JEFFREY SCOTT BEDWELL
Accelerated Age-Related Decline of Visual Processing in Healthy First-Degree Relatives of Persons with Schizophrenia
(Under the Direction of: L. STEPHEN MILLER)

Research focusing on individuals with schizophrenia has noted that a subgroup evidence an accelerated age-related decline in general cognitive performance, particularly on tasks that emphasize visual processing ability. However, there appears to be an absence of literature examining age-related visual processing change in healthy first-degree relatives of persons with schizophrenia. Such research would help determine if similar findings in persons with schizophrenia are primarily related to genetic contributions to the disorder, as opposed to factors such as chronic neuroleptic exposure. Cross-sectional examination of healthy first-degree relatives of persons with schizophrenia between the ages of 21 and 72 revealed that both visual processing and intellectual ability (to a weaker extent) displayed an accelerated age-related decline compared to controls. The findings extend a report of accelerated age-related decline of visual processing in persons with schizophrenia to include healthy first-degree relatives, supporting the notion of genetic contributions to this phenomenon.

INDEX WORDS: Schizophrenia, Visual Processing, Relatives, Aging, Age-Related Decline, Full Scale IQ, Sustained Attention

ACCELERATED AGE-RELATED DECLINE OF VISUAL PROCESSING IN HEALTHY FIRST-DEGREE RELATIVES OF PERSONS WITH SCHIZOPHRENIA

by

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CHAPTER 1

OVERVIEW AND SPECIFIC AIMS OF PROJECT

Examining healthy first-degree relatives of persons with schizophrenia is advantageous because unique biobehavioral characteristics found in these individuals may offer insight into genetic expression in schizophrenia without the confounds of neuroleptic exposure, duration of hospitalization, and active symptom effects (Adler, Freedman, Ross, Olincy, & Waldo, 1999; Weinberger, 1999). This insight may lead to improved identification of members of an affected family that are likely carrying one or more genes associated with schizophrenia, even in the absence of frank psychopathology, thereby adding statistical power to genetic linkage studies (Adler et al., 1999; Freedman, Adler, & Leonard, 1999). Identification of the genes that predispose individuals to schizophrenia paves the way for developing more effective pharmacological treatments and prevention strategies. Such improved treatment and/or prevention strategies have the potential to ease lifelong suffering in countless individuals and save millions of dollars spent annually treating this chronic condition.

Research focusing on individuals with schizophrenia has noted that a subgroup of these individuals evidence an accelerated age-related decline in general cognitive performance (Harvey et al., 1999), particularly on tasks that emphasize visual processing ability (Granholm, Morris, Asarnow, Chock, & Jeste, 2000). However, there appears to be an absence of literature examining accelerated age-related cognitive decline in first-degree relatives of persons with schizophrenia. Such research would help determine if these findings in persons with schizophrenia are primarily related to genetic contributions

to the disorder or whether they are likely related to secondary factors such as chronic neuroleptic exposure and changes in the active symptomology of the disorder. If an accelerated age-related decline in particular cognitive functions does appear to be primarily related to schizophrenia-related gene effects, this can add statistical power to genetic linkage studies, thereby increasing the likelihood that the genes related to schizophrenia will be identified.

To this end, the current study had the following aims:

Specific Aim #1: To investigate whether the aging decline in visual processing is accelerated in first-degree relatives of persons with schizophrenia, as compared to individuals who are not known to have any biological relative with schizophrenia.

Specific Aim #2: If an accelerated age-related decline is found: to describe the age range at which this differential performance is statistically significant.

Specific Aim #3: To investigate whether an accelerated age-related decline is relatively specific to sensory-perceptual processing, as compared to general intellectual ability and sustained attention.

CHAPTER 2

INTRODUCTION

Background and Significance

It is well established that as many as 85% of persons with schizophrenia display impairment in many areas of cognitive functioning (Palmer et al., 1997), and that this dysfunction is present in many patients as early as the first episode (Hoff, Riordan, O'Donnell, Morris, & DeLisi, 1992; Saykin et al., 1994). However, continued progression of cognitive decline after the onset of psychosis in schizophrenia remains controversial. Some studies support a neurodegenerative hypothesis, finding that cognitive decline in older persons with schizophrenia is greater than that found in normal aging (Arnold et al., 1995; Bilder et al., 1992; Davidson et al., 1995; Harvey, Leff, Trieman, Anderson, & Davidson, 1997). Other studies support a neurodevelopmental hypothesis that cognitive deficits found early in the disorder progress only to the extent expected by normal aging (Chaikelson & Schwartzman, 1983; Goldberg, Hyde, Kleinman, & Weinberger, 1993; Hyde et al., 1994; Mockler, Riordan, & Sharma, 1997).

Considering these discordant findings, it is difficult to clearly infer schizophrenia-related gene effects on age-related cognitive decline. One possibility is that an artificial performance ceiling conceals a genetically driven, accelerated, age-related cognitive decline. This ceiling effect may be created through reduced cognitive performance resulting from a number of factors operating in persons with schizophrenia, including psychoactive medications, active symptomology, long-term hospitalization, and reduced cognitive stimulation. This ceiling effect could hypothetically restrict adequate

performance on cognitive tests beginning in the early stages of the disease and continuing through old age. Therefore, cognitive decline may be masked as a result of constrained performance variability. In light of this possibility, among other possible confounds, it may be less informative to examine persons with schizophrenia directly.

As an alternative, examining healthy first-degree relatives of persons with schizophrenia is advantageous because unique characteristics found in these individuals may offer insight into genetic expression in schizophrenia without the confounds of neuroleptic exposure, duration of hospitalization, and active symptom effects. First-degree relatives of individuals with schizophrenia have been found to have a number of neurobiological and neurobehavioral abnormalities similar to those seen in the affected probands. These similar abnormalities appear in structural brain imaging (Seidman et al., 1999; Sharma et al., 1999; Staal, Hulshoff Pol, Schnack, van der Schot, & Kahn, 1998; Staal, Hulshoff Pol et al., 2000), eye tracking (Holzman, 2000), sustained attention (Cornblatt & Keilp, 1994), sensory-perceptual processing (Cornblatt & Keilp, 1994; Green, Nuechterlein, & Breitmeyer, 1997; Maier, Franke, Hain, Kopp, & Rist, 1992), neuropsychological profile (Cannon et al., 1994), P-300 and P-50 auditory event-related potentials (Blackwood, St Clair, Muir, & Duffy, 1991; Freedman et al., 1997), nonverbal social-emotional perception (Toomey, Seidman, Lyons, Faraone, & Tsuang, 1999), and subtle clinical features (Burke, Murphy, Bray, Walsh, & Kendler, 1996; Hain, Maier, Hoechst-Janneck, & Franke, 1995).

The overabundance of these features in first-degree relatives of persons with schizophrenia, compared to the general population, suggests that some of these features may be genetic markers related to schizophrenia. Such features have been termed

"endophenotypes" or "biobehavioral markers" and are thought to be closer to the mechanism of gene action than the clinical phenotype (Cannon et al., 1994). The presence of endophenotypes in first-degree relatives is consistent with the fact that they share 50% of the proband's genes and the notion that schizophrenia is caused by multiple genes of small effect.

Current problems with diagnosis and classification severely limit the power of genetic linkage studies in schizophrenic families (Freedman et al., 1999; McGuffin, 1984). Although family, twin, and adoption studies indicate that schizophrenia has a significant genetic component, these studies also show that the inheritance of schizophrenia is complex, involving an uncertain mode of transmission, incomplete penetrance, and probable genetic heterogeneity (Risch, 1990b; Tsuang, 1993).

Genetic linkage studies determine the statistical likelihood that a specific feature is linked to a particular gene locus through the detection of genetic sequences shared at a higher frequency in affected compared to unaffected family members (Terwilliger & Goring, 2000). If the genetic location of a given trait is unknown, genome-wide scans are used to search for the gene locus that shows the highest statistical likelihood of being related to the given trait. Therefore, identification of reliable biobehavioral markers will considerably improve the prospect of success in genetic linkage studies, as they will help identify family members that carry one or more schizophrenia-related genes, even in the absence of schizophrenia symptomology.

