The relationship between age of onset and clinical severity, community functioning, and cognitive functioning in schizophrenia: A multiplex extended pedigree study

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Schizophrenia is associated with substantial heterogeneity in symptom severity, course of illness, and overall functioning. Earlier age of onset is a consistent predictor of poor outcomes in multiple domains, but the causes of this association are still unknown. We used a multiplex, extended pedigree study (N=773) to determine the heritability of age of onset, to replicate its association with measures of symptom severity and functioning, and to determine the degree to which the genetic effects that influence age of onset are shared with those that influence outcome. We also assessed the degree to which the genetic effects on age of onset might influence functioning in relatives with major depression or those with no psychiatric diagnosis, thus assessing whether or not those genetic factors are transdiagnostic. The current sample consisted of 43 multigenerational families (N=635 relatives) with at least two first-degree relatives diagnosed with schizophrenia (N=103) and 135 matched controls. All participants completed a demographic and symptom interview as well as a cognitive battery with 11 tasks. Although age of onset of schizophrenia was modestly heritable, it was not significant (h^2 = 0.198, p = 0.277). However, age of onset was still significantly correlated phenotypically with negative symptoms, positive symptoms, community functioning, and cognitive functioning. The genetic correlation between age of onset of schizophrenia and negative symptoms was significant, while the genetic relationships between age of onset and positive symptoms, community functioning, and cognitive functioning were non-significant. There was no significant genetic correlation between age of onset in schizophrenia and community or cognitive functioning in depressed relatives, or community and cognitive functioning in relatives with no

psychiatric diagnoses, which is consistent with the proposal that any genetic effects on age of onset in schizophrenia are not transdiagnostic. This study was, to the best of our knowledge, the first of its kind to assess the potential shared genetic effects linking age of onset to relevant outcome measures and to examine their diagnostic specificity. These findings illustrate the potential of such approaches and support further research elucidating the potential causes of heterogeneity within schizophrenia.

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1.0 INTRODUCTION

Schizophrenia is a severe diagnosis defined in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) by positive symptoms (e.g., hallucinations, delusions) and negative symptoms (e.g., blunted affect, avolition). It is also strongly associated with severe and pervasive cognitive impairments and difficulties in social and occupational functioning. There are a number of factors that contribute to the debilitating and costly nature of the disorder. Schizophrenia is often severe and chronic and tends to manifest in adolescence and emerging and early adulthood (typically between the ages of 15 and 35), which is often a time of great social and emotional growth as well as vocational productivity. Furthermore, even before onset of a full psychotic episode and an individual's subsequent diagnosis, there tends to be a "prodromal" period in which sub-threshold cognitive, psychotic, and disorganized symptoms begin to emerge, further interrupting normative development (Hafner et al., 1999).

In terms of overall prognosis, it has been estimated that 20-40% of individuals have poor functional outcomes; however, there is significant variation in symptomatology, cognitive ability, overall functioning, and course, and as many as 40% of individuals with schizophrenia are able to lead relatively independent lives (Lauronen et al., 2007). It is generally difficult to predict which individuals may have a more severe course, but one factor is consistently linked with a host of relevant outcome measures: age of onset. Numerous studies have found earlier age of onset to be correlated with poorer functional outcomes, such as intensity and duration of

symptoms, and level of functional and cognitive impairment. Interestingly, age of onset is also associated with sex differences in schizophrenia. Males generally have a younger age of onset than females, and male gender is a risk factor for symptom severity and poorer outcome.

At this juncture, however, it is unclear why age of onset is correlated with symptom variability and clinical outcome in schizophrenia. Both genetic effects and a variety of different environmental factors could play a significant role in explaining the correlation between age of onset and clinical variation, but their relative contributions are not known. Therefore, the proposed study seeks to increase our understanding of the genetic and environmental causes of the correlations between age of onset and variation in clinical features and general functioning in schizophrenia.

1.1 AGE OF ONSET: METHODOLOGICAL CONSIDERATIONS

Before proceeding, it is important to keep in mind a few methodological considerations regarding age of onset in schizophrenia. Determining the exact age of onset of schizophrenia is not entirely straightforward, due to the presence of prodromal, sub-threshold symptoms that frequently occur but vary both in their intensity and in how long they last before a clear psychotic break (Hafner et al., 1999). Nevertheless, to denote onset, most researchers use records of the individual's first hospitalization, retrospective self-report, or caregiver-report concerning the first full psychotic episode meeting criteria for schizophrenia. Another complication with this extensive literature is that many researchers choose to divide their samples into categorical groups based on age ranges, rather than keeping age as a continuous variable, and the division points for these groups varies widely. Therefore, when comparing studies, it is essential to attend to the definition of age of onset within the studies and the age range to which "early" refers.

Variations in age of onset of schizophrenia have consistently been correlated with differences in many symptom domains and overall functioning (DeLisi, 1992), but the age at which an individual's symptoms or functioning are assessed may be important. In addition, it is possible that duration of illness plays a role in symptom severity and functioning. However, this is typically confounded with age of onset, in that patients with earlier ages of onset will also have a longer duration of illness, if patients are matched for age at assessment (which is a common practice to attempt to adjust for age effects).

The use of adequate control groups is another consideration when evaluating the relationship between age of onset and symptoms or functioning. In studies focused on age of onset and symptom domains specific to schizophrenia (such as hallucinations or blunted affect), differences in symptomatology between early and late onset cannot be examined in reference to a healthy control group. Such studies necessarily confound age of onset effects with either age or duration of illness effects, depending on the design. In contrast, studies of characteristics that can be measured among individuals without a diagnosis of schizophrenia (such as cognition or regional brain volumes) can be compared to a psychiatrically healthy control group, which allows patients with differing ages of onset to be compared to similarly aged controls (thus controlling for age effects)

A final methodological feature to be cognizant of is the issue of sex differences. On average, men tend to have an earlier age of onset than women, which brings up the question of whether or not significant differences in symptomatology or outcomes are actually sex effects, rather than age of onset effects. In addition, sex potentially has varying effects on a number of relevant domains, including negative and affective symptomatology, social functioning, and cognitive functioning (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). To mitigate these

potential confounds, it is important for researchers to attempt to control for sex in analyses and/or to examine sex as a potential moderator.

1.2 PEAK AGE OF ONSET AND THEORIES OF ITS DEVELOPMENTAL TIMING

The developmental timing of onset of schizophrenia varies widely among individuals and between males and females. In general, the peak incidence for the diagnosis of schizophrenia is between 20-24 years old in males and between 25-35 years old in women (with another smaller peak between the ages of 50-54, roughly around menopause) (Welham, Thomis, & McGrath, 2004; Kessler et al., 2005; Lauronen et al., 2007). Figure 1, drawn from a study by Hafner and colleagues (1998), illustrates these sex differences and the distribution of age of onset. A substantial amount of research has been conducted over the years in an effort to explain this peak. Since the 1980s, two theoretical frameworks in particular have been influential in directing this research: the early and late neurodevelopmental models of schizophrenia (Pogue-Geile, 1991). The early model proposes that the causative genetic and environmental factors that are specific to schizophrenia are present from the pre- and peri-natal stages of development, and that the overt signs and symptoms of schizophrenia develop later following additional non-specific triggering events, such as normative developmental brain processes and/or various environmental factors (Weinberger, 1987). The late model suggests that the etiology involves schizophrenia-specific abnormalities in genes that are not expressed until young adulthood and that non-specific environmental events in the pre- and peri-natal period may serve to modify the timing or severity of the disorder (Feinberg, 1982, Pogue-Geile, 1991). In other words, the key difference between these two models is the timing at which brain abnormalities associated specifically with schizophrenia occur: In the early model, abnormalities are present at or before

birth and continue to have deleterious effects before the overt manifestation of psychotic symptoms later in life, whereas in the late model, brain abnormalities specific to schizophrenia only become apparent later in life, closer to the development of overt psychotic symptoms.

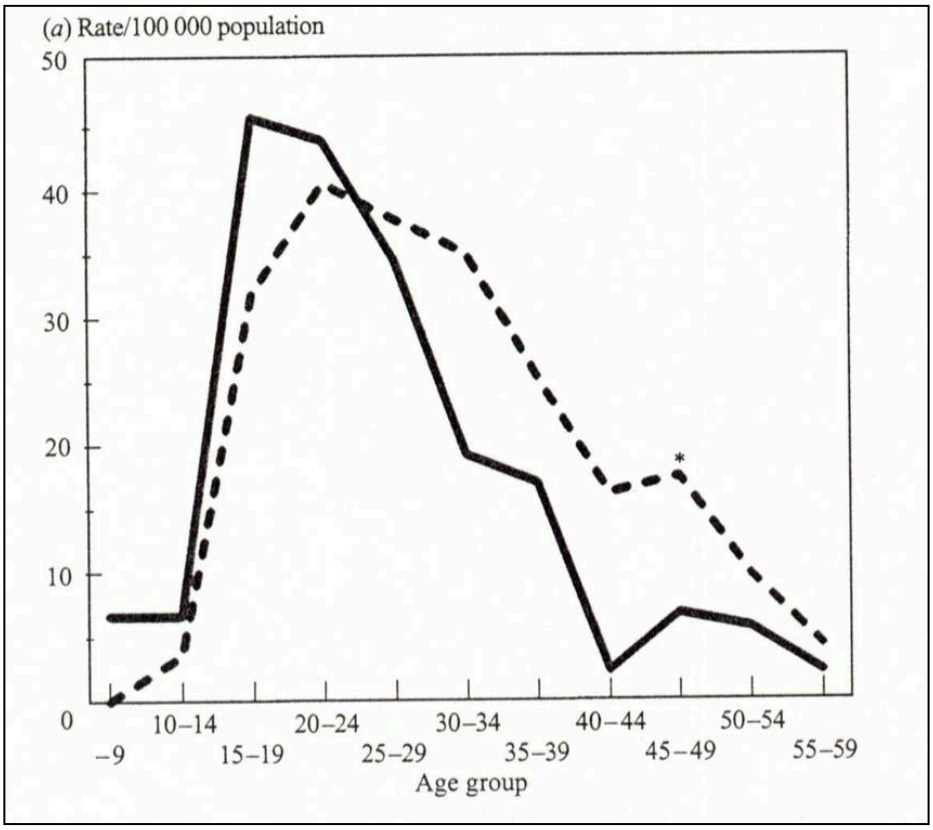

Figure 1: Annual incidence of age of onset in schizophrenia. Note: The heavy bolded line represents males, and the dotted line represents females. Figure drawn from Hafner et al., 1998.

