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Transitive Inference Deficits in Unaffected Biological Relatives of Schizophrenia Patients

Obiora E. Onwuameze, M.D., Ph.D.¹, Debra Titone, Ph.D.², and Beng-Choon Ho, M.D.³

¹Department of Psychiatry, Southern Illinois University Medical School, Springfield, IL, USA

²Department of Psychology, McGill University, Montreal, QC, Canada

³Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Abstract

Currently available treatments have limited efficacy in remediating cognitive impairment in schizophrenia. Efforts to facilitate cognition-enhancing drug discovery recommend the use of varied experimental cognitive paradigms (including relational memory) as assessment tools in clinical drug trials. Although relational memory deficits are increasingly being recognized as a reliable cognitive marker of schizophrenia, relational memory performance among unaffected biological relatives remains unknown. Therefore, we evaluated 73 adolescents or young adults (22 first- and 26 second-degree relatives of schizophrenia patients and 25 healthy controls (HC)) using a well-validated transitive inference (TI) experimental paradigm previously used to demonstrate relational memory impairment in schizophrenia. We found that TI deficits were associated with schizophrenia risk with first-degree relatives showing greater impairment than second-degree relatives. First-degree relatives had poorer TI performance with significantly lower accuracy and longer response times than HC when responding to TI probe pairs. Second-degree relatives had significantly quicker response times than first-degree relatives and were more similar to HC in TI performance. We further explored the relationships between TI performance and neurocognitive domains implicated in schizophrenia. Among HC, response times were inversely correlated with FSIQ, verbal learning, processing speed, linguistic abilities and working memory. In contrast,

Address for correspondence: Dr. Beng-Choon Ho, Department of Psychiatry, W278 GH, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, Phone: 319/384-9299, Fax: 319/353-8656, beng-ho@uiowa.edu.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Contributors

Dr. Onwuameze contributed to data analyses and interpretation, and wrote the first draft of the manuscript. Dr. Titone contributed to instrument design, data interpretation, and manuscript write-up. Dr. Ho takes responsibility for the primary conceptualization of this study, including the study design, data collection, data analyses and interpretation, and manuscript write-up. All authors contributed to and have approved the final manuscript.

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relatives (first-degree in particular) had a differing pattern of TI-neurocognition relationships, which suggest that different brain circuits may be used when relatives encode and retrieve relational memory. Our finding that unaffected biological relatives of schizophrenia patients have TI deficits lends further support for the use of relational memory construct in future pro-cognition drug studies.

Keywords

schizophrenia; family studies; endophenotype; cognition; relational memory; hippocampus

1. Introduction

Schizophrenia is a neuropsychiatric disorder in which cognitive impairment features prominently (Barch, 2005; Goldberg, David, & Gold, 2004; Heinrichs & Zakzanis, 1998; Pelletier, Achim, Montoya, Lal, & Lepage, 2005). Previous studies have implicated episodic memory as a fundamental cognitive deficit in schizophrenia (Barch, 2005; Cirillo & Seidman, 2003; Ranganath, Minzenberg, & Ragland, 2008). Patients showed varying impairments in episodic memory encoding, retrieval or in both. In their integrated model of memory function, Eichenbaum and Cohen have advocated that relational memory provides a fundamental basis for complex memory organization (Eichenbaum & Cohen, 2001). Relational memory refers to the ability to learn the associations between a stimulus and its coincident context (Eichenbaum, 2004; Eichenbaum, Otto, & Cohen, 1994; Howard, Fotedar, Datey, & Hasselmo, 2005). Relational memory not only permits easy retrieval of encoded information it also forms the core requirements for episodic/declarative memory. Relational memory impairment has been observed in schizophrenia patients (Huron & Danion, 2002; Ongur et al., 2006; Smith & Squire, 2005; Titone, Ditman, Holzman, Eichenbaum, & Levy, 2004). Furthermore, the CNTRICS initiative (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia)(Carter & Barch, 2007) has identified relational memory encoding and retrieval as an important facet of long-term memory that warrants translational development; so as to aid in the discovery of cognition-enhancing drugs for schizophrenia treatment (Carter et al., 2007; Ragland et al., 2009).

One form of relational memory is transitive inference (TI). TI is the ability to infer the relationships between indirectly related items that have not been presented together (e.g. inferring $A > C$ from knowing $A > B$ and $B > C$). Initial animal studies assessing TI have shown that disruption of hippocampus-cortical or hippocampus-subcortical pathways prevented rodents from inferring the proper order of odors B and D within a hierarchical set of five odors ($A > B > C > D > E$) (Dusek & Eichenbaum, 1997). Subsequent studies involving healthy human volunteers have confirmed the pivotal role the hippocampus plays in mediating TI (Dusek et al., 1997; Ongur et al., 2005). The hippocampus serves as an important link between the prefrontal cortex and association cortices (including bilateral parietal cortex and pre-motor areas). Diminished activations of the right parietal cortex and the anterior cingulate correlated with TI impairment among schizophrenia patients (Ongur et al., 2006). Relational memory deficits are increasingly recognized as a reliable marker of neurocognitive dysfunction in schizophrenia. A recent commentary even suggested that

memory deficits in schizophrenia stem fundamentally from impairments in relational memory (Lepage, Hawco, & Bodnar, 2015). These authors proposed that memory impairment in schizophrenia patients may be related to ineffective activation of the extended brain networks involved in relational memory.

