Genetic Variation in Cognitive Flexibility Performance and Brain Activation in Schizophrenia: A Multiplex Extended Pedigree Study

by

Petra Emily Rupert

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This thesis was presented

by

Petra Emily Rupert

It was defended on

August 4, 2020

and approved by

Kirk Erickson, Professor, Department of Psychology

Konasale Prasad, Professor, Department of Psychiatry

David Roalf, Assistant Professor, Department of Psychiatry, University of Pennsylvania

Thesis Advisor: Michael Pogue-Geile, Professor, Department of Psychology

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Petra Emily Rupert, M.S.

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On executive tasks of cognitive flexibility, individuals with schizophrenia have poorer performance and often differing patterns of brain activation. The present study sought to examine the degree to which cognitive flexibility performance and its related brain activation may reflect effects of schizophrenia genetic risk using an extended pedigree design. A total of 521 participants, 30 schizophrenia probands, 202 of their relatives (1st to 4th degree), and 289 unrelated controls completed similar versions of a computerized cognitive flexibility task (Penn Conditional Exclusion Test) both out of and in an MRI scanner. Both behavioral performances and brain activation during the task in five regions of interest were analyzed. In order to examine diagnostic specificity, we also investigated genetic correlations between diagnosed depression and PCET performance and brain activation. Cognitive flexibility performance was significantly genetically correlated with schizophrenia both out of (R_g=-0.65, p=0.005) and in the scanner (R_g=-0.56, p<0.001) after false discovery rate (FDR) correction. In contrast, genetic correlations between schizophrenia and ROI brain activation in the Frontal Pole (right Rg=0.30, p=0.30, left Rg=1.00, p=0.01), Anterior Cingulate Gyrus (bilateral Rg=0.39, p=0.18), and Middle Frontal Gyrus (right Rg=1.00, p=0.04, left Rg=0.60, p=0.12) were either not nominally significant or were not significant after FDR correction. Neither behavioral performance nor brain activation measures were significantly genetically correlated with depression. In contrast to some hypotheses, these results suggest that behavioral performance on this measure of cognitive flexibility (PCET) is more sensitive (and also specific compared with depression) to schizophrenia genetic risk effects than fMRI measures of its regional brain activation.

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1.0 Introduction

Schizophrenia is not only highly heritable (Sullivan, Kendler, & Neale, 2003), it is also genetically complex (Birnbaum & Weinberger, 2017), which makes it challenging to identify how genetic variation is involved in the pathology of schizophrenia. Endophenotypes of schizophrenia, phenotypes that are heritable and genetically related to schizophrenia, are proposed to be more associated with genetic etiology than the diagnosis itself (Gottesman & Gould, 2003; Gottesman & Shields, 1972) and thus present a way to better understand genetic risk. Impaired cognitive functioning has been suggested as a promising behavioral endophenotype, as it is widespread and severe (Dickinson, Iannone, Wilk, & Gold, 2004; Dickinson, Ragland, Calkins, Gold, & Gur, 2006; Heinrichs & Zakzanis, 1998; Keefe & Fenton, 2007), seen prior to the onset of schizophrenia (Caspi et al., 2003; Keefe & Fenton, 2007), heritable (Bertisch, Li, Hoptman, & DeLisi, 2010), and seen in unaffected family members (Egan et al., 2001; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004).

Cognitive flexibility may be a particularly important aspect of cognitive impairment in schizophrenia due to its degree of impairment relative to other cognitive domains (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999), its persistence (Albus et al., 1996), and its relation to functional, social, and vocational outcomes (Michael Foster Green, Kern, Braff, & Mintz, 2000; Michael F Green, Kern, & Heaton, 2004). Furthermore, the degree of impairment on cognitive flexibility tasks may differentiate individuals with schizophrenia from those with non-psychotic psychiatric disorders, such as depression (Mahurin et al., 2006; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999).

Individuals with schizophrenia also show differing brain activation compared to controls in functional neuroimaging studies of cognitive flexibility, with mixed evidence supporting hypoactivation (Riehemann et al., 2001; Volz et al., 1997) or hyperactivation (Pedersen et al., 2012; Wilmsmeier et al., 2010) in task related regions of interest. It is currently unclear if abnormal brain activation during cognitive flexibility tasks is only present in individuals with a schizophrenia diagnosis or if it might also occur in relatives of patients, suggesting that it may serve as a biological endophenotype.

By studying individuals who are genetically related to schizophrenia patients, the degree to which cognitive flexibility deficits or brain activation are indicators of increased genetic risk for developing schizophrenia can be examined. Therefore, the current study, utilizing an extended pedigree family design, examined the potential of these measures as endophenotypes, or heritable traits that are genetically correlated with schizophrenia.

1.1 Behavioral Performance on Tasks of Cognitive Flexibility

Tasks of cognitive flexibility require individuals to inhibit responses and shift to new responses or ways of thinking based on information they receive from their environment (Diamond, 2013). The most common test of cognitive flexibility is the Wisconsin Card Sorting Test (WCST) (Anderson, 2002; R. K. Heaton, Chelune, Talley, Kay, & Curtiss, 1993; Milner, 1963; Puente, 1985). The aim of the WCST is to sort stimuli based on a current criterion and throughout the task be able to shift flexibly to new criteria and inhibit old responses when criteria change. In addition to the WCST, other similar tasks have been developed and schizophrenia patients show similar performance deficits. For example, the Penn Conditional Exclusion Test (PCET) has been developed specifically for computerized administration and has shown performance on components of the PCET to be correlated to their analogous measures on the WCST (Kurtz, Ragland, Moberg, & Gur, 2004; Kurtz, Wexler, & Bell, 2004).

1.1.1 Cognitive Flexibility Performance in Schizophrenia

Compared to individuals without a psychiatric diagnosis, individuals with schizophrenia discern fewer rules and make more perseverative errors when rules change (Everett, Lavoie, Gagnon, & Gosselin, 2001; R. Heaton et al., 1994; Nieuwenstein, Aleman, & de Haan, 2001). The WCST has been frequently studied in schizophrenia; large meta-analyses have shown moderate to large effect sizes of impaired performance by schizophrenia patients on the WCST (Heinrichs & Zakzanis, 1998; Laws, 1999; Mesholam-Gately et al., 2009). Poor performance on the WCST compared to control groups has also been seen in first-episode patients (Fey, 1951; Mesholam-Gately et al., 2009). Individuals with schizophrenia also perform more poorly on the PCET compared to controls in both speed and overall accuracy (Calkins et al., 2013; Calkins et al., 2010; R. C. Gur et al., 2015).

Other diagnoses, such as depression, have also shown impairments in cognitive flexibility when compared to healthy controls (Snyder, 2013). However, compared to depression, individuals with schizophrenia perform significantly worse on tasks of cognitive flexibility, including the WCST (Mahurin et al., 2006; Merriam et al., 1999). While impairments in cognitive flexibility may not be solely seen in schizophrenia, the extreme degree of impairment tends to distinguish schizophrenia patients from those with other psychiatric diagnoses.

1.1.2 Cognitive Flexibility Performance in Schizophrenia Relatives

In addition to individuals with schizophrenia showing cognitive flexibility impairments, family members of schizophrenic patients also typically perform worse than healthy controls. When examining cognitive functioning in family members of schizophrenic patients across a wide range of cognitive domains, executive functioning was found to have a larger effect size of impairment compared to other domains (Sitskoorn et al., 2004). Poor performance on the WCST specifically has a moderately large effect size in family members (Snitz, MacDonald, & Carter, 2005).

Compared to unrelated healthy controls, family members of schizophrenic patients are less accurate and take longer to complete tasks of cognitive flexibility (Birkett et al., 2008; Calkins et al., 2013; Calkins et al., 2010; Egan et al., 2001; Faraone et al., 1995; R. E. Gur et al., 2007; Scarone, Abbruzzese, & Gambini, 1993). In addition, performance on the WCST among unaffected family members in multiplex families (more than one schizophrenia patient per family) is worse than those in simplex families (Lin et al., 2011). These same studies indicate that although family members perform worse than unrelated controls, they still perform better than their relatives with schizophrenia.

Studies of offspring of individuals with affective disorders showed that the offspring of depressed mothers (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006), or of parents with either unipolar or bipolar depressive disorders (Wolf, Cornblatt, Roberts, Shapiro, & Erlenmeyer-Kimling, 2002) did not have WCST performance deficits compared to healthy controls, suggesting some diagnostic specificity.

1.2 Neuroimaging of Cognitive Flexibility

1.2.1 In Healthy Control Populations

Among healthy control samples, several brain regions have been proposed to be involved with cognitive flexibility. Of these, the prefrontal cortex is most commonly identified as having higher activation during cognitive flexibility task performance (Buchsbaum, Greer, Chang, & Berman, 2005). Within the prefrontal cortex, both the dorsolateral prefrontal cortex (DLPFC) (Berman et al., 1995; Buchsbaum et al., 2005) and ventrolateral prefrontal cortex (VLPFC) (Graham et al., 2009; Monchi, Petrides, Petre, Worsley, & Dagher, 2001) have shown higher activation during an fMRI version of the WCST. Other tasks of cognitive flexibility, such as the Penn Conditional Exclusion Test, have also replicated higher prefrontal activation (Roalf et al., 2014). These consistent findings have framed the WCST as a prefrontal task; however due to the complexity of cognitive flexibility, studies have found that the inferior parietal cortex, temporal cortex, and anterior cingulate also have higher activation compared to baseline during cognitive flexibility tasks (Berman et al., 1995; Buchsbaum et al., 2005; Lie, Specht, Marshall, & Fink, 2006; Roalf et al., 2014). This widespread higher activation may indicate that different brain regions are involved in different components of cognitive flexibility tasks. For example, the DLPFC may be most activated during trials when individuals were receiving positive feedback and were giving the correct response, but the basal ganglia, caudate nucleus, VLPFC, and mediodorsal thalamus may be more activated during negative feedback periods (Monchi et al., 2001).

1.2.2 Neuroimaging of Cognitive Flexibility in Schizophrenia Patients

In schizophrenia samples, early studies using regional cerebral flood flow (rCBF) and single-photon emission computed tomography (SPECT) identified hypoactivation compared to healthy controls in prefrontal regions in schizophrenia patients when completing the WCST (Berman, Zec, & Weinberger, 1986; Catafau et al., 1994; Ortuño, Moreno-Íñiguez, Millán, Soutullo, & Bonelli, 2006; Parellada et al., 1994; Weinberger, Berman, & Zec, 1986). This has been seen in both un-medicated and medicated first-episode patients (Berman et al., 1986; Eisenberg & Berman, 2010; Steinberg, Devous Sr, Paulman, & Gregory, 1995), suggesting that the prefrontal hypoactivation seen in patients is not due to medication effects. Aside from the prefrontal cortex, schizophrenia patients may also have lower activation compared to healthy controls in the left temporal lobe (Riehemann et al., 2001).