Two studies have already identified genetic loci using this method of identifying biobehavioral markers in schizophrenic families. Using genome-wide linkage analysis and abnormal P-50 auditory-evoked response inhibition as the endophenotype, Freedman

et al. (1997) have demonstrated linkage to a locus on chromosome 15 (15q13-14). Similarly, using eye-tracking dysfunction as the endophenotype, Arolt et al. (1996) reported linkage to two regions on the short arm of chromosome 6. These examples demonstrate the potential for biobehavioral markers to reveal genetic contributions to schizophrenia.

In addition to informing genetic linkage studies and offering insight into genetic expression in schizophrenia, identification of endophenotypes can permit isolation of environmental contributors to illness expression in genotypic carriers, which may lead to prevention or treatment strategies. This identification is achieved by examining environmental factors present in individuals who express the endophenotype, but do not develop schizophrenia, and comparing these with environmental factors present in individuals who both express the endophenotype and develop schizophrenia. These studies are optimally conducted by examining individuals for the presence of the endophenotype before the typical age of onset for schizophrenia (prior to age 16) and then following these individuals longitudinally to assess for the expression of schizophrenia.

An example of a promising endophenotype is performance on a task called the Span of Apprehension (SOA). A common version of the SOA task requires an individual to detect which of two target letters is present in a group of random distracter letters flashed very briefly (50-100 ms) on a visual display. The number of distracter letters is varied systematically and performance is compared across conditions. As the number of distracter letters is increased, there is an increased reliance on visual processing and performance accuracy general declines.

Deficiency on the SOA task has been demonstrated in persons with schizophrenia of all ages (Asarnow, Granholm, & Sherman, 1991; Granholm, Asarnow, Verney, Nelson, & Jeste, 1996; Ito, Kanno, Mori, & Niwa, 1997; Miller, Chapman, Chapman, & Barnett, 1990), however this deficiency is only present with a large number of distracter letters. Similarly, healthy older individuals display a deficiency in performance on the SOA task, again only with a large number of distracter letters (Plude & Hoyer, 1986). As a result, it appears that the more difficult conditions on the SOA task are sensitive to both schizophrenia and healthy aging, suggesting that this task may be able to detect an age-related decline in sensory-perceptual processing in schizophrenia.

First-degree relatives of persons with schizophrenia have also demonstrated deficits on the SOA task (Asarnow, Steffy, MacCrimmon, & Cleghorn, 1977; Maier et al., 1992). Additionally, a study found that individuals within a nonpsychiatric group who performed poorly on the SOA task scored significantly higher on questionnaires that measure subclinical schizotypy (Asarnow, Nuechterlein, & Marder, 1983). A study using nonpsychiatric twins found that the SOA task had high heritability (0.65) and that less than half the genetic effects important for the SOA task were found in common with genetic factors important for IQ (Bartfai, Pedersen, Asarnow, & Schalling, 1991), indicating a unique genetic contribution to SOA performance. These findings support the validity of using the SOA task as a genetic marker for schizophrenia.

In light of these findings, research was recently conducted to examine whether the SOA deficit found in those with schizophrenia displayed an accelerated age-related decline. It is notable that previous studies, discordant in finding accelerated age-related cognitive decline in persons with schizophrenia, used traditional neuropsychological test

batteries and gross cognitive screening measures. In contrast, Granholm et al. (2000) used the SOA task, which has been suggested to be more sensitive to age-related cognitive decline in schizophrenia, as compared to more traditional neuropsychological tests (Niederehe & Rusin, 1987). Using cross-sectional analyses, these investigators found evidence for accelerated age-related decline on a SOA task in a group of outpatients with schizophrenia.

An alternate task of genetic liability for schizophrenia, the Continuous Performance Task (CPT), has been used in many studies examining individuals with schizophrenia. The early versions of this task included the original X (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) and AX (Wohlberg & Kornetsky, 1973) tasks. The X task required a participant to press a button whenever an "X" appeared on the screen in a series of random letters, while the AX task required the participant to press a button when an "X" appeared, but only when preceded by the letter "A". These versions of the tasks were able to support the notion of a sustained attention deficit in persons with schizophrenia, both when ill (Orzack & Kornetsky, 1966), and when in remission (Asarnow & MacCrimmon, 1978; Wohlberg & Kornetsky, 1973).

CPT performance in persons with schizophrenia has shown a decrease in accuracy over the duration of the task that is independent of the degree of stimulus degradation, consistent with a sustained attention deficit (Mass, Wolf, Wagner, & Haasen, 2000). However, these changes in performance were reported to be negatively correlated to neuroleptic drug levels, confounding interpretation of the results. This highlights the advantage of using healthy relatives to aid in isolating effects of the genetic contribution on CPT performance.

A recent study (Elvevag, Weinberger, Suter, & Goldberg, 2000) reported that CPT deficits found in persons with schizophrenia may be influenced by visual processing dysfunction. This study found that persons with schizophrenia produced more omission errors (not responding to target stimuli) on CPT conditions with shorter interstimulus intervals (which requires faster processing), a finding also reported in a previous study (Cornblatt & Keilp, 1994). This suggests that persons with schizophrenia have difficultly in constructing a mental representation of the stimulus, as they have difficulty identifying a target when given little time to process it.

Versions of the CPT that do not use visually complex stimuli are generally not successful in revealing sustained attention deficits in relatives of persons with schizophrenia (Asarnow et al., 1977; Cohler, Grunebaum, Weiss, Gamer, & Gallant, 1977; Egan et al., 2000; Herman, Mirsky, Ricks, & Gallant, 1977). Research using the CPT with relatives began to use more difficult versions. This was accomplished through using more complex visual stimuli such as images of playing cards (Rutschmann, Cornblatt, & Erlenmeyer-Kimling, 1977), requiring participants to respond only to identical versions of complex stimuli (identical pairs version) (Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988), and perhaps more commonly, through degrading the stimuli by blurring them on the screen and superimposing visual noise (Nuechterlein, 1983). These versions of the CPT placed more demand on visual processing and were able to distinguish between relatives of persons with schizophrenia and comparison participants (Chen et al., 1998; Finkelstein, Cannon, Gur, Gur, & Moberg, 1997; Franke, Maier, Hardt, Hain, & Cornblatt, 1994; Laurent et al., 1999;

Maier et al., 1992; Mirsky, Ingraham, & Kugelmass, 1995; Mirsky, Yardley, Jones, Walsh, & Kendler, 1995; Nuechterlein, 1983; Rutschmann et al., 1977).

A large proportion of healthy first-degree relatives of persons with schizophrenia (19-34%) have CPT deficits, which can be predicted from their probands' CPT performance (Chen & Faraone, 2000). CPT performance has displayed a heritable pattern in four family studies of schizophrenia conducted in the United States, Taiwan, Israel, and Ireland (Chen et al., 1998; Egan et al., 2000; Mirsky, Ingraham et al., 1995; Mirsky, Yardley et al., 1995). Relative risk is a measure used in genetics and epidemiology to quantify familial similarity and is calculated based on the equation: (concordant pairs/[concordant pairs + nonconcordant pairs])/percent affected in the comparison group (Egan et al., 2000). Thus, the higher the relative risk, the greater the assumed heritability. The relative risk estimates for these CPT studies ranged from 3.3 (Egan et al., 2000) to as high as 130.3 (Chen et al., 1998). The replication of the genetic contribution to performance on this task supports the validity of using the CPT as a genetic marker of schizophrenia.

The majority of CPT studies in relatives of persons with schizophrenia purport that poor performance on the CPT reflects a deficit in sustained attention. An alternate view, suggested by Nuechterlein et al (1991), is that at least some CPT deficits may involve early perceptual processes. This is supported by previous research, showing that the CPT tasks involving relatively simple visual stimuli (X and AX versions) did not detect a deficit in relatives, while the versions using degraded and complex stimuli were able to detect a deficit. Additionally, first-degree relatives do not generally show a decrease in their accuracy on the CPT task from beginning to end, which would be

indicative of a sustained attention deficit. Instead, they differ from controls in their ability to separate signal from noise stimuli throughout the task, which involves visual processing in the more complex CPT versions (Nuechterlein, Dawson, & Green, 1994).

Unfortunately, there appears to be little research examining the effect of old age on CPT performance. Normative data for a particular CPT software package (Vigil) was collected on healthy individuals across adulthood (age 20-90), which showed that aging was associated with increasing omission and commission errors (ForThought, 1993b). In addition, studies using alternative measures of attention have found that decreases in sustained and selective attention (McDowd & Birren, 1990), as well as visuoperceptual judgment (Eslinger & Benton, 1983; Ska, Poissant, & Joanette, 1990), accompany normal aging.

