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Auditory working memory impairments in individuals at familial high risk for schizophrenia

Larry J. Seidman[1,2,3], **Eric C. Meyer**[4], **Anthony J. Giuliano**[1,5], **Hans C. Breiter**[2,6], **Jill M. Goldstein**[1,2,3,7], **William S. Kremen**[8], **Heidi W. Thermenos**[1,2,3], **Rosemary Toomey**[9], **William S. Stone**[1], **Ming T. Tsuang**[1,8], and **Stephen V. Faraone**[10]

[1]Harvard Medical School, Department of Psychiatry, Massachusetts Mental Health Center Division of Public Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA 02115

[2]Harvard Medical School, Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114

[3]Athinoula A. Martinos Center for Biomedical Imaging (Massachusetts Institute of Technology, Harvard Medical School and Massachusetts General Hospital), Charlestown, MA 02129

[4]Department of Psychiatry and Behavioral Science, Texas A&M Health Science Center, College of Medicine, College Station, TX

[5]Psychology Department, Tewksbury State Hospital, Tewksbury, MA 01876

[6]Northwestern University, Department of Psychiatry and Behavioral Sciences, Chicago, Il, 60611

[7]Harvard Medical School, Department of Psychiatry, Brigham and Women's Hospital, and Departments of Medicine, Division of Women's Health, Connor's Center for Women's Health & Gender Biology, Boston, MA 02115

[8]University of California, San Diego, Department of Psychiatry, Center for Behavior Genomics, and Institute of Genomic Medicine, La Jolla, CA

[9]Boston University, Department of Psychology, Boston, MA 02215

[10]Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY 13210

Abstract

Objectives—The search for predictors of schizophrenia has accelerated with a growing focus on early intervention and prevention of psychotic illness. Studying nonpsychotic relatives of individuals with schizophrenia enables identification of markers of vulnerability for the illness independent of confounds associated with psychosis. The goal of these studies was to develop new auditory continuous performance tests (ACPTs) and evaluate their effects in individuals with schizophrenia and their relatives.

Methods—We carried out two studies of auditory vigilance with tasks involving working memory (WM) and interference control with increasing levels of cognitive load to discern the

Correspondence: Larry J. Seidman, Ph.D., Massachusetts Mental Health Center, Neuropsychology Laboratory, Commonwealth Research Center, 5th Floor, 75 Fenwood Road, Boston, MA 02115; Tel: 617-754-1238; Fax: 617-754-1250, lseidman@bidmc.harvard.edu.

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information processing vulnerabilities in a sample of schizophrenia patients, and two samples of nonpsychotic relatives of individuals with schizophrenia and controls. Study 1 assessed adults (mean age = 41), and Study 2 assessed teenagers and young adults age 13-25 (mean =19).

Results—Patients with schizophrenia were impaired on all five versions of the ACPTs, while relatives were impaired only on WM tasks, particularly the two interference tasks that maximize cognitive load. Across all groups, the interference tasks were more difficult to perform than the other tasks. Schizophrenia patients performed worse than relatives who performed worse than controls. For patients, the effect sizes were large (Cohen's d =1.5), whereas for relatives, they were moderate (d = ~0.40-0.50). There was no age by group interaction in the relatives –control comparison except for participants <31 years of age.

Conclusions—Novel WM tasks that manipulate cognitive load and interference control index an important component of the vulnerability to schizophrenia.

The Importance of Neurocognition in Schizophrenia and the Family High Risk Approach

Schizophrenia is a serious, neurodevelopmental disorder with a multifactorial etiology including both environmental and genetic influences (Tsuang, Stone & Faraone, 1999). Family, twin, and adoption studies provide strong evidence for a spectrum of disorders in which schizophrenia is the most severe expression of an illness that includes non-psychotic features such as neurocognitive deficits in addition to positive symptoms of psychosis (Faraone, Green, Seidman & Tsuang, 2001; Gottesman & Gould, 2003). Neurocognitive dysfunction has come to be regarded as a core component of the disorder (Barch, 2005; Heinrichs & Zakzanis, 1998; Seidman, 1983), supporting the original ideas of Kraepelin (1919) and Bleuler (1911) regarding the central role of cognitive deficits. Neurocognitive dysfunctions are observed in the vast majority of people with the illness and in all phases of the illness (Keefe, Beasley & Poe, 2005; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Palmer et al., 1997; Wilk et al., 2005). Among people with schizophrenia, neurocognitive deficits aggravate overall levels of disability and worsen functional outcomes (Green, 1996; Green, Kern, Braff & Mintz, 2000). Moreover, the relatively modest improvement in neurocognition following antipsychotic treatment (Harvey & Keefe, 2001; Mishara & Goldberg. 2004), suggests that neurocognitive impairments are largely independent of psychosis, thus underscoring the pressing need for effective interventions to address cognitive impairments (Buchanan et al., 2011; Eack et al., 2010).

The "genetic" or family high-risk (FHR) approach is based on the fact that genetic influences are among the best-established risk factors for schizophrenia, with heritability estimated at approximately 60-90% (Gottesman, 1991). Non-psychotic first-degree relatives of people with schizophrenia, who on average share 50% of genes with their ill relatives, are typically unmedicated and free of other confounds associated with psychosis. Thus, studying non-psychotic relatives provides a high fidelity window into understanding the influence of genes on the pathophysiology of schizophrenia. Further, studying relatives at different time points (i.e., during and after the peak risk for psychosis from ages 18-30) allows for identification of markers associated with vulnerability and risk in youth vs. resilience among people who have passed through the peak risk period. Studying younger relatives (i.e., < age 31) provides an additional opportunity to identify developmental differences present prior to the typical age of onset of schizophrenia that may aid in predicting psychosis.

Neurocognitive dysfunctions are well documented in studies of adult non-psychotic relatives (ages 30-70) (Gur et al., 2007; Kremen et al., 1994; Sitskoorn, Aleman, Ebisch, Appels & Kahn, 2004; Snitz, McDonald & Carter, 2006; Szoke et al., 2005; Trandafir, Meary, Schurhoff, Leboyer & Szoke, 2006). In brief, meta-analyses document that adult relatives

manifest deficits on tasks of sustained attention, declarative and working memory, perceptual-motor speed, verbal fluency, and executive functions (EFs), usually intermediate between persons with schizophrenia and controls (Sitskoorn, Aleman, Ebisch, Appels & Kahn, 2004; Snitz, McDonald & Carter, 2006; Szoke et al., 2005; Trandafir et al., 2006). The deficits in executive control processes and memory dysfunctions are stable over time in adulthood (Faraone et al., 1999) and are associated with degree of genetic loading (Faraone et al., 2000). Overall, this literature suggests a common difficulty in high-load executive control processing across tasks during adulthood (Cornblatt & Keilp, 1994; Nuechterlein & Dawson, 1984).

A substantial literature examines cognitive measures among younger relatives, usually offspring < age 31 years. There are at least 30 FHR studies indicating results comparable to that observed in older relatives in similar cognitive domains (reviewed in Agnew-Blais & Seidman, in press; Keshavan et al., 2010; Niemi, Suvisaari, Tuulio-Henriksson & Lonnqvist, 2003; Seidman et al. 2006). Relevant to the current study, vigilance or sustained attention on high-load visual information processing tasks remains consistently impaired throughout late childhood and adolescence in those who go on to develop schizophrenia (Cornblatt, Winters & Erlenmeyer-Kimling, 1989). High loads of information and/or speed of processing demands are common to tests that have the largest effect sizes (ESs) in patients and relatives, such as digit symbol/coding or story memory free recall (Dickinson, Ramsey, & Gold, 2007; Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009).