To date, only three fMRI studies of the WCST have been done in patients with schizophrenia. Of these studies, two replicated previous SPECT and rCBF findings of hypoactivation in the right prefrontal cortex in patients compared to controls (Riehemann et al., 2001; Volz et al., 1997). However, one study using two analytic approaches did not find any regions in which patients had hypoactivation compared to controls, possibly due to the types of analyses done and group characteristics. In one report, patients had higher event related activation in the rostral and dorsal anterior cingulate compared to controls when a set shift was indicated and when they successfully shifted (Wilmsmeier et al., 2010). The second report from the same study showed that higher performing patients showed higher set shifting event related activation in the anterior cingulate compared to controls, whereas lower performing patients did not (Pedersen et al., 2012). These reports suggest that patients with schizophrenia may activate compensatory networks while performing a cognitive flexibility task.

While poor performance on WCST has been shown in depression, although at a lesser extent than seen in schizophrenia patients, individuals with depression do not show the same hypoactivation in frontal brain regions (Berman, Doran, Pickar, & Weinberger, 1993). This may indicate that hypoactivation during the WCST could differentiate between schizophrenia and depression, suggesting relative specificity to schizophrenia.

1.2.3 Neuroimaging of Cognitive Flexibility in Relatives of Schizophrenia Patients

While cognitive flexibility performance in schizophrenia relatives has been extensively examined, the functional neuroimaging literature on similar tasks is sparse. One early study examined the WCST in monozygotic twins discordant for schizophrenia. Compared to their schizophrenic twin, the unaffected cotwins had higher rCBF in prefrontal regions during the WCST (Berman, Torrey, Daniel, & Weinberger, 1992). However, there were no significant differences between the unaffected cotwins and control subjects who did not have a genetic risk for schizophrenia. The Berman et al. study however may have been underpowered to find significant differences, as the sample size included 10 discordant twin pairs, 8 concordant twin pairs, and only 3 healthy control twin pairs.

Other studies that have examined brain activation in nonpsychotic family members of schizophrenia patients have used tests of cognitive control and working memory, both considered as components of executive function that

may share overlapping features with cognitive flexibility (Friedman & Miyake, 2017). A review of eleven fMRI studies in nonpsychotic family members of schizophrenia found mixed results in both cognitive control and working memory (MacDonald, Thermenos, Barch, & Seidman, 2008). While lower activation in family members compared to control groups was implicated in prefrontal regions in some studies, there were about the same number of studies showing no difference or higher activation. The lack of consensus in the studies examining executive functions in nonpsychotic family members of schizophrenic patients may be due to the wide range of tasks used, none of which employed tests of cognitive flexibility. Additionally, the sample sizes for these studies were very small (range 12-30 relatives), suggesting these studies were underpowered.

1.3 Genetic Effects on Cognitive Flexibility Performance and Concurrent Brain Activation

Cognitive flexibility performance on the PCET has been shown to be heritable among family members of schizophrenia patients (Calkins et al., 2013; Calkins et al., 2010; Glahn et al., 2007) and to help locate genes that create an increased risk for schizophrenia, early literature looked for associations between candidate genes, such as COMT, and schizophrenia and the WCST. However, more recent GWAS studies have not replicated studies examining such specific candidate genes and their association with schizophrenia (Johnson et al., 2017). Therefore, the relevance of these genes to schizophrenia and WCST (J. Barnett, Jones, Robbins, & Müller, 2007) is unclear.

More recently, other studies have used polygenic risk scores (PRS) to calculate weighted genetic risk for schizophrenia based on multiple loci. In the general population, increased polygenic risk for schizophrenia has been associated with working memory deficits, another measurement of executive functioning (Krug et al., 2018; Miller et al., 2017; Mistry, Harrison, Smith, Escott-Price, & Zammit, 2018), although none to date have examined cognitive flexibility. One study also examined polygenic scores for general cognitive function and their relation to the WCST, finding a significant association with perseverative errors on the WCST(H. Zhang et al., 2018). Taken together, these PRS studies suggest that both polygenic risk for schizophrenia and cognitive functioning may be related to executive functioning abilities.

Studies of genetic effects on brain activation during cognitive tasks have been limited and mainly focused on working memory. Broadly, these studies show mixed evidence for heritability of brain activation during working memory tasks (Blokland et al., 2008; Blokland et al., 2011). One review has suggested that there is a relationship between schizophrenia PRS and functional brain activation during executive functioning tasks (Dezhina, Ranlund, Kyriakopoulos, Williams, & Dima, 2019), however none of the studies included were tasks of cognitive flexibility. Two additional studies not included in the review found that schizophrenia PRS were related to lower activation in prefrontal areas (Krug et al., 2018; Miller et al., 2017). Therefore, there is some evidence of an association between schizophrenia genetic risk and functional brain activation during executive functioning tasks.

1.4 Shared Genetic Effects Between Schizophrenia and Cognitive Flexibility Performance and Concurrent Brain Activation: The Current Study

Previous research has robustly implicated cognitive flexibility deficits in schizophrenia as well as differing brain activation when performing cognitive flexibility tasks. However, little research has examined the extent to which genetic factors influence brain activation and whether this is specific to schizophrenia or may be found in other psychopathologies. Therefore, the current study used an extended pedigree design to investigate cognitive flexibility as an endophenotype of schizophrenia by investigating the genetic correlation and heritability of both behavioral performance and brain activation. To the best of our knowledge, the genetic correlation of schizophrenia and brain activation during a cognitive flexibility task or the heritability of this brain activation has not been assessed; this may be crucial to identifying an endophenotype that may be closer to the genetic influence than broad diagnostic criteria or behavioral performance. We sought to answer the following questions:

1. Do schizophrenia patients show deficits in cognitive flexibility (for both in and out of scanner tasks) compared to healthy controls? Importantly, do schizophrenia patients perform significantly worse than individuals with depression?
2. While completing a task of cognitive flexibility, do patients with schizophrenia show different activation compared to healthy controls during cognitive flexibility performance? Do schizophrenic patients show different activation compared to depressed individuals?
3. How heritable is performance of cognitive flexibility (both in and out of the scanner)?
4. How heritable is brain activation during a cognitive flexibility task?
5. To what extent do shared genetic effects contribute to both schizophrenia and cognitive flexibility performance (in and out of the scanner)? Between depression and cognitive flexibility performance (in and out of the scanner)?
6. To what extent do shared genetic effects contribute to both schizophrenia and brain activation during a cognitive flexibility task? Between depression and brain activation during a cognitive flexibility task?
7. Is cognitive flexibility performance in the scanner correlated with cognitive flexibility performance out of the scanner? Is cognitive flexibility performance correlated with activation?

2.0 Methods

2.1 Subjects and Procedures

Participants in this project were drawn from an initial sample, the Multiplex Genetic Investigation (MGI 1) study of schizophrenia, and from a second round of data collection (MGI 2) several years later that included neuroimaging. Families recruited for MGI 1 and 2 were multiplex multigenerational families of European-American ancestry and were recruited from two sites, the University of Pittsburgh and the University of Pennsylvania. Probands with a DSM-IV diagnosis of schizophrenia were recruited and included in the study if they met the following inclusion criteria: a first degree relative with schizophrenia or schizoaffective depressive disorder; ability to provide informed consent/assent; permission to contact 10 or more first through fourth degree family members; and English proficiency. Exclusion criteria included: significant medical or neurological disorders associated with psychosis; and intellectual disability or gross neuroanatomic abnormalities. All available first through fourth degree relatives were asked to participate in the study and undergo the same diagnostic and testing procedures as initial probands. Those who participated in both MGI 1 and MGI 2 were diagnostically reevaluated at the second time point.

Unrelated community controls were recruited from geographic locations close to schizophrenia probands and their families and were attempted to be matched to the proband relatives on age and sex. Community controls had the following additional exclusionary criteria: any psychotic disorder in themselves or a first-degree family member; taking any antipsychotic medications; a psychiatric hospitalization or psychiatric medication dose increase in the past month; or received treatment in the past six months with electroconvulsive therapy or for substance abuse. Community controls were not excluded for other psychiatric diagnoses, as proband family members were not excluded on these criteria. All subjects provided consent or assent with parental approval for participants under the age of 18.

For recruitment during MGI 2, additional exclusionary criteria were added concerning MRI scanning (metallic inserts, poor vision, pregnancy, orthopedic circumstances).

2.2 Clinical Assessment

All participants in this study completed the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), which provided diagnostic information and was conducted by trained interviewers. DSM-IV diagnoses were confirmed in a consensus meeting between two investigators who reviewed the assessment files to determine a final diagnosis. Additionally, one member of each family completed the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) to provide the pedigree information. If available, medical records were requested and all participants provided information on current medications.

Positive and negative symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Norman, Malla, Cortese, & Diaz, 1996) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982). The SAPS assessed hallucinations, delusions, bizarre behavior, and positive formal thought disorder using 30 items. The SANS assessed affective flattening/blunting, alogia, avolition/apathy, anhedonia/asociality, and attention using 20 items. Items on both the SAPS and SANS are rated on a 6-point Likert scale from 0-5, where 0 represents no symptoms and 5 represents extreme impairment.

New participants for the MRI study also completed these assessments upon enrollment. Initial participants who returned for the MRI study were assessed for any change in diagnostic status but did not repeat additional clinical assessment measures.

2.3 Penn Conditional Exclusion Test: Out of Scanner Task

Participants were asked to complete a 1-hour Computerized Neurocognitive Battery (CNB) that contained eight tasks measuring: cognitive flexibility, attention, verbal memory, face memory, spatial memory, spatial processing, sensory-motor dexterity, and emotion processing. (R. C. Gur, Ragland, Moberg, Bilker, et al., 2001; R. C. Gur, Ragland, Moberg, Turner, et al., 2001; R. C. Gur et al., 2012; R. C. Gur et al., 2010; Moore, Reise, Gur, Hakonarson, & Gur, 2015). The cognitive flexibility task, the Penn Conditional Exclusion Test (PCET) in the MGI 2 sample is the focus of the current study and has been validated across the different form types, which use different stimuli, and in schizophrenia patients (Kurtz, Ragland, et al., 2004; Kurtz, Wexler, et al., 2004). The PCET has been found to be highly correlated with other tests of cognitive flexibility (r=.77) (Kurtz, Ragland, et al., 2004).

