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Comparing the Functional Neuroanatomy of Proactive and Reactive Control between Patients with Schizophrenia and Healthy Controls

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Abstract

Cognitive control deficits are associated with impaired executive functioning in schizophrenia. The Dual Mechanisms of Control framework suggests that *proactive control* requires sustained dorsolateral prefrontal activity, while *reactive control* marshals a larger network. However, primate studies suggest these processes are maintained by the same dual-encoding regions. To distinguish between these theories, we compared the distinctiveness of proactive and reactive control functional neuroanatomy. In a re-analysis of data from a previous study, 47 adults with schizophrenia and 56 controls completed the Dot Pattern Expectancy task during an fMRI scan examining proactive and reactive control in frontoparietal and medial temporal regions. Areas suggesting specialized control or between-group differences were tested for association with symptoms and task performance. Elastic net models additionally explored their predictive ability regarding performance metrics. Results indicated most regions were active in both reactive and proactive control. However, evidence of specialized proactive control was found in the left middle and superior frontal gyri. Control participants showed greater proactive control in the left middle and right inferior frontal gyri. The elastic net models were moderately predictive of task performance and implicated various frontal gyri regions in controls, with additional involvement

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Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Participants consented to have their data included in analyses to be published.

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of anterior cingulate and posterior parietal regions for performance associated with reactive control. By contrast, the elastic nets for patient participants implicated the inferior and superior frontal gyri, and posterior parietal lobe. Importantly, no specialized cognitive control activity was associated with task performance or schizophrenia symptomatology. Since these results complement aspects of both cognitive control theories, future work is needed to conceptualize the distinctiveness of proactive and reactive control, and clarify its role in executive deficits in severe psychopathology.

Keywords

Cognitive Control; fMRI; Functional Neuroanatomy; Dot Pattern Expectancy Task (DPX); Schizophrenia; Psychosis

Introduction

Cognitive control, the ability to regulate, coordinate, and sequence thoughts and actions to attain desired behavioral outcomes (Braver, 2012; Cohen & Servan-Schreiber, 1992), is a core component of executive cognition. Impaired cognitive control is linked to deficits in subsumed processes, including cognitive flexibility, goal maintenance, and selective attention, and is thought to cause inefficient context processing often observed in serious mental illnesses like schizophrenia (Miller & Cohen, 2001). However, full consensus has not been met regarding the neural mechanisms underlying cognitive control. Some researchers posit a combination of top-down and bottom-up processes with distinct neural signatures (Braver, 2012), at least in terms of the time course of brain activation, if not the spatial location. Another perspective, drawn from monkey electrophysiological research, suggests 'dual encoding' neural clusters drive both actions (Blackman et al., 2016). Determining the distinctiveness of these processes may aid examinations of the connection between cognitive control deficits, like those reported in schizophrenia, and impairments in other domains such as working memory and problem solving.

Primarily, cognitive control is conceptualized as emerging from variable applications of bottom-up and top-down mechanisms supported by frontoparietal brain regions (Barch & Ceaser, 2012; Cohen & Servan-Schreiber, 1992; Koechlin et al., 2003). Most significantly, the Dual Mechanisms of Control (DMC) framework characterizes these mechanisms as *proactive control*, which facilitates anticipatory planning and goal maintenance, and *reactive control*, which inhibits and adjusts responses based on contextual changes (Braver, 2012). The DMC framework postulates that proactive control arises from sustained/anticipatory lateral prefrontal cortex (PFC) activity. By contrast, reactive control is hypothesized to be driven by transient lateral PFC activity, in addition to "accessory structures" such as the anterior cingulate cortex (ACC), posterior parietal lobe (PPL), and medial temporal lobe (Braver, 2012; Braver et al., 2009).

Accordingly, most cognitive control research is informed by the viewpoint that proactive and reactive control alternate in predominance and have distinctive patterns. DMC-informed studies typically examine these processes with tasks derived from the A-X expectancy paradigm (Cohen et al., 1999). The paradigm features two stimuli types: cues ('A' and other

stimuli collectively referred to as 'B') and probes ('X' and other stimuli collectively referred to as 'Y'). Participants follow the 'A-then-X' rule, where the valid sequence depicts an A cue followed by an X probe (AX), and other combinations (AY, BX, BY) are lures. Optimal task accuracy requires efficient marshaling of both proactive and reactive control. The former is considered most necessary for BX trials, as B cues induce preparations to respond 'non-target' regardless of the subsequent probe identity (Cohen et al., 1999). By contrast, AY trials are associated with successful reactive control: Since most trials are AX sequences, AY accuracy requires overcoming the prepotent expectation that an 'X' will follow the 'A' through quick information retrieval, comparison, and adaptation (MacDonald, 2007). Generally, A-X expectancy psychopathology studies show participants with schizophrenia rely on reactive-style strategies more than do controls, whose performances imply increased use of proactive control (MacDonald et al., 2005; Yoon et al., 2008). Consistent with the DMC framework, this difference is associated with greater dorsolateral PFC activity during proactive control in participants without psychopathology (Braver et al., 2009; Lesh et al., 2013; MacDonald et al., 2005; Smucny et al., 2018; Yoon et al., 2008).