Comparing neuropsychological deficits among adolescents versus older relatives is an important strategy for a number of reasons. First, samples of young relatives who have not passed through the peak age of risk for psychosis (< age 31) may contain some future cases, whereas those > age 30 have significantly lower risk of developing schizophrenia. Thus, cognitive impairments may be greater compared to controls in younger relatives. Second, the efficient processing of certain high load tasks such as working memory tends to peak in the 20's in the normal population (Luna, Padmanabhan, & O'Hearn, 2010). Therefore, it is important to determine if those at FHR show a similar developmental trend, or whether development of this function may be disrupted differentially in youth at FHR compared to older relatives. Finally, studying premorbid differences may identify predictors of illness and inform targets for prevention or early intervention.

Development of Novel Auditory Continuous Performance Tasks (CPTs) to Identify Key Neurocognitive Vulnerabilities for Schizophrenia

Vigilance

Problems in vigilance and sustained attention have long been considered key impairments in schizophrenia (Cornblatt, Risch, Friedman & Erlenmeyer-Kimling, 1988; Mirsky, Anthony, Duncan, Ahern, & Kellam, 1991; Nuechterlein & Dawson, 1984; Seidman, 1983). Vigilance, is a "state of readiness to detect and respond to certain small changes occurring at random time intervals" (Mackworth, 1948). Vigilance tasks require subjects to sustain their attention to subtle sensory signals, to minimize distractibility to irrelevant stimuli, and to maintain alertness over time.

Vigilance tasks vary according to stimulus sensory modality, complexity, rate of presentation, signal probability, response type, sensory clarity and memory load (Parasuraman & Davies, 1977). These task parameters can be systematically varied to tax the limited processing capacity of attention (Kahnemen, 1973; Norman & Bobrow, 1975). Overload of information (i.e., that which requires very "effortful" processing; Beatty, 1982) can be induced by increasing working memory (WM) load, dividing attention (e.g., as in dichotic listening or shadowing tasks), increasing interference, or decreasing stimulus

clarity. For example, the original Continuous Performance Test (CPT; Rosvold, Mirsky, Sarason, Bransome & Beck, 1956), a widely used vigilance task, has been made more demanding by degrading the sensory clarity of the stimulus (Nuechterlein, Parasuraman & Jiang, 1983; Seidman, Van Manen et al., 1998) or by increasing memory load to burden working memory (WM) CPTs (Braver et al., 1997; Cohen et al., 1994; Cornblatt, Risch, Faris, Friedman & Erlenmeyer-Kimling, 1988). Because several visual CPTs had already been developed, we developed an auditory CPT (ACPT) battery to complement these tasks and that could be used in subsequent studies involving direct comparisons with visual CPTs (Makris et al., 2008) to determine differential sensitivity. We were also motivated by accumulating data pointing to deficits in auditory processing in schizophrenia, i.e., that auditory processing areas of the temporal lobes (Heschls gyrus and the superior temporal gyrus) are dysfunctional in schizophrenia (Hirayasu et al., 2000), that deficits in abnormal auditory event related potentials (ERPs) including P300 are prominent (Jeon & Polich, 2003), and that auditory stimuli used in prepulse inhibition (Braff et al., 1978), P50 (Adler et al., 1982), and mismatch negativity (Michie, 2001) experiments yield abnormal ERPs in individuals with schizophrenia and their first-degree relatives.

Working Memory

WM refers to a set of processes involving temporary storage and manipulation of information for use in various cognitive operations (Baddeley, 1986; Baddeley & Hitch, 1994; Goldman Rakic, 1987). The information to be retrieved or manipulated must be retained in spite of interference from internal or external distractions (Fuster, 1989; Gevins et al., 1996). WM tasks involve a “central executive” or “supervisory attentional system” that is tapped by CPT tasks requiring manipulation and continuous cognitive updating (D’Esposito et al., 1995; Wager & Smith, 2003).

Several auditory-verbal WM tasks have previously been utilized in studies of patients with schizophrenia and relatives, such as the letter number-sequencing task (Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997; Horan et al., 2009) and dichotic listening tasks (Faraone et al., 1995). However, these tasks involve short-term storage, which is subserved by somewhat different neural substrates than executive WM tasks that require continuous cognitive updating over several minutes (Wager & Smith, 2003). Auditory WM tasks that involve competing information, such as dichotic listening (Faraone et al., 1995) or dichotic shadowing (Spring, 1985) successfully discriminate the performance of relatives from controls. These findings encouraged us to develop updating tasks in which competing information (i.e., “interference”) increases task demands within a continuous cognitive updating (i.e., CPT) framework.

In developing effortful ACPTs, we chose to increase both WM load and interference control demands because, whereas persons with schizophrenia have global attention problems (Nuechterlein & Dawson, 1984; Seidman, 1983), their first-degree relatives exhibit impairment only on more demanding attention tasks (Cornblatt & Keilp, 1994). Both patients and nonpsychotic relatives exhibit deficits in WM (Goldman-Rakic, 1991; Lee & Park, 2005; Park, Holzman & Rakic, 1995). Finally, tasks had to be difficult enough to be sensitive indicators of risk in unaffected relatives but not too difficult for patients to perform. Thus, we created a series of information processing tasks along a continuum of difficulty to maximize the potential for group differentiation.

Principles of Task Design

In addition to behavioral studies, these ACPTs were designed for a blocked design functional magnetic resonance imaging (fMRI) applications that require comparison of a “target experimental” task with a “baseline control” task. Therefore, all task conditions were

closely matched on multiple parameters including: auditory sensory modality, stimuli (letters), target response signal (the letter "A"), warning/cue signal (the letter "Q"), rate of presentation (one letter/second), and sensory clarity. The differences between task conditions were the parameters of interest: degree of WM and interference load. WM load was defined as the number of letters between the warning/cue and the target. Level of interference was defined by the number of distracters ("Q's" and "A's") embedded between the cue and the target. The initial paradigms were designed to evaluate block (time) effects by directly matching them as alternating epochs in one experimental presentation (see Figure 1a). The WM and interference tasks had additional requirements for participants to keep in mind both the identity and order of previously presented letters and to continuously update the mental record as the sequence of letters progressed.

Procedures

For the initial study, we developed five versions of the ACPT named "A" and "QA" (vigilance), "Q3A-MEM" (high WM load/no interference), "Q1A-INT" (low WM load/low interference load), and "Q3A-INT" (high WM load/high interference load). Each task consisted of a baseline and target condition presented in an A-B-A-B format (see Figure 1a). In each condition, letters of the alphabet were presented monaurally at a rate of one/sec for four blocks of 90sec. Subjects were required to respond to all target stimuli by lifting their index finger. The simplest target vigilance condition required subjects to respond to each "A" (i.e., the A task). The next target vigilance condition required subjects to respond to each A only if immediately preceded by a Q (i.e., QA), a typical successive discrimination AX CPT (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Rosvold, Mirsky, Sarason, Bransome & Beck, 1956). Target probability and frequency of "lure" stimuli (individual "A's" or "Q's" not constituting a QA combination) are listed in Figure 1b. For interference tasks, these stimuli were periodically inserted between warning Q's and target A's interspersed with randomly selected letters of the alphabet.