These heuristic neurodevelopmental models both emphasize that developmental processes in the brain during adolescence, emerging adulthood, and early adulthood are related to the development of the overt symptoms of schizophrenia (Walker & Bollini, 2002). There are a number of different lines of biological research that support various neurodevelopmental models of schizophrenia. For example, considerable research has been conducted on synaptic pruning, in which (in normative development) excess synapses are eliminated and existing connections are strengthened throughout adolescence and early adulthood (Thompson, Pogue-Geile, & Grace, 2004). Observations of reduced grey and white matter volume in schizophrenia (at the time of symptom development and after) led to the hypothesis that schizophrenia may be a result of overly aggressive synaptic pruning. Consistent with this theory, a recent study has found that variations in the expression of complement 4 genes (which are at a locus on chromosome 6 recently associated with schizophrenia risk; Ripke et al., 2014) in the brain are related to synaptic pruning in mice, thus identifying a potential mechanism of synaptic pruning with specific relevance to schizophrenia (Sekar et al., 2016). Similarly, decreased numbers of dendritic spines (which are crucial in many excitatory synaptic connections and undergo substantial developmental changes throughout adolescence and early adulthood) may also be a potential source of decreased grey matter in schizophrenia, particularly in the prefrontal and temporal cortices (Bennett, 2011; Glausier & Lewis, 2013). Both of these areas of research align with the late neurodevelopmental theory of schizophrenia in which abnormalities in genes expressed later in development have a deleterious effect on crucial brain developmental processes in adolescence, emerging adulthood, and early adulthood.

It is important to highlight that for the vast majority of these biological phenomena, there are complex interactions with environmental factors that may have a significant impact on the timing and quality of these neural changes and the development of schizophrenia (Brown, 2011).

Beginning with early work by George Brown and colleagues (Brown, Birley, & Wing, 1972), considerable research has examined the role that normative life experiences (such as increased social and emotional stress) during adolescence and young adulthood might play in explaining the peak age of onset in schizophrenia. This research has been buttressed by the extensive literature emphasizing the widespread behavioral and neural changes associated with social, emotional, and executive functioning in normative adolescent development, and the important role of life experiences on these changes (Blakemore, 2008; Casey, Jones, & Hare, 2008; Dahl, 2004). In the schizophrenia literature, environmental stressors throughout childhood and adolescence (such as socioeconomic status, stress, anxiety, trauma, and drug use) have been consistently associated with the manifestation of schizophrenic symptoms and neural abnormalities (e.g., poor dendritic spine formation, hypothalamic-pituitary-adrenal axis dysfunction) (Brown, 2011; Leuner & Shors, 2012; Phillips et al., 2006; Walker & DiForio, 1997). However, it is less clear whether or not these factors influence the timing of psychosis onset.

In sum, the peak incidence of schizophrenia during adolescence, emerging, and early adulthood is well-documented and has stimulated considerable theorizing and empirical study, with the result that some form of neurodevelopmental hypothesis has become the dominant theoretical model of schizophrenia. However, the causes and correlates of variation—as opposed to the mean—in age of onset of schizophrenia have received far less attention.

1.3 VARIATION IN AGE OF ONSET, CLINICAL SEVERITY, AND COMMUNITY AND COGNITIVE FUNCTIONING

As mentioned previously, the clinical profile of schizophrenia varies greatly, and an individual's course and severity of illness can be difficult to predict. However, earlier age of onset in schizophrenia has been consistently correlated with worse functional outcomes. One systematic review of outcome in schizophrenia found that, among individuals unselected for age of onset, 27.1% had a "poor" outcome and 42.2% achieved a "good" outcome (Menezes, Arenovich, & Zipurskey, 2006). By contrast, another systematic review specifically focused on early onset in schizophrenia found that of early onset patients (defined as those whose reported onset occurred before age 18), 60.1% experienced a "poor" outcome and only 15.4% achieved a "good" outcome (with the remaining patients experiencing a "moderate" outcome), based on broad measures of functioning. This was significantly different from outcomes of samples unselected for age of onset (Clemmensen, Vernal, & Steinhausen, 2012). Earlier age of onset has also been associated with less time spent in remission. Using data from the Northern Finland 1966 birth cohort, Juola and colleagues (2013) were able to measure long-term (i.e., at least 10 years after illness onset) outcomes and symptom severity in a population-based sample of individuals with schizophrenia. Specifically, they found that earlier age of onset (i.e., onset before 22 years of age) significantly predicted a lack of long-term remission, as compared to those with onset after 22 years old (Juola et al., 2013).

In addition to these broad functional outcomes, there is also evidence to support that earlier age of onset is associated with a more severe symptom profile (Vassos et al., 2008). In particular, a number of studies have found earlier onset to be associated with more severe disorganized symptoms (such as formal thought disorder and inappropriate affect), negative

symptoms (such as alogia, avolition, dysphoria, and slowed movement), and social deficits (Hafner, 2000; Howard, Castle, Wessely, & Murray, 1993; Kendler et al., 1997; Luoma et al., 2008; Mayer, Kelterborn, & Naber, 1993; Pearlson et al., 1989; Shultz, Ho, & Andreasen 2000). It is less clear whether or not positive symptoms (such as hallucinations and delusions) are more severe with earlier onset, and results are mixed in the studies cited above

Cognitive deficits are one of the hallmarks of the diagnosis, and tend to be both severe and to remain relatively stable over time (Kurtz, 2005; Frangou, Hadjulis, & Vourdas, 2008). Based on results from a recent meta-analysis (which only included studies with healthy control groups), individuals with early onset schizophrenia (i.e., onset before 19 years of age and assessed 2 years after illness onset, on average) performed worse than those with later onset schizophrenia on full-scale IQ tests, speed of processing, tests of executive function, and set-shifting tasks (Rajji, Ismail & Mulsant, 2009). Similarly, in studies that used age of onset as a continuous variable, earlier age of onset was associated with impairments in attention, working memory, verbal memory, IQ, expressive and receptive speech, motor speed/coordination, and overall cognitive ability (Bellino et al., 2004; Bjorck, Sjalin & Nordin, 2000; Hoff et al., 1996; Tuulio-Henriksson et al., 2004; van der Werf et al., 2012). In these studies, individuals were assessed between 5 and 22 years after illness onset and all participants were either compared to a control group or age-based population norms, except for the research involving motor speed/coordination (Bjorck, Sjalin & Nordin, 2000).

1.4 AGE OF ONSET: POTENTIAL CAUSES OF VARIATION

There has been longstanding interest in determining the potential causal factors that influence the peak age of onset of schizophrenia. Less attention has been given to why there might be such

variation in age of onset (i.e., why even though the peak is between 20-35 years old, children as young as 6 and adults as old as 60 can also develop the disorder). Understanding this variation is especially important considering the host of negative outcomes associated with earlier age of onset. There may be overlapping factors that influence both the mean and the variation of age of onset in schizophrenia; however, it is also entirely possible that there are unique factors that contribute to the variability and not to the mean. Therefore, potential causes of variation in age of onset of schizophrenia will be reviewed below.

1.4.1 Environmental effects.

A significant portion of the literature examining environmental effects on schizophrenia is focused on overall risk (i.e., which factors might increase the likelihood of developing schizophrenia) rather than what might affect the developmental timing of the diagnosis. There is some evidence to suggest that obstetric complications and lower childhood IQ may not only be associated with increased risk for psychosis, but that they may also be correlated with earlier onset of psychosis; however, the causality of this relationship is unclear (i.e., the factors that may be influencing earlier age of onset may also be influencing obstetric complications and lower IQ, or these factors could influence age of onset directly) (McDonald & Murray, 2000). In terms of socioemotional stressors, some studies have found a link between stressful life events and the onset of psychotic episodes; however, it is not clear whether or not such stressors affect the developmental timing of the first psychotic episode onset (Howes et al., 2004; McDonald & Murray, 2000). In terms of the role of substance use, a recent meta-analysis found a positive association between earlier age of onset of psychosis and use of tobacco products, as compared to non-smokers (Gurillo, Jauhar, Murray, & MacCabe, 2015), though a slightly older meta-analysis did not find a significant association (Myles et al., 2012). Other research has focused on

substances such as cannabis and methamphetamines (or other substances that affect the dopamine system), and a recent meta-analysis found a positive association between cannabis use and earlier age of onset of psychosis (Large, Sharma, Compton, Slade, & Nielssen, 2011). One major difficulty with this type of correlational research is that it is again difficult to determine causality (i.e., does the substance use decrease the age of onset, or are individuals with earlier onset of psychotic symptoms more likely to use substances).

1.4.2 Heritability of age of onset.

Schizophrenia itself has a strong genetic basis, with twin and family studies estimating heritability at approximately 81% (Sullivan, Kendler, & Neale, 2003). There is also evidence to suggest that age of onset is heritable. Numerous studies have found age of onset to be correlated among concordant twins, siblings, and other first-degree relatives, with stronger correlations occurring with higher genetic relatedness (e.g., correlations are higher in monozygotic twins than in dizygotic twins). To the best of our knowledge, there are 23 family, twin, and pedigree studies that have published age of onset data in schizophrenia since 1925, and the results of their findings are provided in Table 1.