A third type of task that has been used to examine the genetic contributions of schizophrenia is visual backward masking, which has traditionally been used to assess the earliest components of visual processing. In backward masking, a brief visual stimulus (target) is followed very quickly by a second stimulus (mask). The interval between the presentation of the target and mask is called the interstimulus interval (ISI). While participants are usually able to accurately identify the target presented without a mask, the addition of a mask makes identification of the target more difficult. As the mask appears to operate backwards in time, the task is called backward masking.

Although even healthy controls display a masking effect, persons with schizophrenia require a longer ISI to identify the target (Braff & Saccuzzo, 1982; Green & Walker, 1986; Rund, 1993; Saccuzzo & Braff, 1986; Schwartz, Winstead, & Adinoff, 1983; Suslow & Arolt, 1998). This difficulty does not appear to be due to neuroleptic

medications, which instead seem to reduce the deficit (Braff & Saccuzzo, 1982) or have no effect (Butler, Harkavy-Friedman, Amador, & Gorman, 1996). Backward masking deficits appear to be a trait, in addition to state, indicator in schizophrenia, as persons with this disorder often show deficits even when the disorder is in symptomatic remission (Miller, Saccuzzo, & Braff, 1979).

Additional studies have attempted to determine the neuronal dysfunction primarily responsible for the backward masking deficit in schizophrenia. One such study examined whether the deficit is indeed central (brain mediated) as was previously assumed or instead a peripheral (retinal) dysfunction (Saccuzzo, Cadenhead, & Braff, 1996). The authors used both a backward and forward masking task to investigate this question. In the forward visual masking task, the mask precedes the target (instead of following it), and the mechanisms involved in this task are thought to be more peripheral (retinal) than are backward masking tasks, as physiological processes thought to mediate performance do not primarily involve the brain (Turvey, 1973). The results showed that persons with schizophrenia had a selective and differential deficit in backward masking, providing support that this deficit is centrally (brain) mediated in schizophrenia.

Further research has attempted to delineate the conditions in which transient and sustained visual channels are primarily responsible for backward masking**.** The transient visual channel is thought to represent the magnocellular subcortical pathway, while the sustained channel is thought to represent the parvocellular subcortical pathway (Livingstone & Hubel, 1987). Backward masking conditions that require location identification rely more on the transient (magnocellular) channels, while conditions that

use a clearly focused target and require target identification rely more on sustained (parvocellular) visual channels (Green et al., 1997).

Backward masking research examining persons with schizophrenia has hypothesized that the decrement in performance is due to overactive transient visual channels that interrupt icon formation (Green, Nuechterlein, & Mintz, 1994b). This hypothesis is supported by Schwartz et al.(1990) who found that persons with schizophrenia had longer visual persistence linked to peripheral compared to foveal visual field stimulations, suggesting a transient system deficit. Other researchers found that persons with schizophrenia had difficulty in a visual spatial location task, but were not impaired on a task that required discrimination of visual stimuli attributes (Cadenhead, Serper, & Braff, 1998; O'Donnell et al., 1996). This lends further support to the notion that the primary visual processing deficit in schizophrenia resides in the transient visual pathway, which resides on the dorsal processing stream of the cortical visual system.

More recent research on backward masking in persons with schizophrenia extends the explanation for deficits on this task. Green et al. (1999) found that healthy controls showed a pattern of performance during backward masking that oscillated (a fourth-degree polynomial function) over increasing ISIs. This pattern is consistent with cortical activity oscillating in the gamma range (30 to 70 Hz) (Green et al., 1999). Interestingly, the individuals with schizophrenia did not display this oscillating pattern of performance over increasing ISIs, indicating a possible lack of normal oscillation in cortical activation at the gamma range of the sustained (parvocellular) channels.

Using a backward masking task, several investigators have demonstrated visual processing dysfunction in healthy adult siblings of persons with schizophrenia (Green et al., 1997; Keri, Kelemen, Benedek, & Janka, 2001). While Green and colleagues found that siblings performed poorer than controls only at the shorter ISIs, Keri and colleagues reported that siblings performed more poorly at both the shorter and longer ISIs, although the effect was reportedly stronger at the shorter ISIs. In both of these studies, the authors found stronger effects in task conditions that emphasized the transient channels. In contrast, Lieb et al (1996) did not find a difference in backward masking performance at any ISI examined for a small sample (N=17) of adolescents with one parent who had schizophrenia. This null finding may be a result of lack of statistical power due to the small sample, or alternatively, may be do to the younger age of the relatives, as the presumed neural inefficiency responsible for the backward masking deficit in persons with schizophrenia-related genes may become exaggerated with increasing age.

There is ample evidence in the research literature that backward masking task performance decreases as a function of old age in healthy individuals (unrelated to persons with schizophrenia). Studies using a variety of visual backward masking tasks have consistently shown that older participants display greater overall masking effects, resulting in poorer accuracy when identifying target stimuli (Coyne, Burger, Berry, & Botwinick, 1987; Di Lollo, Arnett, & Kruk, 1982; Muise, Watier, DesRosiers, & Caissie, 1999; Schlotterer, Moscovitch, & Crapper-McLachlan, 1984; Seiple, Szlyk, Yang, & Holopigian, 1996; Walsh, Williams, & Hertzog, 1979).

These studies indicate that normal age decline on backward masking tasks: 1) is not due to the color of the stimuli (Muise et al., 1999), 2) is similar for peripherally

located targets as for centrally located targets (Seiple et al., 1996), and 3) appears to be due to a slowdown in visual information processing (Coyne et al., 1987; Di Lollo et al., 1982) that appears to occur at both the early and late stages of central perceptual processing (Walsh et al., 1979). Interestingly, one report concluded that the type of target stimulus effected the difference due to aging, with older individuals displaying the most difficulty with consonant trigrams, followed by individual letters, and then words (Cramer, Kietzman, & van Laer, 1982).

In summary, studies utilizing the SOA, CPT, and backward masking lend support to the notion that visual processing dysfunction is a heritable vulnerability trait for schizophrenia, although the exact nature and neural basis of this deficit is poorly understood. Performance on these tasks appears to decrease over healthy aging and there is some evidence that persons with schizophrenia experience an accelerated age-related decline in visual processing. While there appears to be an absence of published literature examining accelerated age-related cognitive decline in first-degree relatives of persons with schizophrenia, recent unpublished research suggests such a decline in older relatives on tasks that reflect both visual processing and attention (K.H. Nuechterlein, personal communication, August 11, 2000). Research examining first-degree relatives aids in determining whether similar accelerated age-related decline in persons with schizophrenia is primarily due to genetic influences.

The investigator hypothesized that visual processing would display an accelerated age-related decline, but that general intellectual functioning and sustained attention would not show a differential age-related change.

CHAPTER 3

METHOD

Participants

Data were collected from two participant populations: 1) 28 healthy first-degree biological relatives of persons with schizophrenia (N=25) or schizoaffective disorder (N=3), with ages approximately evenly distributed over the range of 21 to 72 (mean=49.1±13.5); and 2) 34 healthy control participants recruited from the community, with ages approximately evenly distributed over the range of 19 to 82 (mean=53.0±16.1). Participants in the relatives groups included: 15 full-siblings, 5 biological parents, and 5 biological children of a person with schizophrenia. Three of the relatives were full-siblings of a person with schizoaffective disorder, a disorder that is believed to be genetically related to schizophrenia (Kendler, Neale, & Walsh, 1995).

The sample size of the relatives group is slightly less than that predicted from an a priori power analysis for multiple regression, which predicted the need for 34 persons in each group; assuming a medium effect size (f^2=0.15; based on similar research), two predictors (age and experimental group), and a 0.80 power ratio.

Participant demographics are listed in Table 1. Although there was no statistically significant difference between the groups on age, gender, state anxiety, and visual acuity, the relatives group contained 64% minorities, while the control group contained a smaller number of minorities (15%). In addition, the estimated IQ and

socioeconomic status were statistically higher in the control group as compared to the relatives group. These demographic differences between groups were primarily due to inadequate response to the community advertisements from persons in the control group who matched persons in the relatives group on these factors.