In the target condition for the "Q1A-INT" task (AX CPT with interference), subjects responded to each A when preceded by a Q separated by one letter (e.g., Q R A), with some Q-A trials containing interspersed "Q's" or "A's" (Figure 1b). There were two versions of the increased memory load CPT in which the warning (Q) and target (A) stimuli were separated by 3 letters ("Q3A-MEM" and "Q3A-INT"). In the target condition for the "Q3A-MEM" task, subjects responded to each A when preceded by a Q separated by three letters (e.g., Q R C T A), and there were never Q's or A's between the Q (warning) and A (target) (i.e., no "interference"). In "Q3A-INT", like Q3A-MEM, randomly selected letters of the alphabet were interspersed throughout the block, including freestanding Q's and A's alone. To make the task more difficult, combinations of the letters, Q, A or QA were periodically embedded in between the Q and the target A. For example, some of the embedded stimuli strings were like the following: "Q Q c q A A b r". In this example, capital Q's and A's are cues and targets respectively, whereas the lower case "q" is a distracter. Trials with interspersed Q's and interleaved series were designed to produce distraction, divide attention, and prevent counting because the subject was episodically required to maintain two separate tracks simultaneously (e.g., constant updating of identification of stimuli from memory).

Previous Work—In initial fMRI studies, we demonstrated that two cohorts of healthy male volunteers performed significantly worse on the Q3A-INT task compared to a simple vigilance QA task (Seidman et al., 1998). In and outside the scanner, the vigilance task was performed virtually without error, while the more demanding WM condition did not show ceiling effects, despite the high education and level of intelligence of the participants. In fMRI studies, these two tasks were subsequently used, respectively, as baseline (vigilance)

and experimental (WM plus interference) tests to elicit group differences in fronto-subcortical circuitry between nonpsychotic relatives of individuals with schizophrenia and controls (Seidman et al., 2007; Thermenos et al., 2004). In two small samples of approximately 10-15 subjects per group, relatives demonstrated impaired performance during scanning on the WM + interference task (Q3A-INT). In this paper, we present for the first time a detailed analysis of performance on the entire battery of ACPT tasks in persons with schizophrenia, first-degree relatives, and healthy controls using two independent samples of participants at substantially different ages to assess for age effects.

Study Goals—The auditory tests were designed to tap these putatively fundamental cognitive deficits in schizophrenia (i.e., the effects of WM + interference) to serve as potential endophenotypic markers for the illness (Tsuang, Seidman & Faraone, 1999). These novel tasks could ultimately be used in future studies to track the probable increase in neurocognitive impairment from the premorbid through the prodromal period and the first episode of psychosis that often characterizes schizophrenia (Seidman et al., 2010). We also designed these tasks to be effectively adapted for fMRI experiments (Goldstein et al., 2005; Seidman et al., 1998; Seidman et al., 2007; Thermenos et al., 2004).

To achieve these goals, we carried out two studies. First, we conducted a study in a sample of adult patients with schizophrenia, their nonpsychotic first-degree relatives, and matched healthy controls using five ACPT task conditions with varying levels of difficulty/load (Study 1). Next, we sought to replicate the Study 1 findings with a younger, independent FHR sample. Because the WM plus interference tasks clearly discriminated relatives from controls in Study 1 and our aim was to develop measures of risk for psychosis, in Study 2 we focused solely on the comparison between relatives and controls and did not evaluate a second sample of patients with schizophrenia. Based on the results of Study 1, in Study 2, we used a shorter version of the ACPT battery consisting of three task conditions with an adolescent sample of nonpsychotic relatives and matched controls. Studies 1 and 2 are complementary in terms of examining the influence of age, as the relatives in Study 1 are largely older than 30 (mean = 41.0), while the relatives in Study 2 are all < 26 years of age (mean = 19.4). We subsequently analysed the combined data sets of both studies to assess the effects of age on condition and group, and also to study the age by group interaction in our largest sample of relatives < age 31.

Based on the literature indicating that high load tasks are most sensitive in eliciting deficits in relatives of persons with schizophrenia, our overarching hypothesis was that the two interference WM tasks would be most sensitive to the presumed vulnerability to schizophrenia observed in first-degree relatives. Thus, we expected to demonstrate task condition, group, and group by condition interaction effects in which patients with schizophrenia would be most impaired compared to controls, and relatives would show milder deficits.

Study 1

Participants

Subjects were 20 patients with DSM-III-R diagnoses of schizophrenia, 63 non-psychotic, first-degree relatives of patients with DSM-III-R diagnoses of schizophrenia, and 56 healthy controls. All subjects gave informed consent, and the study was approved by the Institutional Review Boards at the Massachusetts Mental Health Center (MMHC), Brockton Veterans Administration Medical Center, Massachusetts General Hospital (MGH), and Harvard Medical School (HMS). The subjects were part of previous studies (Faraone et al., 2000; Seidman et al., 2002), but the ACPT data have not been previously published except for a subset of the tests (QA and Q3A-INT) in approximately 30% of the relatives and

controls participating in neuroimaging studies (Seidman et al., 2007; Thermenos et al., 2004). Participants in this study were excluded if they had a diagnosis of substance abuse or dependence within the past six months, neurological disease, history of head injury or medical illness with documented cognitive sequelae, sensory impairments, IQ less than 70, or < eight years of formal education. Relatives and controls were included if they had no lifetime diagnosis of psychotic illness. As previously described (Faraone et al., 1995; Seidman et al., 2002), control participants were recruited through advertisements in the same geographic catchment areas as the hospitals from which the patients were recruited.

Procedures: Diagnostic and Personality Assessment

Patient diagnoses were derived from structured interviews using the Schedule for Affective Disorders and Schizophrenia (SADS, Spitzer & Endicott, 1978), review of the medical record, and clinician information. Two expert clinicians, unaware of the neuropsychological data, reviewed all available information to determine consensus lifetime diagnoses. Relatives were interviewed with the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1987) for Axis I disorders and the Structured Interview for DSM-III Personality Disorders (SIDP) (Stangl & Zimmerman, 1983). The substance use section of the SADS was used to screen for presence of substance abuse. Potential controls underwent a similar screening process as the relatives and patients, with the exception that they were assessed for current psychopathology using a short form of the Minnesota Multiphasic Personality Inventory (MMPI-168; Vincent et al., 1984) rather than a structured diagnostic interview. Controls were excluded if they reported a personal or family history of psychosis or psychiatric hospitalization, or if any MMPI clinical or validity scale, except for Masculinity-Femininity, was above a T-score of 70. The reading subtest of the Wide Range Achievement Test – revised (WRAT-R; Jastak & Jastak, 1985) was used as an estimate of intellectual ability (Kremen et al., 1996).

Data Analysis

Continuously distributed demographic variables such as age, education, WRAT-3 Reading, and parental education (the mean of both parents' years of education or one parent's years of education when only one parent's data was available) were compared among groups using analysis of variance (ANOVA). Sex and ethnicity were compared using Chi-square tests. The dependent measures reported are correct hit rates and signal detection indices ("d prime" or d'). d' is a measure of efficiency that takes into account both hit and false alarm rates (Green & Swets, 1966). The correlations between hit rates and d' were high, ranging from .90 to .98. Because age was expected to influence performance, age was used as a covariate in all analyses except those assessing age by group interactions. We assessed the relationship between ACPT performance and sample characteristics using the Pearson product moment correlation to determine whether the use of additional covariates was warranted.

As stated previously, our *a priori* hypotheses were that there would be directional effects of task Condition (WM interference tasks would yield lower performance), Group effects (patients would perform worst, followed by relatives, compared to controls), and a Group by Condition interaction (WM interference tasks would produce the biggest impairments, especially in the relatives – controls comparison). For these *a priori* directional comparisons, we used $p < .05$ (one-tailed) as the significance level. We also studied the Time (block) effect in exploratory analyses, using $p < .01$ for these contrasts (two tailed, as no specific hypotheses were formulated, and multiple comparisons were conducted). We examined the main effects of Group (schizophrenia, relatives, controls), Condition (five task conditions as in Figure 1a), and Time (i.e., whether performance changed across the two blocks for each task condition), and the interactions using ANOVA and ANCOVA. Next, we conducted

simple pairwise ANOVAs for each task Condition, collapsed across trials. Only the first two (of eight) QA blocks were analyzed in order to maintain comparability with the other conditions, each of which was administered twice (see Figures 1a). ESs were calculated for each pairwise comparison with Cohen's *d* (mean of the control group minus mean of the case group divided by the pooled standard deviation, Cohen, 1988). Adjusted ESs were also calculated using age as a covariate.