Table 1: Heritability of age of onset of schizophrenia

Study	Sample	Sample size (total affected individuals)	MZ twin correlation	First-degree relative correlation	Heritability
First-degree relative studies					
Myerson, 1925	Sibling	148		0.71*	1.0‡
Sjogren, 1935	Sibling	16		0.48	0.96
Stromgren, 1935	Sibling	262		0.19*	0.38
Slater, 1947	Sibling	146		0.55*	1.0‡
Slater, 1953	Sibling	52		0.39*	0.78†
Larsson & Sjorgen, 1954	Sibling	34		0.06	0.11
Tsuang, 1965	Sibling	50		0.68*	1.0‡
Larson & Nyman, 1970	Sibling	186		0.27	0.54
Bleuler, 1978	Sibling	446		non-significant result (not reported)	N/A
DeLisi, Goldin, Maxwell, Kazuba, & Gershon, 1987	Sibling	84		0.39*	0.78
Kendler, Tsuang, & Hays, 1987	First-degree relatives – Iowa Family Study	52		0.15	0.29
Kendler & MacLean,	First-degree relatives	134		0.43	0.86

1990					
Leboyer et al., 1992	Sibling***	97		0.40*	0.80
Burke, Murphy, Bray, Walsh, & Kendler, 1996	Sibling	169		0.24*	0.48
Kendler et al., 1997	Sibling – Irish Study of High Density Schizophrenia Families	512		0.08	0.16
Cardno et al., 1998	Sibling***	109		0.26*	0.52
Vassos et al., 2008	Sibling	291		0.35*	0.69
First-degree relatives total	*17 studies*	*2342*[+]			*0.55***
Twin studies					
Slater, 1953	Maudsley Twin Register (London)	DZ: 26		0.74*	1.0[‡]
Gottesman & Shields, 1972	Maudsley Twin Register (London)	MZ: 24 DZ: 12	0.87	0.80	0.14
Kendler, Tsuang, & Hays, 1987	NAS-NRC Twin Registry (male)	MZ: 60 DZ: 18	0.51*	-0.04	0.94
Cannon et al., 1998	Finnish twin cohort	MZ: 134 DZ: 374	0.76	0.26	1.0
Allan et al., 2009	Maudsley Twin Register (London)	MZ: 88 DZ: 18	0.90*	0.56	0.68
Twin total	*5 studies*	*MZ: 306* *DZ: 448* *Total: 754*			*0.91***

Extended pedigree studies				
Hare et al., 2010	Extended pedigree	717	--	0.33†
Pedigree total	*1 study*	*717*		*0.33*
Overall total	*23 studies*	*3816*+		*0.58***

Note: If no significance value was provided for a correlation, the number stands alone without a distinguishing mark. Heritability calculated by C.M using the following equations: $h^2 = 2(R_{mz} - R_{dz})$*, with* R_{mz} *signifying the correlation between monozygotic twins, and* R_{dz} *signifying the correlation between dizygotic twins; and* $h^2 = 2R_1$*, with* R_1 *signifying the correlation between first-degree relatives. This assumes that shared environmental effects are zero. The average heritability was weighted by number of individuals in the study. Finally, there was an additional extended pedigree study conducted by Wickham et al (2002) that was excluded, because the intraclass correlations between age of onset and clinical characteristics were not separated by degree of relatedness, thus preventing any estimation of heritability.*

* Significant results at $p<0.05$

** Weighted average

*** Includes diagnoses of schizophrenia, schizoaffective, and psychosis NOS

+ Total does not include Bleuler et al, 1978 (N=446) because first degree correlation was not reported

† Statistic calculated by the study authors (all others calculated by C.M.)

‡ Heritability estimates exceed 1.0 and are reported at 1.0.

In the studies cited within Table 1, age of onset heritability estimates range from 0.11 (Larsson & Sjorgen, 1954) to 1.00 (Cannon et al., 1998; Tsuang, 1965; Slater, 1947; Myserson, 1925). The average heritability (weighted by sample size) calculated from the available studies provides us with an estimate of 0.58 (i.e., 58% of the variance in age of onset can be attributed to genetic effects). It may be helpful to break down this broad estimate into the three types of samples utilized, which include first-degree relative studies, twin studies, and extended pedigree studies. Investigations based on first-degree relatives include data from parents, siblings, and offspring, but correlations (and heritability estimates) can be inflated if shared environmental effects are present. Twin studies are frequently considered one of the most powerful

methodologies for estimating genetic effects and heritability, but are also dependent on the assumption that the shared environmental effects are equal between monozygotic and dizygotic twins. Extended pedigree studies, which compare affected relatives with several degrees of genetic relatedness (e.g., first, second, third degree relatives), are also considered a strong methodology for estimating heritability. Both twin studies and extended pedigree studies are generally found to produce similar heritability estimates and are well-established designs for this purpose (Docherty et al., 2015).

From the correlations obtained in the studies in Table 1, the average weighted heritability estimate for first-degree relative studies is 0.55; for twin studies, 0.91; and for the single extended pedigree study, 0.33. This wide range of estimates is somewhat puzzling, and the excessively high estimates from the twin studies are particularly intriguing. It is not entirely clear what might be driving this finding; however, it may suggest that the genetic effects on age of onset are not entirely additive, and that there could be dominance or epistasis effects. Another potential factor could be the smaller number of total participants in the twin studies, as compared with the total number across all study designs (i.e., 754 twins out of 3816 total participants). This relatively small number of participants invites the possibility of increased error associated with the heritability estimates derived from the twin studies. Overall, however, the vast majority of studies (with data from different types of samples) have found that genetic effects play a role in variation of age of onset.

1.4.3 Specific genetic effects on age of onset.

The investigation of potential candidate genes that may influence age of onset in schizophrenia has generated a fair amount of research over the years, but unfortunately, the results have been inconclusive, and many positive findings are still lacking replications. Researchers have recently

used genome-wide association studies (GWAS) to investigate the possible connection of specific genetic variants with age of onset, but again, these studies have not been conclusive and a number of the positive findings have not yet been replicated. In one large study, no genes that met genome wide significance were found to be associated with age of onset, and the gene with the highest significance value was unable to be replicated in a large separate sample (Bergen et al., 2014). In another GWAS, the researchers found one single nucleotide polymorphism (SNP) associated with age of onset in schizophrenia, but were unable to replicate their finding in a separate sample (Wang, Liu, Zhang, Aragam, & Pan, 2010). These inconclusive findings suggest that either larger sample sizes or new approaches may be necessary to identify specific genetic effects of age of onset.

1.4.4 Heritability of age of onset: Diagnostic specificity.

Within the body of research investigating genetic risk for schizophrenia, considerable effort has been made to determine if the schizophrenia phenotype is primarily caused by genetic variations that are unique to schizophrenia, or if there are meaningful genetic factors that increase risk for the development of a range of psychiatric diagnoses, including schizophrenia, bipolar disorder, and major depression. By examining rates of other disorders in family studies of probands with schizophrenia to individuals without a family history of schizophrenia, there is strong evidence for genetic overlap between schizophrenia, schizotypal personality disorder, and psychotic affective disorders (Kendler et al., 1993a; Kendler et al., 1993b; Sham et al., 1994). Historically, the evidence is less strong for genetic overlap between schizophrenia and non-psychotic affective disorders such as major depressive disorder (Kendler et al., 1993a; Kendler et al., 1993b; Huang et al, 2010), but some recent evidence from meta-analyses (Bader & Gershon, 2002) as well as family-based studies and GWAS (Cross-Disorder Group of the Psychiatric Genomics

Consortium, 2013; Fallin et al, 2005; Craddock, Donovan, & Owen, 2006; Moskvina et al., 2009) suggest some overlap in genetic susceptibility for schizophrenia and bipolar disorder. However, even within potential overlapping risk genes, it is not clear if the same polymorphisms are implicated in both schizophrenia and affective disorders (Muller, Zai, Shinkai, Strauss, & Kennedy, 2011).

Surprisingly, the inconclusive evidence cited above has not led to substantial investigations into whether or not there is any overlapping genetic influence on variations in age of onset in schizophrenia and age of onset in other psychiatric diagnoses. One archival study by Husted, Greenwood, and Bassett (2006) seems to report that earlier age of onset in a proband with schizophrenia is associated with earlier age of onset of an affective disorder in a sibling of the probands, and vice versa (i.e., that earlier age of onset in a proband with an affective disorder is associated with earlier age of onset of schizophrenia in a sibling). However, it is unclear whether or not appropriate statistical analyses were used. Other research has focused on the relationship between age of onset and increased disease risk in other diagnoses, rather than the relationship between age of onset in schizophrenia and age of onset of other diagnoses. This potential relationship was investigated in a set of studies by Kendler and colleagues (1987), but they found no significant relationship between age of onset in schizophrenia and risk for other diagnoses (apart from schizophrenia) in their sample. Overall, there may be some evidence to suggest that there is a relationship between age of onset in schizophrenia and age of onset in other diagnoses, but at this point in time, the literature is extremely sparse.

1.5 RELATIONSHIP BETWEEN AGE OF ONSET AND SYMPTOM SEVERITY AND COMMUNITY AND COGNITIVE FUNCTIONING: THE CURRENT RESEARCH PROJECT

Considerable research has been dedicated to understanding potential predictors of variation in clinical and functional outcome in schizophrenia. Earlier age of onset has been found to be consistently associated with a host of negative outcomes, including greater symptom severity, increased cognitive deficits, and poorer overall functioning. However, very little research has sought to assess the underlying causes for why there is such a strong association between age of onset and these outcomes. There is considerable evidence that age of onset is heritable (i.e., that genetic effects play a significant role in individual differences in age of onset); but to our knowledge, no studies have taken this finding one step further and attempted to examine whether or not genetic effects on age of onset are shared with those affecting clinical outcomes and cognitive and community functioning. Additionally, no studies have investigated whether or not these potential effects are diagnostically specific to schizophrenia.

The current project, therefore, has three overall goals. First, we aim to replicate previous findings in the literature that earlier age of onset is associated with increased clinical severity and decreased community and cognitive functioning, and that age of onset is significantly heritable. Second, we will examine novel research questions concerning the potential causes of the association between age of onset and four different aspects of clinical and general functioning (i.e., positive symptom severity, negative symptom severity, community functioning, and cognitive functioning). Third, we will determine if these effects are diagnostically specific to schizophrenia. The specific research questions are as follows:

1. As expected from the body of literature explored previously, is age of onset significantly correlated with positive and negative symptom severity, community functioning, and cognitive deficits in schizophrenia?
2. Is age of onset of schizophrenia significantly heritable in our sample? That is, is age at onset of schizophrenia correlated among concordant relatives according to degree of genetic resemblance?
3. To what extent does the genetic variation underlying age of onset in schizophrenia overlap with the genetic variation underlying positive and negative symptom severity, cognition, and community functioning? In other words, to what extent do pleiotropic genetic effects cause a correlation between age of onset and clinical outcome measures in schizophrenia?
4. To what extent do environmental factors explain the relationship between age of onset and positive and negative symptom severity, cognition, and community functioning?
5. To what extent is the genetic influence on the relationship between age of onset and clinical outcome measures diagnostically specific? In other words, is there a genetic relationship between age of onset in schizophrenia and measures of functioning in another diagnosis, such as major depression?

Does the potential genetic influence on age of onset in schizophrenia also have some manifestation in unaffected relatives? More specifically, does the genetic influence on age of onset in schizophrenia have any effects on community functioning or cognition in unaffected relatives?