Prior studies have reported similar, but less severe neurocognitive, neuroanatomical, electrophysiological and behavioral abnormalities in non-psychotic biological relatives of schizophrenia patients (Boos, Aleman, Cahn, Pol, & Kahn, 2007; Capizzano, Toscano, & Ho, 2011; Ho, 2007; Ho & Magnotta, 2010; Keshavan et al., 2002; Lawrie et al., 1999; McDonald et al., 2004; Steel et al., 2002). Such intermediate phenotypes are likely related to genetic vulnerability factors that biological relatives have in common with schizophrenia patients. To our knowledge, no studies have examined relational memory performance in unaffected biological relatives of patients. Therefore, in the present study we assessed TI functioning in individuals who are at-risk for schizophrenia based on having a family history of the disorder. We hypothesized that biological relatives have impaired TI (i.e. poorer accuracy and longer response time) compared to healthy controls without schizophrenia family history. In addition, we also explored the relationships between TI and neuropsychological functioning. Working memory has been shown to predict TI performance (Libben & Titone, 2008). Recent studies reported moderate correlations between TI accuracy with general intelligence as well as with specific cognitive domains (Armstrong, Kose, Williams, Woolard, & Heckers, 2012a; Armstrong, Williams, & Heckers, 2012b). Schizophrenia patients with severe cognitive deficits were also less likely to achieve adequate learning in relational memory.

2. Materials and methods

2.1. Sample

In this study, we evaluated 73 subjects comprising of 48 unaffected biological relatives (22 first- and 26 second-degree relatives) of schizophrenia patients and 25 healthy controls (HC). Subjects gave written informed consent approved by the University of Iowa Human Subjects Institutional Review Board.

Relatives of schizophrenia patients were recruited either through 1) schizophrenia patients who have participated in research studies or have received psychiatric treatment at the University of Iowa Health Care, or 2) advertisements in local newspapers or mental health advocacy groups. Inclusion criteria for relatives were 13 to 25 years of age, and having at least one first- or second-degree relative with schizophrenia. Presence of schizophrenia family history was verified using Family History-Research Diagnostic Criteria (FH-RDC) interview administered to study participants, or to a parent or legal guardian if the study participant is a minor. The FH-RDC has well-established reliability and validity for assessment of family history of psychiatric disorders (Andreasen, Endicott, Spitzer, & Winokur, 1977). Relatives were interviewed using the SCID-IV (Structured Clinical Interview for DSM-IV)(First, Spitzer, Gibbon, & Williams, 2002), and were excluded if they had a lifetime history of psychiatric disorders (including schizophrenia, schizophrenia-spectrum or psychotic disorders) or substance use disorders currently or within the past year. HC without family history of schizophrenia were assessed using an abbreviated version of

the Comprehensive Assessment of Symptoms and History (CASH)(Andreasen, Flaum, & Arndt, 1992) to exclude subjects with current or past psychiatric illnesses and substance misuse. FH-RDC was also used to confirm the absence of family history of schizophrenia in HC. Additional exclusion criteria for all subjects in this study were: neurological disorders, mental retardation, unstable medical conditions or contraindications for magnetic resonance imaging (MRI). All subjects were from distinct families unrelated to one another.

The mean age for the sample was 19.7 years ($SD=2.9$; Range=13–25). Mean age and handedness were not significantly different between first-degree relatives, second-degree relatives and HC (Table 1; $F=0.25$, $p=0.78$). Although there was a greater preponderance of females among second-degree relatives, this difference was not statistically significant (Table 1; $p=0.38$).

2.2. Transitive Inference Task

The experimental procedure has been used previously in studies of HC and schizophrenia patients (Heckers et al., 2004a; Ongur et al., 2006; Ongur et al., 2005). The paradigm used a 2×2 factorial design to study the effects of inference (novel versus previously learned pairings) and stimulus sequence (overlapping versus non-overlapping pairs) (Figure 1).

