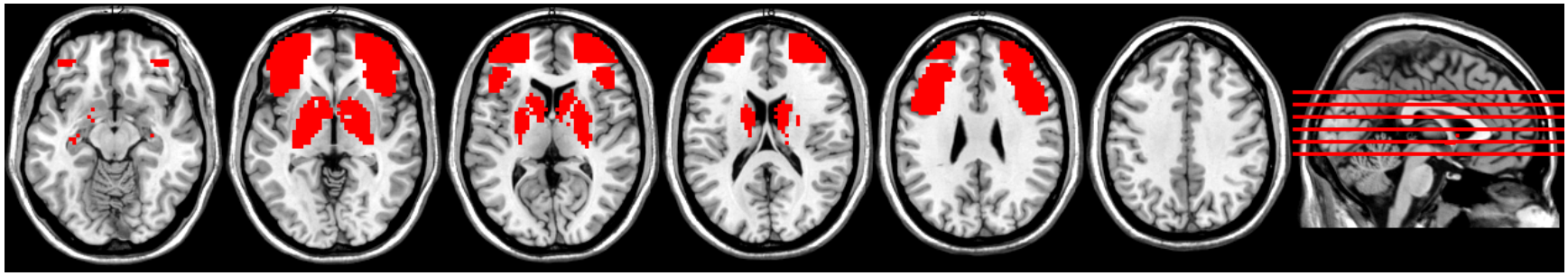
Figure 4.6: **Regions Demonstrating a Diagnosis by Update Trial Type Accuracy interaction.** We plotted the regions in bilateral globus pallidus that demonstrated diagnosis by Update accuracy following the presentation of the update cue. Red lines in the figure represent incorrect trial activity and blue lines represent correct trial activity. For the Update trial type participants are probed with an item they should have updated during the update cue. A “yes” response indicated they made the appropriate update, and a “no” response suggests that they did not. For both regions of the globus pallidus patients demonstrated significantly less activity during incorrect trials when compared with correct trials, again consistent with the idea that increases of brain activity in these regions are associated with information updating. However, for controls we again found the opposite pattern to patients when comparing correct and incorrect trial activity. Controls, on the other hand, demonstrated the opposite pattern of patients, such that activity in the left globus pallidus during incorrect trials following the presentation of the update cue was significantly greater than activity during correct trials. Activity in the right globus pallidus for controls did not significantly differ when comparing correct and incorrect Update activity following the presentation of the update cue.

Figure 4.7: **Scatter Plots Depicting the Relationship Between ASI and Brain activity during Incorrect Resist Distracter Lure Trials.** We observed a significant positive correlation between ASI and brain activity in the right lateral putamen during incorrect Resist Distracter Lure trials for patients but not controls, such that, as predicted, the brain activity for patients who were susceptible to distraction increased as ASI symptoms increased. If anything, putamen activity of controls demonstrated a non-significant correlation in the opposite direction. While we also observed a positive correlation between MFG activity during incorrect Resist Distracter Lure trials and ASI scores for patients, this correlation did not reach significance.

Figure 4.8: **Scatter Plots Depicting the Relationship Between ASI and Brain activity during Incorrect Update Trials.** We observed a significant positive correlation between ASI and brain activity during correct Update trials in the left and right lateral globus pallidus for patients but not controls, such that the brain activity for patients during updating increased as ASI symptoms increased. This relationship was not expected, and suggests basal ganglia reactivity more broadly is associated with increased ASI. For controls, we found no significant relationship between brain activity and ASI in these same regions.