Results

Sample Characteristics

Table 1 presents sample characteristics. Participants ranged in age from 20 to 75, and age did not differ across groups. There were significantly fewer males among the relatives than the schizophrenia and control groups. The sample was primarily White, and the control group had a significantly higher proportion of White participants than the schizophrenia and relatives groups. Controls had significantly more years of education than the schizophrenia and relatives groups. However, the groups did not differ in parental education, which may be viewed as a proxy for SES. Controls exhibited higher WRAT-R Reading scores than the relatives. Age was not associated with performance on A or QA, but was negatively associated with Q3A-MEM (r = -.27, p < .005) and Q3A-INT (r = -.26, p < .005). Parental education was associated with Q1A-INT (r = .19, p < .05) and Q3A-INT (r = .21, p < .05). Sex was not associated with ACPT performance. Non-White race was negatively associated with performance on Q1A-INT only (r = -.18, p = .038). Because race differed across groups and was also associated with performance on the ACPT, it was used as a covariate in addition to age.

Tests of *a priori* Hypotheses

Task Condition

Table 2 gives the results of the ANOVAS and ANCOVAs. There was a significant main effect of task Condition, which remained significant after covarying age and race. Post hoc contrasts for d' indicated that performance on Q3A-INT was lower than performance on all other conditions (p's < .001). Performance on Q1A-INT was lower than all other conditions (p's < .001) except Q3A-INT. Performance on Q3A-MEM was lower than QA and A (p's < .001). Performance on QA did not differ from A. This linear trend is apparent in all 3 groups (see Figure 2 and Table 3).

Group

There was a main effect of Group that remained significant after covarying age and race. The schizophrenia group performed worse than relatives (p < .001) and controls (p < .001). Relatives performed worse than controls (p = .034).

Group X Condition

The interaction between Group and Condition was significant. This interaction remained significant after covarying age and race. ESs controlling for both age and race are not shown because the results are very comparable to controlling for age alone. Simple pair-wise comparisons and ESs by group and task condition are presented in Table 3. *Schizophrenia versus control:* As expected, the schizophrenia group performed significantly worse than controls on all task conditions. Unadjusted ESs were large, ranging from 0.87 to 1.60. These effects remained significant with large effects across all task conditions after controlling for age and race (d's from 1.11 to 1.87).

S*chizophrenia versus relatives*

The schizophrenia group performed significantly worse than the relatives on all task conditions. Unadjusted ESs were large, ranging from 0.80 to 1.32. These large effects remained significant across all conditions after controlling for age and race (*d*'s from 0.83 to 1.74).

Relatives versus controls

The relatives did not differ from controls on A or QA. On Q3A-MEM, relatives performed worse on d' after adjusting for age (*d* = 0.35) but not on hit rate. As predicted, relatives performed significantly worse than controls on the two interference tasks. On Q1A-INT, d' (*d* = 0.46) and hit rate (*d*= 0.38) both remained significant after covarying age and race. On Q3AINT, relatives performed worse than controls (*d* = 0.36 for d', *d* = 0.43 for hit rate). This remained significant after covarying age (*d* = 0.51 hit rate, *d* = 0.43 for d').

Exploratory Analyses

None of the exploratory analyses examining hit rate or d' reached the significance level of $p < .01$ after controlling for age and race. Of note, for the Time X Group interactions, in which there was a marginal trend (overall analyses $p < .024$, two tailed), the performance of the schizophrenia group did not differ across trials, whereas the performance for both the relatives and controls improved from trial 1 to 2 (both *p*'s < .001).

Study 2

Participants

Study 2 data were collected as part of the Harvard Adolescent Family High Risk Study between 1998 and 2007. This sample and its ascertainment procedures were described previously (Seidman et al., 2006). In brief, participants for this study were the biological children and siblings of schizophrenia probands (our FHR sample), and the biological children and siblings community control probands. All participants were between the ages of 13 and 25 at the time of their ACPT assessment. The FHR group comprised 41 children and siblings of adult probands least 18 years of age) diagnosed according to DSM-IV criteria with either schizophrenia or schizoaffective disorder, depressed type, using the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al 2004) and the Family Interview for Genetic Studies (FIGS; Maxwell, 1996). The control group comprised 55 children of parents diagnosed according to DSM-IV criteria with no mental illness (n = 25), major depressive disorder (n = 8), mood disorder due to general medical condition (n = 1), or cannabis abuse (n = 1) using the DIGS and FIGS. The adult control probands were drawn from respondents to local newspaper advertisements and announcements posted in the sites from which FHR probands were recruited (e.g., local hospital and clinics). The children and siblings of probands were subsequently ascertained to determine their eligibility and willingness to participate as subjects in the study.

Exclusion criteria were similar to Study 1. FHR participants were excluded if they had any lifetime diagnosis of psychotic illness, substance dependence, or neurological disease, a history of head injury or medical illness with documented cognitive sequelae, sensory impairments, current psychotropic medication use, or a full-scale IQ estimate of less than 70 based on eight sub-tests of the WISC-III (Wechsler, 1991) or WAIS-III (Wechsler, 1997). Participants in the control group were screened with the same criteria, with an additional exclusion criterion of any first- or second-degree biological relatives with lifetime history of a psychotic disorder. Offspring and siblings of control and schizophrenia probands were screened for presence of psychosis with the Washington University Kiddie SADS (KSADS;

Geller, Zimmerman, Williams & Frazier, 1994). The Psychosis, Substance Abuse and Mood Disorders modules of the WASH-U-KSADS were administered along with a Neurodevelopmental Questionnaire (Faraone et al., 1995) to establish other inclusion and exclusion criteria. The reading subtest of the Wide Range Achievement Test – third edition (WRAT-3; Wilkinson, 1993) was used as an estimate of intellectual ability.

Participants age 18 and older gave informed consent, while subjects younger than 18 years of age gave assent in conjunction with informed consent provided by a parent. Subjects received an honorarium. The study was approved by the human research committees of the MMHC, MGH, HMS, and other recruitment sites.

Measures and Procedures

The ACPT task battery was modified slightly from Study 1 in the following ways: Only the "QA", "Q3A-MEM", and "Q3A-INT" task conditions were administered in order to shorten the battery based on data that "A" and "QA", and "Q1AINT" and "Q3AINT" respectively, had comparable discriminating utility in Study 1. While the tasks contained the identical stimuli as in Study 1, one of the blocks of QA was eliminated (we had administered 8 blocks of QA task in Study 1), as data analysis by block showed no change over time on QA performance (See Figure 1a, tasks 5A-8A). Otherwise, stimuli were the same and the administration identical to Study 1.

Data Analysis

Data analytic procedures were similar to Study 1. Continuously distributed demographic variables (age, education, WRAT-3 Reading, parental SES as measured by the Hollingshead (1975) four factor scale, were compared between groups using ANOVA, while sex and ethnicity were compared using Chi-square tests. Age was used as a covariate in all analyses. The main dependent measures were hit rate and d'. The correlations between d' and raw hit rates ranged from .89 to .97.