However, the literature's tendency to prioritize characterizing proactive control raises a potential limitation. Despite the DMC framework's popularity, the comparative lack of reactive control research limits conclusions about its accuracy. Certainly, several studies have examined reactive control within the context of inhibition. For example, Go/No-go and Stop Signal paradigm research implicate regions such as the inferior frontal and middle frontal gyri, insula, inferior parietal lobule, and pre-motor supplementary area (Hughes et al., 2012; Ray Li, 2006; Swick et al., 2011). However, this focus on inhibitory activity does not fully capture the DMC framework, which posits reactive control as a *general* adaptation to the environmental context (Braver, 2012), with inhibition being only one outcome of such processes. Nor does it allow us to compare proactive and reactive functional neuroanatomy or its impairment in psychopathology within the same task. In Stroop Task studies, reactive control is primarily associated with conflict-monitoring activity in the anterior cingulate cortex (ACC), with some involvement of the dorsolateral PFC (Becker et al., 2008; Haupt et al., 2009; Lesh et al., 2013; Marinkovic et al., 2012; van Veen & Carter, 2005). While switching Stroop paradigms do engage both proactive and reactive control (Carter et al., 2012; MacDonald et al., 2000), such paradigms are less useful for demonstrating cross-species relationships due to their complexity, and may be less well suited for demonstrating specific context-processing deficits in psychopathology. The AX-expectancy paradigm addresses some of these issues; however, comparatively little research has leveraged these advantages to thoroughly examine reactive control in schizophrenia. One study (Ryman et al., 2019) found evidence of reactive control-specific dorsomedial and dorsolateral PFC activity, and ventrolateral PFC activity associated with both reactive and proactive control. However, these findings were obtained within a non-psychiatric sample. Two others (Braver et al., 2009; Paxton et al., 2008) identified lateral PFC activity in response to probes, but specifically within the context of healthy cognitive aging.

Contrary to the DMC framework, nonhuman primate electrophysiological models challenge the distinctiveness of cognitive control processes. Most notably, single-cell recordings suggest the predominance of prefrontal dual-encoding neurons – during both proactive and reactive control – in monkeys trained on the Dot Pattern Expectancy task (DPX; see Figure

1A), an A-X expectancy variant whose stimuli feature dots instead of letters (Blackman et al., 2016; MacDonald, 2007). These findings also indicate proactive control (i.e., in response to B cues) is largely characterized by transient spikes in activity, instead of the sustained activity described by the DMC framework. Dual-encoding neurons have also been identified in the posterior parietal lobe and mediodorsal thalamic nuclei, and are thought to facilitate cognitive flexibility, decision-making, and response selection (Chakraborty et al., 2019; DeNicola et al., 2020; Goodwin et al., 2012). The multiplicity of implicated regions suggests non-prefrontal regions may play significant roles in both proactive and reactive control. However, even though administering ketamine to monkeys has been shown to elicit cognitive control impairments (Blackman et al., 2013), it is unclear if these cognitive control findings generalize to humans or serve as adequate analogues for schizophrenia functional neuroanatomy.

Consequently, both DMC and dual-encoding theories have supporting evidence and areas of uncertainty. This ambiguity is compounded by the hypotheses being grounded in research with different species. Therefore, clarity may be found through determining the extent to which brain regions identified in the DMC framework engage in specialized cognitive control (outsized involvement in proactive over reactive control, or vice-versa) versus equivalent involvement. Results that find areas of specialized cognitive control would support the DMC framework, especially given the implication that the neuroanatomical network facilitating reactive control is greater than that serving proactive control (Braver, 2012). However, results showing little difference in both the location and dynamics of activity in regions engaged in reactive and proactive control, especially in non-prefrontal areas, would imply the DMC framework does not fully characterize the dynamics at play. This would lend credence to the potential importance of dual-encoding within human cognitive control processes. Therefore, even though the methods used in dual-encoding primate research cannot be replicated in humans, results suggesting similarity in location and response profiles of regions involved in proactive and reactive control may justify future exploration of dual encoding in humans using electrophysiological means.

Given this challenge, examining this question using a task suited for translational research seemed prudent. The DPX was selected due to its status as a well-established cognitive control measure in animal and human psychopathology research (Carter et al., 2012; Henderson et al., 2012). DPX studies replicate other AX-Expectancy findings, such that people with schizophrenia and bipolar disorder tend to misidentify BX trials more than other trial types (Chun et al., 2018; Jones et al., 2010; Smucny et al., 2019). Conversely, healthy controls tend to find BX trials relatively easy, and AY trials challenging (Henderson et al., 2012; Jones et al., 2010). Additionally, the novelty of DPX stimuli creates degradation effects more efficiently than other AX-Expectancy variants – especially within healthy controls – making it a more sensitive tool for examining cognitive control deficits (MacDonald, 2007). This study used the dataset published by Poppe and colleagues (2016), which established impairments in the frontoparietal networks of people with schizophrenia that were associated with decreased BX trial accuracy. However, like other studies mentioned here, it did not further address the possibility that proactive and reactive control were subserved by distinct or similar brain regions as posited by these competing theories.

FInally, deepened understanding of cognitive control mechanisms may bear relevance for schizophrenia treatment, given the link between impaired cognition and symptoms associated with poor prognosis (Addington et al., 2017; Lesh et al., 2011; Ventura et al., 2010). Therefore, we sought to examine the extent to which DPX-based cognitive control predicted clinical indicators of cognitive dysfunction. Disorganization symptoms served as our measure of clinically relevant cognitive impairment (American Psychiatric Association, 2013). This choice was made because disorganization symptoms are thought to reflect disjointed, inefficient thought processes, and have been previously linked with cognitive control performance (e.g. Barch et al., 2003; Lesh et al., 2013; Niendam et al., 2014). Positive symptoms were also included to clarify if potential associations between cognitive control and disorganization reflected conceptual similarities, as opposed to general schizophrenia symptomatology.

Ultimately, our goals were threefold. First, we aimed to determine the extent to which brain regions displayed 'specialized' preference for proactive or reactive control. Drawing from literature based on the DMC framework, we hypothesized that dorsolateral PFC activity would be associated with specialized proactive control, and that specialized reactive control would be associated with medial temporal and/or posterior parietal regions. Second, we sought to explore potential differences in specialized cognitive control between individuals with schizophrenia and healthy controls. We hypothesized participants with schizophrenia would show fewer areas of specialized activity, reflecting inefficient cognitive control processing. Our final goal was to determine if a relationship existed between specialized cognitive control and behavioral metrics and clinical symptoms. We hypothesized that regions associated with specialized cognitive control would predict DPX performance and disorganization symptoms, but not positive symptoms.