During this task, four shapes appear on the screen and participants are asked to select the shape that does not belong. The shapes can differ on the following categories: shape, size, and thickness of outline. The first rule to be inferred is to select the shape that is different from the others; the second rule is to select the size that is different from the others; the third rule is to select the width of outline that is different. Participants receive feedback after their selection as to whether they answered correctly or incorrectly. When they successfully select the correct response based on the current rule 10 times in a row, the test moves on to the next rule without informing the participant of the change. After 40 incorrect responses, or correct selection of each rule 10 times in a row, the test ends. Accuracy is calculated by multiplying the ratio of correct to incorrect responses by the number of categories achieved. Cognitive performance efficiency scores were computed by averaging a participant's accuracy and reaction time z-scores (reaction time was subtracted from accuracy as lower z-scores reflect better performance) (standardized based on the total sample) to give a single cognitive performance measure that equally reflects a participant's accuracy and reaction time.

2.4 Penn Conditional Exclusion Test: In Scanner Task

After completing the CNB out of the scanner (typically several hours to a day earlier), participants completed an adapted version of the PCET inside the MRI scanner (along with other adapted tasks from the CNB). The fMRI version of this task has been shown to activate brain regions that we would expect during a cognitive flexibility task (Roalf et al., 2014). As in the out of scanner PCET, participants see four shapes appear on the screen and are asked to choose the shape that does not belong. Feedback is provided as to whether or not they chose correctly. There are 6 total trial blocks that contain 8 trials each. Each trial is presented for 5 seconds. Trial blocks are separated by an 18 second fixation point. One sorting criterion applies to all trials in a block and continues until the end of the block regardless of how the participant responds. Each of the three sorting criteria appear twice in a pseudorandom order across all blocks and is fixed across subjects. The total runtime for the task is 6 minutes and 54 seconds. Accuracy is calculated as the total percentage of correct responses over all 48 trials. Individuals who responded to less than 75% of trials were excluded from analyses. An efficiency score for cognitive performance within the scanner was computed in the same way as the measure for out of scanner performance (described above).

2.5 Functional MRI Procedures and Data Collection

Prior to beginning the fMRI, participants practiced the task to become familiar with timing and using the response device, which was a scroll wheel fiber-optic response panel (FORP; Current Designs, Inc., Philadelphia, PA) that allowed subjects to scroll through potential responses and make selections. In addition, all participants wore earplugs to minimize scanner noise. Participants viewed the task through a mirror mounted on the head coil that allowed them to see the task that was rear-projected using a PowerLite 7300 video projector (Epson America, Inc.; Long Beach, CA). Respiratory and cardiac activity were also monitored throughout the task.

The functional scan was a BOLD (blood oxygen level dependent) scan with single-shot gradient-echo (GE) echo-planar (EPI) sequence acquired on Siemens Tim Trio 3T scanners (Erlangen, Germany) using an 8-channel head coil. The following parameters were in place for the scan: repetition time/echo time=3000/35 msec; field of view=220x220mm; matrix=64x64; flip angle=70 degrees; slice thickness/gap=3/0 mm; 40 slices; and effective voxel resolution of 3.44x3.44x3.0 mm.

Before task collection, a 5-minute magnetization-prepared rapid acquisition gradient echo T1-weighted (MPRAGE) image was acquired. The following acquisition parameters were in place for the MPRAGE: repetition time/echo time=1680/4.67msec, field of view=180x240mm, matric 192x256; flip angle=15 degrees, effective voxel resolution=0.96x0.96x1mm. The structural MPRAGE scan was acquired to aid spatial normalization to a standard space. Scanner equipment and procedures at both Pitt and Penn were identical and were found to have inter-site reliability (Roalf et al., 2014).

2.6 fMRI Preprocessing

All fMRI data preprocessing and analyses were completed using FSL 6.0.3 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). A study specific standardized template was created using a subset of participants to address differences between our study sample (older and with substantial psychiatric diagnoses) and the participants used for the MNI-152 template (younger and with no psychiatric diagnoses), to improve registration (Fillmore, Phillips-Meek, & Richards, 2015; Huang et al., 2010). First, non-brain areas were removed using BET (brain extraction tool, Smith, 2002). Next, scans were identified as usable for the study specific template if their T1-weighted scan was free from artifacts, by consensus of three independent raters (Rosen et al., 2018). These scans were then registered to the MNI-152 template using FLIRT (FMRIB's Linear Image Registration Tool) (Greve & Fischl, 2009; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) with a 12 degrees of freedom affine transformation and all registrations were visually inspected. Next, the study specific template was created by averaging the registered scans. Within FSL, FEAT (fMRI Expert Analysis Tool) Version 6.00 was used. All images were motion corrected using MCFLIRT (Jenkinson et al., 2002), where all volumes were matched with the middle volume of a run, using a tri-linear interpolation with 6 degrees of freedom. Additionally, preprocessing included a high pass filter (100s), spatial smoothing (6mm FWHM), and scaling using mean-based intensity normalization. During the preprocessing stages, non-brain areas were removed using BET (Smith, 2002). All functional scans were registered to the study specific standardized template and all registrations were visually inspected. Whole brain activation results were generated for each participant using FILM (FMRIB's Improved General Linear Model) (Woolrich, Ripley, Brady, & Smith, 2001). Participant-level task activation was modeled in the general linear model, considering the hemodynamic response and its temporal derivative. Output of participant-level analysis was a contrast image revealing task activation averaged across all trial blocks relative to the average of all inter-block fixation. Due to the use of a block design, only the effects of task activation compared to fixation could be examined and the contributions of other cognitive functions (such as attention) could not be distinguished.

2.7 Brain Activation Regions of Interest

ROI selection used a joint anatomical and functional approach. First, based on previous research on cognitive flexibility as described in the introduction, three a priori anatomical regions were selected within the Harvard-Oxford Structural Atlas (HOSA): the frontal pole, anterior cingulate gyrus, and middle frontal gyrus. A group level functional activation map from a subset of the control subjects in this study was created to identify functional areas that were active during the PCET compared to baseline (following methods from Roalf et al., 2014). The resulting functional activation map included control participants contrast maps from their lower level analysis, which were entered into the group-level analysis to locate regions with significant activation across all included participants (Figure 1), with a corrected significance threshold of p=0.0001 (Worsley, 2001). Overlap between this group-level functional activation

map and each a priori HOSA anatomical region was identified (Figure 2) and only functionally active regions within each of the anatomical regions was used as an ROI (Figure 3) in the following analyses. For each subject, the signal intensity averaged across all voxels within each ROI was used for analysis with resulting contrast parameter estimates converted to percent signal change. Masks were created for both left and right hemispheres and were analyzed separately if their Pearson correlation was less than 0.75 but were combined to create a bilateral mask if their correlation was greater than 0.75.

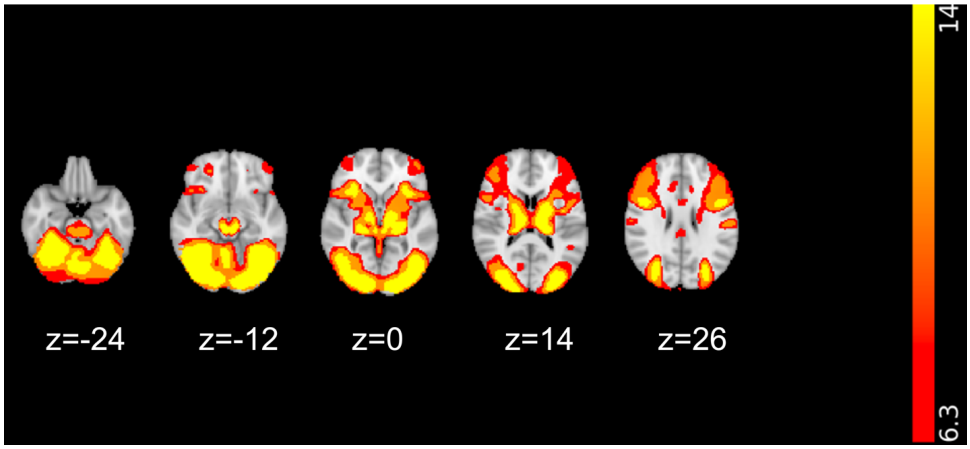

Figure 1: Group Level Activation Map in Controls

Whole brain task activation for task compared to fixation-baseline for the Penn Conditional Exclusion Task in controls. This image is presented in radiologic standard, with the right hemisphere on the left side of the image and the left hemisphere on the right side of the image.

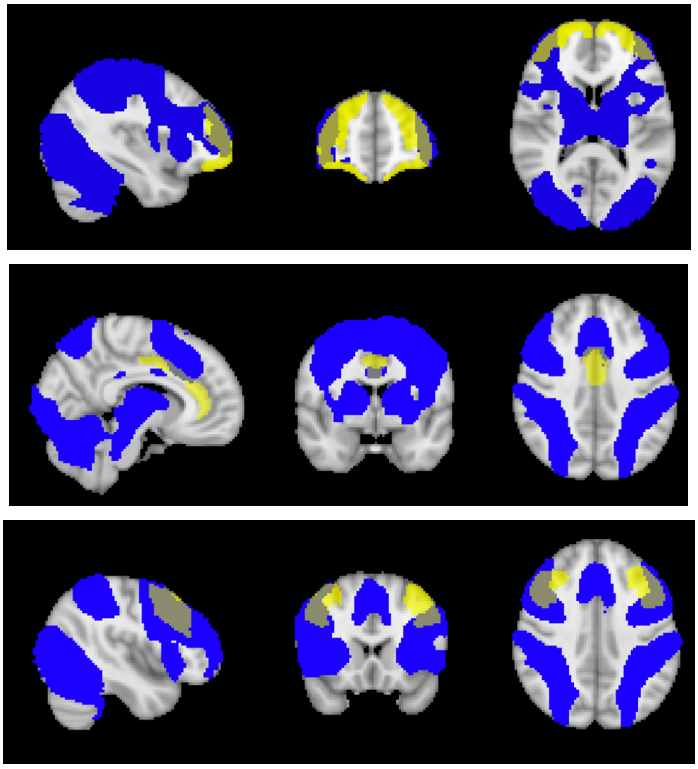

Figure 2: Overlay of Functional Activation Map from Controls with Anatomical Regions of Interest

These images are presented in radiologic standard, with the right hemisphere on the left side of the image and the left hemisphere on the right side of the image.

Each image shows the functional brain activation map from Figure 1 in blue overlaid with a Harvard Oxford Atlas anatomical region in yellow; overlap between the two are shown in a dull yellow-grey.