Appendix A

Multislice image of anatomical masks of the prefrontal cortex and basal ganglia



Appendix B

Regions from the Current Data Set that Demonstrated Diagnosis by Condition Effects Within the Whole Brain

X	Y	Z	Size	Hemi	Region	BA	Effect at frames 8-12			Direction (Patients)		Direction (Controls)	
							Analysis	*F*	*p*	*Upgreen vs. Upempty*	*Upred vs. Upempty*	*Upgreen vs. Upempty*	*Upred vs. Upempty*
Condition													
-43	-69	-6	81	Left	Inferior Occipital Gyrus	19							
35	-77	3	196	Right	Middle Occipital Gyrus	19							
-39	-40	40	69	Left	Inferior Parietal Lobule	40							
-39	0	52	24	Left	Middle Frontal Gyrus	6							
Diagnosis													
-20	-5	11	33	Left	Putamen								
19	-17	7	122	Right	Thalamus								
-18	-17	0	62	Left	Thalamus								
-47	-50	-12	29	Left	Fusiform Gyrus	37							
45	-49	-7	25	Right	Sub-Gyral	37							
-42	16	4	234	Left	Insula	13							
36	15	4	62	Right	Insula	13							
-55	-36	1	23	Left	Middle Temporal Gyrus	22							
-40	44	10	80	Left	Middle Frontal Gyrus	46							
-31	-53	35	173	Left	Inferior Parietal Lobule	40							
-45	-2	36	107	Left	Precentral Gyrus	6							
37	6	32	23	Right	Precentral Gyrus	9							
27	-64	32	21	Right	Precuneus	7							
-4	11	57	240	Left	Superior Frontal Gyrus	6							
29	-68	-37	261	Right	Inferior Semi-Lunar Lobule								
-23	-70	-46	76	Left	Inferior Semi-Lunar Lobule								
-2	-74	-40	24	Left	Inferior Semi-Lunar Lobule								
-34	-67	-31	23	Left	Pyramis								
Condition X Diagnosis													
18	-43	43	30	Right	Precuneus	7	Dx X Cond	16.42	<0.001	no diff	G < E**	no diff	R < E**
Condition X Time													
18	5	11	85	Right	Putamen								

-19	-4	9	290	Left	Lateral Globus Pallidus	
0	-68	15	5869	Left	Posterior Cingulate	31
21	33	-11	30	Right	Middle Frontal Gyrus	11
-40	-8	-14	22	Left	Sub-Gyral	21
11	60	-6	21	Right	Superior Frontal Gyrus	10
-51	12	-1	54	Left	Superior Temporal Gyrus	22
-19	-34	-2	44	Left	Parahippocampal Gyrus	27
-56	-37	-3	36	Left	Middle Temporal Gyrus	21
18	-33	0	63	Right	Parahippocampal Gyrus	27
-2	-42	17	226	Left	Posterior Cingulate	29
-7	11	41	2292	Left	Cingulate Gyrus	32
5	-79	21	38	Right	Cuneus	18
47	-33	23	22	Right	Insula	13
-3	-36	46	49	Left	Precuneus	7
29	21	8	24	Right	Claustrum	
-28	23	4	34	Left	Claustrum	
32	-65	-46	28	Right	Inferior Semi-Lunar Lobule	
Diagnosis X Time						
18	-23	24	31	Right	Caudate	
-18	-5	23	22	Left	Caudate	
32	-90	-16	36	Right	Inferior Occipital Gyrus	18
47	-58	-11	94	Right	Fusiform Gyrus	37
-45	-76	-13	64	Left	Fusiform Gyrus	19
-23	-86	-8	125	Left	Inferior Occipital Gyrus	18
3	33	3	208	Right	Anterior Cingulate	24
27	28	-4	24	Right	Inferior Frontal Gyrus	47
-51	0	21	475	Left	Inferior Frontal Gyrus	44
-39	43	7	114	Left	Middle Frontal Gyrus	46
-31	24	3	41	Left	Inferior Frontal Gyrus	45
-5	-100	7	50	Left	Cuneus	18
55	1	8	22	Right	Precentral Gyrus	6
-41	33	24	59	Left	Middle Frontal Gyrus	46
-44	-62	18	24	Left	Middle Temporal Gyrus	39
25	7	27	50	Right	Middle Frontal Gyrus	8
52	-8	30	73	Right	Precentral Gyrus	6