Participants first underwent a set of training trials. They viewed pairs of pattern fills (Figure 1; e.g. a and b, c and d, A and B, B and C etc.) on a computer screen. These visual images consisted of 13 distinct pattern fills: 8 non-overlapping pairs (Condition ‘P’) and 5 overlapping sequence pairs (Condition ‘S’). The participants were unaware of the ordered relationships of the overlapping or non-overlapping patterns. In the beginning, participants were informed that they would see pattern pairs, and that a ‘smiling face’ was behind one of the pairs. Their task was to pick and remember the correct pattern hiding the smiling face. Participants indicated their choice of pattern fill by a button press on a response pad. During training, participants received immediate feedback about their responses. If the participant guessed correctly, the selected pattern moved to uncover the smiling face. If the participant was wrong, the selected pattern moved but no smiling face appeared. Participants were first trained on the non-overlapping pairs condition (‘P’) followed by overlapping pairs (‘S’). Each condition comprised of 144 training trials divided into 3 blocks of 60, 60 and 24 trials (Titone et al., 2004). On completion of training, participants were tested to ensure they had achieved adequate learning ($>80\%$ correct responses). To assess this, participants were presented with a single block of 48 trials (24 non-overlapping and 24 overlapping pairs). One additional training session was administered if learning criterion was not met initially. If $>80\%$ learning was still not achieved at the second training session, the subject was excluded from the study.

The experiment proper comprised of 160 trials of previously seen pairs (Figure 1; ‘P’ and ‘S’) and novel inference pairs (‘IP’ and ‘IS’). There were 16 blocks of 10 trials presented in a fixed order: P, IP, S, IS, P, IP, S, IS, P, IP, S, IS, P, IP, S and IS. Participants were therefore presented with 40 trials in each trial type (i.e. P, IP, S or IS). They were asked to recall the correct responses in previously seen pairs and to infer which pattern in novel pairs hid the ‘smiling face’. Unlike the training trials, participants did not see the smiling face

reinforcement during these 160 trials. The entire study paradigm took approximately 30 minutes to complete.

We further contrasted IS novel pairs that differ based on the number of items with an ambiguous prior reinforcement: one ambiguous item (non-BD pairs) or two ambiguous items (BD pairs) (Figure 1).

To avoid bias resulting from object shape (i.e. pentagon versus ellipsoid), pattern (i.e. order of the 13 patterns selected from a larger set of 16 fills) was rotated with each subsequent subject) or position (i.e. left or right 'smiling face' position), these factors associated with visual stimuli were systematically varied across subjects in a pseudo-randomized fashion. The software program controlling the experimental paradigm was written in Presentation Control Language. Presentation software version 11.3 (Neurobehavioral Systems, Inc., Albany, CA) was installed on an Intel Pentium 4 machine running Windows XP operating system. To prevent interfering with the precise timing, the machine was not connected to any computer network and was dedicated to this experiment. Additionally, the button-press response latency was hardware-based and used the response pad (Model RB530 by Cedrus Corporation), which has built-in timer with 1 millisecond resolution. The accuracy and response latency for each trial were stored in a CSV-file for subsequent analyses.

2.3. Neuropsychological Test Battery

Subjects underwent neurocognitive assessment using a battery of standardized neuropsychological tests (Table 1). A psychometrist trained in standardized assessments and scoring procedures administered these neuropsychological tests. The neurocognitive test battery was selected because these tests tap into cognitive domains (i.e. verbal learning, working memory, processing speed, linguistic abilities and problem solving) in which schizophrenia patients have consistently shown impairment (Heinrichs et al., 1998). To assess general indices of mental abilities, subjects were also administered the Wechsler Adult Intelligence Scale 3rd Edition (WAIS; or Wechsler Intelligence Scale for Children 4th Edition (WISC) for subjects under age 16 years) to derive Full Scale IQ scores. In the current study, Wechsler Memory Scale 3rd Edition (WMS-III) Logical Memory referred to the total number of items from delayed recall. Working Memory Index comprised of WAIS/WISC Letter-Number Sequence and Digit Span subtests. Processing Speed Index was derived based on WAIS/WISC Digit Symbol Coding and Symbol Search subtests. Controlled Oral Word Association Test (COWAT) was the total number of items, and Tower of London total number of moves made.

2.4. Statistical Analysis

Response accuracy rates (percent correct) for each trial type (i.e. P, IP, S or IS) were calculated based on the number of correct responses out of 40 trials per trial type expressed as a percentage. This generated 292 observations of response accuracy (73 subjects x 4 trial types). Given its skewed distribution, response accuracy rates were log-transformed to normalize the data and to minimize the effects of outliers. Of the 11,680 observations of response time (millisecond; 73 subjects x 4 trial types x 40 trials), only trials in which subjects responded correctly (N=10,857 correct-only observations for P, IP, S and IS trial

types respectively: N=833, 747, 801 and 711 (22 first-degree relatives); N=1030, 1030, 994 and 902 (26 second-degree relatives); N=988, 971, 946 and 904 (25 HNC)) were used in the statistical analyses.