2.0 METHODS

2.1 PARTICIPANTS

The current study is part of a larger multisite project (the Multiplex Multigenerational Investigation; MGI) based at the University of Pittsburgh and the University of Pennsylvania. Probands were included in the study if they: had a diagnosis of schizophrenia; had at least one other first-degree relative with schizophrenia or schizoaffective disorder (depressed type) who could be contacted; had at least 10 first to fourth degree relatives who could be contacted; were at least 18 years old; were of European-American descent; were proficient in English; had not suffered from a traumatic brain injury or other disorder that severely impairs cognition; and were able to provide informed consent. All participants were recruited through the University of Pittsburgh or the University of Pennsylvania via mental health clinics and organizations in Pennsylvania, New Jersey, Delaware, Ohio, West Virginia, Kentucky, Michigan, and Indiana. All available first, second, third, and fourth degree relatives of the probands were assessed.

European-American individuals aged 18-84 were recruited for inclusion in a control group. Individuals were excluded if they or a first-degree relative were diagnosed with a schizophrenia spectrum or a psychotic disorder. Individuals were also excluded if they: were

taking any antipsychotic medications; experienced any recent exacerbation of non-psychotic psychiatric symptoms (e.g., psychiatric hospitalization or psychiatric medication dose increase in the past month); were treated in the last six months with electroconvulsive therapy or for substance abuse; had a medical condition that could produce psychiatric symptoms or cognitive deficits (e.g., Alzheimer's disease); or had a history of a serious head injury. At the University of Pittsburgh site, controls were matched by approximately the geographic area in which the relatives of the schizophrenia probands lived by randomly calling landline telephones in specific zip codes. Controls were also attempted to be matched to the relatives of the schizophrenia probands by average age and sex. All controls at the University of Pittsburgh completed the Diagnostic Interview for Genetic Studies, 2.0 (Nurnberger et al., 1994; see below). At the University of Pennsylvania, controls were recruited via advertisements, and were administered a screening interview.

The total MGI sample includes 773 participants, with 638 pedigree members from 43 multiplex, multigenerational families, and 135 controls.

2.2 DIAGNOSTIC INTERVIEW FOR GENETIC STUDIES (DIGS)

All pedigree participants were assessed using the Diagnostic Interview for Genetic Studies, 2.0 (DIGS) (Nurnberger et al., 1994) in-person via trained interviewers who were not blind to participant proband status. The DIGS is a comprehensive assessment used for genetic studies that documents demographic information, medical history, the presence of major psychiatric disorders, and detailed information pertaining to schizophrenia and psychotic disorders, such as severity of positive, negative, and schizotypal personality symptoms. This information was supplemented by inspection of medical records when possible.

2.3 AGE OF ONSET ASSESSMENT

Age of onset of psychosis was determined by self-report (or by medical records, when available), from the DIGS (Section K, Item number 64), and was defined as the age of the individual's first psychotic symptoms. Age of onset of depression was also determined by self-report from the DIGS (Section F, Item 40). For individuals who reported exceptionally low ages of onset (i.e., less than or equal to 11 years old), the accuracy of their self-report was considered as questionable; therefore, the age at first psychiatric hospitalization (DIGS Section K, Item 6c) was used as a more objective measure.

2.4 NEUROCOGNITIVE BATTERY

Participants were administered a computerized neurocognitive battery (CNB) that has been used with healthy controls (Gur et al., 2001b) and patient samples (Gur et al., 2001a). The battery takes approximately 60 minutes to complete, and tasks were administered in a fixed order. Each task measures both accuracy and reaction time and scores were standardized based on scores from individuals without any psychiatric diagnosis in the Control group (N=95). Next, efficiency scores were calculated by subtracting standardized reaction time (which was defined as median reaction time for correct responses) from standardized accuracy, divided by two. In this way, higher efficiency scores represent better accuracy and faster performance. The battery assesses eight domains: abstraction and mental flexibility, attention, verbal memory, facial memory, spatial memory, spatial processing, sensorimotor dexterity, and emotion processing. Each task is described below, along with definition of accuracy (which is specific to each task). Refer to Table 2 for a brief summary of the measures.

Table 2: Study measures

Measure	Assessment	Subscales	Score used in analyses
Age of onset	Structured clinical interview (DIGS)	N/A	Age (years)
Negative symptoms	Scale for the Assessment of Negative Symptoms (SANS)	Affective flattening/blunting Alogia Avolition/apathy Anhedonia/asociality Attentional impairment	Pro-rated average of items and subscale global scores
Positive symptoms	Scale for the Assessment of Positive Symptoms (SAPS)	Hallucinations Delusions Bizarre behavior Positive formal thought disorder	Pro-rated average of items and subscale global scores
Community functioning	Diagnostic Interview for Genetic Studies, 2.0 (DIGS)	Marital status; living situation; occupational status; Global Assessment of Functioning scale (GAF)	Factor scores (see Methods section)
Cognitive functioning	Penn Computerized Neurocognitive Battery*	Abstraction & mental flexibility (Penn Conditional Exclusion Task)	Factor scores (see Methods section)
		Attention (Penn Continuous Performance Test)	
		Verbal memory (Penn Word Memory Test)	
		Spatial memory (Visual Object Learning Test)	
		Spatial processing (Judgment of Line Orientation task)	
		Sensorimotor dexterity	
		Facial memory (Penn Face Memory Test)	
		Emotion processing (The Penn Emotion Intensity Discrimination Test)	
	Other cognitive measures	Attention & processing speed (The Trail Making Task)	
		Verbal memory (The California Verbal Learning Test)	
		Verbal IQ (Word Reading subtest of the Wide Range Achievement Test)	

*As described in the Methods section, the factor scores were derived from accuracy and speed efficiency scores. These scores were standardized (based on individuals without any psychiatric diagnosis) and used to calculate an overall efficiency score for each measure.

Abstraction and mental flexibility. In each trial, the Penn Conditional Exclusion Task (PCET; Kurtz, Ragland, Moberg, & Gur, 2004) presents four objects simultaneously, and the participant is asked to select which object does not belong with the other three based on one of three sorting heuristics. After each trial, the participant is given feedback about whether or not his/her selection was correct. Accuracy was represented by: (number of categories completed + 1) * (number of correct responses / total number of responses).

Attention. In the Penn Continuous Performance Test (PCPT; Kurtz, Ragland, Bilker, Gur, & Gur, 2001), participants are asked to respond any time a set of seven vertical and horizontal lines form a number. Performance on each trial does not depend on any information from previous trials (i.e., there is no working memory load). Accuracy was defined as the number of correct responses.

Verbal memory. In the Penn Word Memory Test (PWMT; Gur et al., 1993), participants are first presented with 20 target words. Then, those target words are interspersed with 20 distractor words, and the participants are asked to recognize the original target words. Finally, after 20 minutes, there is a delayed recognition trial. The distractor words are matched with the target words on frequency, length, concreteness, and low imageability, based on Paivio's norms. Both accuracy (number of correct responses) and response time were averaged across the immediate and delayed conditions.

Face memory. In the Penn Face Memory Test (Gur et al., 1993), participants are first presented with 20 target faces. Then, those target faces are randomly interspersed with 20 distractor faces, and the participants are asked to recognize the original target faces. Finally, after 20 minutes, there is a delayed recognition trial. Both accuracy (number of correct responses) and response time were averaged across the immediate and delayed conditions.

Spatial memory. In the Visual Object Learning Test (VOLT; Glahn, Gur, Ragland, Censits, & Gur, 1997) participants are first instructed to memorize a set of 10 geometric objects. Then, the target objects are interspersed with 10 distractor objects, and the participants are instructed to recognize the original 10 objects. Finally, after 20 minutes, there is a delayed recognition trial. Both accuracy (number of correct responses) and response time were averaged across the immediate and delayed conditions.

Spatial processing. In this version of the Judgment of Line Orientation Task (JLO; Benton, 1975), participants are shown a series of 11 lines (numbered 1-11) fanned out in a semi-circle and each 18 degrees apart. Then, participants are shown two lines with differing orientations, and asked to match each of those two stimulus lines to the appropriate angle in the semi-circle below. Accuracy was defined as the number of correct responses.

Sensorimotor dexterity. Participants are asked to use a mouse to click on a square appearing at different locations on the computer screen, and the squares become progressively smaller as the task continues (Gur et al., 2001a). Accuracy was defined as the number of correct responses.

Emotion processing. The Emotion Intensity Differentiation task involves 40 trials showing participants two of the same face side by side that varied by emotion intensity. The participants are asked to indicate which of the two faces displays a more intense emotion, and 40 face pairs (20 happy, 20 sad) were used (Gur et al., 2006). The Emotion Recognition Test (Kohler et al., 2003; Gur et al., 2001) randomly presents 40 digitized male or female faces displaying five different emotions (anger, fear, sadness, happiness, or neutral) at either a mild or extreme intensity. The participant is asked to select the more intense expression. Sets were balanced for gender, age, and ethnicity. The scores from these two tasks were averaged to create

an overall Emotion Processing measure. Accuracy for each was defined as the total number of correct responses.

All participants also completed three additional non-computerized tasks (described below).

Attention and processing speed: The Trail Making Task. The Trail Making Task (part A; Reitan, 1958) requires participants to connect a series of circled numbers in sequential order as quickly as possible and with a single line (i.e., without picking the pencil up off of the paper). In part B, the circles contain both numbers and letters, and the participants must connect them in alternating sequential and alphabetical order (e.g., 1, A, 2, B). These two tasks are thought to measure visual scanning, information processing, hand-eye coordination, and executive functioning. The total time (in seconds) taken to complete each task is recorded and multiplied by -1, so that higher scores reflect better (i.e., faster) performance.

The California Verbal Learning Test. In the California Verbal Learning Test (CVLT; Delis et al., 1987), participants are read a series of 16 words and asked to repeat back as many as they can over the course of five attempts. The final number of words recalled on the fifth (final) attempt was used as a measure of verbal memory.

Finally, participants were administered the Word Reading subtest of the Wide Range Achievement Test (WRAT; Wilkinson, 1993), which was used as a broad estimate of verbal IQ. Scores were based on age-standardized norms, which go up to 75 years of age. For those individuals who completed the WRAT but were over 75 years old, their scores were standardized based on the 75 year-old norms.

All scores from the above cognitive measures were adjusted for age and sex and factor scores were used for all analyses (see Preliminary Analyses section below).

2.5 COMMUNITY FUNCTIONING

Community functioning was assessed via four separate measures: marital status, living situation, occupational status, and global functioning. All four measures were combined using factor analysis (see Preliminary Analyses section below) to create overall scores to reflect community functioning. Each item was scored such that higher scores reflected better functioning. The exact ranking system (described below) within each category is based on previous work by Kuo (2014, unpublished manuscript) and varies slightly from the ranking in the DIGS.