Top row: Frontal pole [x, y, z :-36, 52, 12]
Middle row: Anterior cingulate gyrus [x, y, z: 8, 0, 38]
Bottom row: Middle frontal gyrus [x, y, z: 43, 18, 38]

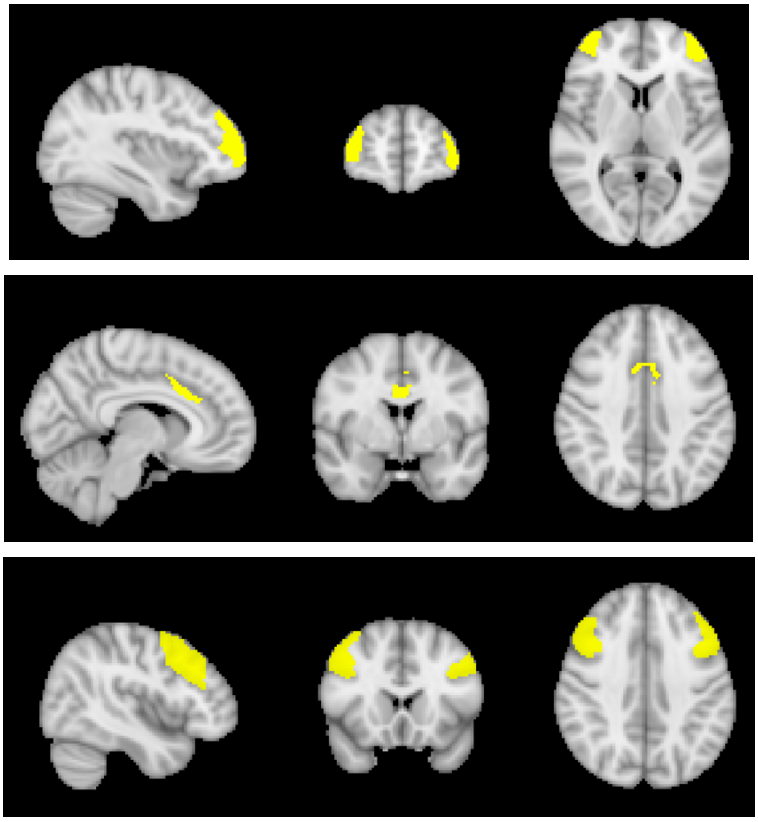

Figure 3: Final Regions of Interest

These images are presented in radiologic standard, with the right hemisphere on the left side of the image and the left hemisphere on the right side of the image.

Each region of interest was created from the overlap between the functional activation map (from Figure 1) and the Harvard Oxford anatomical region shown in Figure 2.

Top row: Frontal pole [x, y, z :-36, 52, 12]
Middle row: Anterior cingulate gyrus [x, y, z: 8, 0, 38]
Bottom row: Middle frontal gyrus [x, y, z: 43, 18, 38]

3.0 Results

3.1 Overall Sample

Initial recruitment for the MGI 1 study included 645 pedigree members (43 families ranging from 2-71 members) and 220 unrelated controls. As noted above, a second round of data collection (MGI 2) occurred two years later in which an additional 113 new pedigree members from 28 of the initial families, 31 pedigree members from 9 new families, and 297 new controls consented to participate. The combined total sample for this study includes 1306 participants (789 pedigree members and 517 unrelated controls).

During the second round of data collection that included cognitive and neuroimaging measures, participants from the initial sample were also asked to participate again. From the initial sample, 165 pedigree members from 28 families and 28 controls consented to participate again. These, plus the new participants (144 pedigree and 297 controls), yielded a total of 634 participants (309 pedigree members and 325 controls) who consented to participate in the second round of data collection, MGI 2.

Of the 634 participants in MGI 2, 538 (245 pedigree members and 293 controls) completed both the out of scanner cognitive flexibility task and the in scanner cognitive flexibility task. Fifteen participants (schizophrenia (SC)=5, relatives (REL)=6, controls (CTL)=4) were excluded from data analysis for not completing both tasks with valid data. In addition, one participant (REL) was excluded for having invalid behavioral data for the out of scanner task and one participant (SC) was excluded for not responding at least 75% of the time during the in scanner cognitive flexibility task. With these exclusions, the final cognitive assessment sample with both adequate in and out of scanner cognitive flexibility performance was 521 participants (SC=30, REL=202, CTL=289) (Figure 4).

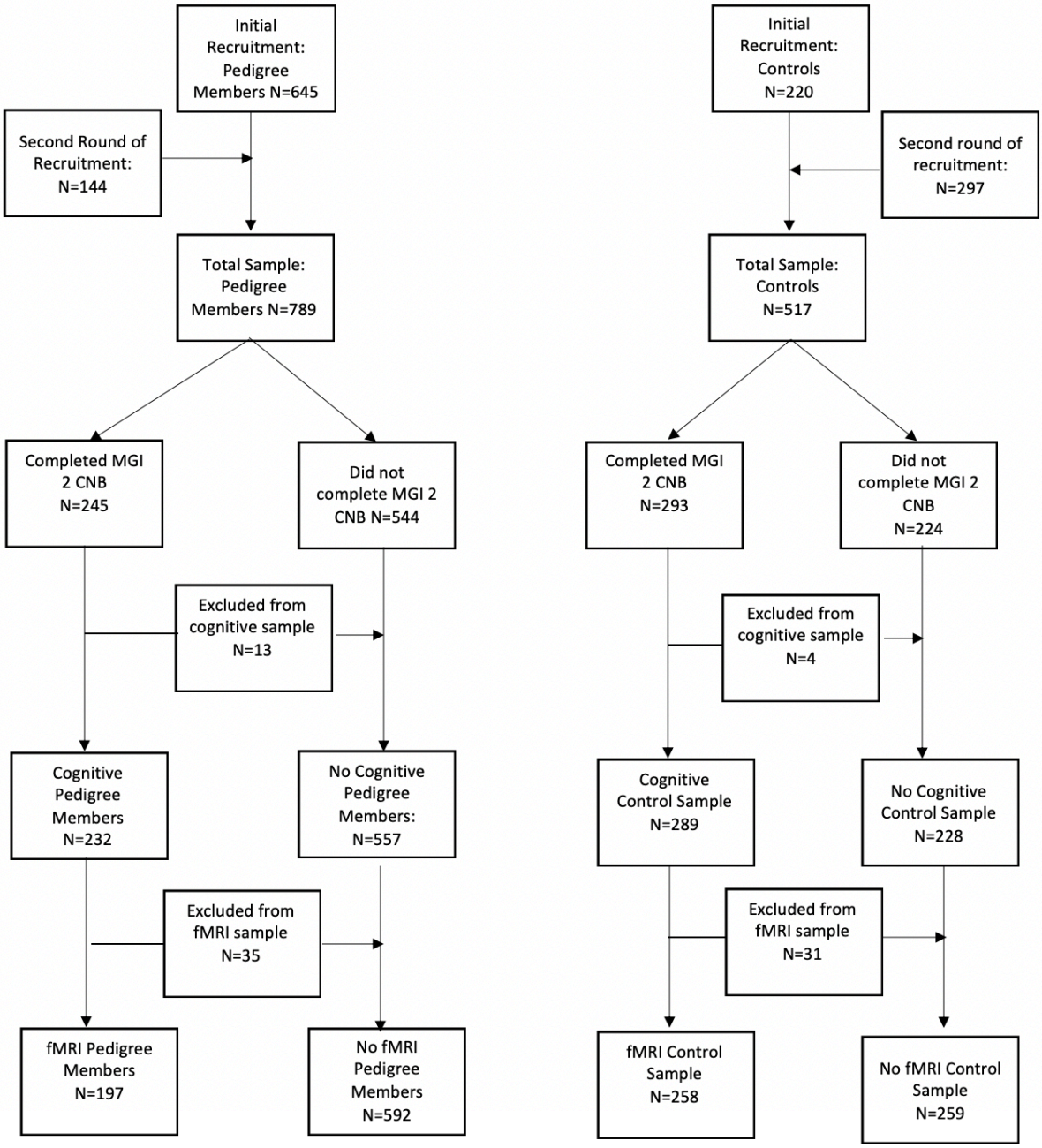

Figure 4: Data Collection Flow Chart

3.2 Demographic and Clinical Characteristics

Participants in the schizophrenia group with cognitive data either had a diagnosis of schizophrenia (N=28) or schizoaffective disorder (N=2). Secondary diagnoses for the schizophrenia group are presented in Table 1. Of the 30 participants in the schizophrenia group, nine had a comorbid diagnosis; three with major depressive disorder and six with a substance use disorder.

Table 1: Comorbid Diagnoses in the Schizophrenia Group with Cognitive Data

	Schizophrenia
Total	**30**
Major Depressive Disorder	**3**
Substance Use	**6**
Alcohol	(2)
Cannabis	(2)
Polysubstance	(1)
Unspecified Substance	(1)
No comorbid diagnosis	**21**

This sample includes 30 patients with a diagnosis of schizophrenia (N=28) or schizoaffective disorder (N=2) who completed both the in scanner and out of scanner cognitive flexibility task. Each cell represents the number of individuals with a secondary diagnosis in that category.

Diagnostic information for all participants with cognitive data is presented in Table 2. In total, 97 relatives and 85 controls had a diagnosis with the two most common for both groups being depressive and substance use disorders. For the purposes of later analyses, participants in the non-schizophrenia relatives and control groups were assigned to one of three mutually exclusive diagnostic categories: Major Depressive Disorder (MDD, REL=36, CTL=33), Other Diagnosis, which includes all non MDD diagnoses, (OTH, REL=61, CTL=52), and No Diagnosis (ND, REL=105, CTL=204). Individuals with depressive disorder not otherwise specified or major depressive disorder with psychotic features were included in the Other Diagnosis category.

Table 2: Diagnoses in Relatives and Controls with Cognitive Data

	Relatives	Controls
Total	**232**	**289**
Schizophrenia	**30**	**0**
Major Depressive Disorder	**36**	**33**
Other Diagnoses	**61**	**52**
Depressive Disorder NOS	(11)	(8)
Bipolar Disorder	(3)	(0)
Mood Disorder NOS	(2)	(1)
Alcohol	(15)	(20)
Cannabis	(7)	(9)
Cocaine	(1)	(2)
Opioid	(3)	(0)
Polysubstance	(1)	(1)
Hallucinogen	(0)	(1)
Anxiety Disorder	(1)	(4)
Brief Psychotic Disorder	(1)	(0)
Paranoia-delusional disorder	(1)	(0)
Schizotypal Personality	(1)	(0)
Unspecified Psychosis	(1)	(0)
ADHD	(4)	(0)
Adjustment Disorder	(3)	(1)
Bereavement	(2)	(0)
Asperger's	(1)	(0)
Intermittent Explosive Disorder	(1)	(0)
Delusional Disorder	(1)	(0)
Observation of other Mental condition	(1)	(2)
Eating Disorder	(0)	(1)
Reading Disorder	(0)	(2)
No Diagnosis	**105**	**204**

Sample includes 202 relatives and 289 controls who completed both the in scanner and out of scanner cognitive flexibility task. Each cell represents the number of relatives or controls who have a specific diagnosis as their primary diagnosis. Major depressive disorder (MDD) is placed higher in the diagnostic hierarchy, where individuals with MDD could have secondary diagnoses but individuals with other diagnoses could not have MDD as a secondary diagnosis.