Methods and Materials

Subjects

The sample had been examined in a previous DPX study (Poppe et al., 2016) and consisted of 47 chronic, medicated adults with schizophrenia (SZ; mean age = 35.6 years) and 56 healthy controls (HC; mean age = 34.8 years) recruited through the Cognitive Neuroscience Test Reliability and Clinical applications for Serious Mental Illness consortium (CNTRaCS; Gold et al., 2012) consisting of laboratories in: Washington University, St. Louis; University of Minnesota; University of California, Davis; Baltimore Psychiatric Research Center; and Rutgers University. As stated in previous analyses, participant groups did not differ with respects to sex, age, handedness, socioeconomic status, or premorbid intelligence (Poppe et al., 2016). SZ participants completed the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 2002) and the Brief Psychiatric Ratings Scale (BPRS; Overall & Gorham, 1962; Ventura et al., 2000) to confirm diagnoses and assess symptom severity, and had been receiving a fixed dose of medication for at least a month. In accordance with prior DPX literature, all participants passed *a priori* task performance standards: at least 10% accuracy in AX, AY, and BX trials, and at least 50% accuracy in BY trials. Table S1 elaborates additional criteria for participant removal. This study was approved by institutional review

boards at all participating CNTRaCS sites. Participants gave informed consent prior to data collection in accordance with IRB protocols at each participating site.

Procedure

Each participant completed four blocks of 40 DPX trials in a 3-Tesla scanner after adequate practice. With a button box, participants were instructed to press one button whenever a cue image appeared on the screen regardless of its identity, and then press one of two other buttons either to indicate the probe stimulus completed the target AX sequence, or if the resulting sequence was non-target (AY, BX, or BY). Figure 1A depicts the manner in which the stimuli are presented. Every block consisted of 60% AX trials, 15% AY trials, 15% BX trials, and 10% BY trials. Cue and probe display times lasted 500 milliseconds each. Each trial had jittered inter-stimulus intervals lasting between 2.5 seconds and 3.5 seconds. Inter-trial intervals ranged from 2.5 seconds to 12.5 seconds. Participants did not receive performance feedback outside practice sessions.

fMRI Data Collection and Preprocessing—Specific acquisition steps have been previously described (Poppe et al., 2016) and are included as supplementary material. All preprocessing occurred with the FMRIB Software Library (FSL) packages (Woolrich et al., 2009). Steps included motion correction (Jenkinson et al., 2002), brain extraction (S. M. Smith, 2002), prewhitening, high-pass temporal filtering (100s sigma), B0 field unwarping, spatial smoothing with a 5 mm FWHM Gaussian kernel, and spatial normalization and linear registration (Smith et al., 2004) to the Montreal Neurological Institute (MNI) 152 standard brain.

Behavioral Analyses—We chose to examine cognitive control with two DPX performance metrics. d' context, the normalized difference between AX hits and BX false alarms, served as our proactive control measure (Cohen et al., 1999; Servan-Schreiber et al., 1996). This metric indicates the extent to which target accuracy is attributable to maintaining the context provided by the cue stimulus, and is calculated as follows, assuming Z (p) represents the inverse of variable *p* under the cumulative Gaussian distribution:

$$\text{d' context} = Z(\text{proportion of correct AX trials}) - Z(\text{proportion of BX errors})$$

Previous studies have found people with schizophrenia consistently have lower d' context than nonpsychiatric controls (Chun et al., 2018). We created a parallel metric to investigate reactive control, drawing from the d' context formula and the considerable prepotent response inhibition literature (e.g. Bedard et al., 2002; Vink et al., 2015). The resulting metric, 'd' expectancy', distinct from other measures of reactive control (e.g. Gonthier et al., 2016), measures the normalized difference between AX hits and AY false alarms:

$$\text{d' expectancy} = Z(\text{proportion of correct AX trials}) - Z(\text{proportion of AY errors})$$

We calculated mean d' context and d' expectancy scores for each participant, adjusting accuracy proportions of 1 and 0 to 0.999 and 0.001, respectively, to facilitate Z calculations. Previous parametric analyses of this sample indicated greater d' context in controls (Poppe

et al., 2016). To examine if results would replicate under greater stringency, we used Wilcoxon rank-sum tests to determine if HC participants had greater d' context and d' expectancy values than SZ participants. To examine the extent to which these relationships varied across the task and in order to aggregate sufficient numbers of appropriate trials, we compared blocks 1 and 2 to blocks 3 and 4 in a mixed ANOVA with main factors Group (HC, SZ) and Half (first, second), and dependent variable Performance Metric (d' context, d' expectancy).

Finally, to examine the relationship between DPX performance and clinical symptoms, we conducted 4 partial correlations between d' context and d' expectancy, and disorganization and positive symptoms. Each correlation in this series controlled for the effect of the metric and symptom not being directly examined. For example, the correlation between d' context and disorganization partialled out the effect of d' expectancy and positive symptoms.

Neuroimaging Modeling—Neuroimaging analyses were conducted with regressors for cues and probes associated with correct responses for all trial types, and centered on three contrasts considered representative of different cognitive control mechanisms. In accordance with established practices (Braver et al., 2009; Lesh et al., 2013; Lopez-Garcia et al., 2016), we designated regions in which B-cue activity overshadowed A-cue activity (B > A) as proactive control areas. This contrast isolates cue activity specifically associated with the preparation to reject lures trials. Reactive control regions were conceptualized as areas in which AY activity was greater than AX activity (AY > AX). This captured activity driving timely adaptation separate from that associated with the 'default' prepotent response. Finally, cognitive control specialization was quantified by areas with significant differences between proactive and reactive control, i.e. (B > A) – (AY > AX) and (AY > AX) - (B > A). Threshold-Free Cluster Enhancement (TFCE; Smith & Nichols, 2009) identified group-level activity significance while minimizing family-wise error rates.