Individuals were examined through the age of 82, as the latter age range (roughly over 50) is related to the most prominent age-related decline in sensory-perceptual ability in healthy individuals (Lezak, 1995). The large majority (all but two) of persons in the relatives group were at least 30 years old, which is considered to be beyond the age of greatest risk for developing schizophrenia (Cornblatt, Green, & Walker, 1999). None of the relatives reported past or present symptoms of schizophrenia, indicating that it is unlikely that any differences on the dependent variables in the relatives group were due to the presence of the schizophrenia phenotype.

First-degree relatives of persons with schizophrenia were recruited via the Advantage Behavioral Health Systems (ABHS), Athens, GA through within-agency requests to the probands (persons with schizophrenia). Probands agreeing to participate signed a consent form agreeing for a staff psychiatrist at ABHS (Sharon Esposito, M.D.) to review their medical records for the purpose of confirming the diagnosis of schizophrenia or schizoaffective disorder. In addition, probands agreeing to participate signed a second consent form, on which they indicated particular first-degree relatives that could be contacted. Relatives of probands agreeing to participate were contacted (by telephone) by the primary investigator, requesting their participation. In order to ensure confidentiality, the primary investigator was not given the names or records of the

probands, but instead was given an identification number linking the relatives to the proband records (stored by Dr. Esposito).

Healthy controls were recruited from the local community using: 1) printed advertisements posted at various places throughout the community; 2) computerized advertisements placed on a local university cable television channel; and 3) phone calls to persons who had previously given consent for future contact after participating in University of Georgia Psychology Department studies in the past.

Two relatives were included through a different recruitment method, as they independently contacted the investigator after seeing an advertisement targeting the control group. In both of these cases, the participant asked their relative with schizophrenia to sign a release, allowing the proband's private psychiatrist to mail summary psychiatric records to Dr. Esposito, so that she could confirm the diagnosis of schizophrenia. Dr. Esposito confirmed a diagnosis of schizophrenia in these two individuals, as well as in the rest of the proband group.

Exclusionary criteria for the control group included: 1) any individual with a past or present Axis I psychiatric diagnosis (with the exception of a single past major depressive episode; substance abuse occurring over three months prior; substance dependence ending before ten years prior, and social phobia ending before ten years prior) as determined through a SCID-I diagnostic interview; 2) current use of psychoactive medication; 3) corrected visual acuity less than 20/50 based on the Snellen visual acuity chart; and 4) past or present history of a neurological disorder (as determined by self-report); 5) the presence of schizophrenia spectrum Axis II disorder (schizotypal or paranoid personality disorder) as determined by SCID-II diagnostic

interview; and 6) biological relation (however distant) to a person with probable psychosis (by self-report).

Exclusionary criteria for the relative group included: 1) any individual with a past or present history of mania or any psychotic disorder as determined through a SCID-IV diagnostic interview; 2) corrected visual acuity less than 20/50; and 3) past or present history of a neurological disorder (as determined by self-report). The exclusionary criteria for the relative group was more liberal, as schizophrenia-related genes may cause other psychopathology and the goal of this study was to examine persons with such genes in the absence of schizophrenia.

The resulting group of relatives included three persons with Major Depressive Disorder, two persons with Paranoid Personality Disorder, and one person with Dysthymic Disorder. In addition, three persons were on antidepressants and one person was on clonidine. Three relatives had a past history of Panic Disorder and one had a past history of Post Traumatic Stress Disorder; however, these individuals did not report active symptoms of these disorders at the time of evaluation.

Each participant was reimbursed $20 for the average two hours of research procedures (one session). All research procedures were conducted in the Neuropsychology and Memory Assessment Laboratory (Room 415) of the Psychology Building, University of Georgia. Participants from both experimental groups were screened over the telephone for exclusionary criteria. Those passing this brief screen were scheduled for an appointment time to participate in the research. Further exclusionary screening was conducted during the research session, which resulted in the exclusion of two controls for inadequate visual acuity.

This project was approved by the institutional review boards of the University of Georgia, Advantage Behavioral Health System (Athens, GA), and the Human Resources Department of the State of Georgia. All participants in the study were asked to read and sign a consent form in compliance with the Federal Department of Human Services regulations. All consent forms were reviewed and approved by the three institutional review boards.

The only identifiable risk to participants from the study was a slight possibility of emotional distress during the diagnostic interview. To minimize the risk of emotional distress, the study was explained to participants, both verbally and in writing, and it was ascertained that they freely consented to participate. In addition, participants were told that they may refuse to answer any question during the diagnostic interview, without giving an explanation. Participants were made aware prior to data collection of their right to withdraw from the study at any time without penalty.

Because some of the study tasks were extremely difficult, steps were taken to minimize feelings of anxiety and helplessness related to test performance. Before all tests, every participant was cautioned that some tasks would be very difficult and that most people get many items wrong. It was emphasized that it was important only that they continue to try their best on all tasks.

Independent Measures and Covariates

Age and a priori group membership (controls or relatives) were the main independent variables of interest. However, many other variables were collected for secondary correlative analysis.

These covariates included:

1) Visual Acuity Chart (Snellen Scale – Carolina Biological Supply Company, Burlington, NC). The Snellen scale provides a basic measure of the ability of the eyes to focus (visual acuity), by requiring an individual to read rows of random letters of progressively smaller size. The chart was placed on a wall at eye level, 20 feet from the individual. Each participant was asked to cover one eye and read one line at a time from the top of the chart. This procedure was repeated for each eye and the last line that the individual was able to read without error was recorded. If there was a difference between the visual acuity of each eye, the score from the better eye was used.

   Each line on the chart represents a distinct focus ability level that was established with healthy individuals. As all participants stood exactly 20 feet from the chart, visual acuity was represented as a ratio of distance needed to adequately focus. For example, 20/40 represents that a person can focus at 20 feet from a target to roughly the same degree as a healthy individual at 40 feet from a target. In order to make statistical comparisons with these scores, each ratio was changed into a number by dividing the top number by the bottom (e.g,. 20/40 was converted to 0.50). Thus, the higher the resulting number, the better the visual acuity.

2) Demographic questionnaire (see Appendix A). Questions were asked orally and directly entered by the experimenter into a form in Microsoft Access 2000 (Microsoft, 1999). These questions pertained to basic demographic information.

3) Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)/Non-patient Edition-Version 2.0 (First, Spitzer, Gibbon, & Williams, 1998). This interview was in the form of a booklet that the investigator completed by asking questions orally of each participant. The interview booklet contained directions for scoring answers to derive DSM-IV Axis I diagnostic labels. The SCID-I has been shown to be a reliable and valid means of identifying DSM-IV Axis I diagnoses. While research has not been conducted on the SCID-I non-patient edition, a research study has examined the interrater reliability and diagnostic accuracy (validity) of the SCID-I patient edition (for DSM-IV), which is very similar to the non-patient edition (Ventura, Liberman, Green, Shaner, & Mintz, 1998). This study found that interrater reliability was excellent (kappa = 0.85, range = 0.71 to 0.97) and that diagnostic accuracy, compared to the "gold standard" of consensus diagnosis, was very good (82%). There is evidence that the SCID-I is a valid instrument for the diagnosis of schizophrenia in particular, as SCID-I schizophrenia diagnosis displayed good sensitivity (.89), specificity (.96), and agreement (.86) when compared to best-estimate diagnosis made by psychiatrists on first-admission psychotic patients (Fennig, Craig, Lavelle, Kovasznay, & Bromet, 1994).

In addition, research has demonstrated reliability in its predecessor, the SCID-I for DSM-III-R disorders. This research demonstrated mean kappa values for a nonpatient sample of .37 for current and .51 for lifetime diagnoses (Williams et al., 1992). While these kappa values are relatively low, they are roughly comparable to those obtained with other structured diagnostic instruments.

4) Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). Only the sections pertaining to Schizotypal and Paranoid Personality Disorder sections were completed for each participant. The participant was given the SCID-II screening form and asked to circle yes or no to each statement. All questions that the participant responded affirmatively to prompted further questioning by the investigator using the SCID-II investigator manual questions (First et al., 1997). This manual contained scoring criteria that were used to assign diagnoses. The validity of deriving diagnoses using this screening method has been established by a study that found a low false negative rate across every diagnosis (Jacobsberg, Perry, & Frances, 1995). The SCID-II has been shown to be a reliable means of identifying DSM-IV personality disorders, as research has demonstrated interrater reliability coefficients ranging between .48 to .98 for categorical diagnosis (Cohen kappa) and from .90 to .98 for dimensional judgments (intraclass correlation coefficient) (Maffei et al., 1997). In addition, this study also showed that internal consistency coefficients were satisfactory (.71 to .94).
5) State-Trait Anxiety Inventory (STAI-Form Y-1; state portion only) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). This questionnaire consisted of 20 items that tap the individual's current level of anxiety. Each item is rated from 1 (not at all) to 4 (very much so). The total score can range from 20 to 80. Test-retest reliability for one hour between testing is .16 to .31. Tests of internal consistency under stressful conditions yield alpha coefficients from .90 to .93 for college females. Construct validity studies show that the STAI successfully

discriminated between persons undergoing stressful events and those who were not (Spielberger et al., 1983).

Dependent Measures

Three computer-based tests were administered: a visual backward masking task, the Span of Apprehension Test, and the Continuous Performance Test. These tasks were administered in the beginning of the session and the order of presentation was counterbalanced for each participant to control for carryover effects. Performance on these computer-based tests generated the main dependent variables of interest.

Backward Masking Task

The backward masking task was created using E-Prime software (Beta 5 version; Psychology Software Tools) and was based on parameters outlined by Green et al (1997, 1999). A desktop PC and monitor were used to present all stimuli. Participants sat in a chair, which was placed in a position so that the eyes were 100 cm from the screen and the chair height/position was adjusted so that the eyes were approximately center to the screen both laterally and vertically. Participants were asked to remain as still as possible during the test.

Directions were presented on the screen and explained in detail by the investigator. Prior to each target presentation, a fixation cross was presented in the middle of the screen for 400 ms and ended 200 ms before target presentation. Next, one of four letters (S, C, O, or Q) was presented at any one of four locations on the screen (top, right, bottom, left), which was 3.7 cm from the center. Each letter was approximately 0.5 cm wide and 0.7 cm high, and was presented as white text on a gray

background. This was followed by an interstimulus interval (ISI) during which the screen was blank. The mask (four clusters of “X”s - each 0.5 cm wide, 0.7 cm high; white on a gray background) then appeared, covering all possible areas that the target may have appeared.

The task included two masking conditions, designed to differentially emphasize the sustained/parvocellular (target identification) or transient/magnocellular (location identification) visual channels. The two conditions were presented in a counterbalanced order by participant. Each condition is comprised of the following parameters:

1. *Target identification with a high-energy mask*: After each trial, the participant was asked to state aloud the letter that appeared before the mask. A large card was placed in front of the participant that listed the possible choices (S, C, O, Q). Participants were encouraged to "guess the first of these letters that came to their mind" if they did not see a letter. The investigator entered the participant's stated answer using a numeric keypad.

   The “energy” of the mask refers to the duration of the mask in relation to the duration of the target. In this condition, the energy of the mask was twice the energy of the target (27 ms mask with a 13 ms target). Five different ISIs were presented in a random order, with each ISI consisting of 16 trials. The ISIs (13, 27, 40, 80, and 93 ms) were based on previous backward masking studies (Green et al., 1997; Green et al., 1999; Keri et al., 2001) and were limited by the refresh rate of the computer monitor (listed as 50 to 60 Hz).

2. *Location identification*: After each trial, the participant was asked to state aloud the location that the letter appeared before the mask. The participant was encouraged to point with their hands if they reported left/right confusion. Participants were encouraged to "guess the first of these locations that came to their mind" (up, down, left, right) if they did not see the letter. The investigator entered the participant's stated answer using a numeric keypad.

   Since locating a target is generally easier than identifying one, the target-mask ratio was 1:1 (13 ms for both target and mask) to prevent a ceiling effect. In addition, the ISIs (13, 27, 40, 80 ms) did not include the longest interval of 93 ms, as the masking function has been shown to be truncated in this easier location condition in previous studies (Green et al., 1997). Each ISI was presented in a random order, each consisting of 16 trials.

Targets, locations, and ISIs were selected in a block-randomized manner, with the constraint that the same variable (target, location, and ISI) cannot be presented in succession.

For practice, the targets were presented with a mask at an ISI of 140 ms, an interval in which very little masking function was expected based on previous studies (Green et al., 1997; Green et al., 1999). Participants were required to correctly identify at least four out of five targets at this ISI before proceeding with the task.

Formal reliability measures have yet to be established for the backward masking task. However, a decrement in performance in target identification (as measured by accuracy score) under backward masking conditions has been well replicated for persons with schizophrenia and their relatives (Butler et al., 1996; Cadenhead et al., 1998; Green et al., 1997; Green, Nuechterlein, & Mintz, 1994a; Saccuzzo et al., 1996), as well in healthy older adults (Coyne et al., 1987; Cramer et al., 1982; Di Lollo et al., 1982; Muise et al., 1999; Schlotterer et al., 1984; Seiple et al., 1996; Walsh et al., 1979). This high degree of replication of the backward masking phenomenon supports the notion of high reliability, particularly in these populations.

The validity of using this task to measure visual processing has been supported through well-controlled laboratory studies that systematically varied backward-masking conditions to derive a fine-grained analysis of specific processes that underlie backward masking performance (Breitmeyer, 1984; Breitmeyer & Ganz, 1976; Michaels & Turvey, 1979).

Span of Apprehension Task

The SOA task was created using E-Prime software (Psychology Software Tools, 2000), based on parameters described by Granholm et al. (2000). A desktop PC and monitor were used to present all stimuli. Participants sat in a chair, which was placed in a position so that the eyes were 115 cm from the screen and the chair height/position was adjusted so that the eyes were approximately center to the screen both laterally and vertically. Participants were asked to remain as still as possible during the test.

Participants were told that either a “T” or an “F” would be presented among a group of other random letters and instructed to state their choice aloud. Participants were informed that only one target (either one “T” or one “F” and never both) would be presented on every trial and were asked to guess either "T" or "F" if they did not see either one. The investigator entered the participant's stated answer using a numeric keypad.

The target letter was located in random spatial locations among arrays containing either zero (one-letter condition), 5 (six-letter condition), or 11 (12-letter condition) distracter letters, which were randomly selected from all other letters in the alphabet. Letters occupied spatial locations within a 5x5 matrix, constrained by: 1) an equal number of target letters (T and F) appeared in each array size condition; and 2) target letters appeared equally in each spatial matrix location within each array size condition.

Ten trials of each array-size condition were presented in counterbalanced blocks in the following sequence (# of letters): 1, 6, 12, 1, 12, 6, 6, 12, 1. A central fixation cross remained in the middle of the screen during the entire task and participants were asked to keep their eyes fixated on this cross. Each stimulus presentation was presented rapidly (94 ms) as gray letters on a slightly darker gray background. Each letter was approximately 5.3 cm high and 3.7 cm wide. The letters were located in a matrix that was 26.2 cm high and 36 cm wide. There was a five-second interval between each stimulus presentation during which the participant stated the answer. This resulted in a task duration of 8.91 minutes. For practice, the one letter condition was presented for 5 trials. Participants were required to correctly identify the target on 4 of 5 trials to continue with the task.

The sustained attention measure (SA) reflects the stability in performance over the duration of the task and is calculated by subtracting the total number of errors from the last third of the task duration from the total number of errors from the first third of the task duration. This measure, along with # of correct responses within each array-size condition, was used to derive the summary scores.

Reliability of the SOA task accuracy scores has been well established in persons with schizophrenia (test-retest correlation range: .74 to .78 over 12 weeks) and healthy controls (split-half reliability: .88 to .99) (Asarnow et al., 1991). The validity of using this task to infer genetic effects is supported by studies finding high heritability, both between nonpsychiatric twins (r = 0.65) (Bartfai et al., 1991) and between persons with schizophrenia and their mother (r = 0.58) (Asarnow et al., 1991). Additionally, SOA accuracy scores have been used to show an accelerated age-related decline in persons with schizophrenia (Granholm et al., 2000), which supports the validity of using this task to measure aging effects.