Differences in response accuracy and in response time (correct-only trials) between the 3 groups were assessed using mixed linear models (with repeated measures for subject). Mixed model repeated measures (MMRM) analysis offers several advantages over more traditional analyses (De Ketelaere, Lammertyn, Molenberghs, Nicolaï, & De Baerdemaeker, 2003; Krueger & Tian, 2004). In previous studies (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004b; Ongur et al., 2006; Titone et al., 2004), investigators tested group differences in response accuracy and group differences in mean response time for each trial type separately. In contrast, MMRM analytic approach is not only more flexible, it also provides a more comprehensive statistical model. MMRM allows simultaneous inclusion of both within-subject and between-subject differences that contribute to variance in the outcome measure of interest (Cnaan, Laird, & Slasor, 1997; De Ketelaere et al., 2003). Furthermore, response time observations for incorrect trials were excluded from the statistical analysis thereby creating “missing data” at inconsistent trial number within the 40 trials from each trial type. MMRM is able to handle such “missing data” by modeling the most appropriate within-subject variance-covariance structure (see below; (Krueger et al., 2004; Littell, Pendergast, & Natarajan, 2000)).

In these mixed models, the dependent measures were either log-transformed response accuracy or response time (correct trials only). Fixed effects were trial type, group and trial type-by-group interaction term. Subjects were treated as random effects for which we modeled within-subject response accuracy and within-subject response time using an autoregressive of order 1 (AR(1)) variance-covariance structure. With AIC as the deciding criterion (Littell, Milliken, Stroup, & Wolfinger, 1996), AR(1) covariance structure consistently provided the best fit. A significant main effect of group would suggest that the dependent measure (response accuracy or response time) differed significantly between groups. A significant main effect of trial type indicates that the dependent measure differed significantly between trial types. A significant main effect of trial type-by-group interaction term suggests that the relationship between response accuracy (or response time) and group membership differed significantly across trial type. When the MMRM analysis yielded significant main effects of group membership, post-hoc pair-wise group comparisons (i.e. first- versus second-degree schizophrenia relatives, first-degree relatives versus HC, and second-degree relatives versus HC) used the Tukey’s method (Q statistic) to adjust for multiple comparisons.

As exploratory analyses, we also examined the relationships between TI performance and cognitive domains in which schizophrenia patients are known to be impaired. We performed similar mixed models statistical tests. We restricted these additional analyses to only response time because compared to response accuracy the former appears to be more sensitive in detecting group differences (see below). In these MMRM within-subject response time analyses, the primary fixed effects of interest were individual neuropsychological test score (NP) and NP x group interaction. A significant main effect of NP would suggest that TI response time and neuropsychological performance are correlated.

Statistically significant main effect of NP x group interaction indicates that TI response time-NP performance relationships differed across the 3 comparison groups. Age, gender and Full Scale IQ were included as covariates in these mixed linear models because these variables are known to contribute to the variance in cognitive performance.

3. Results

Relational memory learning capability was good. Only 15.1% of the sample (3 first- and 3 second-degree relatives and 5 HC) failed to achieve the >80% accuracy learning criterion. Learning capability did not differ significantly across the 3 comparison groups (Fisher's Exact Test $p=0.71$). Following administration of a second training session, all 11 subjects were able to achieve at least 80% accuracy.

On response accuracy, there were statistically significant main effects of trial type (P, IP, S versus IS; $F=6.29$, $df=3,210$, $p=0.0004$) and group ($F=6.64$, $df=2,70$, $p=0.002$). Trial type-by-group interaction effects on response accuracy were not statistically significant ($F=1.55$, $df=6,210$, $p=0.16$). Compared to non-overlapping trials (P and IP), subjects were generally less accurate during the overlapping trials (S and IS) (Figure 2A and Table 2). First-degree relatives had consistently lower mean accuracy scores compared to HC and second-degree relatives across all trial types (Figure 2A and Table 2). The largest group differences were in the novel trials (IP and IS). Compared to HC, first-degree relatives had lower mean accuracy on IP (Mean=97.1% versus 84.9% respectively) and IS (Mean=90.4% versus 80.8% respectively) trials. These differences approached but did not achieve statistical significance ($p=0.06$; Table 2). First-degree relatives were significantly less accurate for IP trials than second-degree relatives ($Q=2.22$, $df=46$, $p=0.03$). Second-degree relatives did not differ significantly from HC on response accuracy (Table 2; $Q=1.38$, $df=49$, $p=0.18$).