Confirmatory Analyses.: ROIs were chosen *a priori* based on research implicating their involvement in cognitive control processes and identification in the DMC framework (Braver, 2012; Carter et al., 1998; Paxton et al., 2008). Structures included the anterior cingulate cortex (ACC), hippocampus (HPC), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), parahippocampus (PHG), posterior parietal lobe (PPL), and superior frontal gyrus (SFG). Using the Harvard-Oxford cortical and subcortical structural atlases for reference, we combined all ROIs into an omnibus mask thresholded at 0.30 (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006). To determine significant activity within the omnibus mask, we used the FSL *randomise* package to conduct a permutation test with 5000 permutations and a one-tailed significance level of 0.05 within the entire participant sample (Winkler et al., 2014). This process was repeated for each of the three contrasts. Regions with significant clusters were examined for between-group differences with 10,000-permutation two-sample unpaired t-tests (Winkler et al., 2014).

Exploratory Analyses.: Examining whole-brain proactive and reactive control can provide a more comprehensive conceptualization. Accordingly, we used *randomise* to assess each contrast of interest across the whole brain (cluster threshold $p < .05$, voxel threshold $z > 3.09$

[p < .001]) (Winkler et al., 2014). Within-group and between-group methods mirrored those used for confirmatory analyses.

Relationship between Functional Activity and Behavioral and Clinical Metrics

—To determine if cognitive control activity predicted variance in d' context and d' expectancy, the regressors of ROIs associated with significant proactive, reactive, and/or specialized control within the combined sample were introduced into elastic net regression models using the *caret* and *glmnet* R packages (Friedman et al., 2010; Kuhn, 2008). The choice to use elastic net regression stemmed from noted difficulties with accuracy and parsimony in ordinary least squares, particularly with large numbers of predictors – which was highly relevant to our confirmatory analysis (Zou & Hastie, 2005). Moreover, an elastic net's simultaneous automatic variable selection and continuous shrinkage, and ability to select groups of correlated variables, combines the benefits of other regularization techniques such as ridge and lasso regression (Zou & Hastie, 2005). Ultimately, this method yielded four separate models: HC and SZ d' context (calculated with proactive or specialized proactive regressors), and HC and SZ d' expectancy (calculated with reactive or specialized reactive regressors). Each model was tested with 10-fold cross-validation repeated 5 times (alpha = seq[0.1, length=10], lambda = seq[0.0001, 0.2, length = 5]).

Results

Behavioral Analyses

Similarly to parametric analyses previously conducted with the current sample (Poppe et al., 2016), non-parametric between-group comparisons found the HC group had greater overall d' context (W = 1779.5, p = .001, r = .303) and d' expectancy (W = 1586, p = .037, r = .176) values than the SZ group. As illustrated in Figure 1B, the mixed ANOVA found main effects for Group (HC vs. SZ, $F_{1,101} = 6.18$, p = .015) and Metric (d' context vs. d' expectancy, $F_{1,101} = 4.89$, p = .029), and an interaction between Group and Metric ($F_{1,101} = 5.10$, p = .026). There were no significant effects for Half (first vs. second, $F_{1,101} = .087$, p = .769); accordingly, all other analyses conducted for this study used overall d' context and d' expectancy scores. Simple main effects of Metric revealed a significant difference between d' context and d' expectancy, such that d' context was greater than d' expectancy within the HC group (p = .026), but not within the SZ group (p = .983).

Partial correlations within the SZ group found no association between the d' metrics and either disorganization or positive symptoms (all ps >.2). A secondary interest concerned the utility of response time metrics for investigating cognitive control. Relevant methods and results are detailed in the supplementary material.

fMRI Analyses

Previous analyses of this dataset found no effect of scanning location on neuroimaging results (Poppe et al., 2016). Table 1 and Figure 2 summarize combined sample testing results across all three contrasts. Both B > A and AY > AX were generally associated with activity in bilateral dorsolateral PFC and posterior parietal regions. Specialized proactive control ((B>A) - (AY>AX)) was most evident in the left MFG (peak z score = 5.16) and the left

SFG (z = 4.53) confirmed by significant post-hoc testing. No regions showed evidence of specialized reactive control. A post-hoc conjunction analysis confirmed the presence of regions active for both B>A and AY>AX (Figure 2). Across all *a-priori* regions, only B>A within the left MFG (z = 3.31) and the right IFG (z = 2.81) yielded between-group differences; HC activity was greater than SZ activity in both circumstances (Figure 3). No other significant between-group differences were found within the other contrasts.

Whole-brain analyses found significant activity associated with all contrasts apart from specialized reactive control (Table 2, Figure S1). B>A was associated with activity in the left occipital lobe, brain stem, and temporal lobe. AY>AX was associated with the left insula, posterior supramarginal gyrus, and inferior temporal gyrus, and the right middle frontal gyrus. Lastly, specialized proactive control was associated with the middle frontal, superior frontal, right occipital fusiform, and anterior supramarginal gyri.

Relationship between fMRI and Behavioral and Clinical Measures

Elastic net results were summarized separately for each group (Table 3). Within the HC group, the d' context model of best fit (alpha = 1.10, lambda = 0.10; RMSE =1.18) identified the right MFG (B>A), left IFG (B>A), and left SFG ((B>A) - (AY>AX)) as the most important predictors. This model accounted for approximately 25% of d' context variance. The HC d' expectancy model (alpha = 1.10, lambda = 0.20, RMSE =1.13) identified the right IFG (AY>AX) as the most significant predictor alongside the left PPL, right ACC and MFG, and bilateral SFG, and accounted for approximately 37% of variance. Within the SZ group, the d' context model (alpha = 1.10, lambda = 0.20; RMSE =1.53) had the right IFG (B>A) as its sole predictor and accounted for 33% of variance. The SZ d' expectancy model (alpha = 1.1, lambda = 0.15, RMSE = 1.17) identified the left SFG and PPL (both AY>AX), accounting for approximately 49% of variance. To aid interpretability, four additional elastic nets were conducted on the cue/probe regressors associated with significant contrast activation. The HC d' context model solely identified right MFG B-cue activity, suggesting it drove 21% of d' context variance ($R^2 = 0.21$). The SZ d' context model identified right IFG B-cue activity as its only predictor ($R^2 = 0.32$). D' expectancy models also differed between groups, as the HC model ($R^2 = 0.29$) identified right IFG AY activity only, whereas the SZ model ($R^2 = 0.37$) identified the left PPL (for both AX and AY) and left SFG (AX only).