We hypothesized that there would be directional Condition effects (WM interference tasks would be performed worst), Group effects (relatives would be impaired compared to controls), and a Group by Condition interaction (the Q3A-INT task would produce the largest impairment in the relatives). These comparisons we used $p < .05$ (one-tailed) as the significance level. We also studied the Time effect in exploratory analyses, using $p < .01$ for these contrasts (two-tailed as no specific hypotheses had been formulated and multiple comparisons were conducted). We examined the main effects of Group (relatives, controls), Condition (three task conditions), and Time (i.e., whether performance changed across the two blocks for each task condition), and the interactions using ANOVA and ANCOVA. Next, we conducted simple pairwise ANOVAs for each task condition, collapsed across trials. As in Study 1, only the first two QA trials were analyzed. Adjusted and unadjusted ESs were calculated for each pairwise comparison, with age as a covariate.

Results

Sample Characteristics

Sample characteristics are presented in Table 4. Participants ranged in age from 13 to 25; the FHR relatives were significantly older than controls. The sample was evenly split in terms of sex, and the groups did not differ on race or years of education. Controls reported higher parental SES. There was a marginal trend for normal controls having higher WRAT-3 Reading scores. Age was associated with performance on Q3A-INT ($r = .22$, $p < .05$). Parental SES was associated with performance on Q3A-MEM ($r = .35$, $p < .05$) and Q3A-INT ($r = .41$, $p < .001$).

Tests of *a priori* Hypotheses

Task condition

The results of ANOVAs and ANCOVAs are presented in Table 5. There was a significant main effect of task Condition, which remained significant after covarying age. Post hoc contrasts conducted on d' indicated that performance on Q3A-INT was lower than performance on Q3A-MEM, which was lower than performance on QA (p's < .001). This linear trend is apparent in both groups (Figure 3).

Group

There was a significant effect for both hit rate and d'. The relatives performed significantly more poorly than controls after adjusting for age.

Condition X Group

There was a significant interaction between Condition and Group for hit rate and a non-significant trend for d' (p = .059). Simple pairwise comparisons and ESs by group and task condition are presented in Table 6. The relatives and controls did not differ on QA. On Q3A-MEM, relatives performed worse than controls on hit rate and d' after covarying age. On Q3A-INT, relatives performed significantly worse than controls after covarying age on both hit rate and d", and the ES was greater after covarying age than before.

Exploratory Analyses—None of the exploratory analyses (Time, Time X Condition, Time X Group, Time X Group X Condition) reached the significance level of $p < .01$ for either hit rate or *d'* after age was controlled.

Ability of task conditions to discriminate between relatives and controls in the combined sample

Logistic regression examined the ability of the different task conditions to differentiate between relatives and controls in the combined sample (relatives n = 104; controls n = 111). Q3A-INT hit rate was a significant predictor of group status (B = 2.41, SE = 0.83, p = .004, 95% CI = 2.18-56.82), correctly classifying 58.6% of participants. Neither QA nor Q3A-MEM was a significant predictor of group membership, and adding them did not increase the predictive validity of the model, nor attenuate significant results. To determine if these findings wereaccounted for by a generalized deficit in cognition, we examined whether Q3A-INT would continue to be a significant predictor of group membership after covarying scores on WRAT-3 Reading. WRAT-3 Reading is a general measure of intellectual ability shown to differentiate between relatives and healthy controls (Agnew-Blais & Seidman, in press), was significantly different in our combined sample, and was moderately associated with Q3A-INT hit rate in the combined sample (r = .31, $p < .001$). After covarying WRAT-3 Reading, Q3A-INT hit rate remained a significant predictor of group membership (B = 1.73, SE = 0.88 p = .049, 95% CI = 1.01-31.69), with the model correctly classifying 63.5% of subjects. WRAT-3 Reading was also a significant predictor of group membership (p = .006) after covarying Q3A-INT suggesting that both variables uniquely predicted group membership.

To examine whether psychometric properties of the task conditions influenced their ability to discriminate between relatives and controls, we examined the correlations for hit rate between blocks 1 and 2 for each condition as a measure of reliability. The intraclass correlations were as follows: QA r = .33, Q3A-MEM r = .54, and Q3A-INT r = .69. Restricted range (i.e., ceiling effects) likely contributed to the lower correlation for QA.

Age By Group Interactions in the Combined Sample

To more directly examine the effect of age on performance for Q3A-INT, two-way between-groups ANOVAs with age and group as the independent variables were conducted on hit rate and d'. There was no interaction between group and age for hit rate ($F = 0.70$, $p = .864$) or d' ($F = 0.59$, $p = .943$) for the overall sample. However, for the combined sample under age 31 (relatives n = 53; controls n = 65), a statistically significant age by group interaction was found. Participants were separated into those age 13-20 (relatives n = 25; controls n = 43) and age 21-30 (relatives n = 28; controls n = 22). There was a significant interaction between group and age for hit rate ($F = 4.93$, $p = .028$) and d' ($F = 5.24$, $p = .024$). These effects are presented in Figure 4 and indicate that performance improved as a function of age to a greater extent among controls compared to relatives.

DISCUSSION

We carried out two studies of auditory vigilance with tasks involving WM and interference to identify the information processing vulnerabilities in people with schizophrenia and two independent samples of nonpsychotic relatives of individuals with schizophrenia and control groups. Results are summarized below.

Summary of Study 1

In this study of adults up to age 75, the results supported the hypotheses. First, the interference tasks were more difficult than the other tasks, and the memory task was intermediate in difficulty, while the simple vigilance tasks were easiest for all groups. Second, relatives and controls performed comparably on both vigilance tasks (A and QA), while QA was more difficult than A only among patients. Third, there was a clearly observable trend for schizophrenia patients to perform worse than relatives who, in turn, performed worse than controls. The differences between relatives and controls were only significant on the WM tasks, especially the two interference tasks, and the effect magnitude was modest ($d = \sim 0.40\text{-}0.50$). For patients, the ESs were quite large, averaging approximately $d = 1.5$ compared to controls, and they were impaired on all 5 versions of the ACPT. Finally, as the tasks had been designed to allow for analysis of learning/practice effects, there was a non-significant trend for the overall Time X Group interaction, with improved performance in the second block compared to the first for the relatives and controls only (patients did not improve from the first to the second trial). The overall pattern of results was consistent with that of the patients having a general deficit compared to the comparison groups. Significant impairment among the relatives emerged mainly when memory and interference were combined at low (Q1A-INT) or high (Q3A-INT) levels of difficulty.

Summary of Study 2

In this study of youth ages 13-25, results supported the hypotheses and were comparable to Study 1. The interference task was more difficult than the memory task, which was more difficult than the vigilance task. The relatives and controls did not differ on vigilance. As in Study 1, group differences began to emerge on the memory task, with relatives performing worse than controls after covarying age. As in Study 1, the ESs on the interference task were larger than on the memory task, with relatives performing significantly worse than controls. The ESs were moderate and similar but slightly larger in magnitude to those observed in Study 1. There was no significant effect of Time or Time x Group interaction. Overall, the results were consistent with the hypothesis that the task condition that combined memory and interference most clearly differentiated relatives from controls. Given the relatively large combined samples of more than 100 relatives and 100 controls, the data strongly

support the idea that these novel auditory WM + interference tasks tap an important component of the vulnerability to schizophrenia across a wide age range.