On response time (correct trials only), there were significant main effects of trial type ($F=450.8$, $df=3,210$, $p<0.0001$), group ($F=24.7$, $df=2,70$, $p<0.0001$) and trial type-by-group interaction ($F=3.48$, $df=6,210$, $p=0.003$). Similar to response accuracy, mean response time for overlapping trials (S and IS) were longer than non-overlapping trials (P and IP; Figure 2B and Table 2). Again, mean response time in first-degree relatives was longer in all trial types compared to the other 2 groups. Post hoc analyses found that first-degree relatives had significantly longer response times than second-degree relatives on each of the 4 trial types (Figure 2B and Table 3; $Q=2.71$, $p=0.02$), and significantly longer response times than HC on P and IS trials ($Q=2.47$, $p=0.04$). Compared to HC, second-degree relatives had significantly shorter response times on P, IP and S trials ($Q=2.62$, $p=0.03$).

3.1. BD Trials

Because previous studies found schizophrenia patients had selective deficits in responding to the BD probe pairs (but not to non-TI probe pairs) (Ongur et al., 2006; Titone et al., 2004), we further analyzed accuracy and response time within the IS trials subdivided into BD versus non-BD trials (Table 2 and Figure 3).

During BD trials, first-degree relatives were significantly less accurate compared to HC (75.0% versus 88.5% respectively; $Q=2.06$, $p=0.04$; Table 2 and Figure 3A) and had longer

mean response time (1,488.5 msec versus 1,272.8 msec respectively; $Q=1.96$, $p=0.05$; Table 2 and Figure 3B). Second-degree relatives had comparable BD accuracies and response times compared to first-degree relatives and to HC ($Q=1.43$, $p=0.16$). Although second-degree relatives had lower BD accuracy and longer response time than HC, these differences were not statistically significant ($Q=1.42$, $p=0.16$).

During non-BD trials, pair-wise group comparisons did not find any statistically significant differences in accuracy rates or in response times (Table 2; $Q=1.73$, $p=0.09$). This is consistent with previous findings in schizophrenia patients where selective deficits in TI were restricted to only BD trials.

3.2. Exploratory correlational analyses of TI performance and neurocognition

The 3 groups did not differ significantly on IQ or on neurocognitive performance (Table 1; $F=1.49$, $p=0.23$). There were no statistically significant main effects of IQ or IQ-by-trial type interaction on response time (Table 3; $F=0.51$, $p=0.67$). However, main effects of IQ-by-group interactions on response time were statistically significant ($F=22.62$, $p<0.001$) indicating that the relationships between IQ and response time differed between groups. For HC, higher IQ correlated with shorter response time (Figure 4A and Table 3; partial Pearson's $r=-0.26$). In contrast, schizophrenia relatives showed a different pattern of IQ-response time relationships. Higher IQ was associated with longer response time among first-degree relatives (partial Pearson's $r=0.28$). Among second-degree relatives, IQ-response time relationship was intermediate between the other 2 comparison groups (partial Pearson's $r=0.08$).

On almost every cognitive domain we examined (except for problem solving/Tower of London), there were significant main effects of neuropsychological measure on response time (Table 3; $F=3.87$, $p=0.05$). There were no statistically significant neuropsychological measure-by-Trial Type effects ($F=1.94$, $p=0.12$; except for Logical Memory and COWAT (see below)). There were statistically significant neuropsychological measure-by-group interaction effects on response time (Table 3; $F=6.73$, $p=0.002$), which suggests that neuropsychological performance-response time relationships differed between the 3 groups. For HC, better performance in working memory, processing speed and problem solving were associated with shorter response time (Table 3 and Figure 4B, 4C and 4D). In general, schizophrenia relatives showed a different pattern of neuropsychological performance-response time relationships than HC (Table 3 and Figure 4; e.g. partial Pearson's r for working memory= 0.40 and 0.12 in first- and second-degree relatives respectively versus $r=-0.09$ in HC).

Since there were statistically significant neuropsychological measure-by-trial type interaction effects as well as significant neuropsychological measure-by-group interaction effects on response time for Logical Memory and for COWAT, we analyzed these neuropsychological performance-response time relationships separately by trial type (see Supplemental Results, Supplemental Figure S1 and Supplemental Table S1 for more details). Verbal Learning- and Linguistic Abilities-response time relationships in relatives again showed a different pattern as those in HC.

4. Discussion

In this study, we determine whether unaffected biological relatives of schizophrenia patients have TI deficits akin to relational memory impairment previously reported in schizophrenia patients. We found that first-degree relatives had poorer TI performance showing significantly lower accuracy and longer response times than HC when responding to TI probe pairs (BD trials) but not during non-TI probe pairs. First-degree relatives of schizophrenia patients also had longer response times compared to second-degree relatives. These findings indicate that relational memory deficits are associated with schizophrenia risk, and suggest that TI performance is an endophenotypic feature of schizophrenia. In addition, we found moderate correlations between TI performance and several neurocognitive domains among HC. This is consistent with previous observations that TI is subserved by distributed brain networks in HC. In contrast, biological relatives of schizophrenia patients (particularly first-degree relatives) showed a different pattern of TI-neurocognition relationships.