As a secondary interest, elastic net models were also conducted for reaction time metrics of cognitive control. These models identified a wide array of predictors and are further described in tables S2a and S2b.

Regarding clinical symptoms, disorganization symptoms were entered into a multiple regression with beta weight estimates of the left MFG and right IFG as independent variables. Neither predictor was significant ($F_{2, 40} = 0.56$, p = .58). Similar results occurred for positive symptoms ($F_{2, 40} = 1.35$, p = .27). *Post-hoc* analyses examined if symptoms were predicted by the d' metrics, but yielded non-significant results for both disorganized ($F_{2, 40} = 0.84$, p = .44) and positive ($F_{2, 40} = 1.69$, p = 0.20) symptoms.

Discussion

We used fMRI and the DPX to characterize the functional neuroanatomy of reactive and proactive cognitive control, and to determine the extent of their distinctiveness from each other. We then examined between-group differences within 47 individuals with schizophrenia and 56 healthy controls. The results found several prefrontal and parietal regions were implicated in both proactive and reactive control, such as the MFG, IFG, SFG, and PPL. Our hypothesis regarding the existence of specialized engagement in cognitive control was partially confirmed, as portions of the MFG and SFG showed greater activation levels for proactive control than for reactive control. No regions showed evidence for specialized reactive control. Regarding between-group differences, control participants showed greater proactive control in the left MFG and right IFG than did the schizophrenia group. However, neither region was strongly correlated with behavioral measures of proactive (d' context) or reactive (d' expectancy) processes in the DPX. Exploratory elastic net regressions did identify the right IFG activity as a significant predictor of behavioral outcomes, but this differentially related to proactive control for HC d' expectancy, but reactive control in SZ d' context. Moreover, several other regions were deemed to be more important predictors. Future work will be vital in assessing the potential significance of this divergence, and its associations.

These results are intriguing to consider with regard to the DMC framework and the dual-encoding hypothesis. Our confirmatory analysis found evidence of specialized proactive control in the left MFG and SFG, which is consistent with the DMC framework's emphasis of lateral PFC activity in proactive control (Braver, 2012). However, generalized proactive control was also associated with anterior PFC and PPL regions, which contradicted our expectations from DMC. These findings indicate the DMC framework needs further refining, especially since it currently conceptualizes posterior parietal activity as an accessory feature of reactive control only (Braver, 2012). Similarly, our results simultaneously support and challenge the dual-encoding hypothesis. The implication of several prefrontal and posterior parietal regions in both proactive and reactive control is fairly consistent with nonhuman primate findings (Blackman et al., 2016). The PPL's significance is especially notable, given prior research has found significant clusters of dual-encoding neurons within the region that substantially contribute to cognitive control (Goodwin et al., 2012). Additional support is given by the fact that even though results found ROIs involved in specialized proactive control, proactive control in these regions were uncorrelated with clinical symptoms and largely did not predict DPX performance metrics (the sole exception is discussed further on). However, conclusions are limited by our traditional fMRI-based approach to examining this research question – fMRI operates under a relatively-slow timecourse, and temporal acuity is crucial to both hypotheses. For instance, sustained vs. transient dorsolateral PFC activity is a key component of the DMC framework's conceptualization of proactive vs. reactive control (Braver, 2012) and we could not examine time course effects in the current study. Moreover, dual-encoding studies have depended on nonhuman single-cell recordings that would be extremely difficult to replicate in humans. One ambitious possibility might be to observe implanted electrode recordings in neurosurgery patients; however, a project of that nature is beyond the scope of this study.

Therefore, future attempts to quantify the distinctiveness of cognitive control processes will greatly benefit from combined imaging and electrophysiological methods, such as simultaneous EEG and fMRI.

Confirmatory analyses aside, interesting patterns emerged within the elastic net models despite their exploratory nature. For one, d' context was primarily dependent on B-cue MFG activity in controls, and IFG activity in the SZ group. Neither involvement is surprising. For example, the MFG is frequently highlighted as an enabler of proactive control (e.g. Goghari & MacDonald, 2009; Niendam et al., 2014; Poppe et al., 2016; Ray Li, 2006). And the IFG has been linked with both context processing and inhibitory processes in cognitive control literature (Derrfuss et al., 2005; Goghari & MacDonald, 2009; Marklund & Persson, 2012; Tops & Boksem, 2011). However, between-group differences abound. As expected, the SZ IFG coefficient was positive, implying greater B>A discrepancies facilitate increased d' context. By contrast, this relationship was negative within the HC group. This difference may reflect a genuine pathology-based difference; however, such a conclusion should be conclusive given the exploratory nature of this analysis.

Additional differences were evident within the d' expectancy models. Within the HC group, d' expectancy was primarily predicted by the IFG, followed by various frontal and posterior parietal regions that were deemed less essential. The SZ d' expectancy model only identified the left SFG and PPL regions, and both regions were considered important in follow-up analyses. Contrary to our expectations, these results imply better HC d' expectancy is associated with more 'superfluous' ROI activity compared to SZ counterparts. Furthermore, while the PPL has been associated with executive processes such as attention switching, task switching, and overcoming prepotent inhibition in healthy controls, the cause of the region's greater impact within our SZ group is uncertain (Barber & Carter, 2005; Cusack et al., 2010). However, the way abnormal PPL functioning uniquely contributes to cognitive control deficits in schizophrenia is uncertain. Compared to the HC elastic net models, the SZ results implied d' expectancy was more associated with activation during 'default' stimuli states, such as A cues and AX trials. Perhaps cognitive control deficits in schizophrenia are associated with effortful-yet-inefficient processing, as opposed to overall reduced activity. This interpretation complements previous findings that link schizophrenia with reduced ability to terminate visual processing in the face of distractor stimuli (Silverstein et al., 2009). However, complications arise from the absence of a direct association between region-related activity and clinical symptoms or task-based metrics. It is possible that our SZ participants had low variance in symptom severity, especially with regards to disorganization symptoms. The exploratory nature of these results, however, may reflect a more complicated relationship between cognitive control and schizophrenia-spectrum symptoms (Lesh et al., 2013; MacDonald et al., 2005; Niendam et al., 2014; Poppe et al., 2016; Yoon et al., 2008). Certainly, there is more to learn about how aberrant activity in these brain regions affect lived experiences.