Of interest, the simple vigilance CPT task was quite easy in that almost all non-patients achieved perfect performance beginning with the first block, and no significant improvement occurred due to ceiling effects. This pattern is typical of traditional “”X” and AX” CPTs (Nuechterlein, 1991). In contrast, although a few subjects were able to perform perfectly, there were no ceiling effects on the interference WM CPTs. Improvement was achieved over time within task (except in schizophrenia patients) but did not reach ceiling. Among controls, the pattern of results on the QA vigilance task and the Q3AINT WM tasks in these samples of average intelligence are consistent with that observed in two independent cohorts of highly educated, healthy male controls participating in fMRI studies (Seidman et al., 1998). Significantly poorer performance on the WM than vigilance task is consistent with that found by others who have shown that error rates increase with memory load (Barch et al., 1997; Braver et al., 1997; Gevins et al., 1996). Of note, the reliability of the WM+INT task across blocks was the highest of the three task conditions used in both studies, probably contributing to their enhanced discriminating power.

The CPT tasks, especially the interference tasks, had an ES as large as the most discriminating tasks (such as digit symbol coding) for schizophrenia (Dickinson, Ramsey & Gold 2007; Mesholam-Gately, Giuliano, Faraone, Goff & Seidman 2009), even though the mean IQ in this schizophrenia sample was about 100, somewhat higher than is typical (Aylward, Walker & Bettes 1984; Woodberry, Giuliano & Seidman 2008). Similarly, the effect for the interference task in relatives, which was moderate (i.e, d ~0 .40-0.50), was roughly equivalent to the largest ESs in meta-analyses of neurocognitive impairment among nonpsychotic relatives (e.g., Snitz, MacDonald & Carter, 2006). This suggests that the interference tasks are sensitive in terms of tapping into an important component of vulnerability to schizophrenia.

Task performance on the memory and interference tasks was negatively correlated with age across the whole sample, consistent with a large literature suggesting that aging is associated with decline in cognitive function (Salthouse, 1994). However, there was no significant group by age interaction across the entire sample, suggesting the group differences were largely comparable across age. We carried out an exploratory analysis for the age range of 13-30 based on hypotheses that deficits may be largest in the period when the onset of schizophrenia peaks (late teens to late 20’s). In that epoch, containing approximately half of the overall sample, there was a significant age by group interaction; controls improved with age whereas the relatives did not, suggesting a failure of developmental maturation. The absence of improved performance in relatives may reflect an increasing failure to respond to higher load task demands.

Future research should clarify how findings from these auditory CPTs compare to those from other CPTs used in most endophenotype studies. There are no published direct comparisons between this set of tasks and other complex CPTs, however, we can infer relative sensitivity based on two comprehensive reviews of CPTs (Snitz et al., 2006; Gur et al. 2007). Indeed, differing conclusions as to whether FHR individuals show deficits in vigilance may be due to an inability of simpler versions of the CPT to identify subtle deficits. Several studies using simple CPTs (Asarnow, Steffy, MacCrimmon & Cleghorn, 1977; Cohler, Grunebaum, Weiss, Gamer & Gallant, 1977) found no difference between FHR and controls. This is comparable to our observation of no significant differences in relatives-control comparisons on the two auditory vigilance tasks (A and QA) used in the current study. This pattern led investigators to focus on high-load, effortful CPTs.

The two most frequently used high load CPTs in the FHR literature are both visual, the degraded stimulus CPT (Nuechterlein, Parasuraman, & Jiang, 1983) and the CPT-IP (Cornblatt, Risch, Friedman. & Erlenmeyer-Kimling, 1988). Overall, meta-analyses report moderate ESs for these two tasks; d ~= 0.43-0.54 for CPT d' in complex, high-load versions (Snitz et al., 2006; Gur et al., 2007). The CPT-IP is closer conceptually to the auditory CPT battery because it manipulates WM load, whereas the degraded stimulus CPT burdens perceptual processing. Agnew-Blais & Seidman (in press) reported that the mean ES across 5 studies of FHR youth below age 30 for the CPT-IP digits was -0.29 and for CPT-IP shapes was -0.26, both somewhat smaller than the ES for the WM + interference CPT in the current study 2, and smaller than the meta-analyses cited above suggest. Neither study of adolescents at FHR (Cosway et al.,2002; Seidman et al. 2006) found significant impairments in the CPT-IP, although some similar studies did successfully discriminate using CPT-IP digits (Myles-Worsley et al, 2007) with moderate ESs (d=-0.61). Moreover, in successive rounds of testing in Sample B of the New York HR Study, using the CPT-IP, FHR participants had significantly poorer discriminability compared to controls and to individuals at FHR for affective disorders, replicating the earlier finding in the double-digit Task B CPT (Erlenmeyer-Kimling & Cornblatt, 1992). Thus, because the variability of findings across studies makes it difficult to make definitive conclusions, direct comparisons between CPT tasks are necessary to address the issue of comparative sensitivity and specificity.

Additional questions need to be addressed to help investigators choose among various tests for endophenotype studies. For example: 1. Do the tests identify the same subjects as impaired or non-impaired?; 2. For which populations are the tests appropriate? For example, the auditory Q3A-INT may be too difficult for younger children. 3. How heritable are the different tests, and are they associated with the same genetic processes or neural substrates? These questions are beyond the scope of this paper, but they highlight issues that need to be addressed to determine the differential utility of these tests.

Strengths and limitations—This study has a number of strengths, including a novel battery of auditory CPT tasks designed within a conceptual framework oriented to identifying core information processing deficits in schizophrenia. A large sample of relatives and controls was studied. By studying two independent samples of relatives across a wide age range, replication could be achieved, and impairments across the wide age range from 13 to 75 were demonstrated. There were also some limitations. These include a fixed order of tasks within each study. However, very similar results in two separate studies of relatives, which had different task orders argues against a fatigue or order effect (see figure 1a). Moreover, the fact that both relatives and controls showed comparable learning over time argues against a substantial fatigue effect. In addition, the schizophrenia participants did not show a decline over time, consistent with results reported by Lenzenweger, Cornblatt, & Putnick (1991) on the visual CPT-IP.

Another limitation of the study is the generalized deficit problem (Chapman & Chapman, 1978). The current results appear to be at least partially explained on the basis of a general deficit: patients< relatives< controls, with the deficit growing as task difficulty increases for all groups. That is, tasks with increasing difficulty (and better reliability) had better discriminating power in patients and relatives. Of note, however, the WM + INT task continued to differentiate relatives from normal controls even after accounting for a general measure of intellectual ability and for simple vigilance. The current study design does not allow us to precisely pinpoint the mechanisms underlying the impairment on the most sensitive tasks (i.e,, WM +INT). One of the questions generated by this study is whether WM alone or WM + interference are central to the cognitive vulnerability to schizophrenia. While our study design was not set up to optimally test for differential deficit, it is notable that whereas controls were equivalent in performance on Q3A-MEM and Q1A-INT in Study

1, relatives exhibited impairment only on the interference task. However, the group by condition effect was not significant using these two tasks with these two groups. If this initial finding of equivalent performance amongst controls on these two tasks can be replicated in a larger, independent sample, this would allow us to test for differential deficit in future studies. Moreover, comparison with other well-established cognitive vulnerability indicators (i.e., verbal declaratve memory) on the same subjects would help identify whether there are selective deficits in these cognitive processes.

Future Directions—Future work could evaluate the differential sensitivity of these WM interference tasks compared to matched visual CPT tasks, and directly compare the differential sensitivity to other neurocognitive tasks that have been shown to be sensitive to genetic risk for schizophrenia (e.g., digit symbol coding, dichotic listening, story recall etc.). Prospective, longitudinal studies could also examine whether performance on these ACPTs enhances prediction of conversion to psychosis among at-risk participants (e.g., Seidman et al., 2010) or changes over time. It remains important to determine the relationships among these tasks and functional outcome, symptoms, and other clinical features in relatives and patients with schizophrenia. Identifying whether these tasks are useful in discriminating other disorders (e.g., schizotypal personality disorder, attention-deficit/hyperactivity disorder) with presumed problems in WM and effortful attention processing would be useful for determining the specificity of the deficits observed in these studies. Finally, such tasks could be tested in treatment studies and imaging studies to determine the malleability or reversibility of the deficits (Barch & Smith, 2008).