As a group, schizophrenia patients have significant impairments in episodic memory (Cirillo et al., 2003). Episodic memory deficits in schizophrenia patients may be principally due to impairment in relational memory encoding (Ragland et al., 2012); which in turn have been associated with reduced dorsolateral prefrontal and hippocampal activations (Ragland et al., 2015). With regards to TI (a form of relational memory), schizophrenia patients performed poorly compared to healthy volunteers, and lower mean accuracy and longer mean response time (Armstrong et al., 2012a; Armstrong et al., 2012b; Coleman et al., 2010; Ongur et al., 2006; Rowland, Griego, Spieker, Cortes, & Holcomb, 2010; Titone et al., 2004). Furthermore, patients have greater difficulties in attaining adequate learning of the relational memory task (Armstrong et al., 2012a). Approximately one-third of patients did not achieve a priori learning criterion during the training phase of the experiment (22% – 39%) (Armstrong et al., 2012a; Coleman et al., 2010) versus 8.8% in HC (Williams, Avery, Woolard, & Heckers, 2012)). Among schizophrenia patients, “poor learners” also have significantly greater cognitive deficits and greater symptom severity than “good learners” (Armstrong et al., 2012a). In the current study, relational memory learning capabilities and neuropsychological performance were equivalent across our 3 comparison groups. Although 15% of the sample failed to meet the >80% accuracy learning criterion initially, all subjects (including relatives of schizophrenia patients) achieved adequate learning following a second training session.

Our study indicates that biological relatives of schizophrenia patients have deficits in TI. Response accuracy was consistently lower among first-degree relatives for all trial types with significantly lower accuracy with the TI probe pairs (BD trials). In contrast, second-degree relatives were (non-significantly) more accurate than first-degree relatives and had comparable response accuracy as HC. For response time, first-degree relatives were slower than the other 2 comparison groups, and had significantly longer mean response time during BD trials compared to HC. Second-degree relatives were significantly quicker in responding during P, IP and S trials than HC. In general, second-degree biological relatives performed better than their first-degree counterparts, and were more similar to HC in relational memory performance. These observations are consistent with a previous finding by our group

(Capizzano et al., 2011); where we found that first-degree relatives of schizophrenia patients had more severe abnormal magnetic resonance spectroscopy (MRS) metabolite levels in limbic brain regions than second-degree relatives. Thus, our current study provides additional evidence that deviations in endophenotypic features of schizophrenia among unaffected biological relatives increase with greater familial proximity to the schizophrenia proband.

Animal studies indicate that the hippocampus plays a pivotal role in relational memory formation (Dusek et al., 1997). Lesions involving hippocampal-subcortical pathways or those disrupting hippocampal-cortical connections disrupt the acquisition of memory for orderly odor relations in rodents (Bunsey & Eichenbaum, 1996; Dusek et al., 1997). Functional MRI studies of healthy human volunteers provide further support regarding the role of the hippocampus in mediating TI (Heckers et al., 2004b) and relational memory (Ragland et al., 2015). In schizophrenia patients, reduced left hippocampal activation during BD trials suggests that TI deficits are likely related to hippocampal dysfunction (Ongur et al., 2006). Although the hippocampus is vital for TI, anterior cingulate cortex and parietal brain regions have also been implicated in relational memory and in TI deficits in schizophrenia patients (Acuna, Eliassen, Donoghue, & Sanes, 2002; Heckers et al., 2004a; Ongur et al., 2006).

In our study, we found that neuropsychological performance-response time relationships differed significantly between the 3 groups. In general, shorter TI response times in HC correlated with higher FSIQ, better verbal learning abilities, processing speed, linguistic abilities and working memory. These TI-neurocognitive performance correlations are consistent with the premise that relational memory is subserved by distributed neural circuits involving the hippocampus. WMS Logical Memory tests have been shown to require the hippocampus (Damasio, 1996; Levy, Mendell, & Holzman, 2004). Lesions studies indicate that diverse brain regions (including the prefrontal cortex, temporal and parietal cortices) mediate task performance in standardized neuropsychological tests examined in the current study (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Damasio, 1996; Koenigs, Barbey, Postle, & Grafman, 2009; Levy et al., 2004). Our study is limited in that such neurocognitive tests serve only as indirect assessments of brain circuits. Nonetheless, our results are in keeping with in vivo neuroimaging findings and animal studies implicating the hippocampus and distributed network of brain circuits in mediating relational memory formation.