It is prudent to consider study methods that may influence our results. For one, we conceptualized reactive control as that which occurs during the AY > AX contrast to prioritize specificity and maintain consistency with the canonical proactive conceptualization of the B > A contrast. One may argue that our behavioral analogue,

d' expectancy, may not solely reflect reactive control due to the potential influences of the prepotent AX sequence. However, similar concerns could be raised with d' context (an established proactive measure), which highlights the difficulty of creating factor-pure cognitive control measures. Other studies have measured reactive control differently, including decreased cue activity followed by increased probe activity (Braver et al., 2009), comparing the relative balance of AY and BX trial interference (Braver et al., 2009; Gonthier et al., 2016), general AY trial activity (Ryman et al., 2019), and with different paradigms altogether, such as the Stroop task (Smucny et al., 2018). Despite the idiosyncratic strengths and drawbacks of these approaches, it is possible that our results would differ had we used similar methods.

Other considerations include task choice. For example, prior research has linked the AX-CPT with greater insula activity, and the DPX with greater PFC-medial temporal lobe connectivity (Lopez-Garcia et al., 2016). However, it is uncertain if these differences induce observable differences between proactive and reactive control performances. Finally, unlike other studies, we conducted region-specific testing in several *a priori* non-prefrontal regions. Non-prefrontal regions are implicated in various cognitive control tasks, such as task switching, overcoming inhibitory responses, and error-related processing (Esterman et al., 2009; Ide & Li, 2011; Sdoia et al., 2020). Following the broader framework hypothesized by the DMC framework (Braver, 2012) increased our power to detect non-PFC activity that may have been less noticeable in a whole-brain exploratory analysis.

Similarly, some limitations affect the study's generalizability. For example, our sample size may have been too small to detect subtle effects that did not survive permutation testing. Additionally, the decision to conduct initial testing within the combined participant sample meant only voxels that showed sufficient consistency in the total sample were scrutinized further. While not necessarily a negative by itself, this conservative approach does raise the possibility of Type-II error. Finally, as discussed above, the absence of electrophysiological data diminished our ability to fully examine temporal characteristics that play significant parts in both DMC framework and dual-encoding hypotheses.

This study aimed to characterize the distinctiveness between proactive and reactive control, and explore their relationships with clinical symptoms. Results found some evidence of specialized proactive control processing within the PFC, and no specialized reactive control. Moreover, these specialized control regions were not associated with individual differences in task performance metrics, nor with schizophrenia symptoms theoretically associated with impaired cognitive control, implying that specialized cognitive control is not a crucial component of either cognitive control process. These results, complementary to dual-encoding findings from nonhuman primate research, provide a potential refining point for the DMC framework. However, future examinations of the electrophysiological signature of lateral prefrontal activity would clarify the sustained vs. transient nature of this region during proactive and reactive control, respectively. Ultimately, the neuroanatomical focus of this study may provide a stepping stone for more comprehensive research that teases apart the cognitive processes underlying executive functioning deficits in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and materials:

Researchers interested in access to the data may contact Angus MacDonald at angus@umn.edu. The author will assist with any reasonable replication attempts for two years following publication.

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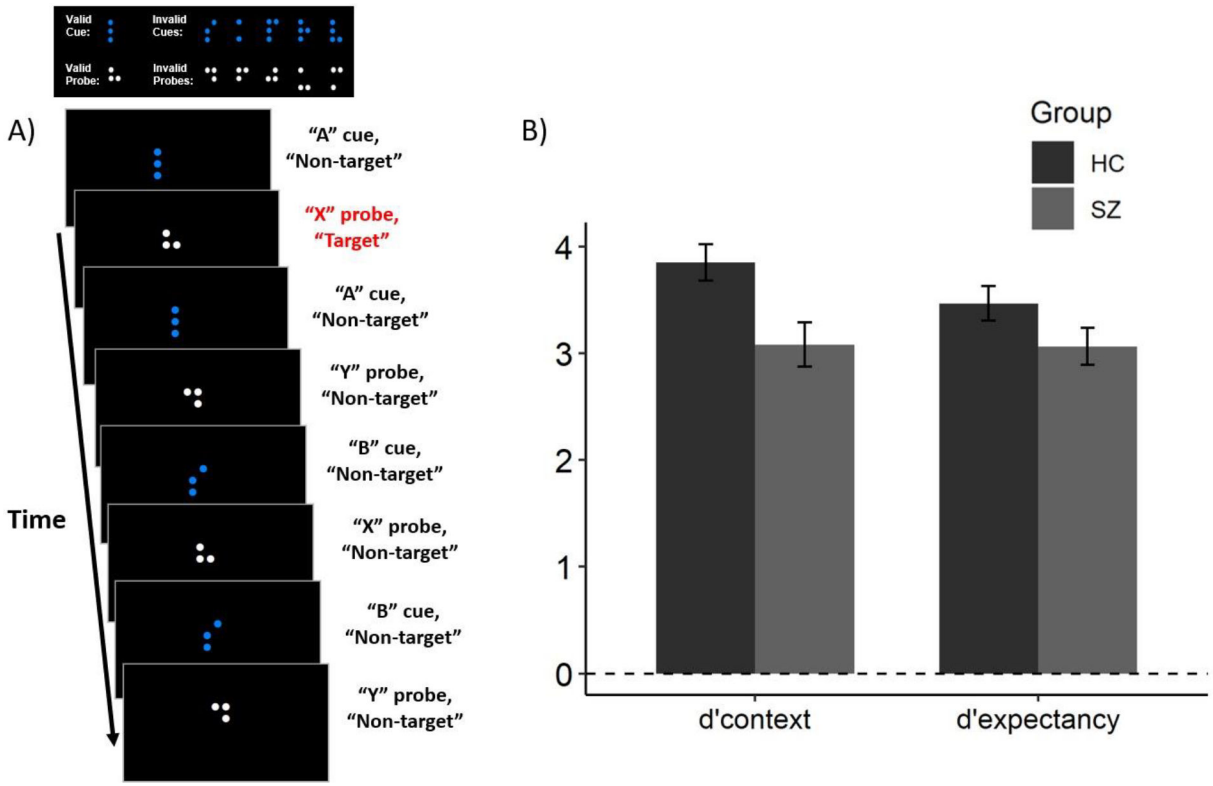