Current marital status (DIGS Section A, Item 7). Marital status provides a measure of interpersonal functioning, and participants were ranked as follows: 1) never married; 2) separated or divorced; 3) married or widowed.

Current living situation (DIGS Section A, Item 8). Participants were ranked depending on their level of independence: 1) living in a residential treatment facility; 2) living in a home with relatives; 3) living alone or with roommates; 4) living with an unmarried partner for at least one year; 5) living in his/her own home with a spouse and/or children.

Current occupational status (DIGS Section A, Item 10). Participants were categorized into one of 10 potential employment rankings as a measure of vocational functioning: 1) unemployed and under the age of 65; 2) on disability support; 3) homemaker; 4) operator, fabricator, or laborer; 5) farming, forestry, fishing, production, craft and repair; 6) service; 7) full-time student; 8) technical, sales, or administrative support; 9) professional; 10) managerial positions. For individuals who were retired (e.g., unemployed and over the age of 65), they were coded based on their previous job that required the highest level of responsibility according to the ordered ranking.

Current global functioning (DIGS Section T, Item 3). The Global Assessment of Functioning scale (GAF; Endicott, Spitzer, Fleiss, & Cohen, 1976) measures an individual's lowest level of functioning in the past month on a scale of 1 to 100, with 1 representing the most impairment (e.g., "Needs constant supervision for several days to prevent hurting self or others, or makes no attempt to maintain minimal personal hygiene, or serious suicide act with clear intent and expectation of death"), and 100 representing the highest level of adaptive and independent functioning (e.g., "Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his warmth and integrity. No symptoms").

2.6 SYMPTOM ASSESSMENT

Current negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982), which has 20 items across five domains: affective flattening/blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. Additionally, each domain has a global rating item (for a total of 25 ratings). Each item is scored by a 6-point Likert scale (from 0-5, with 0 representing no symptoms and 5 representing extreme impairment). All items (including the global items) were averaged to create an overall score, which was prorated for the number of completed items in order to adjust for any missing data. Any cases missing more than 50% of the items (i.e., missing 14 or more out of 25) were treated as missing for this measure.

Positive symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Norman, Malla, Cortese, & Diaz, 1996), which has 30 items across four

domains: hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Additionally, each domain has a global rating item (for a total of 34 total ratings). Each item is scored by a 6-point Likert scale (from 0-5, with 0 representing no symptoms and 5 representing extreme impairment). All items (including the global items) were averaged to create an overall score, which was prorated for the number of completed items in order to adjust for any missing data. Any cases missing more than 50% of the items (i.e., missing 18 or more out of 34) were treated as missing for this measure.

3.0 RESULTS

3.1 SAMPLE

The total sample from the MGI study included 773 participants (638 pedigree members and 135 controls) who had diagnostic information and at least one of the four functioning measures or one of the 11 cognition measures. These criteria were then refined such that individuals were only included if they had more than 50% of the 11 cognitive measures or more than 50% of the four functioning measures. With these additional criteria, two unrelated individuals diagnosed with schizophrenia were excluded, for a final sample of 771 participants (636 pedigree members and 135 controls).

Pedigree participants were assigned to one of four hierarchical, mutually exclusive diagnostic groups: Schizophrenia (SC; N = 103)[1], Depression (MDD; N = 110)[2], Other (Other; for all other diagnoses; N = 167)[3], and No Diagnosis (ND; N = 256). Please refer to Appendix Table A1 for comorbidity information.

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[1] This includes individuals with a diagnosis of schizophrenia (N=89) and schizoaffective disorder (N=14).
[2] Individuals with a diagnosis of major depression with psychosis (N = 3), major depression and comorbid schizotypal personality disorder (N = 5), major depression with comorbid paranoid personality disorder (N = 1), and a primary diagnosis of substance use disorder with a secondary diagnosis of major depressive disorder (N = 2) were excluded from the Depression diagnostic group and placed in the Other group, in order to reduce the potential overlap between the Schizophrenia and Depression groups.
[3] One pedigree member with a diagnosis of schizophrenia was placed in the Other group, due to a comorbid diagnosis of mild mental retardation.

3.2 DEMOGRAPHIC CHARACTERISTICS

Demographic information for all groups is presented in Table 3. All omnibus tests of group differences in the five demographic variables (recruitment site, sex, age, years of education, and parental education) were significant. Post-hoc tests of significance indicated that, compared to the Control group, the Schizophrenia group had a significantly smaller percentage of participants from the Pitt site, significantly more male participants, were significantly younger, and had significantly fewer years of education. Compared to the Depression group, the Schizophrenia group had significantly more male participants and significantly fewer years of education.

Table 3: Demographic characteristics

		Site	Sex	Age	Education, years (self)	Education, years (Average parental)*
	Total N	**% Pitt (N)**	**% Male (N)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Total sample	771	46.6% *(359)*	46.3% *(357)*	46.84 *(17.62)*	13.46 *(2.93)*	11.93 *(3.24)*
Pedigree members	636	42.6% *(271)*	48.3% *(307)*	45.17 *(17.36)*	13.15 *(2.93)*	11.76 *(3.27)*
SC	103	38.8%[a] *(40)*	58.3%[a] *(60)*	46.63[a] *(12.54)*	12.44[a] *(2.72)*	12.34[ab] *(2.90)*
MDD	110	49.1%[ab] *(54)*	27.3%[b] *(30)*	43.42[a] *(14.45)*	13.65[b] *(2.88)*	12.10[ab] *(3.56)*
Other	167	37.1%[a] *(62)*	67.1%[a] *(112)*	43.28[a] *(17.10)*	12.73[ab] *(2.99)*	11.43[a] *(3.00)*
ND	256	44.9%[a] *(115)*	41.0%[b] *(105)*	46.56[a] *(20.04)*	13.50[b] *(2.92)*	11.61[ab] *(3.42)*
CTL	135	65.2%[b] *(88)*	37.0%[b] *(50)*	54.71[b] *(16.75)*	14.92[c] *(2.43)*	12.61[b] *(3.02)*
Statistic		27.83	58.43	9.94	15.16	3.36
df		4	4	4, 766	4, 764	4, 684
p-value		< 0.001	< 0.001	< 0.001	<0.001	0.01

* Parental education is the average of maternal and paternal years of education. For those individuals that were missing one, the other was substituted. 82 individuals were missing both maternal and paternal education.

Note: Group abbreviations: SC = Schizophrenia; MDD = Depression; Other = Other diagnoses; ND= No diagnosis; CTL= Control. Results of one-way ANOVAs for age and education are reported with the F statistic, and results for site and sex are reported with the Pearson chi-square statistic. Post-hoc Tukey's pairwise tests were conducted to compare each group. Values sharing the same superscripts did not differ significantly ($p \geq 0.05$) from one another (i.e., are within the same homogeneous subset).

3.3 DATA PREPARATION

Of the 103 individuals in the Schizophrenia group, 85 had available age of onset of psychosis data. Six of these individuals reported exceptionally low ages of onset (1, 5, 6, 7, 9, and 11 years old), and due to the questionable nature of these self-reported ages, each individual's age at first hospitalization was used instead as a more objective measure. In the Depression group, 84 individuals reported age of first depressive episode onset. Three individuals in the Depression group reported ages of onset later than their current age, in which case, age of onset was changed to match current age.

As mentioned previously, all participants missing diagnostic information or more than 50% of the cognition variables and more than 50% of the functioning variables were excluded from analyses**.** The efficiency scores for the eight CNB cognitive tasks, the raw scores for the CVLT, Trails A, and Trails B, and the standardized WRAT scores were all evaluated for outliers. Any score that was more than three deviations beyond the mean and more than two standard deviations beyond the next closest score was Winsorized (e.g., assigned the next score closest to the mean). One score each was changed in this way for the Verbal Memory task, the Spatial Memory task, and the Trails A task, and two scores were changed for the Sensorimotor task. The distributions of each variable were also assessed for skewness and kurtosis and transformations were considered unnecessary.

3.4 PRELIMINARY ANALYSES

The Schizophrenia group had an average age of onset of 21.53 years old (*SD*=7.75, N=85) and an average duration of illness of 24.29 years (*SD*=13.27, N=85). The distribution of age of onset is provided in Figure 2. Males had a mean age of onset of 20.32 years old (*SD*=5.83, N=50) and females had a later mean age of onset of 23.26 years old (*SD*=9.71, N=35), although this difference was not significant ($F(1,83)=3.029$, $p=0.086$). The Depression group had an average age of onset of depression of 25.09 years old (*SD*=11.83, N=88) and an average duration of illness of 17.62 years (*SD*=12.47, N=88).

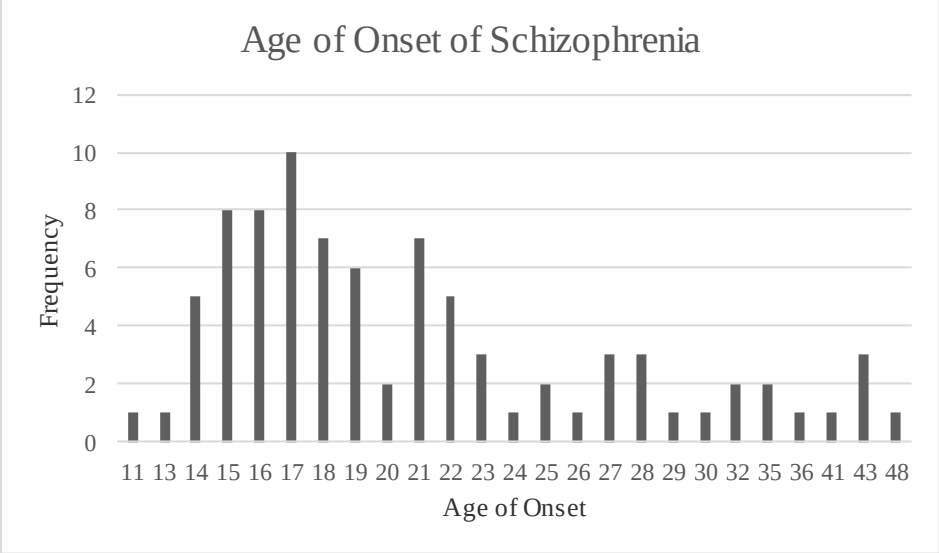

Figure 2: Frequency distribution of age of onset for Schizophrenia group

Table 4 presents the cognition scores. The Other diagnosis group was dropped from all further analyses, as it is not relevant to the current project. One-way ANOVAs were conducted with age and sex as covariates, and there were significant overall group differences for each cognitive measure. Post-hoc comparisons with Bonferroni correction indicated that the Schizophrenia group performed significantly worse than the Depression group, No Diagnosis group, and Control group on every measure.