27	-66	33	97	Right	Precuneus	7							
-31	-52	35	254	Left	Inferior Parietal Lobule	40							
49	21	27	33	Right	Middle Frontal Gyrus	46							
0	40	41	49	Left	Medial Frontal Gyrus	8							
-1	-46	37	47	Left	Precuneus	31							
37	-43	47	114	Right	Inferior Parietal Lobule	40							
-26	1	48	47	Left	Middle Frontal Gyrus	6							
-5	8	61	154	Left	Superior Frontal Gyrus	6							
-2	-25	64	28	Left	Medial Frontal Gyrus	6							
-16	-27	65	22	Left	Precentral Gyrus	4							
-28	-34	67	28	Left	Postcentral Gyrus	2							
-14	-40	-46	29	Left	Cerebellar Tonsil								
31	-64	-49	27	Right	Inferior Semi-Lunar Lobule								
-36	-60	-47	24	Left	Cerebellar Tonsil								
-24	-53	-46	49	Left	Cerebellar Tonsil								
33	-65	-29	81	Right	Tuber								
-22	-58	-25	50	Left	Culmen								
Condition X Time X Diagnosis													
-41	-74	-9	21	Left	Fusiform Gyrus	19	Dx X Cond	3.64	0.04	G > E**	R > E**	G > E**	R > E**
-40	-45	43	45	Left	Inferior Parietal Lobule	40	Dx X Cond	5.98	0.004	no diff	no diff	G > E**	no diff
-5	10	58	72	Left	Superior Frontal Gyrus	6	Dx X Cond	8.58	<0.001	no diff	no diff	G > E**	no diff

Regions from the current data set that demonstrated task effects in the whole brain. They are organized on the left side under headings like "Diagnosis" or "Condition X Time" based on whether they demonstrated these effects when examining all 15 time frames of the trial. Because we were only interested in regions that demonstrated effects that interacted with both diagnosis and condition we only conduced follow up tests on these regions. Statistics from the update cue response analysis can be found under the heading "Effect at frames 8-12". G = Upgreen trials, E = Upempty trials, and R = Upred trials. *p<0.05 and **p<0.01, uncorrected. "no diff" signifies no statistically significant difference.

Appendix C

Regions Demonstrating an Effect of Diagnosis by Resist Distracter Lure Trial Type Accuracy within the Whole Brain

X	Y	Z	Size	Hemisphere	Region	BA	Effect at frames 8-12			Correct vs. Incorrect	
							Analysis	*F*	*p*	*Patients*	*Controls*
Diagnosis											
-43	-6	34	105	Left	Precentral Gyrus	6					
-26	-58	32	52	Left	Angular Gyrus	39					
-8	22	41	21	Left	Cingulate Gyrus	32					
23	-2	41	25	Right	Middle Frontal Gyrus	6					
-5	9	58	63	Left	Superior Frontal Gyrus	6					
43	-64	-26	30	Right Cerebellum	Tuber						
Accuracy											
-30	-59	39	29	Left	Angular Gyrus	39					
-34	-26	54	59	Left	Precentral Gyrus	4					
Diagnosis X Accuracy											
34	14	38	23	Right	Middle Frontal Gyrus	8	Dx X Acc	21.56	<0.001	cor < incor	cor > incor
47	-10	45	25	Right	Precentral Gyrus	4	Dx X Acc	11.69	0.002	cor < incor	cor > incor
Accuracy X Time											
17	-18	8	47	Right	Thalamus						
-11	-21	12	54	Left	Thalamus						
2	61	0	77	Right	Middle Frontal Gyrus	10					
-34	12	2	24	Left	Insula	13					
-50	-16	14	129	Left	Postcentral Gyrus	43					
-33	-14	11	22	Left	Insula	13					
-4	-54	7	28	Left	Posterior Cingulate	30					
10	-68	28	59	Right	Cuneus	7					
-4	-66	45	217	Left	Precuneus	7					