Continuous Performance Task

The CPT task was created using the Vigil software package (ForThought, 1993a). Stimuli were presented using a PC computer and monitor and responses were collected with a standard keyboard. The CPT task was modeled after the A-X version (Wohlberg & Kornetsky, 1973), in which a series of random single letters are presented and the participant is asked to press the spacebar after observing a target sequence of two letters. In this study, the target was when the letter "K" was immediately followed by the letter "A", which occurred approximately 20% of the time. Stimuli were presented in the

middle of the screen at a constant rate of one per 998 ms, with the target appearing for the first 43 ms and a blank screen appearing for the remaining 955 ms. Each letter was approximately 1.2 cm wide and 2 cm high. Two conditions were administered in a counterbalanced order. The first, termed the "clear condition", presented white letters on a black background, while the second, termed the "noise condition", presented white letters on a background of white noise. The white noise was automatically generated by the software package, utilizing a software program setting of stimuli noise = 25 and background noise = 25. Each condition consisted of 150 trials, resulting in condition duration of 2.5 minutes.

Response to target trials ("K" followed by "A") was considered a correct detection. A response to a trial that is not the target is considered a commission error, while failure to respond to a target trial is an omission error. Each condition also includes 30 “catch” trials in which the stimulus presented was either "K" followed by a letter other than "A" or "A" preceded by a letter other than "K". Response to a “catch” trial is considered a false alarm (a specific type of commission error).

The dependent variables used in deriving the summary scores included a sustained attention measure (SA) and a perceptual sensitivity measure (A'). A' is a non-parametric measure similar to the traditional parametric measure D', and is calculated based on the conditional probabilities of correct detections and false alarms (Rutschmann et al., 1977)**.** The higher A', the better the ability to separate signal from noise. The sustained attention measure (SA) reflected the stability in performance over the duration of the task and was calculated by subtracting the A' measure from the last third of the task duration from the A' measure from the first third of the task duration. A negative value

indicated a decrease in accuracy over the duration of the trial, while a positive value indicated an increase in accuracy.

Construct validity has been established by the developers of the CPT software program used in this study (ForThought, 1993a) through comparison with performance on tests thought to measure similar constructs, which included the Mesulam Figure Cancellation Task and the FAS test. These tasks showed a fair degree of correlation with the number of errors of omission and commission on a simple degraded target identification CPT condition (r = .45 to .59) (ForThought, 1993b). In addition, the software developers demonstrated reliability of the degraded AX version with high test-retest correlation (over three month interval) in errors of commission (r = .70) and omission (r = .69).

In addition, numerous studies examining first-degree relatives of persons with schizophrenia (Chen et al., 1998; Finkelstein et al., 1997; Franke et al., 1994; Laurent et al., 1999; Maier et al., 1992; Mirsky, Ingraham et al., 1995; Mirsky, Yardley et al., 1995; Nuechterlein, 1983; Rutschmann et al., 1977) and healthy older individuals (ForThought, 1993b), have found the degraded stimuli CPT task to distinguish these populations from controls, particularly using the perceptual sensitivity score.

Full Scale IQ Estimate

Vocabulary and matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) were used to estimate Full Scale IQ. These subtests have been found to be a valid estimate of Full Scale IQ, as the developers reported that performance on these subtests accounts for approximately 76% of the variance of

performance on the full battery of the Wechsler Adult Intelligence Scale-3rd Edition. In addition, the developers found the subtests to be reliable, as test-retest correlations (over an interval of one month) were .85 for the vocabulary subtest and .77 for the matrix reasoning subtest (Wechsler, 1999).

CHAPTER 4

RESULTS

Dependent Variable Construction

Before data analysis was begun, all dependent measures used in deriving summary scores were first rescaled to standard equivalents (z transformations). For both experimental groups, z-scores were based on the raw score distribution of the control group - a method used by other researchers conducting neuropsychological studies on relatives of persons with schizophrenia (e.g, Cannon et al., 1994; Staal, Hijman, Hulshoff Pol, & Kahn, 2000). While alternative methods of calculating z-scores are possible, it was felt that adjusting the mean of the control group to zero would best depict differences in the group of relatives. In addition, this method of transformation produced equivalent interaction and main effects compared to those resulting from examination of the raw data on individual measures (e.g., Full Scale IQ).

The dependent variables in the regression analyses included:

1) Visual Perception Summary Score (VPSS): This score reflected the impact of visual perception processing on performance and was derived from the mean of z-scores from: 1) The A' measure from the degraded stimuli condition of the Continuous Performance Test (CPT), 2) the number of accurate responses on the 6 and 12 letter conditions (pooled together) of the Span of Apprehension task (SOA), and 3) the number of accurate responses from all ISI intervals of both conditions of the backward masking task. A coefficient alpha level demonstrated

that these factors were sufficiently correlated with each other across both groups (Cronbach's alpha = .84).

2) Sustained Attention Summary Score from the SOA (SASS-SOA): This score reflected the impact of sustained attention on task performance and is the average z-score from the sustained attention measure on the 6 and 12 letter conditions (pooled together) of the SOA task. This measure displayed a statistically significant, but negative, correlation with VPSS (r = -.46, p < .01) in the controls.
3) Sustained Attention Summary Score from the CPT (SASS-CPT): This score also reflects the impact of sustained attention on task performance and is the average z-score from the sustained attention measure on the two conditions of the CPT. This measure was not related with VPSS (r = .16, *ns*) in the controls.
4) Full Scale IQ Estimate (FSIQ): Vocabulary and matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) were used to estimate Full Scale IQ. FSIQ was not related to VPSS (r = .27, *ns*) or SASS-SOA (r = -.29, *ns*) in the controls, but did show a statistically significant positive correlation with SASS-CPT in the controls (r = .56, p = .001).

* Note: Initially, a sustained attention summary score was created based on the combination of the two sustained attention dependent variables mentioned above. However, a coefficient alpha level demonstrated that these variables were not sufficiently correlated with each other (Cronbach's alpha = .41). As a result, it was decided to examine the two sustained attention measures separately.

Descriptive Statistics

Data were screened for missing and invalid data points. A data point was missing for one person in the relatives group for the CPT clear condition performance due to a corrupt computer data file. In addition, data points were missing for two controls and one relative who stated that they could not see the stimuli during the CPT noise condition. No data points were missing or invalid for any other measure. If a person was missing data from a particular measure that comprised the VPSS, the summary score was determined from the average of the remaining constituent measures. No participant had missing data points for more than one measure. Descriptive statistics for demographic variables is listed in Table 1.

Data were analyzed to determine whether each dependent measure followed a normal distribution. Results of this analysis revealed that the VPSS approximated a normal distribution in both the control (Shapiro-Wilk statistic = 0.97, *ns*) and relatives (Shapiro-Wilk statistic = 0.95, *ns*) group. Similarly, the analysis showed that the SASS-SOA approximated a normal distribution in both the control (Shapiro-Wilk statistic = 0.98, *ns*) and relatives (Shapiro-Wilk statistic = 0.97, *ns*) group. The SASS-CPT did not follow a normal distribution in the control group (Shapiro-Wilk statistic = 0.89, $p < .05$), but did approximate a normal distribution in the relatives group (Shapiro-Wilk statistic = .97, *ns*). As well, FSIQ did not follow a normal distribution in the control group (Shapiro-Wilk statistic = 0.92, $p < .05$), but did approximate a normal distribution in the relatives group (Shapiro-Wilk statistic = 0.93, *ns*).

Levene's test of equality of error variances revealed homogeneity of variance across groups for the VPSS: $F(1,60) = 3.68$; SASS-SOA: $F(1,60) = 0.01$; SASS-CPT: $F(1,60) = 2.86$; and FSIQ: $F(1, 60) = 0.49$.

Demographic Correlates of Dependent Variables

Age, gender, visual acuity, state anxiety, socioeconomic status (SES), race, and the four dependent measures were intercorrelated to examine for significant relationships within each experimental group (see Table 2). After using a Bonferroni correction for multiple comparisons, correlations within the control group revealed a statistically significant positive correlation between visual acuity and the VPSS ($r_s = .55$, $p = .001$), as well as between IQ estimate and SASS-CPT ($r = .56$, $p = .001$). A statistically significant negative correlation was found between age and VPSS score ($r = -.67$, $p < .001$). Race ($r = -.56$, $p = .001$) and SES ($r = -.65$, $p = .001$) were correlated with the IQ estimate, in the direction of higher SES (e.g., lower Hollingshead category) and non-minority status relating to higher IQ.