Table 4: Cognitive measures by diagnostic group

	SC	**MDD**	**ND**	**CTL**	***F***	***df***	***p***
Overall N	103	110	256	135			
Abstraction and Mental Flexibility[1]	-0.80[a] *(0.93)*, N=76	0.24[b] *(0.68)*, N=99	0.06[b] *(0.82)*, N=232	0.04[b] *(0.89)*, N=135	40.80	5, 536	<0.001
Attention[1]	-1.14[a] *(1.35)*, N=70	0.08[b] *(0.74)*, N=99	0.01[b] *(0.82)*, N=223	0.06[b] *(0.70)*, N=132	41.29	3, 518	<0.001
Verbal Memory[1]	-0.98[a] *(1.53)*, N=77	0.01[bc] *(0.80)*, N=99	-0.11[b] *(1.03)*, N=237	0.01[c] *(0.84)*, N=135	22.72	3, 542	<0.001
Facial Memory[1]	-0.72[a] *(1.41)*, N=80	0.21[c] *(0.82)*, N=99	-0.11[b] *(0.99)*, N=238	0.02[bc] *(0.83)*, N=134	21.34	3, 545	<0.001
Spatial Memory[1]	-0.41[a] *(1.06)*, N=73	0.21[b] *(0.79)*, N=97	0.10[b] *(0.86)*, N=234	0.09[b] *(0.76)*, N=135	16.07	3, 533	<0.001
Spatial Processing[1]	-0.80[a] *(1.51)*, N=67	0.10[b] *(0.82)*, N=101	0.04[b] *(0.87)*, N=235	0.07[b] *(0.77)*, N=134	26.47	3, 531	<0.001
Sensori-motor Dexterity[1]	-1.18[a] *(1.82)*, N=75	0.16[bc] *(0.71)*, N=97	0.01[b] *(1.00)*, N=229	0.04[c] *(0.91)*, N=135	40.55	3, 530	<0.001
Emotion Processing[1]	-0.80[a] *(0.91)*, N=69	0.12[bc] *(0.66)*, N=99	-0.08[b] *(0.91)*, N=234	0.02[c] *(0.77)*, N=135	29.36	3, 531	<0.001

Trails A[2]	51.26[a] *(29.66)*, N=77	30.22[b] *(11.39)*, N=101	34.24[b] *(18.55)*, N=237	32.37[b] *(14.58)*, N=135	27.87	3, 544	<0.001
Trails B[2]	134.31[a] *(76.81)*, N=73	69.14[b] *(31.00)*, N=102	76.02[b] *(48.35)*, N=233	76.33[b] *(45.97)*, N=134	36.17	3, 536	<0.001
CVLT[3]	9.37[a] *(3.41)*, N=70	12.18[b] *(2.87)*, N=95	12.03[b] *(2.80)*, N=230	12.00[b] *(2.73)*, N=96	16.09	3, 485	<0.001
WRAT[4]	92.44[a] *(15.94)*, N=78	101.43[b] *(12.00)*, N=103	103.44[b] *(12.81)*, N=237	108.34[b] *(8.43)*, N=115	24.13	3, 527	<0.001
Cognitive Factor Score	-3.12[a] *(2.37)*, N=77	-0.41[bc] *(0.82)*, N=99	-0.73[b] *(1.28)*, N=238	0.00[c] *(0.89)*, N=135	87.90	3, 543	<0.001

Note: SC=schizophrenia; MDD=depression; Other=all other diagnoses; CTL=control group. Mean first and standard deviation in parentheses. All efficiency scores are z-scores based on individuals in the Control group without any diagnoses (N=95). One-way ANOVAs with age and sex entered as covariates. Post-hoc mean comparisons were conducted with Bonferroni corrections, and items sharing a superscript were not significantly different ($p \geq 0.05$) from one another. The Other group (N=167) has been excluded from subsequent analyses because it is not relevant to the main hypotheses.

[1] Efficiency scores; [2] Seconds; [3] Words recalled; [4] Standard scores

Table 5 presents the community functioning scores. One-way ANOVAs were conducted with age and sex as covariates, and there were significant group differences for each community functioning measure. Post-hoc comparisons with Bonferroni correction indicated that the Schizophrenia group reported significantly poorer functioning than each group on every measure.

Table 5: Community functioning measures by diagnostic group

	SC	MDD	ND	CTL	*F*	*df*	*p*
Overall N	103	110	256	135			
Current Marital Status[1]	1.60 [a] *(0.76)* N=102	2.31[b] *(0.86)* N=110	2.32[b] *(0.89)* N=253	2.33[b] *(0.89)* N=88	27.21	3, 547	<0.001
Current Living Situation[2]	2.43[a] *(1.38)* N=91	4.04[b] *(1.25)* N=108	3.90[b] *(1.32)*, N=249	4.12[b] *(1.16)*, N=84	38.60	3, 526	<0.001
Current Occupational Status[3]	1.83[a] *(2.11)* N=103	6.17[b] *(2.88)* N=110	6.50[bc] *(2.72)*, N=251	7.31[c] *(2.73)*, N=88	90.20	3, 546	<0.001
Current Global Functioning[4]	46.13[a] *(17.14)* N=93	78.82[b] *(11.00)* N=103	86.63[c] *(8.07)*, N=234	85.95[c] *(10.48)*, N=84	303.15	3, 508	<0.001
Community Functioning Factor Score	-8.63[a] *(1.83)*, N=103	-1.50[b] *(1.18)*, N=110	-0.13[cd] *(0.53)*, N=251	0.000[d] *(0.50)*, N=88	1780.28	3, 546	<0.001

Note: Mean first and standard deviation in parentheses. One-way ANOVAs with age and sex entered as covariates. Post-hoc mean comparisons were conducted with Bonferroni corrections, and items sharing a superscript were not significantly different ($p \geq 0.05$) from one another. The Other group (N=167) has been excluded from subsequent analyses because it is not relevant to the main hypotheses. Higher scores reflect better functioning for all measures.

[1] Range: 1 to 3.
[2] Range: 1 to 5.
[3] Range: 1 to 10.
[4] Range: 1 to 100.

The average negative symptom score based on the SANS was 1.56 (*SD*=1.04, N=90) and the average positive symptom score based on the SAPS was 0.93 (*SD*=0.73, N=89). As mentioned previously, both the SANS and the SAPS use a 0-5 Likert scale, with higher scores indicating increased symptom severity. These relatively low symptom severity scores are not unexpected considering the use of an outpatient community sample.

To create unified outcome measures for global cognitive and community functioning, exploratory and confirmatory factor analyses were conducted. All cognitive scores were first adjusted for age based on the control sample (our estimate of the general population). Specifically, for each measure, age was used in a regression equation to predict the cognitive score in a subset of the control group that was not diagnosed with any psychiatric disorder (N=95). The age-corrected cognitive score for each participant in the entire sample was then created by multiplying the regression equation unstandardized beta weight for age by the individual's age, then adding the regression equation constant, and subtracting that value from the individual's cognitive score. In the same way, the scores were then adjusted for sex. These age- and sex-adjusted scores were then used in exploratory factor analyses and confirmatory factor analysis using the Mplus program (Muthén & Muthén, 2011). The same procedure was implemented for the community functioning measures.

3.5 EXPLORATORY FACTOR ANALYSES

The exploratory factor analysis (EFA) for the Schizophrenia diagnostic group was conducted using a maximum likelihood estimator, geomin rotation (non-orthogonal), and parallel analysis with 500 iterations. The variables were age- and sex-adjusted efficiency scores that were

standardized based on the control group for the 11 cognitive measures. A scree plot of the Eigenvalues favored a one-factor solution (Eigenvalues: Factor 1 = 6.246, Factor 2 = 1.072, Factor 3 = 0.875) and a parallel analysis indicated that only the first factor explained more variance than randomly generated data (95 percentile Eigenvalues of randomly generated data: Factor 1 = 1.931; Factor 2 = 1.622; Factor 3 = 1.440). However, from a model fit index perspective, the three-factor model fit best (CFI = 0.999, TLI = 0.997, RMSEA=0.017), compared to the two-factor model (CFI = 0.972, TLI = 0.954, RMSEA = 0.064) and the one-factor model (CFI = 0.884, TLI = 0.855, RMSEA = 0.113). (The four-factor model did not converge.) Given the difficulty of achieving overall model fit with 11 variables and the clear preference of a single factor from the parallel analysis, we chose to adopt a one-factor solution to proceed with the confirmatory factor analysis.

Separate EFAs were completed for cognition in the Depression, No Diagnosis, and Control diagnostic groups as well, and similar determinations were made. A one-factor model was generally preferred by parallel analysis in all groups, which we used as the basis for proceeding with the confirmatory factor analyses using all four groups in a single dataset. Appendix Table A2 provides the 1-factor solution factor loadings for each diagnostic group, and Appendix Table A3 provides the results from the parallel analyses.

The same approach was used to complete a geomin-rotated EFA for community functioning in the Schizophrenia group. The Eigenvalues supported a one-factor model (Eigenvalues: Factor 1 = 2.071, Factor 2 = 0.985, Factor 3 = 0.624) and the parallel analysis indicated that only the first factor explained more variance than randomly generated data (95 percentile Eigenvalues of randomly generated data: Factor 1 = 1.382; Factor 2 = 1.158; Factor 3 = 0.997). The overall fit was moderate (CFI = 0.911, TLI = 0.733, RMSEA = 0.182). As with the

analyses of cognitive functioning, separate EFAs for community functioning were completed in the Depression, No Diagnosis, and Control groups and a single factor solution was considered appropriate. Appendix Table A2 provides the 1-factor solution factor loadings for each diagnostic group, and Appendix Table A3 presents the results of the parallel analysis.