Figure 1. Dot Pattern Expectancy Task and associated Behavioral Metrics.

Note: A) Diagram of the Dot Pattern Expectancy Task (DPX), modified from Henderson et al., 2012. B) Bar charts comparing d' context and d' expectancy within participant groups across task halves. "HC" and "SZ" refer to "healthy controls" and "individuals with schizophrenia", respectively.

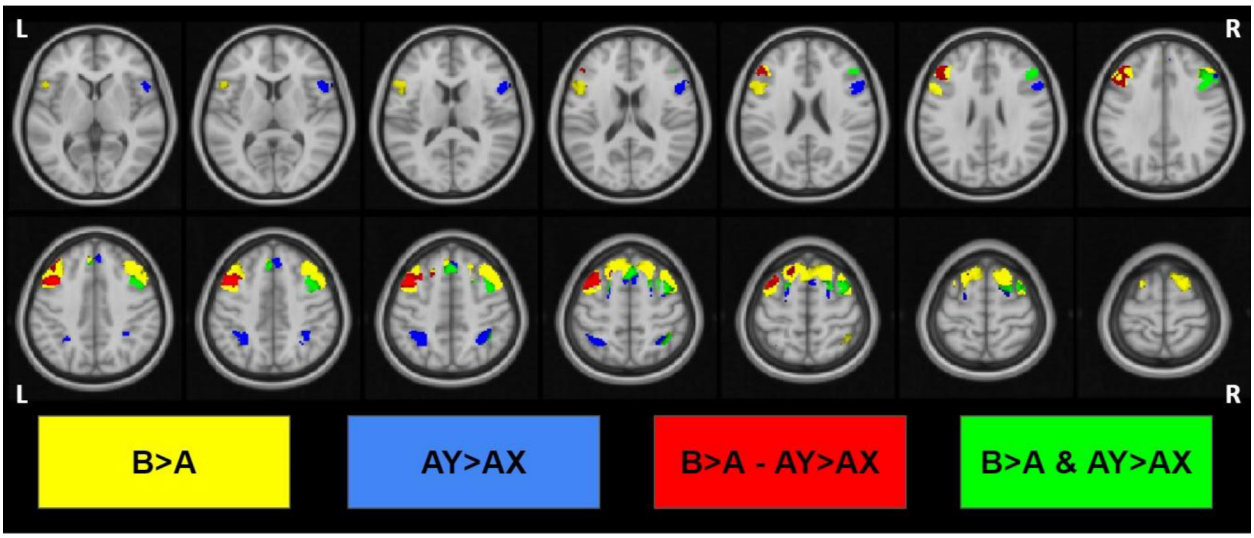

Figure 2. Regions of Significant Activity within the Combined Participant Sample.

Note: Proactive control (B>A) is depicted in yellow, reactive control (AY>AX) in blue, and specialized proactive control ((B>A) – AY>AX)) in red. No regions showed significant specialized reactive ((AY>AX) – (B>A)) control. Regions in green are the results of a conjunction analysis of regions associated with both proactive and reactive control.