Demographic information for all participants with cognitive data is shown in Table 3. There were no significant differences among groups for recruitment site or handedness. However, there were overall significant group differences in sex, age, education, and parental education. Post-hoc tests indicated that patients were more likely to be

male and were significantly older than both relatives and controls. Both patients and relatives had significantly fewer years of education and parental education than controls.

Table 3: Demographic Characteristics for Participants with Cognitive Data

	Schizophrenia	Relatives	Controls	F/X^2	df	p
Total N	30	202	289			
Site (%Pitt)	50.0%[a]	53.0%[a]	52.6%[a]	.09	2	0.95
Sex (%Male)	70.0%[b]	49.5%[a]	45.7%[a]	6.56	2	0.04
Handedness (%Right)	83.3%[a]	89.1%[a]	88.6%[a]	3.08	2	0.65
Age (Mean, SD)	51.30 (9.93)[b]	43.33 (18.07)[a]	40.26 (16.07)[a]	6.95	2, 518	0.001
Education (Mean, SD)	13.00 (1.91)[a]	13.70 (2.66)[a]	15.23 (2.36)[b]	28.99	2, 518	<.001
Parental Education* (Mean, SD)	12.52 (2.95)[a]	12.34 (2.91)[a]	13.75 (2.66)[b]	15.92	2, 516	<.001
Intracranial Volume*	1542434[a]	1545435[a]	1551048[a]	0.11	2,448	0.89
SANS^ (Mean, SD)*	1.27 (0.93)	NA	NA	-		
SAPS^ (Mean, SD)*	0.85 (0.64)	NA	NA	-		
CPZ Equivalent, mg (Mean, SD)	810.08 (1085.04)	NA	NA	-		

Sample includes 521 participants who completed both the in scanner and out of scanner cognitive flexibility tasks. Results for age, education (self), and education (parental) are reported with ANOVAs and results for site, sex, and handedness are reported with chi-square tests. Post-hoc independent two sample t-tests were conducted to compare differences between groups. Values that share the same superscript were not significantly different from each other (p≥.05).

^Abbreviations: SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Postive Symptoms; CPZ: Chlorpromazine

***Two participants were missing parental education. Six controls and 2 relatives were missing intracranial volume. 8 schizophrenia patients were missing SANS and SAPS; 5 schizophrenia patients were missing CPZ equivalent.**

Schizophrenia patients had average SANS scores of 1.27 (SD=0.93) and SAPS scores of 0.85 (SD=0.64) on a Likert scale from 0-5, with higher scores indicating more severe symptoms. These scores indicate mild symptom severity for both negative and positive symptoms, which is expected as this is an outpatient patient sample. The schizophrenia patients who had medication data available (n=23) were prescribed the equivalent of 810.08 mg of chlorpromazine on average (SD=1085.04, range 0-5,000) (Woods, 2003), with 3 patients not being prescribed any anti-psychotic medication at the time of data collection.

The remaining 557 pedigree members and 228 controls who either did not complete or had poor quality cognitive assessments provided diagnostic and demographic information that were included in SOLAR analyses to improve estimation of heritabilities and genetic correlations between diagnostic groups and cognitive assessments (Table 4).

Table 4: Family Members and Controls with Diagnosis and Demographics but without MGI2 Cognitive Data

	Family Members	Controls
Total N	557	228
Schizophrenia (N)	89	0
Major Depressive Disorder (N)	98	29
Other Diagnosis (N)	150	23
No Diagnosis	220	176
Site (%Pitt)	56.7%	59.2%
Sex (%Male)	46.6%	46.5%
Handedness (%Right)	87.7%	88.4%
Age (Mean, SD)	46.10 (18.32)	44.39 (18.77)
Education (Mean, SD)	13.02 (2.98)	14.99 (2.48)
Parental Education (Mean, SD)	11.73 (3.25)	12.66 (2.99)

This sample includes 557 family members and 228 controls who do not have MGI 2 cognitive data who are included in analyses to improve calculations of genetic correlations.
Of the family members, 3 are missing sex, 38 are missing handedness, 2 are missing education, and 80 are missing parental education.
Of the controls, 116 are missing handedness and 88 are missing education and parental education.

Participants from the cognitive assessment sample whose fMRI data were excluded due to quality control are shown in Table 5. Functional imaging quality control measures were: temporal signal to noise ratio, relative motion displacement, signal drift over time, and voxel intensity outliers (Roalf et al., 2016; Roalf et al., 2014). Participants were excluded if the fMRI sequence was not completed (N=22), they were over 75 years old (N=11), or had quality control measures more than 2.5 standard deviations from the mean (N=33). With these exclusions, the final sample with acceptable fMRI measures (as well as both in and out of scanner cognitive performance) was 455 participants (SC=27, REL=170, CTL=258).

Table 5: fMRI Exclusions

			fMRI QC (+/- 2.5 S.D.)						
	Scan incomplete	Over 75	Low SNR	High Motion	High Drift	High Outcount	Excluded N	Final N	Original N
All	22	11	4	10	6	13	66	455	521
SC	1	0	0	2	0	0	3	27	30
REL	8	7	1	4	4	8	32	170	202
CTL	13	4	3	4	2	5	31	258	289

SNR= signal to noise ratio; SNR Mean (SD): 59.77 (16.38); SNR 2.5 SD Cutoff: 18.82
Motion Mean (SD): 0.10 (0.09); Motion 2.5 SD Cutoff: 0.325
Drift Mean (SD): 0.005 (0.004); Drift 2.5 SD Cutoff: -0.005; 0.015
Outcount Mean (SD): 6.57 (8.79); Outcount 2.5 SD Cutoff: 28.545

Demographic differences between participants who were included versus excluded based on fMRI are shown in Supplemental Table 1. Excluded participants did not differ from included participants based on site, sex, handedness, education or parental education, but as expected, were significantly older and had significantly lower cognitive performance both in and out of scanner. Supplemental Table 2 describes the fMRI groups' demographics. As above, the remaining 592 pedigree members and 259 controls who did not have adequate fMRI data provided diagnostic and demographic information that were also included in the SOLAR fMRI analyses to improve estimation of heritabilities and genetic correlations between diagnostic groups and imaging measures. Demographic differences between these additional participants (35 relatives and 31 controls) and those in the initial non-cognitive diagnostic sample are shown in Supplemental Table 3. The additional participants did not differ from initial participants based on sex, handedness, age, or parental education, although the additional participants had significantly fewer from Pitt and had fewer years of education (Supplemental Table 3).

3.3 Data Characterization

Cognitive performance efficiency scores for both out and in scanner performance were examined for outliers in the total sample and all values were within 3 standard deviations of the mean. Efficiency score distributions in the total sample were also assessed for skewness (-0.31 and -0.55, out and in scanner respectively) and kurtosis (-0.85 and -0.53, out and in scanner respectively) and were within acceptable limits.

Pearson correlations between left and right hemisphere ROIs were high for the anterior cingulate gyrus (.80, CI: 0.76-0.83), but more moderate for the frontal pole (0.56, CI: 0.49-0.62) and middle frontal gyrus (0.67, CI: 0.61-0.71). Therefore, all subsequent analyses will include a bilateral ROI for the anterior cingulate gyrus and left and right hemisphere ROIs for the frontal pole and middle frontal gyrus. Percent activation change for all five ROIs was assessed for skewness (FP right 0.61; FP left 0.39; ACG 0.41, MFG right 0.23, and MFG left 0.57) and kurtosis (FP right 0.17; FP left 1.19; ACG 1.08; MFG right 0.12; MFG left 1.06) and were all within acceptable limits (Lei & Lomax, 2005; West, Finch, & Curran, 1995).

3.4 Correlations with Demographics: Covariates

Phenotypic correlations between task performance and activation and demographic variables in the total sample are presented in Table 6. Age, education, and parental education were all significantly correlated with both out and in scanner tasks, with higher efficiency scores associated with younger age, more years of education and parental education. Additionally, for the out of scanner task, females had significantly higher efficiency scores and for the in-scanner task, larger intracranial volume was significantly associated with higher efficiency scores. Site, handedness, depression, other diagnosis, SAPS, SANS, and chlorpromazine equivalent dosage were not significantly correlated with either in or out of scanner performance.

Table 6: Phenotypic Correlations with Demographics

	PCET Efficiency	fPCET Efficiency	Frontal Pole Right	Frontal Pole Left	Anterior Cingulate Gyrus	Middle Frontal Gyrus Right	Middle Frontal Gyrus Left
Site	-0.02	0.06	0.03	-0.32	-0.003	-0.02	-0.04
Sex	0.13^{**}	0.05	-0.16^{**}	-0.11	-0.10	-0.10	-0.11^{*}
Handedness	-0.08	-0.04	-0.03	-0.03	0.12	-0.04	-0.02
Age	-0.46^{***}	-0.57^{***}	0.23^{***}	0.18^{***}	0.23^{***}	0.33^{***}	0.30^{***}
Education	0.10^{*}	0.18^{***}	-0.16^{**}	-0.04	-0.10	-0.11^{*}	0.001
Parental Education	0.27^{***}	0.38^{***}	-0.21^{***}	-0.16^{**}	-0.10^{*}	-0.21^{***}	-0.13^{**}
MDD	0.03	0.13	0.03	-0.005	0.07	-0.07	-0.07
Other diagnosis	-0.04	-0.10	0.03	-0.08	-0.09	0.08	0.002
Intracranial Volume	0.06	0.11^{*}	-0.04	-0.03	0.005	-0.06	-0.07
SAPS[#^]	-0.21	0.14	-0.48	-0.48	-0.08	-0.07	0.04
SANS[#^]	0.07	-0.19	0.34	-0.03	0.21^{**}	0.44^{**}	0.28
CPZ[#^]	-0.02	0.37	-0.06	0.02	0.12	0.13	0.31

All correlations except parental education use the entire sample of 521 individuals. Two participants (CTLs) were missing parental education.
PCET=Penn Conditional Exclusion Test out of scanner; fPCET= functional Penn Conditional Exclusion Test in scanner
Phenotypic correlations were conducted in SOLAR and used the t-distribution. No covariates were included. Categorical demographic variables were coded as follows: Site: Pitt=0, Penn=1; Sex: Male=1, Female=2; Handedness: Right=1; Other=2; Depression: No=0; Yes=1; Other diagnosis: No=0; Yes=1.
*p<.05; **p<.01; ***p<.001
[#]SAPS, SANS, and CPZ correlations were calculated within the schizophrenia participants only.
^Abbreviations: SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Postive Symptoms; CPZ: Chlorpromazine

Age and parental education were significantly correlated with activation for all five ROIs, with higher activation associated with older age and fewer years of parental education. Additionally, sex and personal education were significantly correlated with activation for the right frontal pole, with higher activation associated with being male and fewer years of personal education; higher activation was also associated with being male for the left middle frontal gyrus. SANS score was significantly positively correlated with activation in the anterior cingulate gyrus and right middle frontal gyrus, with higher activation associated with higher symptom score. Site, handedness, depression, other diagnosis, intracranial volume, SAPS, and chlorpromazine equivalent were not significantly correlated with any of the ROI activations.