The same analyses within the relatives group revealed a statistically significant positive correlation between IQ estimate and VPSS ($r = .71$, $p < .001$). Statistically significant negative correlations were found between age and VPSS score ($r = -.75$, $p < .001$), as well as between SES and IQ estimate ($r = -.62$, $p < .001$), in the direction of higher SES (e.g., lower Hollingshead category) relating to higher IQ.

Regression Analyses

Data were screened for outlying data points that had unreasonable influence on the dependent measures in the primary regression analyses. Examination of Cook's D revealed that no data points in any of the regression analyses were greater than the rule-of-thumb cutoff value (>1.0) for influential data points. However, examination of the Studentized Residuals revealed individuals with values above the rule-of-thumb cutoff (>2.0), distributed in the following manner: 1) VPSS - 3 relatives; 2) SASS-CPT - 1 control and 1 relative; 3) SASS-SOA – 2 controls; and 4) FSIQ - 3 controls and 1 relative. These outlying values generally occurred both above and below the regression line within each group, suggesting that any influence was relatively balanced. Considering the combination of these factors, it was decided to include all data points in the regression analyses.

For all dependent variables described below, linear regression was used to examine the interaction of age and experimental group (see Table 3a). To assess the independent contribution of the interaction, age and group were entered before the interaction term in the regression. As visual acuity may account for performance on these measures and is not the feature of interest, the estimate of visual acuity was entered as the first term in the regression to control for basic visual focus ability.

While both groups displayed an age-related decline in visual processing after controlling for visual acuity, a linear regression displayed an accelerated age-related decline in the relatives. The slope of age and the VPSS in the relatives group (β = -0.064, t = 6.31, $p < .001$) was greater than the slope in the control group (β = -0.026, t = 3.28, $p < .01$), resulting in a statistically significant interaction, $F(1, 57) = 9.58$, $p < .01$ (see

Table 3a and Figure 1). Further analysis of the regression interaction using the Johnson-Neyman technique (Johnson & Neyman, 1936) and Potthoff's extension (Potthoff, 1964) indicated that the absolute difference in VPSS between groups was statistically significant only after the age of 46, with controls performing better (see Table 4).

As seven of the relatives had either a current psychiatric diagnosis or were taking psychoactive medications, the interaction analysis with VPSS was conducted again, excluding these individuals. While the effect size was somewhat less, possibly due to loss of statistical power, the VPSS score continued to display a statistically significant age-related decline in the relatives, $F(1, 50) = 7.13$, $p = .01$ (see Table 3b). Consequently, it is unlikely that the differential presence of these factors in the relatives group had a significant impact on the accelerated age-related decline.

This interaction was not found with either the SASS-CPT, $F(1, 57) = 0.89$, or the SASS-SOA, $F(1,57) = 0.65$, indicating that an accelerated age related decline was not found in measures of sustained attention (see Table 3a and Figures 2 and 3). In addition, neither the control or relatives group displayed a performance relationship with age on either the SASS-CPT ($t = 0.21$; $t = 1.31$, respectively) or the SASS-SOA ($t = 0.25$; $t = 0.79$, respectively).

The main effect of group membership on sustained attention was examined using ANCOVA, controlling for the effects of visual acuity and age, which revealed no statistically significant group difference in either the SASS-CPT, $F(1,57) = 0.10$, or the SASS-SOA, $F(1,57) = 0.06$ (see Table 5). As with the VPSS score, the SASS interaction analyses were conducted again, excluding the seven relatives who had current diagnoses or were on psychoactive medication. The effect size was similar and both the SASS-

CPT: $F(1,50) = 0.96$, and the SASS-SOA: $F(1,50) = 0.46$, continued to display no statistically significant age-related decline in the relatives (see Table 3b).

Linear regression examining FSIQ suggested accelerated age-related decline in the relatives (see Table 3a and Figure 4). While the interaction of age and group on FSIQ did not reach statistical significance after a Bonferroni correction, $F(1,57) = 5.09$, $p = .03$), the controls displayed no evidence of an age-related decline in FSIQ ($\beta = 0.009$, $t = 0.88$, *ns*), while the relatives displayed a statistically significant decline of FSIQ over age ($\beta = -0.029$, $t = 2.10$, $p < .05$). Analysis of the interaction with the Johnson-Neyman procedure revealed that that the difference between groups on FSIQ became statistically significant only after the age of 33 (see Table 4). The interaction analysis was conducted again, excluding the seven relatives who had current diagnoses or were on psychoactive medication. The interaction was similar, but the effect size was weaker $F(1,50) = 2.81$, $p = .10$), possibly as a result of loss of statistical power due to the reduced sample size (see Table 3b).

The individual z-score components of the VPSS were then examined using linear regression for the interaction of group and age (see Table 5). The individual z-score components were first examined for the normality of the distribution and homogeneity of variance across groups. The SOA test performance evidenced a normal distribution (Kolmogorov-Smirnov statistic = .09, *ns*) and displayed homogeneity of variance across groups, $F(1,60) = 0.05$, *ns*. The backward masking test performance did not follow a normal distribution (Kolmogorov-Smirnov statistic= .11, $p = .04$), but did display homogeneity of variance across groups, $F(1,60) = 2.56$, *ns*. Performance from the noise condition of the CPT did not follow a normal distribution (Kolmogorov-Smirnov statistic

= .21, $p < .001$) and did not show homogeneity of variance across groups, $F(1,60) = 5.58$, $p < .05$. Therefore, these factors should be considered in the interpretation of the following regression results.

Performance on the SOA test (6 and 12 letter conditions combined) displayed the strongest accelerated age-related decline in the relatives, with a statistically significant interaction of group and age, $F(1,57) = 16.21$, $p < .001$ (see Table 6). Backward masking performance (identification and location conditions combined) displayed the next strongest accelerated age-related decline in the relatives, but did not reach statistical significance after a Bonferroni correction for multiple comparisons, $F(1,57) = 4.32$, $p < .05$). Performance on the noise condition of the CPT was not quite statistically significant, displaying a trend towards accelerated age-related decline in the relatives, $F(1, 54) = 3.61$, $p = .06$.

The z-scores of the SOA test were further examined using linear regression to determine the relative influence of the 6 and 12 letter conditions on the accelerated age-related decline in the relatives (see Table 6). The 12 letter condition displayed the strongest accelerated age-related decline in the relatives, $F(1,57) = 14.27$, $p < .001$ (see Figure 5), although the 6 letter condition evidenced a similar result, $F(1,57) = 8.41$, $p < .01$. Further analysis with the Johnson-Neyman procedure revealed that on the 6 letter condition, performance differences between groups were statistically significant only after the age of 45 (with controls performing better), while on the 12 letter condition, these differences were statistically significant only before the age of 25 (with relatives performing better) and after the age of 46 (with controls performing better) (see Table 4).

As the backward masking summary score displayed a statistically significant interaction prior to a Bonferroni correction, the z-scores were further examined using linear regression to determine the relative influence of the identification and location conditions on the accelerated age-related decline of performance in the relatives (see Table 6). Performance from the identification condition displayed a normal distribution (Kolmogorov-Smirnov statistic = .06, *ns*), but did not show homogeneity of variance across groups, $F(1,60) = 4.55$, $p < .05$. Performance from the location condition did not display a normal distribution (Kolmogorov-Smirnov statistic = .15, $p < .01$), but did evidence homogeneity of variance across groups, $F(1,60) = 1.47$, *ns*.

Only performance on the identification condition displayed an accelerated age-related decline in the relatives, $F(1,57) = 6.45$, $p = .01$, as the interaction on performance in the location condition was not statistically significant, $F(1,57) = 0.98$. Further analysis using the Johnson-Neyman procedure on the identification condition revealed that differences in performance between the groups were statistically significant only under the age of 24 (with relatives performing better) and over the age of 55 (with controls performing better). As the interaction was not statistically significant with the location condition, an ANCOVA was used to examine the main effect of group after controlling for visual acuity and age, which revealed no statistically significant difference between the groups on this condition, $F(1,58) = 0.64$ (see Table 5).