-3	26	34	21	Left	Cingulate Gyrus	32
-39	-26	55	58	Left	Postcentral Gyrus	3
5	-51	-1	57	Right Cerebellum	Culmen	
17	-65	-16	56	Right Cerebellum	Declive	
Diagnosis X Time						
-22	-7	28	21	Left	Caudate	
0	-33	9	36	Right	Thalamus	
49	-61	-12	116	Right	Fusiform Gyrus	37
33	-39	-15	21	Right	Fusiform Gyrus	20
-43	-75	-13	33	Left	Fusiform Gyrus	19
-15	41	-4	65	Left	Anterior Cingulate	32
-41	44	11	26	Left	Middle Frontal Gyrus	10
-37	32	18	25	Left	Middle Frontal Gyrus	46
46	19	24	33	Right	Middle Frontal Gyrus	46
-11	-22	70	88	Left	Medial Frontal Gyrus	6
-35	42	30	57	Left	Middle Frontal Gyrus	9
-25	-64	31	37	Left	Precuneus	7
27	-66	31	32	Right	Precuneus	7
39	-42	50	196	Right	Inferior Parietal Lobule	40
27	-15	63	115	Right	Precentral Gyrus	6
-42	15	40	24	Left	Precentral Gyrus	9
-36	-45	47	43	Left	Inferior Parietal Lobule	40
0	-72	-13	23	Left Cerebellum	Declive of Vermis	
-24	-80	-25	35	Left Cerebellum	Uvula	

Regions from the current data set that demonstrated diagnosis by Resist Update Lure accuracy. They are organized on the left side under headings like “Diagnosis” or “Accuracy” based on whether they demonstrated these effects when examining all 15 time frames of the trial. We only conducted follow up analyses for the update cue period on regions that demonstrated a significant interaction of accuracy and diagnosis. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. “cor” = correct trials and “incor” = incorrect trials. *p<0.05 and **p<0.01, uncorrected. “no diff” signifies no statistically significant difference.

Appendix D

Regions Demonstrating an Effect of Diagnosis by Update Trial Type Accuracy with the Whole Brain

X	Y	Z	Size	Hemisphere	Region	BA	Effect at frames 8-12			Correct vs. Incorrect	
							Analysis	*F*	*p*	*Patients*	*Controls*
Diagnosis											
1	-16	6	912	Right	Thalamus						
-45	23	6	239	Left	Inferior Frontal Gyrus	45					
25	28	-2	25	Right	Inferior Frontal Gyrus	47					
-30	20	3	50	Left	Insula	13					
32	15	4	46	Right	Insula	13					
-46	-4	33	204	Left	Precentral Gyrus	6					
49	-11	23	28	Right	Precentral Gyrus	6					
0	-29	29	33	Left	Cingulate Gyrus	23					
-27	-63	29	30	Left	Precuneus	7					
-39	-46	41	81	Left	Inferior Parietal Lobule	40					
-4	12	56	283	Left	Superior Frontal Gyrus	6					
-30	-1	52	33	Left	Middle Frontal Gyrus	6					
1	-29	67	66	Right	Paracentral Lobule	6					
-6	-21	-13	54	Left Brainstem	Red Nucleus						
-28	-40	-43	32	Left Cerebellum	Cerebellar Tonsil						
33	-69	-45	38	Right Cerebellum	Inferior Semi-Lunar Lobule						
-29	-70	-46	52	Left Cerebellum	Inferior Semi-Lunar Lobule						
Diagnosis X Accuracy											
-20	-21	2	39	Left	Thalamus		Dx X Acc	10.98	0.002	no diff	cor < incor**
13	-25	2	25	Right	Thalamus		Dx X Acc	8.63	0.006	no diff	cor < incor*
-5	-27	-11	27	Left Brainstem	Red Nucleus		Dx X Acc	5.43	0.03	cor > incor*	cor < incor*
Accuracy X Time											
0	42	-5	36	Left	Anterior Cingulate	32					