The following analyses were first conducted using a set of basic covariates (sex, age, and age squared) that, although significantly correlated with a diagnosis of schizophrenia and with the outcome measures, are unlikely to contribute to the cause of schizophrenia. Basic covariates for the fMRI analyses additionally included site. Analyses were repeated using a second set of conservative covariates (sex, age, age squared, education) that were all significantly correlated both with schizophrenia and the outcome measures, but included education which may be causally related to schizophrenia. Conservative covariates for the fMRI analyses additionally included site.

The false discovery rate (FDR) method of Benjamini and Hochberg (1995) was used to adjust for multiple comparisons with the five ROIs or two performance measures, and only results that remain significant after correction will be interpreted.

3.5 Diagnostic Differences

Table 7 presents out and in scanner cognitive performance and fMRI measures for individuals with schizophrenia, depression, and controls without depression. ANCOVAs indicated significant group differences for both cognitive performance measures using both sets of covariates with schizophrenia patients performing significantly worse on both tasks compared to the depressed and control groups, who did not differ significantly. For the brain activation measures, there were no significant group differences after FDR correction.

Table 7: Diagnostic Differences in Cognitive Flexibility Performance and Brain Activation

				Basic Covariates			Conservative Covariates		
	Schizophrenia	Depression	Controls	F	df	p	F	df	p
Total N	30	69	256						
PCET Efficiency	-1.38 (0.71)[b]	-0.12 (0.78)[a]	0.00 (0.85)[a]	38.93	5,349	<.001	32.67	6,348	<.001
fPCET Efficiency	-1.39 (0.50)[b]	0.02 (0.91)[a]	-0.03 (0.93)[a]	63.18	5,349	<.001	58.21	6,348	<.001
Frontal Pole Right	0.47 (0.41)[a]	0.45 (0.33)[a]	0.42 (0.37)[a]	0.42	6,310	0.66	0.43	7,309	0.65
Frontal Pole Left	0.48 (0.47)[a]	0.41 (0.35)[a]	0.38 (0.36)[a]	1.07	6,310	0.34	1.07	7,309	0.34
Anterior Cingulate Gyrus	0.26 (0.27)[a]	0.21 (0.18)[a]	0.17 (0.19)[a]	3.32	6,310	0.03	3.36	7,309	0.04
Middle Frontal Gyrus Right	0.56 (0.36)[a]	0.47 (0.26)[a]	0.50 (0.34)[a]	0.71	6,310	0.50	0.72	7,309	0.48
Middle Frontal Gyrus Left	0.55 (0.42)[a]	0.44 (0.29)[a]	0.46 (0.29)[a]	1.50	6,310	0.22	1.51	7,309	0.22

Cognitive sample includes 355 individuals who completed the cognitive performance tasks and had a diagnosis of schizophrenia, depression, or were controls without depression. Basic covariates included sex, age, age squared. Conservative covariates additionally included education
fMRI sample includes 27 patients, 63 depressed, and 227 controls. Basic covariates included sex, age, age squared, and site. Conservative covariates additionally included education
ANCOVAs were conducted in R. Post-hoc ANCOVAs were conducted to compare differences between groups that included basic covariates. Results for post-hoc ANCOVAs between groups did not differ when using conservative covariates.
Values that are significant after controlling for false discovery rate based on Benjamini and Hochberg 1995 are indicated with different superscripts. For performance measures, FDR correction included 2 tests each for basic and conservative covariates. For ROIs, FDR correction included 5 tests each for basic and conservative covariates.

3.6 Heritabilities

Quantitative genetic analyses were conducted using the Sequential Oligogenic Linkage Analysis Routines – Eclipse (SOLAR-Eclipse) programs (Almasy & Blangero, 1998), which uses maximum-likelihood estimation for parameter estimates and likelihood-ratio tests to determine the significance of these parameters. In this study, SOLAR-Eclipse uses genetic relationships between 1st-4th degree family members to estimate heritabilities of the outcome measures and phenotypic, genetic, and environmental correlations between outcome measures and diagnosis.

Table 8 presents the heritabilities for out and in scanner performance and fMRI ROIs. Both performance measures showed moderate and significant heritabilities (range .27 to .50) with both sets of covariates. In contrast to the performance measures, there were no significant heritabilities for ROI activations after FDR correction.

3.7 Phenotypic Correlations Between Schizophrenia and Cognitive Performance and fMRI ROIs

As expected, based on the diagnostic comparisons, schizophrenia was robustly and significantly correlated with lower cognitive performance both out and in scanner with both sets of covariates (range -.46 to -.57) (Table 8). In contrast, there were no significant phenotypic correlations between schizophrenia and any of the ROI activation measures after FDR correction.

3.8 Genetic Correlations Between Schizophrenia and Cognitive Performance and fMRI ROIs

Shared genetic effects significantly accounted for covariance between schizophrenia and lower out and in scanner cognitive performance with both sets of covariates (R_g range -0.48 to -0.65) (Table 8). Again, in contrast, there were no significant genetic correlations between schizophrenia and any of the ROI activation measures after FDR correction. The genetic correlations between schizophrenia and the left frontal pole were estimated at the upper limit (R_g=1.00) using both sets of covariates and although nominally significant, they did not survive FDR correction. This relatively low significance level is likely explained by the low heritability and low phenotypic correlations, which affect the significance of the genetic correlation.

Table 8: Heritabilities and Correlations with Schizophrenia

	h^2 (p)	R_p (p)	R_g (p)	R_e (p)
PCET Efficiency				
Basic covariates	0.30 (0.003)*	-0.50 ($1.24x10^{-24}$)*	-0.65 (0.005)*	-0.90 (0.07)
Conservative covariates	0.27 (0.007)*	-0.46 ($1.58x10^{-08}$)*	-0.57 (0.002)*	-0.90 (0.01)*
fPCET Efficiency				
Basic covariates	0.50 (0.000005)*	-0.57 ($2.87x10^{-12}$)*	-0.56 (0.000002)*	-0.90 (0.04)
Conservative covariates	0.47 (0.00004)*	-0.50 ($1.30x10^{-09}$)*	-0.48 (0.0007)*	-0.90 (0.06)
Frontal Pole Right				
Basic Covariates	0.36 (0.05)	-0.03 (0.76)	0.30 (0.30)	-1.00 (0.18)
Conservative Covariates	0.33 (0.09)	-0.09 (0.39)	0.10 (0.74)	-1.00 (0.33)
Frontal Pole Left				
Basic Covariates	0.04 (0.42)	0.07 (0.50)	1.00 (0.01)	-1.00 (0.04)
Conservative Covariates	0.04 (0.43)	0.07 (0.50)	1.00 (0.02)	-1.00 (0.06)
Anterior Cingulate Gyrus				
Basic Covariates	0.10 (0.10)	0.10 (0.32)	0.39 (0.19)	-0.44 (0.43)
Conservative Covariates	0.10 (0.08)	0.06 (0.55)	0.33 (0.26)	-0.58 (0.33)
Middle Frontal Gyrus Right				
Basic Covariates	0.10 (0.50)	-0.02 (0.89)	0.90 (0.25)	-0.89 (0.26)
Conservative Covariates	0.10 (0.50)	-0.07 (0.42)	-0.08 (1.00)	-0.46 (0.50)
Middle Frontal Gyrus Left				
Basic Covariates	0.14 (0.25)	0.04 (0.71)	0.58 (0.08)	-0.90 (0.11)
Conservative Covariates	0.16 (0.23)	0.03 (0.74)	0.46 (0.15)	-0.90 (0.18)

h^2=univariate heritability; R_g=genetic correlation between schizophrenia and cognitive performance; R_p=phenotypic correlation between schizophrenia and cognitive performance; R_e= environmental correlation between schizophrenia and cognitive performance; PCET=out of scanner; fPCET= in scanner
Demographic variables coding: Schizophrenia=1, No schizophrenia=0
All analyses were conducted in SOLAR and used the t-distribution.
Basic covariates included sex, age, and age squared (and site for ROIs). Conservative covariates additionally included education.
Basic covariates: sample included 1303 participants: 521 with cognitive performance measures and 554 family and 228 NCs without cognitive performance measures.
Conservative covariates: sample included 1213 participants: 521 with cognitive performance measures and 552 family and 140 NCs without cognitive performance measures.
Values that are significant after controlling for false discovery rate based on Benjamini and Hochberg 1995 are indicated with an asterisk (*). For performance measures, FDR correction included 2 tests each for basic and conservative covariates. For ROIs, FDR correction included 5 tests each for basic and conservative covariates.
Schizophrenia heritability: basic covariates: h^2=0.98 ($p<0.001$); conservative covariates: h^2=1.00 ($p<0.001$)

3.9 Environmental Correlations Between Schizophrenia and Cognitive Performance and fMRI ROIs

Only out scanner performance, using conservative covariates, showed significant correlated environmental effects with schizophrenia. (Table 8). There were no significant environmental correlations between schizophrenia and any of the ROI activation measures after FDR correction.

3.10 Phenotypic, Genetic, and Environmental Correlations between Depression and Cognitive Performance and fMRI ROIs

A diagnosis of depression was significantly phenotypically correlated only with in-scanner performance using the conservative covariates, such that depression was associated with higher performance (Table 9). Correlated genetic effects between depression and cognitive performance measures were not significant using either set of covariates, although correlated environmental effects with higher in-scanner performance were significant using conservative covariates. There were no significant phenotypic, genetic, or environmental correlations between depression and any of the ROI activation measures after FDR correction.