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Task Design

		Condition and Duration of Stimuli			
		90 sec	90 sec	90 sec	90 sec
Study 1/ Order of Task	Task Name	Baseline Trial 1	Target Trial 1	Baseline Trial 2	Target Trial 2
1. Vigilance	A/QA	A	QA	A	QA
2. WM + High Load Interference	Q3A-INT	QA	Q3A-INT	QA	Q3A-INT
3. WM	Q3A-MEM	QA	Q3A-MEM	QA	Q3A-MEM
4. WM + Low Load Interference	Q1A-INT	QA	Q1A-INT	QA	Q1A-INT
Study 2/Order of Task		90 sec Target Trial 1	90 sec Baseline Trial 1	90 sec Target Trial 1	-
1. Vigilance	QA	QA	-	-	-
2. WM	Q3A-MEM	Q3A-MEM	QA	Q3A-MEM	-
3. WM + High Load Interference	Q3A-INT	Q3A-INT	QA	Q3A-INT	-

Figure 1a.
Experimental Design and Continuous Performance Task Stimuli Task Design

Task Condition	Task Instructions, Stimuli, and Response	Target probability	% distractor stimuli (outside Q-A sequences)	% interfering stimuli (inside Q-A sequences	Total
A	"Respond to *a*." s j t l e z A c o p A …	~20	0	-	0
QA	"Respond to *a* preceded immediately by *q*." o a s q A w q y p q A c …	~20	~12	-	12
Q3A-MEM	"Respond to *a* preceded by *q* four letters previously." r q s p b A q t o c n q c z o A …	~13	~11	-	11
Q1A-INT	"Respond to *a* preceded by *q* two letters previously." q s q a A c g a q q A A m s r …	~20	~14	7	21
Q3A-INT	"Respond to *a* preceded by *q* four letters previously." q s q b r a A c g q z q h A p A m ..	~20	~8	14	22

Figure 1b.
ACPT Task Stimuli, Instructions, Response, and Design for Study 1 and 2

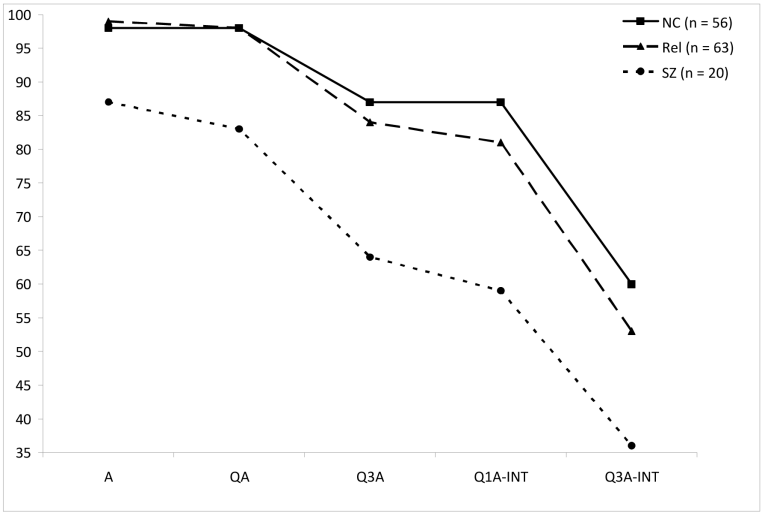

Figure 2.

Study 1. Hit rates for ACPT by group and task condition. The A and QA task conditions are vigilance tasks. Q3A-MEM is a working memory task. Q1A-INT combines low levels of working memory and interference control. Q3A-INT combines working memory and a high level of interference control. NC = Normal Control; Rel = Relatives; SZ = Schizophrenia.

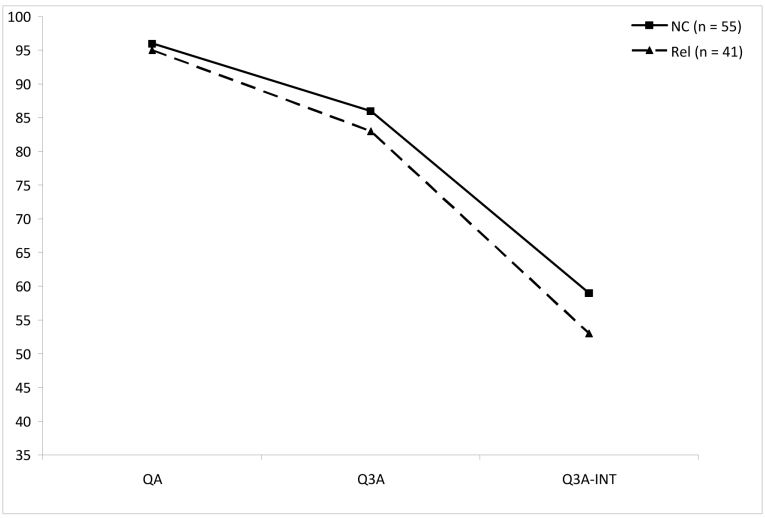

Figure 3.
Study 2. Hit rates for ACPT by group and task condition. QA is a vigilance task. Q3A-MEM is a working memory task. Q3A-INT combines working memory and high levels of interference control. NC = Normal Control; Rel = Relatives.

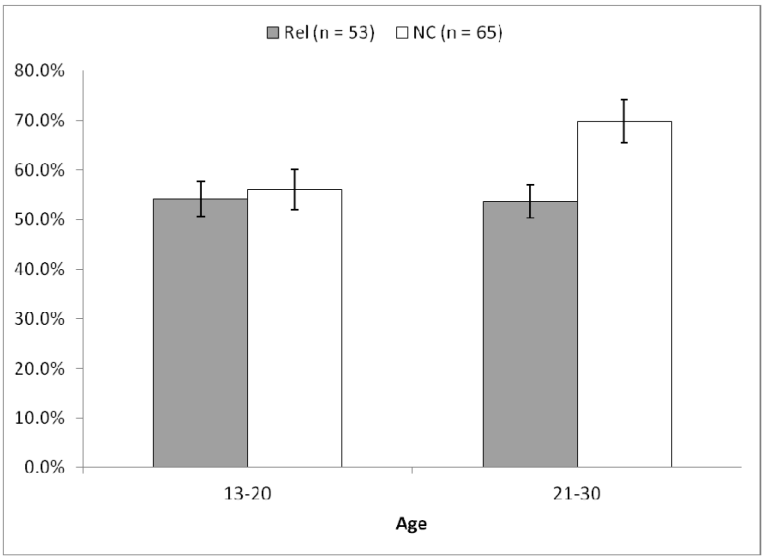

Figure 4.
The interaction of group and age on Q3A-INT hit rate in the Combined Sample of individuals 30 or younger. Q3A-INT combines working memory and interference control. Error bars represent standard errors (Rels = relatives, NC = Normal Controls).