-44	10	30	21	Left	Inferior Frontal Gyrus	9			
-36	-31	43	57	Left	Inferior Parietal Lobule	40			
23	24	40	59	Right	Middle Frontal Gyrus	8			
25	-4	44	56	Right	Middle Frontal Gyrus	6			
-27	1	50	124	Left	Middle Frontal Gyrus	6			
-24	-43	-9	33	Left	Parahippocampal Gyrus	36			
-20	-70	42	59	Left	Precuneus	7			
-3	15	55	203	Left	Superior Frontal Gyrus	6			
36	-41	9	30	Right	Superior Temporal Gyrus	41			
Diagnosis X Time									
-8	-70	32	33	Left	Cuneus	7			
52	-59	-18	27	Right	Fusiform Gyrus	37			
-40	44	3	124	Left	Inferior Frontal Gyrus	10			
-35	-45	45	21	Left	Inferior Parietal Lobule	40			
1	-92	-14	55	Right	Lingual Gyrus	18			
0	38	40	31	Left	Medial Frontal Gyrus	8			
-3	-26	65	26	Left	Medial Frontal Gyrus	6			
-43	8	47	48	Left	Middle Frontal Gyrus	6			
-55	11	9	23	Left	Precentral Gyrus	44			
-54	-3	20	23	Left	Precentral Gyrus	6			
42	17	35	22	Right	Precentral Gyrus	9			
29	-67	29	39	Right	Precuneus	19			
36	-42	37	23	Right	Sub-Gyral	40			
-6	12	60	120	Left	Superior Frontal Gyrus	6			
-48	-66	-16	30	Left Cerebellum	Declive				
Diagnosis X Accuracy X Time									
25	42	5	23	Right	Medial Frontal Gyrus	10	Dx X Acc	2.33	0.14

Regions within our anatomical masks from the current data set that demonstrated diagnosis by Update accuracy. They are organized on the left side under headings like “Diagnosis” or “Accuracy” based on whether they demonstrated these effects when examining all 15 time frames of the trial. We only conducted follow up analyses for the update cue period on regions that demonstrated a significant interaction of

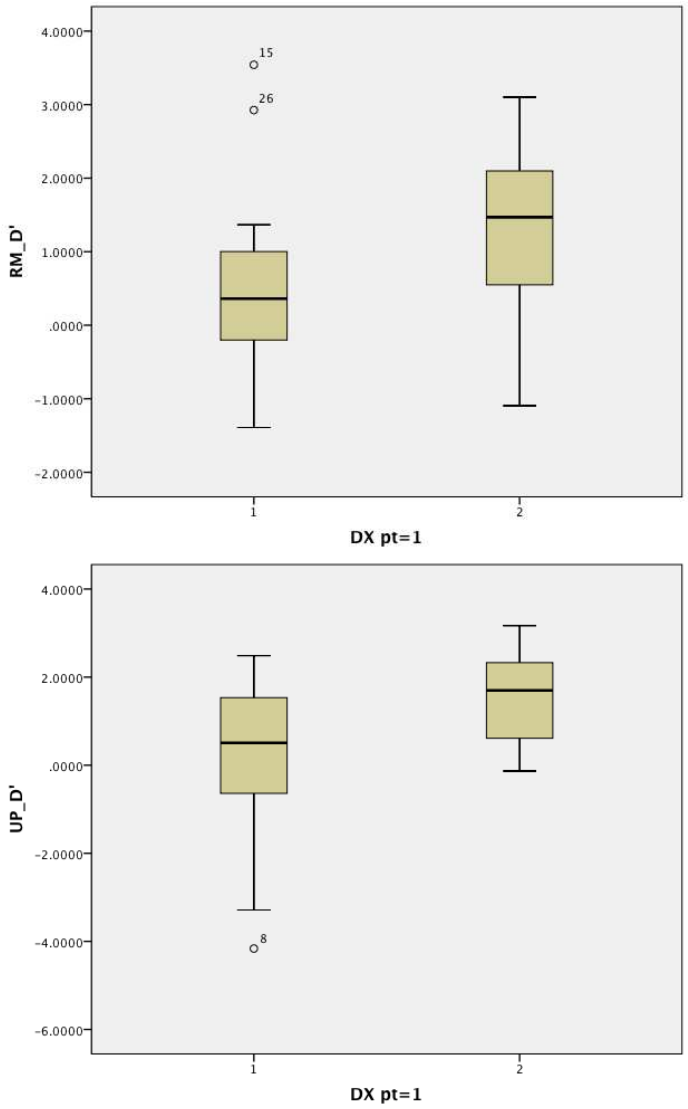
accuracy and diagnosis. Statistics from the update cue response analysis can be found under the heading “Effect at frames 8-12”. “cor” = correct trials and “incor” = incorrect trials. *p<0.05 and **p<0.01, uncorrected. “no diff” signifies no statistically significant difference.