Table 9: Correlations with Major Depressive Disorder

	R_p (p)	R_g(p)	R_e(p)
PCET Efficiency			
Basic Covariates	0.01 (0.85)	-0.24 (0.47)	0.14 (0.43)
Conservative covariates	0.03 (0.67)	-0.23 (0.54)	0.15 (0.16)
fPCET Efficiency			
Basic Covariates	0.13 (0.05)	-0.21 (0.46)	0.38 (0.06)
Conservative covariates	0.16* (0.02)	-0.16 (0.62)	0.38* (0.001)
Frontal Pole Right			
Basic Covariates	0.05 (0.55)	0.69 (0.11)	-0.32 (0.20)
Conservative Covariates	0.03 (0.66)	0.84 (0.08)	-0.38 (0.13)
Frontal Pole Left			
Basic Covariates	0.03 (0.66)	0.89 (0.43)	-0.10 (0.63)
Conservative Covariates	0.03 (0.73)	0.90 (0.31)	-0.14 (0.47)
Anterior Cingulate Gyrus			
Basic Covariates	0.09 (0.23)	0.67 (0.13)	-0.15 (0.46)
Conservative Covariates	0.08 (0.30)	0.61 (0.14)	-0.16 (0.44)
Middle Frontal Gyrus Right			
Basic Covariates	-0.06 (0.48)	0.90 (0.46)	-0.20 (0.27)
Conservative Covariates	-0.07 (0.35)	1.00 (0.38)	-0.24 (0.03)
Middle Frontal Gyrus Left			
Basic Covariates	-0.07 (0.35)	0.41 (0.35)	-0.32 (0.17)
Conservative Covariates	-0.08 (0.34)	0.45 (0.30)	-0.34 (0.14)

R_g=genetic correlation between depression and cognitive performance; R_p=phenotypic correlation between depression and cognitive performance; R_e= environmental correlation between depression and cognitive performance; PCET=out of scanner; fPCET= in scanner

Demographic variables coding: Depression=1, No depression=0

All analyses were conducted in SOLAR and used the t-distribution.

Basic covariates included sex, age, and age squared (and site for ROIs). Conservative covariates additionally included education.

Basic covariates: sample included 1303 participants: 521 with cognitive performance measures and 554 family and 228 NCs without cognitive performance measures.

Conservative covariates: sample included 1213 participants: 521 with cognitive performance measures and 552 family and 140 NCs without cognitive performance measures.

Values that are significant after controlling for false discovery rate based on Benjamini and Hochberg 1995 are indicated with an asterisk (*). For performance measures, FDR correction included 2 tests each for basic and conservative covariates. For ROIs, FDR correction included 5 tests each for basic and conservative covariates.

Depression heritability: basic: h^2=0.39 (p=0.001); conservative: h^2=0.38 (p=0.002)

3.11 Correlations between Performance and Activation Measures

Out and in scanner performance were significantly phenotypically correlated in the total sample with both covariate sets (Table 10). The genetic correlations between them were also high and significant, although the environmental correlations were not.

Using the basic set of covariates, higher in scanner cognitive performance was significantly phenotypically correlated with lower activation for the right and left frontal pole and right and left middle frontal gyrus using either basic or conservative covariates. Higher in scanner performance was significantly genetically correlated with only lower left frontal pole activation and left middle frontal gyrus activation with the basic covariates. There were no significant environmental correlations between in scanner cognitive performance and activation measures.

Out of scanner performance was not significantly phenotypically, or genetically correlated with activation for any of the ROIs (Supplemental Table 4). Only activation in the left middle frontal gyrus was significantly and positively environmentally correlated with out of scanner performance.

Table 10: Correlations with In-Scanner Task Performance

	R_p (p)	R_g (p)	R_e (p)
PCET Efficiency			
Basic covariates	0.54* ($9.58x10^{-43}$)	1.00* (0.00009)	0.29 (0.06)
Conservative covariates	0.52* ($9.61x10^{-37}$)	0.90* (0.0003)	0.32 (0.11)
Frontal Pole Right			
Basic covariates	-0.21* ($5.08x10^{-6}$)	-0.42 (0.11)	-0.05 (0.79)
Conservative covariates	-0.18* (0.0002)	-0.41 (0.16)	0.001 (0.99)
Frontal Pole Left			
Basic covariates	-0.17* (0.0002)	-0.90* (0.002)	-0.0004 (0.99)
Conservative covariates	-0.16* (0.0005)	-0.86 (0.08)	0.05 (0.78)
Anterior Cingulate Gyrus			
Basic covariates	0.03 (0.54)	0.34 (0.28)	-0.12 (0.41)
Conservative covariates	0.07 (0.13)	0.28 (0.37)	-0.03 (0.81)
Middle Frontal Gyrus Right			
Basic covariates	-0.19* (0.00002)	-1.00 (0.17)	-0.09 (0.53)
Conservative covariates	-0.16* (0.0005)	-1.00 (0.27)	-0.08 (0.58)
Middle Frontal Gyrus Left			
Basic covariates	-0.19* (0.00003)	-0.52* (0.0002)	-0.02 (0.77)
Conservative covariates	-0.19* (0.00005)	-0.65 (0.05)	0.05 (0.78)

R_g=genetic correlation between in scanner performance and fPCET activation; R_p=phenotypic correlation between in scanner performance and fPCET activation; R_e= environmental correlation between in scanner performance and fPCET activation

Analyses with basic covariates included 521 individuals with fMRI and cognitive data and basic covariates.

Analyses with conservative covariates included 521 individuals with fMRI and cognitive data and conservative covariates.

All analyses were conducted in SOLAR and used the t-distribution.

Basic covariates included sex, age, age squared, and site (for ROIs). Conservative covariates additionally included education.

Values that are significant after controlling for false discovery rate based on Benjamini and Hochberg 1995 are indicated with an asterisk (*). For performance measures, FDR correction included 2 tests each for basic and conservative covariates. For ROIs, FDR correction included 5 tests each for basic and conservative covariates.

4.0 Discussion

The heritability of schizophrenia is estimated around 80% (Hilker et al., 2018), indicating that in aggregate, genetic contributions to schizophrenia risk are large. However, the extent to which there are shared genetic effects between schizophrenia and cognitive performance and functional brain activation is not well understood. Therefore, the present study used a multiplex extended pedigree design to address these questions. Our results show that cognitive flexibility performance on the Penn Conditional Exclusion Test (PCET) is quite sensitive to genetic effects whereas the task-based activation in three a priori regions of interest (frontal pole, anterior cingulate gyrus, middle frontal gyrus) was not. Specifically, we found that cognitive performance on the PCET – both in and out of scanner – was moderately and significantly heritable, while regional brain activation was not. Schizophrenia was phenotypically correlated with lower performance and shared genetic effects significantly accounted for covariation between schizophrenia and performance measures, however, there were no significant phenotypic or genetic correlations between schizophrenia and our ROI measures of brain activation. We additionally did not find any evidence to support phenotypic or genetic correlations between depression and any of our outcome measures, suggesting that cognitive flexibility performance may specifically share genetic effects with schizophrenia.

Our findings are consistent with previous studies showing robust evidence that individuals with schizophrenia have lower performance on the PCET (Calkins et al., 2013; Calkins et al., 2010; R. C. Gur et al., 2015) as well as similar tasks of cognitive flexibility, such as the Wisconsin Card Sorting Task (Everett et al., 2001; Zhang, Zhang, Qin, & Tan, 2018). We additionally show that lower performance is seen with an in-scanner version of the PCET, which was also significantly correlated with out of scanner performance. These results indicate that in scanner performance is also able to differentiate between those with and without a diagnosis of schizophrenia, and that in and out of scanner performance are likely measuring similar cognitive functions evoked by the PCET. As the tasks are similar, but not identical, further investigation of the similarities and differences between the two tasks may be useful to identify specific and common components of the task that differentiate between schizophrenia patients and controls. This may also be useful in identifying whether in scanner PCET performance can be used as an endophenotype independently from typical computerized performance measures. Our results are also consistent with prior literature on the WCST, showing that schizophrenia patients perform significantly more poorly than individuals with depression (Mahurin et al., 2006; Merriam et al., 1999), indicating that PCET performance is able to differentiate between schizophrenia and other non-psychotic disorders. Similar to the findings in the current study, individuals with a history of depression have also been found to not differ from healthy controls on the WCST (Degl'Innocenti, Ågren, & Bäckman, 1998).

Our estimated heritabilities both for in and out of scanner performance (ranging from 0.27-0.50 (Table 8)), are consistent with previous pedigree studies of schizophrenia, which estimated out of scanner PCET heritability to be between 0.09-0.46 (Calkins et al., 2013; Calkins et al., 2010; Glahn et al., 2015; Greenwood et al., 2007). It is important to note that the broad range of heritabilities from these previous studies may reflect the different ways that individual studies quantified performance (i.e. categories achieved, accuracy, and efficiency (accuracy and reaction

time)). In the current study, we also provide novel evidence that in scanner performance is heritable, highly correlated with out of scanner performance, and that shared genetic effects strongly and significantly account for covariance between performance on the two tasks (Table 10). Interestingly, our estimated heritability for in scanner cognitive flexibility was somewhat higher than the estimate for out of scanner heritability, potentially suggesting that in scanner performance may be even more sensitive than out of scanner performance to genetic effects.

In the current study, we found strong evidence for shared genetic effects between schizophrenia and PCET performance, both in and out of scanner (R_g=-0.48 to -0.65). While no other studies have specifically calculated the genetic correlation between schizophrenia and the PCET or WCST, performance of family members on these tasks has been examined. Unaffected family members of schizophrenia patients do more poorly on the PCET (R. E. Gur et al., 2007) and WCST (Egan et al., 2001; Saoud et al., 2000; Wolf, Cornblatt, Roberts, Shapiro, & Erlenmeyer-Kimling, 2002), suggesting that having a genetic risk for schizophrenia, not just having a diagnosis of schizophrenia, is related to cognitive flexibility performance. Wolf et al. 2002 also found that children of individuals with affective disorders did not perform significantly worse than controls, potentially indicating that it is specifically genetic risk for schizophrenia that is related to poor cognitive flexibility performance. While specific mechanisms or the amount of genetic risk that accounts for poorer behavioral performance is unclear, these previous studies and the current study implicate shared genetic effects between schizophrenia and cognitive flexibility performance. Schizophrenia polygenic risk scores (PRS) have also been associated with poorer cognitive performance in general across the lifespan, despite evidence linking the PRS scores to specific components of cognition being more mixed (Mistry et al., 2018). When looking more specifically at tasks of executive functioning, schizophrenia PRS has been found to be associated with lower performance on working memory tasks (Krug et al., 2018; Miller et al., 2017). While early studies of candidate genes found evidence of the relationship between polymorphisms and WCST performance, meta-analyses have not shown substantive evidence of specific polymorphisms being related to WCST performance (J. Barnett et al., 2007; J. H. Barnett, Scoriels, & Munafò, 2008). As both cognition and schizophrenia are influenced by many genes, individual polymorphisms likely only account for very small percentage of the variance in these traits. Therefore, studies that examine aggregate genetic effects for polygenic traits, such as extended pedigree or GWA studies, are better powered to find effects than candidate gene studies.