Table 1

Sample characteristics for Study 1

	Schizophrenia n = 20 *M (SD)*	Relatives n = 63 *M (SD)*	Normal Control n = 56 *M (SD)*	Test Statistic (*p*-value)
Age	43.2 (8.3)	41.0 (11.2)	43.2 (12.8)	$F = 0.62$ (.540)
Subject Education	12.3 (2.1)	13.2 (2.6)	15.1 (2.2)	$F = 15.25$ (< .001)
Parental Education [a]	12.1 (2.7)	11.6 (3.0)	11.5 (2.8)	$F = 0.26$ (.771)
WRAT-3 Reading	99.7 (17.5)	98.8 (13.0)	105.5 (12.4)	$F = 3.79$ (.025)
Sex % Male (n)	65.0 (13)	31.7 (20)	50.0 (28)	$\chi^2 = 8.24$ (.016)
Race % White (n)	75.0 (15)	81.0 (51)	92.9 (52)	$\chi^2 = 6.46$ (.040)

[a] SZ (schizophrenia) n = 16; Rel (Relatives) n = 60; NC (normal controls) n = 53

Table 2

Results of condition x group analyses for the Auditory Continuous Performance Test for Study 1

	Condition [a] *F (p)*	Group [a] *F (p)*	Condition X Group [a] *F (p)*
Correct hit %	301.37 (< .001)	30.57 (< .001)	3.90 (< .001)
Correct hit % (adjusted for age)	13.04 (< .001)	32.51 (< .001)	4.24 (< .001)
Correct hit % (adjusted for Age and Race)	2.29 (=.003)	30.32 (< .001)	3.36 (<.001)
d' ANOVA	338.02 (< .001)	33.37 (< .001)	2.55 (=.005)
d' ANCOVA (Adjusted for Age)	16.10 (< .001)	35.12 (< .001)	2.86 (=.002)
d' (Adjusted for Age and Race)	4.71 (<.001)	32.75 (< .001)	2.24 (=.012)

Note. Results of three-way ANOVAs and ANCOVAs with two within-subjects variables (5 task conditions, 2 trials per condition) and one between-subjects variable (3 groups). Interactions with Time are not shown as they were not statistically significant.

d' is a measure of efficiency that takes into account both hit and false alarm rate.

[a]Analyses evaluated at $p < .05$ (one-tailed).

Table 3

Task performance and effect sizes by group and task condition for the Auditory Continuous Performance Test for Study 1

Task condition	Schizophrenia *M (SD)*	Relatives *M (SD)*	Normal Controls *M (SD)*	Schizophrenia vs Normal Control		Schizophrenia vs Relatives		Relatives vs Normal Control	
				d [a]	*d* [b]	*d* [a]	*d* [b]	*d* [a]	*d* [b]
A correct hit %	.87 (.16)	.99 (.02)	.98 (.05)	0.87 ^{**e}	1.11 ***	0.99 ^{**e}	1.42 ***	0.24	0.29
QA correct hit %	.83 (.19)	.98 (.03)	.98 (.03)	1.10 ^{***e}	1.51 ***	1.09 $^{** e}$	1.50 ***	0.03	0.03
Q3A-MEM correct hit %	.64 (.26) d	.84 (.13)	.87 (.13)	1.14 ***	1.39 ***	1.00 ***	1.21 ***	0.22	0.29
Q1A-INT correct hit %	.59 (.22) d	.81 (.15)	.87 (.13)	1.53 ***	1.81 ***	1.17 ***	1.28 ***	0.38 *	0.41 *
Q3A-INT correct hit %	.39 (.21)	.53 (.15)	.60 (.18)	1.13 ***	1.21 ***	0.80 ***	0.83 **	0.43 *	0.51 **
A d’	3.54 (.75)	4.19 (.24)	4.17 (.24)	1.13 ***	1.44 ***	1.16 ***	1.52 ***	0.07	0.07
QA d’	3.35 (.85)	4.18 (.26)	4.24 (.23)	1.42 ***	1.87 ***	1.32 ***	1.74 ***	0.23	0.22
Q3A-MEM d’	2.75 (.91) d	3.53 (.53)	3.68 (.48)	1.27 ***	1.55 ***	1.05 ***	1.24 ***	0.29	0.35 *
Q1A-INT d’	2.49 (.79) d	3.32 (.64)	3.60 (.58)	1.60 ***	1.78 ***	1.14 ***	1.18 ***	0.46 **	0.50 **
Q3A-INT d’	1.79 (.70)	2.48 (.47)	2.67 (.56)	1.38 ***	1.56 ***	1.16 ***	1.28 ***	0.36 *	0.43 *

Note. Means and standard deviations are unadjusted. *d* = Cohen’s *d*. d’ is a measure of efficiency that takes into account both hit and false alarm rate.

* $p < .05$;

** $p < .01$;

*** $p < .001$ (one tailed)

[a] *p*-values based on planned contrasts (unadjusted)

[b] *p*-values based on ANCOVAs controlling for age. Cohen’s *d* based on least squared means.

[d] n = 18 due to missing data

[e] *p*-values based on t-test with unequal variance

Table 4

Sample characteristics for Study 2

	Relatives n = 41 ***M (SD)***	**Normal Controls n = 55** ***M (SD)***	**Test Statistic (*p*)**
Age	19.4 (3.8)	17.0 (3.6)	$F = 10.31$ (.002)
Subject Education	11.4 (2.7)	10.8 (3.3)	$F = 1.15$ (.287)
WRAT-3 Reading SS	102.5 (10.3)	106.6 (9.5)	$F = 3.87$ (.052)
Hollingshead (SES)	38.8 (16.5) [a]	47.5 (15.6)	$F = 6.62$ (.012)
Sex % Male (n)	48.8% (20)	45.5% (25)	$\chi^2 = 0.10$ (.747)
Race % White (n)	58.5% (24)	60.7% (34)	$\chi^2 = 0.11$ (.745)

[a] Relatives n = 37

Table 5

Results of condition x group analyses for the Auditory Continuous Performance Test for Study 2

	Condition[a] *F (p)*	Group[a] *F (p)*	Condition X Group[a] *F (p)*
Correct hit %	324.41 (< .001)	3.03 (.043)	1.65 (.098)
Correct hit % (adjusted for age)	26.58 (< .001)	6.85 (.005)	2.95 (.028)
d’	387.17 (< .001)	2.38 (.063)	1.05 (.176)
d’ (adjusted for age)	29.68 (< .001)	6.02 (.008)	2.16 (.059)

Note. Results of three-way ANOVAs and ANCOVAs (adjusted for age) with two within-subjects variables (3 task conditions, 2 trials per condition) and one between-subjects variable (2 groups). Exploratory analyses not shown as none were statistically significant.

d’ is a measure of efficiency that takes into account both hit and false alarm rate.

[a]Analyses evaluated at $p < .05$ (one-tailed).

Table 6

Task performance and effect sizes by group and ACPT task condition for Study 2

	Relatives *M (SD)*	Normal Controls *M (SD)*	*d* [a]	*d* [b]
QA correct hit %	.95 (.07)	.96 (.07)	0.22	0.31
Q3A-MEM correct hit %	.83 (.12)	.86 (.14)	0.20	0.35*
Q3A-INT correct hit %	.53 (.17)	.59 (.18)	0.38*	0.54**
QA d’	4.03 (.34)	4.09 (.32)	0.17	0.27
Q3A-MEM d’	3.47 (.57)	3.58 (.59)	0.21	0.36*
Q3A-INT d’	2.41 (.62)	2.62 (.58)	0.36*	0.57**

Note. Means and standard deviations are unadjusted. *d* = Cohen’s *d*. d’ is a measure of efficiency that takes into account both hit and false alarm rate.

* $p < .05$;

** $p < .01$;

*** $p < .001$ (one tailed)

[a] ANOVAs and effect sizes based on unadjusted group means and standard deviations

[b] ANCOVAs controlling for age;

Cohen’s *d* based on least squared means.