3.6 FACTOR INVARIANCE ACROSS GROUPS: CONFIRMATORY FACTOR ANALYSES

The primary goal of these analyses was to determine if it was reasonable to use cognition scores and community functioning scores from a single-factor model across diagnostic groups (i.e., to determine if there was factor invariance across the four diagnostic groups). Confirmatory factor analysis (CFA) allowed us to assess the fit of a 1-factor model across all diagnostic groups and to compare "strong" and "weak" invariance models. Conceptually, the "weak" model tests to see if it is reasonable to keep the same number of factors (in this case, 1 factor) across groups while allowing all other parameters to vary across groups, while the "strong" model tests if the factor loadings can be set equal across groups. Strong factor invariance implies that any observed group differences can be attributed to latent mean differences, not just variations in the factor structure. These two models can be compared using the Bayesian Information Criterion (BIC), which provides a general estimate of the quality of the model by indicating how much information is lost (or not represented) in the current model (and incorporates a penalty for overfitting a model). Therefore, lower BIC scores are preferred when comparing models.

Maximum likelihood CFA with one factor was completed for cognition using scores from the Schizophrenia, Depression, No Diagnosis, and Control groups. In the "weak invariance"

model, the number of factors was constrained to one and the latent mean was set to zero in each diagnostic group, but the variance, factor loadings (i.e., paths), residuals, and intercepts were all free to vary across groups. In the "strong invariance" model, the number of factors was constrained to one, all factor loadings and intercepts were set to equal one another in each group (e.g., the factor loading on abstract thinking and flexibility was set to be equal in the Schizophrenia, Depression, No Diagnosis, and Control groups, along with their intercepts), the latent mean was set to zero and the variance was set to one in the base group and both were free to vary in the other groups. The fit of both models was somewhat poor based on standard fit indices (weak model: CFI = 0.831, TLI = 0.788, RMSEA = 0.104; strong model: CFI = 0.785, TLI = 0.800, RMSEA = 0.101), but the BIC preferred the strong model over the weak model (weak model BIC = 22490.912, strong model BIC = 22243.160). Therefore, factor scores for each individual in all four groups were generated using the strong invariance model. (See Table 4 for the mean factor scores by group. As expected, the Schizophrenia group performed significantly more poorly than all other diagnostic groups.)

The same procedure was used for community functioning. The marriage status and living status measures were fairly highly correlated (R=0.653), and a model in which the residuals of marriage and living were allowed to covary was preferred by the BIC, as compared to the model in which they were uncorrelated (9220.379 and 9529.694, respectively). Both the weak and strong models fit moderately well (weak model: CFI = 0.969, TLI = 0.906, RMSEA = 0.108; strong model: CFI = 0.915, TLI 0.918, RMSEA = 0.101), but the BIC preferred the strong model (9270.558 and 9202.290, respectively). Factor scores for each individual in the four groups were generated using the strong model allowing the residuals of marriage and living

status to covary. (Table 5 presents the descriptive statistics of the factor scores for each group. As expected, the Schizophrenia group performed more poorly than all other diagnostic groups.)

3.7 THE RELATIONSHIP BETWEEN AGE OF ONSET AND CLINICAL SEVERITY IN SCHIZOPHRENIA

Within the Schizophrenia group, phenotypic correlations were calculated using SOLAR (Almasy & Blangero, 1998) with age and sex as covariates, and the data are presented in Table 6. As predicted, earlier age of onset was significantly associated with increased severity of negative symptoms, positive symptoms, poorer community functioning, and poorer cognitive functioning.

Table 6: Correlations and heritabilities in the Schizophrenia group

	Age of onset (AOO)	Negative symptoms (SANS)	Positive symptoms (SAPS)	Cognitive Functioning	Community Functioning
Phenotypic correlation with AOO	--	-0.196 (0.003)*	-0.228 (0.045)*	0.295 (0.030)*	0.318 (0.008)*
Univariate heritability	0.198 (0.277)	0.977 (<0.001)*	0.853 (0.003)*	0.835 (0.013)*	0.320 (0.182)
Genetic correlation with AOO	--	-1.00 (0.007)*	-1.00 (0.296)	1.00 (0.120)	1.00 (0.590)
Environmental correlation with AOO	--	1.00 (0.078)	0.103 (0.889)	-0.106 (0.840)	-0.248 (0.388)

Note: Heritabilities and correlations are listed first with the *p* value in parentheses below. Analyses were conducted in SOLAR and age and sex were entered as covariates.
* significant at $p = 0.05$

3.8 HERITABILITY OF AGE OF ONSET, SYMPTOM SEVERITY, AND COMMUNITY AND COGNITIVE FUNCTIONING IN SCHIZOPHRENIA

Table 6 also presents the heritabilities of age of onset, negative symptoms, positive symptoms, community functioning, and cognitive functioning within the Schizophrenia group. Although approximately 20% of the variation in age of onset in our sample could be attributed to genetic effects, this was not statistically significant ($p = 0.277$). Negative symptoms, positive symptoms, and cognitive functioning were all significantly heritable. Although 32% of the variance in community functioning was attributed to genetic factors, this was not significant ($p = 0.182$).

3.9 SHARED GENETIC VARIATION IN AGE OF ONSET AND CLINICAL SEVERITY IN SCHIZOPHRENIA

With this key research aim, our goal was to examine if the genetic effects that contributed to variation in age of onset of psychosis were in any part shared with those genetic effects that contributed to our outcome measures of interest. We assessed this overlap using the genetic correlations between age of onset and our outcome measures of interest, and these results are presented in Table 6. Genetic effects explained a significant proportion of the shared variation between earlier age of onset and increased severity of negative symptoms ($R_g = -1.00$, $p = 0.007$). While the genetic correlations between age of onset and positive symptoms, community functioning, and cognitive functioning were all estimated at the upper limit (e.g., $R_g = 1.00$ or -1.00), these genetic correlations were not significant, perhaps due to the lower heritability of the measures individually.

3.10 CORRELATED ENVIRONMENTAL VARIATION IN AGE OF ONSET AND CLINICAL CHARACTERISTICS IN SCHIZOPHRENIA

Table 6 presents the environmental correlations between age of onset and the outcome measures of interest, which were all fairly low and not significant, with the exception of the correlation between age of onset and negative symptoms, which was estimated at the upper limit and also not significant.

3.11 RELATIONSHIP BETWEEN AGE OF ONSET IN SCHIZOPHRENIA AND CLINICAL SEVERITY IN DEPRESSED RELATIVES

The purpose of this research aim was to assess whether or not there is evidence for shared genetic effects between age of onset in individuals with schizophrenia and functioning in their relatives with depression. As presented in Table 7, the genetic correlations between age of onset in schizophrenia and community or cognitive functioning in depressed relatives were small and not significant for community functioning, and while the genetic correlation was at its upper limit for cognitive functioning (i.e., at 1.00), this was not significant (p=0.836).

3.12 RELATIONSHIP BETWEEN AGE OF ONSET IN SCHIZOPHRENIA AND GENERAL FUNCTIONING IN RELATIVES WITH NO PSYCHIATRIC DIAGNOSES

We wanted to know if the genetic effects that may be influencing community functioning and cognition via age of onset in schizophrenia may also be predictive of community or cognitive functioning in relatives without any psychiatric diagnosis (Table 8). Similar to the previous analyses, the genetic correlation with community functioning was small and not significant and the genetic correlation was at its upper limit but non-significant for cognitive functioning.

Table 7: Heritabilities and correlations between the Schizophrenia and Depression groups

	Cognitive Functioning in MDD	Community Functioning in MDD
Univariate heritability	0.385 (0.189)	0.555 (0.051)
Genetic correlation with AOO in SC	1.00 (0.836)	0.160 (0.891)

Note: SC=schizophrenia; MDD=depression. Heritabilities and correlations are listed first with the *p* value in parentheses below. Analyses were conducted in SOLAR and age and sex were entered as covariates.

Table 8: Heritabilities and correlations between the Schizophrenia and No Diagnosis groups

	Cognitive Functioning in ND	Community Functioning in ND
Univariate heritability	0.131 (0.148)	0.430 (0.0009)*
Genetic correlation with AOO in SC	1.00 (0.778)	-0.137 (0.776)

Note: SC=schizophrenia; ND=no diagnosis. Heritabilities and correlations are listed first with the *p* value in parentheses below. Analyses were conducted in SOLAR and age and sex were entered as covariates.

4.0 DISCUSSION

Schizophrenia is a heterogeneous diagnosis in terms of both genetic influences and clinical presentation. Age of onset is among the most useful indicators in predicting the course and severity of the disorder. Consistent with the prior literature, this study found that earlier age of onset was significantly associated with increased severity of positive and negative symptoms, and poorer community functioning and global cognitive functioning. While the estimates of the heritability of age of onset range considerably in literature, the weighted average of 23 studies suggested that age of onset is roughly 60% heritable (Table 1). The heritability of age of onset in this particular study was around 20%, however. While the reasons for this discrepancy are not entirely clear, there are a number of potential factors that could affect this estimate. In terms of comparison to other similar studies, only one other study utilized an extended pedigree design with multiplex ascertainment (as compared to a twin or first-degree relative study; Hare et al., 2010), and their heritability estimate was 33% (Table 1). Our finding of 20% is lower than theirs, but the range of other estimates is substantial. While our sample size was considerable, the number of affected individuals with usable age of onset data (N=85) was smaller than the other extended pedigree study (N=717), and this smaller sample size could lead to less precise estimates. Our age of onset assessment itself also could have contributed to error, in that the report was retrospective and only 85 out of the 103 individuals with schizophrenia provided age of onset data that was not highly questionable (e.g., one individual reported an age of psychosis

onset of 1 year old). These estimates were corroborated with medical records when possible, but these data are largely retrospective and self-reported, and potentially subject to error. However, the vast majority of other studies have also relied on retrospective reports of age of onset as well. Finally, it could be the case that various environmental influences (e.g., birth complications, drug use) contributed more strongly to phenotypic variation than genetic influences; however, we do not have the measures necessary to test this particular theory in our sample, and it is unclear why this sample would differ from other studies on these factors. Future research that utilizes multiple types of study designs and datasets could be helpful in explaining the range of estimates for the heritability of age of onset.

There is strong evidence from this study and many others that 1) age of onset is a useful predictor of symptom severity, community functioning, and cognitive functioning and 2) schizophrenia risk, age of onset of schizophrenia, symptom severity, and cognitive functioning are all influenced by genetic effects. Are the genetic effects that influence variation in age of onset shared with those that influence functional and clinical outcomes in schizophrenia? The current study is inconclusive, but there is some evidence to suggest that there may be shared genetic variance, which could help explain the correlation between age of onset of schizophrenia and outcome measures such as symptom severity, community functioning, and cognitive functioning. All estimates of the shared genetic variance were estimated at the upper limit (e.g., R_g = -1.00 or 1.00; Table 6), but the only relationship that was significant was between age of onset and negative symptom severity. Since the heritability of age of onset was lower than expected (and not significant), it could be that the proportion of genetic variance that is shared between age of onset and our other outcome measures of interest was high, but that the total amount of variance explained was so small that these relationships were not significant.