In contrast to HC without family history of schizophrenia, biological relatives of schizophrenia patients showed a different pattern of TI-neurocognitive performance relationships. Unlike HC where the majority of TI response time-neurocognitive performance relationships were inverse correlations, relatives either showed positive correlations (e.g. on working memory-related tasks) or no correlations (e.g. Logical Memory performance and IS trial response times). We interpret this to indicate that similar to schizophrenia patients (Rowland et al., 2010), individuals at-risk for schizophrenia likely utilize alternative strategies and/or different brain circuits to achieve relational memory. Rowland et al showed that compared to HC, schizophrenia patients have different patterns of fMRI activations following relational learning. These differences include bilateral parietal

activations, absence of hippocampal activation and lack of positive activations in frontal, medial temporal and parietal regions of schizophrenia patients (Rowland et al., 2010). Albeit speculative, individuals at-risk for schizophrenia may either utilize brain circuits that are distinct from those used by HC or they use alternative cognitive strategies to attain relational memory (Wendelken & Bunge, 2010). To confirm this, future studies involving concurrent brain activation measurements will be needed.

In conclusion, relatives of schizophrenia patients have impaired relational memory performance. Such deficits in transitive inference are likely mediated by genetic factors underlying schizophrenia that disrupt prefrontal and hippocampus-linked neural circuits. Transitive inference impairment in unaffected biological relatives of schizophrenia patients, therefore, lend further support for using of the construct of relational encoding and retrieval in pro-cognition drug discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Transitive Inference Paradigm: Stimulus set & task conditions. During training, participants were asked to pick the pattern fill hiding the smiling face (P and S), and indicated their choice of by a button press on a response pad. Subjects learned to discriminate non-overlapping pairs (P) and an overlapping sequence of pairs (S). The reinforced item in each pair is shown on the left. During the experiment itself, subjects recollected the “correct response” for pairs (P and S) they have previously seen during training, and to infer the correct response for novel non-overlapping pairs (IP) and overlapping pairs (IS).

Figure 2.

Column scatterplots (black bar: group mean) comparing transitive inference performance (A) Response Accuracy (percent correct) and (B) Response Time (milliseconds; Correct responses only; Subject Mean over 40 trials) between first-degree biological relatives of schizophrenia patients (1°; square), second-degree biological relatives of schizophrenia patients (2°; triangle) and healthy controls (HC; circle) subdivided by trial type (P: non-overlapping trials, IP: novel non-overlapping trials, S: overlapping trials, IS: novel overlapping trials).

Figure 3.

Column scatterplots (black bar: group mean) of IS trials comparing non-BD pairs (i.e. with one ambiguous item) versus BD pairs (two i.e. with two ambiguous items): (A) Response Accuracy (percent correct) and (B) Response Time (milliseconds; Correct responses only; Subject Mean) between first-degree biological relatives of schizophrenia patients (1°; square), second-degree biological relatives of schizophrenia patients (2°; triangle) and healthy controls (HC; circle).

Figure 4.

Relationships between Mean Response Time (correct responses from all trial types) and neurocognitive performance (A) Full Scale IQ (FSIQ), (B) WAIS Working Memory Index, (C) WAIS Processing Speed Index and (D) Tower of London (total number of moves made) among first-degree biological relatives of schizophrenia patients (1°; red), second-degree biological relatives of schizophrenia patients (2°; blue) and healthy controls (HC; green) (r: Pearson's partial correlation coefficient (covariates: age, gender and IQ except for FSIQ which adjusted for age and gender only)).

Table 1

Sociodemographic characteristics and neurocognitive performance of sample

	First-degree Relatives	Second-degree Relatives	Healthy Controls	Statistic ^a (p)
N	22	26	25	
Sex (Males N (%))	12 (55.6)	10 (38.5)	14 (56.0)	1.91 (0.38)
Age (years)	20.3 (2.66)	19.8 (3.13)	19.7 (3.47)	0.25 (0.78)
Handedness ^b (Right, %)	90.9	88.5	88.0	0.03 (1.00)
IQ	107.6 (11.97)	112.3 (11.33)	108.9 (9.40)	1.36 (0.26)
WMS-III Logical Memory	27.0 (6.94)	28.8 (7.47)	28.4 (6.19)	0.23 (0.79)
Working Memory Index	98.7 (10.58)	102.6 (13.60)	103.4 (11.22)	0.91 (0.41)
Processing Speed Index	110.1 (13.81)	112.1 (15.35)	104.8 (16.10)	1.49 (0.23)
COWAT	40.8 (9.27)	39.4 (9.70)	37.9 (12.27)	0.81 (0.45)
Tower of London	84.6 (5.87)	87.6 (11.14)	87.5 (9.98)	0.40 (0.67)

^a sex (χ^2); handedness (Fisher's Exact); age and cognitive measures (F)