Appendix E

D' Analysis of Behavioral Data

We also examined our behavioral data using d', where correct responses during Update trials were considered "hits" and incorrect responses during Resist Maintenance were considered "false alarms". Both hits and false alarms were z-scored and then subtracted from one another (zHits-zFalse Alarms) to create the d' of updating (UP_D'). Similarly, we created d' using the same method for distracter trials by using correct responses of Resist Distracter trials as hits and incorrect responses of Resist Distracter Lure trials as false alarms (RM_D'). These two d' prime variables give an account of the signal to noise ratio when participants are tasked with making an update or ignoring distracting information. Box plots of the d' scores for each variable and each group can been seen in the figures below. To determine if d' differed between trials and between groups we conduced a 2 x 2 ANOVA with trial d' (UP_D' and RM_D') and diagnosis (patients and controls) as factors. We also included age and ethnicity as covariates, given that these demographic variables were found to differ between diagnostic groups. We found a significant main effect of diagnosis ($F(1,38) = 16.99$, $p < 0.001$), but no main effect of trial type ($F(1,38) = 0.21$, $p = 0.65$) and no interaction of trial type and diagnosis ($F(1,38) = 1.39$, $p = 0.25$). With regard to the effect of diagnosis, d' scores for patients were lower than controls (as seen in the box plots). This was true for both trial conditions. We also examined the correlation between d' and symptom scores separately for patients and controls. For patients, we found that RM_D' did not correlate with any symptoms measures we examined (including aberrant salience). When examining UP_D', we again did not find a significant correlation with aberrant salience, but found a significant negative correlation with physical anhedonia ($r = -0.57$, $p = 0.005$). For controls, however, we found significant negative correlations between RM_D' and aberrant salience ($r = -0.49$, $p = 0.03$) and magical ideation ($r = -0.57$, $p = 0.009$), and

significant correlations between UP_D' and aberrant salience (r= -0.52, p = 0.02) and magical ideation (r= -0.54, p = 0.006).



Box plots of d' scores for RM_D' (top) and UP_D' (bottom). Patients are group 1 and controls are group 2. Cases identified as outliers were examined and were found to be high performing patients for the RM_D' condition and a patient who performed poorly during the false alarm trial for the UP_D' condition. The upper and lower bound of the box represent the 75th and 25th percentile, respectively. The dark line in the box represents the median for each group. Upper and lower whiskers represent the maximum and minimum values, respectively. Outliers were values that fell outside of 1.5 times the inner quartile range.

Appendix F

A Breakdown of the Number of Trials for Each Task Condition and Trial Type

Upempty		Upred			Upgreen			
20		48			52			
SMAIN	**SMAINNP**	**RMAIN**	**RMAINUP**	**RMAINNP**	**UPDATE**	**UPDATEOP**	**UPDATENP**	**UPDATEOP2**
14	6	20	20	8	20	20	8	4