Simulation studies indicate that the power to detect the genetic correlation is a function of the heritability of each individual phenotype (Verhulst, 2017); therefore, if the univariate heritability is low for one or both of the individual measures, there is less power to detect genetic correlations between the two measures. Consistent with this hypothesis, in our sample, the negative symptom measure had the highest univariate heritability of any of the outcome measures (Table 6), and this was the only genetic correlation to reach significance.

We did not find evidence for correlated effects due to the environment between age of onset and any of our outcome measures of interest. The fact that we did not find significant correlated environmental effects or shared genetic effects (for the most part) suggests that our sample may be underpowered.

We did not find evidence in support of a genetic relationship between age of onset in schizophrenia and community or cognitive functioning in their depressed relatives. The main purpose of these analyses was to determine if any genetic effects on age of onset in schizophrenia have significant overlap with the genetic variance that influences functional outcomes in relatives with depression. Our non-significant results suggest that any genetic variance that influences age of onset is not transdiagnostic. However, as we did not find evidence of significant heritability for age of onset in schizophrenia or for a significant genetic relationship between age of onset and community and cognitive functioning within the schizophrenia group, the non-significant findings in the Depression group could be an indication of an absence of age of onset genetic effects in schizophrenia or low power, rather than diagnostic specificity.

We were also interested in assessing whether or not any genetic variation that influenced age of onset in schizophrenia may be related to community and cognitive functioning in their

relatives without any psychiatric diagnoses. In line with our previous findings for depressed relatives, our results did not support a relationship between any genetic effects on age of onset in schizophrenia and community or cognitive functioning in relatives with no psychiatric diagnoses. Again, this is consistent with the proposal that any genetic factors that may be influencing age of onset in schizophrenia are not transdiagnostic. However, given the non-significant findings in schizophrenia, this may also reflect an absence of genetic effects or low statistical power.

While not a main goal of the current study, the heritabilities for the various measures are also interesting. Negative and positive symptoms were both strongly and significantly heritable in the schizophrenia group (Table 6), in spite of the cross-sectional nature of the measures and the waxing and waning nature of symptomatology (and of positive symptoms, in particular). Cognition was also significantly heritable in the Schizophrenia group, but not in the Depression (Table 7) or No Diagnosis group (Table 8), which was unexpected. This could be due to increased variation in cognitive functioning in the schizophrenia group (Levene's test of equality of variance for: Schizophrenia, Depression, No Diagnosis, Control groups $F(3, 548) = 74.735$, $p < 0.001$; Schizophrenia and Depression, $F(1, 211) = 11.894$, $p = 0.01$; Schizophrenia and No Diagnosis, $F(1, 352) = 155.848$, $p < 0.001$; and Schizophrenia and Control, $F(1, 189) = 69.135$, $p < 0.001$). Interestingly, community functioning was significantly heritable in the Schizophrenia and Depression groups and approached significance in the No Diagnosis group, in spite of similarly increased variance in the Schizophrenia group ($F(2, 461) = 85.879$, $p < 0.001$). The low heritabilities for cognition and community functioning in the Depressed and No Diagnosis groups could also contribute to low power to detect genetic correlations with age of onset in the Schizophrenia group.

4.1 LIMITATIONS

The current study has many strengths, including the: extended pedigree sample; thorough measures of many different aspects of symptom, cognitive, and community functioning; age and sex adjustments based on the control group; use of factor invariance analyses to create more accurate composite measures (i.e., factor scores) for our community and cognitive functioning measures; and novel research questions. However, there are also limitations that should be considered. First, it should be noted that the depressed individuals and relatives without any diagnosis may not be typical, due to their genetic relation to at least two individuals diagnosed with schizophrenia. This could bias our results against finding diagnostic specificity of effects. This limitation is unavoidable, however, as it is necessary to have related individuals in order to assess genetic cross-correlations, and in spite of this potential bias, we did not find transdiagnostic effects.

Second, as mentioned previously, our estimate of the heritability of age of onset could be attenuated due to our somewhat small sample size or the self-reported and retrospective age of onset measure.

Third, the current dataset is cross-sectional, and without longitudinal data, it is not possible to determine the causal nature of any shared genetic effects. For example, significant genetic correlations, such as those found between age of onset and negative symptoms, could arise due to: genetic effects on age of onset, which then directly causes negative symptoms; genetic effects on negative symptoms, which then directly cause age of onset; or genetic effects that affect both age of onset and negative symptoms.

A final consideration is the potential influence of medication effects. The participants with schizophrenia were currently or had been prescribed psychotropic medications, but there is

considerable variation in medication type, dosage, and in how consistently each individual takes the medication as prescribed (and we do not have thorough measures of this variability in our sample). Although this could serve to increase noise in the outcome data and may make it more difficult to find significant correlates of age of onset, we were able to find significant phenotypic correlations with all outcome measures.

4.2 CONCLUSION

The heterogeneity of the schizophrenia diagnosis has been of interest to researchers for decades, and even though age of onset is one of the most useful predictors of outcome, there has been limited research to date explaining why this relationship might exist. We were able to replicate previous findings that earlier age of onset is associated with more severe symptomatology and poorer community and cognitive functioning, and were able to do so in an extended pedigree sample with in-depth measurement techniques. To the best of our knowledge, this study was the first to examine the potential genetic relationship between age of onset and functioning in schizophrenia. We found significant overlap of genetic variance between age of onset and negative symptoms in schizophrenia, and while no other genetic correlations reached significance, neither did any of our environmental correlations, which suggests that the current study may be somewhat underpowered to detect such effects. Due to the extended nature of our sample, we were also able to assess diagnostic specificity, and our findings are consistent with the proposal that any genetic effects influencing age of onset in schizophrenia are not transdiagnostic.

APPENDIX A

A.1 TABLE A1: MUTUALLY EXCLUSIVE DIAGNOSTIC GROUPS AND COMORBIDITIES

Table A1: Mutually exclusive diagnostic groups and comorbidities

Diagnostic group & Comorbid diagnoses	Total diagnoses (N)	Total participants (N)
Pedigree members		
Schizophrenia (SC)	--	103
No comorbid diagnosis	65	
Substance dependence or abuse	42	
Depressive disorder NOS	9	
Mood disorder NOS	1	
Antisocial personality disorder	1	
Borderline Intellectual Functioning	1	
Caffeine related disorder NOS	1	
Depression (MDD)	--	110
No comorbid diagnosis	76	
Substance dependence or abuse	38	
Dysthymic disorder	3	
Personality disorder NOS	2	
Panic disorder with agoraphobia	2	
Bulimia nervosa	1	
Borderline personality disorder	1	
Unspecified adjustment disorder	1	
Oppositional defiant disorder	1	
Other	--	167
Substance dependence or abuse	143	
Depressive disorders	48	
Psychotic disorders and Schizotypal PD	36	
Adjustment disorders	10	
Personality disorders	9	
Bipolar disorders	7	
Externalizing disorders	5	
Dementia and other cognitive disorders	4	
Anxiety disorders	3	
Eating disorders	1	
No Diagnosis (ND)	--	256
Total	--	636
Non-pedigree members		
Control (CTL)	---	135
No diagnosis	96	
Depressive disorders	32	
Substance dependence or abuse	21	
Adjustment disorders	4	
Personality disorders	1	
Entire sample total		771

A.2 TABLE A2: SEPARATE EFA 1-FACTOR SOLUTION FACTOR LOADINGS FOR COGNITION AND COMMUNITY FUNCTIONING IN SC, MDD, ND, AND CTL GROUPS

Factor Item	Factor loadings, 1-factor solution	Factor loadings, 1-factor solution	Factor loadings, 1-factor solution	Factor loadings, 1-factor solution
	SC group	MDD group	ND group	CTL group
Cognitive measures				
Abstraction and Mental Flexibility	0.623*	0.594*	0.546*	0.495*
Attention	0.648*	0.391*	0.587*	0.340*
Verbal Memory	0.859*	0.598*	0.610*	0.681*
Facial Memory	0.900*	0.661*	0.742*	0.546*
Spatial Memory	0.776*	0.547*	0.530*	0.563*
Spatial Processing	0.733*	0.551*	0.626*	0.589*
Sensorimotor Dexterity	0.733*	0.414*	0.637*	0.395*
Emotion Processing	0.658*	0.403*	0.682*	0.403*
Trails A	0.693*	0.421*	0.588*	0.462*
Trails B	0.741*	0.430*	0.676*	0.603*
CVLT	0.419*	0.409*	0.146	0.454*
Community Functioning Measures				
Marital status	0.672*	0.653*	1.069*	0.931*
Living situation	0.969*	1.002*	0.675*	0.804*
Occupation	0.317*	0.102*	0.207*	-0.171
GAF	0.394*	0.302*	-0.006	0.271*

* = significant at p=0.05.

Note: Separate EFAs were conducted for each diagnosis and for each diagnosis (i.e., 8 separate EFAs were completed and are displayed in the table above).

A.3 TABLE A3: RESULTS FROM EFA: EIGENVALUES (λ) AND 95% RANDOMLY-GENERATED EIGENVALUES VIA PARALLEL ANALYSIS (λp)

	Factor 1		Factor 2		Factor 3	
	λ	**λ_p**	**λ**	**λ_p**	**λ**	**λ_p**
SC						
Cognitive Functioning	6.246	1.931	1.072	1.622	0.875	1.440
Community Functioning	2.071	1.382	0.985	1.158	0.624	0.997
MDD						
Cognitive Functioning	3.493	1.770	1.554	1.535	1.106	1.374
Community Functioning	1.840	1.372	1.050	1.154	0.776	0.999
ND						
Cognitive Functioning	4.466	1.459	1.142	1.327	0.929	1.242
Community Functioning	1.808	1.232	1.098	1.095	0.822	0.926
CTL						
Cognitive Functioning	3.574	1.652	1.173	1.450	1.12	1.324
Community Functioning	1.923	1.397	0.993	1.162	0.846	0.993

Note: The parallel analysis produces Eigenvalues based on a randomly-generated dataset with the same dimensionality as the observed dataset. The Eigenvalues presented here (λ_p) represent the 95th percentile from the randomly-generated dataset; therefore, any Eigenvalues from the observed dataset (λ) that are larger than (λ_p) are significant at p=0.05.

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