^b Annett Scale of Hand Preference

IQ: Full Scale IQ based on Wechsler Adult Intelligence Scale 3rd Edition or Wechsler Intelligence Scale for Children 4th Edition (WAIS/WISC) depending on subject's age; WMS-III (Wechsler Memory Scale 3rd Edition) Logical Memory: total number of items delay recall; Working Memory Index: WAIS/WISC Letter-Number Sequence and Digit Span subtests; Processing Speed Index: WAIS/WISC Digit Symbol Coding and Symbol Search subtests; COWAT (Controlled Oral Word Association Test): total number of items; Tower of London: total number of moves made

Table 2

Transitive inference (TI) performance (mean accuracy (%)) and mean response time (milliseconds) and pair-wise independent group comparisons (Tukey's test Q (p)) for non-overlapping (P and IP) and overlapping (S and IS) trials between first-degree relatives of schizophrenia patients (1°), second-degree relatives of schizophrenia patients (2°) and healthy controls without family history of schizophrenia (HC)

Trials		TI Performance (Mean (SD))			Pair-wise Comparison (Q (p))		
		1°	2°	HC	1° vs. 2°	1° vs. HC	2° vs. HC
Accuracy (%)							
P		94.7 (14.5)	99.0 (1.9)	98.8 (1.6)	1.54 (.13)	1.46 (.15)	0.47 (.64)
IP		84.9 (26.8)	99.0 (2.0)	97.1 (6.7)	2.22 (.03)	1.97 (.06)	1.38 (.18)
S		91.0 (15.8)	95.6 (3.6)	94.6 (8.3)	1.54 (.13)	1.11 (.27)	0.67 (.50)
IS*		80.8 (24.3)	86.7 (17.7)	90.4 (15.6)	1.12 (.27)	1.74 (.09)	0.77 (.45)
Non-BD		82.2 (24.4)	89.9 (14.8)	90.9 (16.0)	1.66 (.10)	1.73 (.09)	0.09 (.93)
BD		75.0 (29.9)	74.0 (33.2)	88.5 (24.7)	0.67 (.50)	2.06 (.04)	1.42 (.16)
Response Time (msec)							
P		852.0 (10.4)	781.9 (94.0)	817.0 (96.0)	4.99 (<.0001)	2.47 (.04)	2.62 (0.03)
IP		862.1 (16.0)	804.8 (13.8)	866.4 (14.1)	2.71 (.02)	0.20 (.98)	3.11 (.007)
S		1165.8 (16.0)	1071.9 (14.3)	1130.9 (14.7)	4.36 (.0001)	1.60 (.25)	2.87 (.01)
IS*		1254.9 (24.6)	1160.3 (21.7)	1129.8 (22.0)	3.79 (.0009)	3.79 (.0009)	0.99 (.59)
Non-BD		1238.7 (272.1)	1151.2 (246.3)	1110.0 (256.0)	1.17 (.25)	1.71 (.09)	0.57 (.57)
BD		1488.4 (395.2)	1329.8 (393.3)	1272.8 (330.3)	1.43 (.16)	1.96 (.05)	0.53 (.60)

* Based on the number of items with an ambiguous prior reinforcement, IS novel pairs were sub-categorized into either non-BD pairs (i.e. with one ambiguous item) or BD pairs (two ambiguous items).

Table 3

Mixed models analysis examining the relationships between transitive inference (TI) performance (response time) and neurocognition.

Cognitive Domain	Neuropsychological (NP) Measure	Main Effects on Response Time (F (p))			Pearson's partial r^2		
		NP Measure	NP x Trial Type	NP x Group	1°	2°	HC
General Cognition	IQ	0.02 (0.88)	0.51 (0.67)	22.62 (<0.001)	0.28	0.08	-0.26
Verbal Learning	WMS-III Logical Memory	13.31 (<0.001)	3.93 (0.01)	18.75 (<0.001)	-	-	-
Working Memory	Working Memory Index	3.87 (0.05)	0.17 (0.92)	8.24 (<0.001)	0.40	0.12	-0.09
Processing Speed	Processing Speed Index	106.87 (<0.001)	1.94 (0.12)	16.08 (<0.001)	-0.44	-0.19	-0.57
Linguistic Ability	COWAT	27.83 (<0.001)	4.71 (0.003)	6.92 (0.002)	-	-	-
Problem Solving	Tower of London	1.11 (0.30)	1.48 (0.22)	6.73 (0.002)	-0.09	-0.14	0.23

IQ: Full Scale IQ based on Wechsler Adult Intelligence Scale 3rd Edition or Wechsler Intelligence Scale for Children 4th Edition (WAIS/WISC); WMS-III (Wechsler Memory Scale 3rd Edition) Logical Memory: total number of items delay recall; Working Memory Index: WAIS/WISC Letter-Number Sequence and Digit Span subtests; Processing Speed Index: WAIS/WISC Digit Symbol Coding and Symbol Search subtests; COWAT (Controlled Oral Word Association Test): total number of items; Tower of London: total number of moves made)

^a partialing for age, gender and IQ (except for general cognition which adjusted for age and gender only)