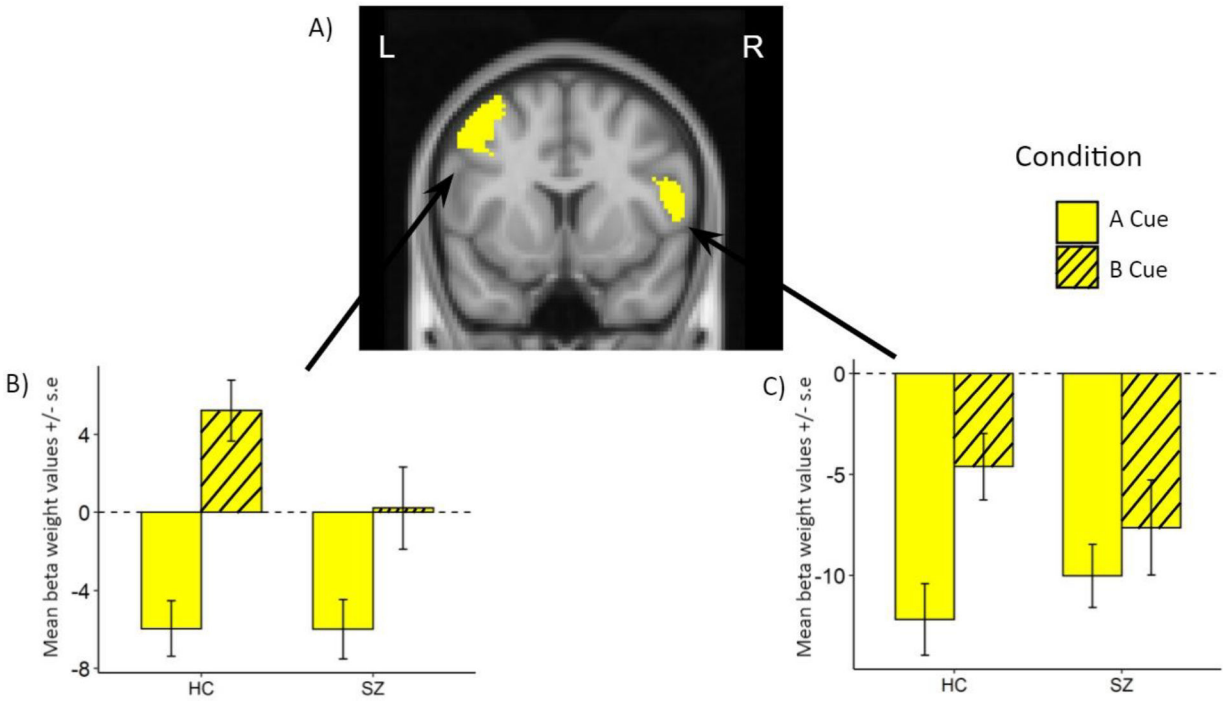

Figure 3. Regions of Significant Between-Group Activity.

Note: A**)** Between group differences in B>A activity were found in the *B)* left middle frontal gyrus and *C)* right inferior frontal gyrus. The bar charts compare patterns accompanying beta weight regressors for A Cues and B Cues. "HC" and "SZ" refer to "healthy controls" and "individuals with schizophrenia", respectively. Differences in activity were significantly higher in the HC group for both regions.

Table 1

Clusters of Significant Activity Detected during Confirmatory Testing within the Combined Sample.

Contrast	Cluster	Voxels	Peak Voxel Z Score	Region	MNI Coordinates		
					X	Y	Z
B>A	7	2105	7.52	R Superior Frontal Gyrus	24	20	56
	6	1823	7.31	R Middle Frontal Gyrus	30	14	56
	5	1784	7.4	L Middle Frontal Gyrus	−52	14	40
	4	664	5.21	R Posterior Parietal Lobe	42	−50	54
	3	511	5.73	L Inferior Frontal Gyrus, pars op.	−54	16	28
	2	111	4.72	R Inferior Frontal Gyrus, pars op.	52	12	28
	1	87	5.54	L Posterior Parietal Lobe	−34	−58	44
AY>AX	9	997	7.72	R Middle Frontal Gyrus	30	6	54
	8	462	6.66	R Inferior Frontal Gyrus, pars op.	50	14	28
	7	456	7.27	R Superior Frontal Gyrus	8	24	50
	6	369	8.38	L Posterior Parietal Lobe	−40	−48	46
	5	305	8.3	R Posterior Parietal Lobe	38	−50	44
	4	190	7.8	R Superior Frontal Gyrus	24	6	54
	3	115	6.52	L Superior Frontal Gyrus	−22	0	56
	2	37	4.6	L Middle Frontal Gyrus	−40	32	22
	1	32	4.59	R Anterior Cingulate Cortex	4	24	38
(B>A) – (AY>AX)	3	1338	5.16	L Middle Frontal Gyrus	−40	14	44
	2	233	4.53	L Superior Frontal Gyrus	−20	22	52
	1	3	4.2	R Superior Frontal Gyrus	26	20	62

Note: “L” and “R” refer to the “left” and “right” hemisphere, respectively. “*pars op.*” refers to *pars opecularis*. “MNI” refers to the Montreal Neurological Institute.

Table 2

Clusters of Significant Wholebrain Activity Detected within the Combined Sample.

Contrast	Cluster	Voxels	Peak Voxel Z Score	Region	MNI Coordinates		
					X	Y	Z
B>A	4	81,367	9.56	L Lateral Occipital Cortex, Inf	−46	−74	−10
	3	254	3.77	R Temporal Pole	46	6	−44
	2	124	3.11	Brain Stem	−12	−28	−30
	1	2	2.84	L Occipital Pole	−16	−92	46
AY>AX	4	18,071	9.2	L Posterior Supramarginal Gyrus	−40	−50	44
	3	17,835	8	R Middle Frontal Gyrus	28	6	56
	2	1,011	4.86	L Insular Cortex	−30	22	−2
	1	70	4.45	L Interior Temporal Gyrus	−42	−60	−6
(B>A) – (AY>AX)	4	34.341	7.22	R Occipital Fusiform Gyrus	32	−80	−10
	3	3,193	4.91	R Anterior Supramarginal Gyrus	52	−20	30
	2	165	4.25	R Superior Frontal Gyrus	26	22	60
	1	58	4.03	R Middle Frontal Gyrus	36	32	48

Note: “L” and “R” refer to the “left” and “right” hemisphere, respectively. “Inf” refers to “Inferior”. “MNI” refers to the Montreal Neurological Institute.

Table 3

Elastic Net Model Characteristics for d' context and d' expectancy within HC and SZ Participant Groups.

Group	Metric	Region	Contrast	Coefficient	Model parameters			
					α	λ	RMSE	R^2
HC	d' context	R Middle Frontal Gyrus	B>A	0.025	1.1	0.10	1.18	0.25
		L Inferior Frontal Gyrus	B>A	−0.006				
		L Superior Frontal Gyrus	(B>A) – (AY>AX)	−0.005				
	d' expectancy	R Inferior Frontal Gyrus	AY>AX	−0.062	0.1	0.20	1.13	0.37
		L Posterior Parietal Lobe	AY>AX	0.019				
		R Superior Frontal Gyrus	AY>AX	0.014				
		R Anterior Cingulate Cortex	AY>AX	0.011				
		R Middle Frontal Gyrus	AY>AX	−0.005				
		L Superior Frontal Gyrus	AY>AX	−0.001				
SZ	d' context	R Inferior Frontal Gyrus	B>A	0.009	1.1	0.20	1.53	0.33
	d' expectancy	L Superior Frontal Gyrus	AY>AX	0.048	1.1	0.15	1.17	0.49
		L Posterior Parietal Lobe	AY>AX	−0.043				

Note: "L" and "R" refer to the "left" and "right" hemisphere, respectively.