The current literature on functional brain imaging during cognitive flexibility tasks is small and inconclusive, with some studies showing hypoactivation and some hyperactivation in schizophrenia patients completing cognitive flexibility tasks. Many early studies using regional cerebral blood flow (rCBF), single-photon emission computed tomography (SPECT), and fMRI found that compared to controls, individuals with schizophrenia had lower activation in prefrontal regions during the WCST (Berman et al., 1986; Catafau et al., 1994; Riehemann et al., 2001; Volz et al., 1997; Weinberger et al., 1986). Other studies did not replicate the hypoactivation and found that patients actually had higher activation, specifically in the anterior cingulate (Toone, Okocha, Sivakumar, & Syed, 2000). A more recent fMRI study using an event related design also found hyperactivation in individuals with schizophrenia when they were able to successfully switch responses and if they had higher overall performance (Pedersen et al., 2012; Wilmsmeier et al., 2010). We did not find evidence to support either hypoactivation or hyperactivation in the frontal pole, anterior cingulate gyrus, or middle frontal gyrus. This may be due to our study sample of outpatients who were generally less

acutely ill during testing, in contrast to participants in many of the earlier studies who were more often inpatients. Although our study sample only had 27 individuals with schizophrenia it had 227 controls with acceptable fMRI data, yielding a power of .79 to detect a medium effect size of 0.5 but only a power of .25 to detect a small effect of .20 (Faul, Erdfelder, Lang, & Buchner, 2007). Lower in scanner performance was also correlated with higher activation in right and left frontal pole and right and left middle frontal gyrus in the total sample

This was the first study to examine the heritability of brain activation during a cognitive flexibility task and its genetic correlation with schizophrenia. Our findings showed non-significant heritabilities for regional brain activation in the frontal pole, anterior cingulate gyrus, and middle frontal gyrus and non-significant genetic correlations (Table 8). Based on a calculation in SOLAR using our sample structure, we have power of .45 to detect a low heritability of 0.25 and .91 power to detect a moderate heritability of 0.50. Several studies, have also examined the heritability of brain activation during other executive functioning tasks, such as working memory and an interference processing task, finding mixed results from non-significantly low to moderate (0.14-0.30) (Blokland et al., 2008) to significant and moderate (0.37-0.65) (Blokland et al., 2011; Matthews et al., 2007). To date, there have been no studies that have examined genetic correlation between schizophrenia and brain activation on the PCET or WCST and there has been only one study of monozygotic twins discordant for schizophrenia, which found no significant difference between unaffected twins and controls (Berman et al., 1992), suggesting that genetic risk for schizophrenia may not affect brain activation on the WCST. Looking at genetic risk for schizophrenia in brain activation more broadly, a review found that higher schizophrenia PRS was associated with hyperactivation in executive functioning working memory tasks in the left dorsolateral and ventrolateral prefrontal cortex (Dezhina et al., 2019). However, two studies not included in the review found that schizophrenia PRS was related to hypoactivation in prefrontal areas (Krug et al., 2018; Miller et al., 2017). Although we did not find evidence to suggest that there is a genetic correlation between schizophrenia and cognitive flexibility regional brain activation or that brain activation was heritable, the mixed results from other studies suggest that further investigation is still needed. Variation in fMRI analysis methods can provide a wide range of results (Botvinik-Nezer et al., 2020) and may influence the ability to detect significant heritability of brain activation. Interestingly, one study examined the extent to which different methods of choosing an ROI can affect the detection of genetic effects and found the strongest genetic effects for ROIs that included only the highest activated voxels within a region of interest (Tong et al., 2016).

4.1 Limitations

There are several strengths of the current study including: the novelty of the research questions; use of an extended pedigree design; measures of performance both in and out of the MRI scanner as well as activation during the task; large sample size; examination of diagnostic specificity; and use of a clinically stable patient sample. However, several limitations should also be considered. First, the in scanner cognitive flexibility task is a block design in which we were able to compare only overall task activation to baseline activation. This means we were unable to

investigate the complexity of the cognitive flexibility task, which may mask differences in schizophrenia and control activation, such as successful switching or receiving feedback. As described previously, choices in fMRI analysis and creating and using metrics from specific regions of interest may also have influenced our ability to detect genetic influences on brain activation. Finally, while we have a large sample size, it may not have been large enough to detect small shared genetic effects between schizophrenia and brain activation, despite using a multiplex design which may be enhanced for genetic risk variants. The low heritabilities and phenotypic correlations of brain activations with schizophrenia also reduced power to detect genetic correlations (Verhulst, 2017).

4.2 Conclusion

The ability to detect genetic effects on the pathology of schizophrenia has been challenging. In the current study, we examined cognitive flexibility performance and concurrent brain activation as potential endophenotypes of schizophrenia. Consistent with previous studies, we show that cognitive flexibility performance, both in and out of scanner, is heritable and phenotypically and genetically correlated with schizophrenia. These results were only seen in schizophrenia, and cognitive flexibility performance was not phenotypically or genetically correlated with a diagnosis of depression, suggesting diagnostic specificity of behavioral performance. We also did not find significant heritability of brain activation or significant phenotypic or genetic correlations with schizophrenia. Overall, these results suggest that behavioral performance on this measure of cognitive flexibility (PCET) is more sensitive (and also more specific compared with depression) to schizophrenia genetic risk effects than fMRI measures of its regional brain activation.

Appendix A Supplemental Tables

Appendix Supplemental Table 1: Demographic Characteristics of Included/Excluded fMRI Participants

	Included	Excluded	t/X^2	df	p
Total N	455	66			
Site (%Pitt)	51.2%[a]	62.1%[a]	2.33	1	0.13
Sex (%Male)	48.8%[a]	47.0%[a]	0.02	1	0.88
Handedness (%Right)	89.2%[a]	83.3%[a]	1.43	1	0.23
Age (Mean, SD)	41.35 (16.05)[b]	47.20 (20.66)[a]	2.66	519	0.008
Education (Mean, SD)	14.52 (2.58)[a]	14.44 (2.68)[a]	-0.21	519	0.83
Parental Education* (Mean, SD)	13.20 (2.90)[a]	12.64 (2.53)[a]	-1.45	515	0.15
PCET Efficiency	-0.13 (0.90)	-0.42 (0.90)	4.92	519	0.01
fPCET Efficiency	-0.13 (0.95)	-0.56 (1.08)	10.56	519	0.001

Sample includes 455 participants who have good quality fMRI data and 66 participants who were excluded for poor fMRI quality. Results for age, education (self), and education (parental) are reported with independent samples t-tests and results for site, sex, and handedness are reported with chi-square tests. Values that share the same superscript were not significantly different from each other ($p \geq .05$).
***Two participants were missing parental education.**

Appendix Supplemental Table 2: Demographic Characteristics for Participants who Passed fMRI Data Quality Control

	Schizophrenia	Relatives	Controls	F/X^2	df	p
Total N	27	170	258			
Site (%Pitt)	51.9%[a]	53.5%[a]	49.6%[a]	0.63	2	0.73
Sex (%Male)	74.1%[b]	48.2%[a]	46.5%[a]	7.47	2	0.02
Handedness (%Right)	85.2%[a]	90.6%[a]	88.8%[a]	0.85	2	0.66
Age (Mean, SD)	50.96 (10.32)[b]	42.27 (16.72)[a]	39.73 (15.73)[a]	6.60	2,452	0.001
Education (Mean, SD)	13.04 (1.83)[a]	13.66 (2.66)[a]	15.24 (2.35)[b]	26.9	2,452	<.001
Parental Education* (Mean, SD)	12.48 (3.01)[a]	12.38 (2.98)[a]	13.82 (2.68)[b]	14.27	2,450	<.001

Sample includes 455 participants who have good quality fMRI data. Results for age, education (self), and education (parental) are reported with ANOVAs and results for site, sex, and handedness are reported with chi-square tests. Post-hoc independent two sample t-tests were conducted to compare differences between groups. Values that share the same superscript were not significantly different from each other (p≥.05).
***Two participants were missing parental education.**
****One control was missing intracranial volume**

Appendix Supplemental Table 3: Demographic Characteristics of Additional Family Members and Controls without Cognitive Data versus Without Cognitive or fMRI Data

	Initial Non-cognitive sample	Without fMRI	t/X^2	df	p
Total N	783	66			
Site (%Pitt)	57.5%	37.9%	8.76	1	0.003
Sex (%Male)	46.6%	47.0%	2.6x10-31	1	1
Handedness (%Right)	87.8%	83.3%	0.71	1	0.40
Age (Mean, SD)	45.60 (18.46)	47.20 (20.66)	.67	846	0.50
Education (Mean, SD)	13.42 (2.99)	14.44 (2.68)	2.67	756	0.008
Parental Education* (Mean, SD)	11.94 (3.22)	12.64 (2.53)	1.72	681	0.09

***91 of the initial sample missing education, 166 missing parental education**

Appendix Supplemental Table 4: fPCET ROI Activation: Correlations with Out of Scanner Task Performance

	R_p(p)	R_g(p)	R_e(p)
Frontal Pole Right			
Basic covariates	-0.11 (0.02)	0.03 (0.93)	-0.19 (0.30)
Conservative covariates	-0.08 (0.08)	0.18 (0.66)	-0.20 (0.26)
Frontal Pole Left			
Basic covariates	-0.02 (0.66)	-0.90 (0.25)	0.12 (0.03)
Conservative covariates	-0.01 (0.86)	-0.90 (0.27)	0.13 (0.33)
Anterior Cingulate Gyrus			
Basic covariates	0.006 (0.90)	0.009 (0.99)	0.008 (0.90)
Conservative covariates	0.03 (0.53)	-0.206 (0.77)	0.06 (0.35)
Middle Frontal Gyrus Right			
Basic covariates	-0.10 (0.03)	-0.90 (0.50)	-0.04 (0.82)
Conservative covariates	-0.008 (0.11)	-1.00 (0.71)	-0.04 (0.71)
Middle Frontal Gyrus Left			
Basic covariates	-0.08 (0.10)	-0.90 (0.06)	0.19* (0.002)
Conservative covariates	-0.07 (0.13)	-1.00 (0.04)	0.21 (0.13)

R_g=genetic correlation between out of scanner performance and fPCET activation; R_p=phenotypic correlation between out of scanner performance and fPCET activation; R_e= environmental correlation between out of scanner performance and fPCET activation
Analyses with basic covariates included 521 individuals with fMRI and cognitive data and basic covariates. Analyses with conservative covariates included 521 individuals with fMRI and cognitive data and conservative covariates.
All analyses were conducted in SOLAR and used the t-distribution.
Basic covariates included sex, age, age squared, and site. Conservative covariates additionally included education.
Values that are significant after controlling for false discovery rate based on Benjamini and Hochberg 1995 are indicated with an asterisk (*). FDR correction included 5 tests for basic covaraites and 5 tests for conservative covariates.

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