The z-scores from performance on each of the five interstimulus intervals (ISIs) from the identification condition of the backward masking test were examined using linear regression to determine the relative influence of particular ISIs on the accelerated age-related decline in performance of the relatives (see Table 7). The Kolmogorov-

Smirnov test for normality revealed a non-normal distribution for the z-scores from the 13 ms (Kolmogorov-Smirnov statistic = .13, $p < .05$), 27 ms (Kolmogorov-Smirnov statistic = .17, $p < .001$), and 40 ms (Kolmogorov-Smirnov statistic = .13, $p < .01$) ISIs. The groups displayed homogeneity of variance on all but one ISI: 40 ms, $F(1,60) = 8.70$, $p < .01$.

After a Bonferroni correction for multiple comparisons using linear regression, only performance on the 93 ms ISI displayed evidence of an accelerated age-related decline in the relatives, $F(1,57) = 13.42$, $p = .001$ (see Figure 6). Further examination with the Johnson-Neyman revealed that performance was statistically different only before the age of 38 (with relatives performing better) and after the age of 54 (with controls performing better) (see Table 4).

In addition, the 27 ms ISI approached statistical significance for an accelerated age-related decline in the relatives, $F(1,57) = 3.90$, $p = .05$. The remaining ISI intervals were examined with an ANCOVA to assess the main effect of group after controlling for visual acuity and age. The ANCOVA revealed no statistically significant group differences in the 13ms - F(1,60) = 0.002; 40 ms - F(1,60) = 0.14; and 80 ms – F(1,60) = 0.05 ISIs (see Table 5).

The z-scores from performance on each of the four interstimulus intervals (ISIs) from the location condition of the backward masking test were examined using linear regression to determine the relative influence of particular ISIs on the accelerated age-related decline in performance of the relatives (see Table 8). The Kolmogorov-Smirnov test for normality revealed a non-normal distribution for the z-scores for all four ISIs (Kolmogorov-Smirnov statistic = .15, $p < .01$; .13, $p < .05$; .20, $p < .001$; and .26, $p <$

.001; for 13, 27, 40, and 80 ms intervals respectively). The groups displayed homogeneity of variance on all but one ISI -13 ms – $F(1,60) = 7.35$, $p < .01$.

None of the ISIs from the location condition displayed evidence of a statistically significant accelerated age-related decline in the relatives. However, the longest ISI (80 ms) approached statistical significance for this interaction, $F(1,57) = 3.25$, $p = .08$. The remaining ISI intervals were examined with an ANCOVA to assess the main effect of group after controlling for visual acuity and age. The ANCOVA revealed no statistically significant group differences in the 13ms – $F(1,60) = 0.57$; 27 ms – $F(1,60) = 0.03$; and 40 ms – $F(1,60) = 0.54$ ISIs (see Table 5).

CHAPTER 5

DISCUSSION

The results of this study support the a priori hypothesis that the genetic component of schizophrenia relates to an accelerated age-related decline in visual perception that does not occur in sustained attention. Unexpectedly, an accelerated age-related decline was also suggested in the full-scale IQ of the relatives. However, considering that the data displayed no statistically significant relationship between IQ and visual processing in the controls ($r = .27$), it is intriguing that such a relationship was found in the relatives ($r = .71$, $p < .01$) and that both visual perception, $F(1,57) = 9.58$, $p < .01$, and IQ, $F(1,57) = 5.09$, $p < .05$, declined faster with age in the relatives compared to the controls. In addition, IQ displayed no evidence of age-related decline in controls ($r = .08$), as was expected considering that scores are age-adjusted for cognitive changes in healthy adults. These relationships, taken together, suggest that it is unlikely that IQ change is the primary cause of visual perception change in the relatives and raise the possibility that both IQ and visual perception may be independently influenced by age-related brain changes related to genetic loading for schizophrenia.

Analysis of the interaction using the Johnson-Neyman procedure suggests that the accelerated age-related decline in the relatives does not occur until after the age of 46 in visual perception and after the age of 33 in IQ. Considering that deficits in visual perception and IQ are often present early in life in those who develop schizophrenia

(Asarnow et al., 1991; Green & Walker, 1986; Hyde et al., 1994; Miller et al., 1990; Mockler et al., 1997), the results of this study raise the possibility that some of the brain changes that may occur at a younger age in persons who develop schizophrenia become more apparent at a later age in healthy first-degree relatives. However, there is controversy regarding whether schizophrenia-related brain changes continue to occur during late aging in persons with schizophrenia, as some studies report a continued decline in visual perception (Granholm et al., 2000) and IQ (Davidson et al., 1995; Harvey et al., 1999), while others suggest an early brain insult which shows impaired, but stable cognitive functioning after the onset of the disorder (Goldberg et al., 1993; Hyde et al., 1994; Mockler et al., 1997). Therefore, it is unclear whether such later age changes in relatives occur during a similar age range as persons with the disorder or represent a delayed manifestation of such processes.

When the Visual Perception Summary Score (VPSS) was further analyzed to determine which of the constituent components were primarily responsible for the accelerated age-related decline in the relatives, several factors emerged. The task that showed the strongest effect size for accelerated age-related decline in the relatives was the combination of the 6 and 12 letter conditions of the Span of Apprehension test (SOA), $F(1,57) = 16.21$, $p < .001$. Further examination of data from the SOA task showed that the 12 letter condition displayed the stronger effect size, $F(1,57) = 14.27$, $p < .001$, while the 6 letter condition displayed a weaker, but still statistically significant, accelerated age-related decline in the relatives, $F(1,57) = 8.41$, $p < .01$. Further analysis of the interaction with the Johnson-Neyman procedure revealed that the differences between groups in the 12-letter performance were statistically significant only before the age of 25 (with

relatives performing better) and after the age of 46 (with controls performing better). However, only two participants were younger than 25, preventing generalization of differences found before age 25. The results of regression analyses on SOA performance are likely valid as the accuracy scores displayed a normal distribution and homogeneity of variance across groups.

This finding with the SOA task is consistent with a previous study that found accelerated age-related decline in performance, again primarily in the 12-letter condition, in persons with schizophrenia (Granholm et al., 2000). The Granholm et al. study examined a similar age-range and used a similar cross-sectional design, task stimuli, and task timing parameters. Thus, the present study is an important extension of the Granholm et al. study, as it expands the finding to include a population of relative, which reduces the confounds present when examining persons with schizophrenia directly.

The backward masking task was further examined, as accuracy from the combination of the identification and location conditions displayed evidence for accelerated age-related decline in the relatives, $F(1,57) = 4.32$, $p < .05$. Regression analyses revealed that only accuracy on the identification condition was related to an accelerated age-related decline in the relatives, $F(1,57) = 6.45$, $p = .01$, as accuracy on the location condition did not approach statistical significance for the interaction, $F(1,57) = 0.98$. It should be noted that while the accuracy scores from backward masking demonstrated homogeneity of variance across groups, they did not follow a normal distribution, which may have reduced the statistical power in related regression analyses.

Accuracy from the five interstimulus intervals (ISIs) of the identification condition was examined. These regression analyses showed that performance from the

longest ISI (93 ms) displayed the strongest effect size for accelerated age-related decline in the relatives, $F(1,57) = 13.42$, $p = .001$. This is consistent with findings in persons with schizophrenia, which show that persons with schizophrenia require a longer ISI to "escape" the masking effect (Braff & Saccuzzo, 1982; Green & Walker, 1986; Rund, 1993; Saccuzzo & Braff, 1986; Schwartz et al., 1983; Suslow & Arolt, 1998). Healthy controls usually show a notable increase in performance as the ISI exceeds 70 ms, as this interval appears sufficiently long to reduce the ability of the mask to interrupt the processing of the target (Breitmeyer, 1984). Analysis of the interaction using the Johnson-Neyman procedure revealed that performance difference in the 93 ms condition became statistically significant only before the age of 38 (with relatives performing better) and after the age of 54 (with controls performing better). It is not clear why relatives would perform better than controls on this condition prior to the age of 38, but examination of the distribution reveals relatively few participants younger than 38 and two particular outlying data points (good performance by the youngest relative and relatively poorer performance by the youngest control) that may be skewing the data.

The 27 ms ISI was the only remaining ISI in the identification condition to approach statistical significance in showing an accelerated age-related performance decline in the relatives, $F(1,57) = 3.90$, $p = .05$). This finding is of particular interest, as the ISI of 27 ms is the only ISI in the study that produced a frequency of stimulus presentation that occurred within the gamma range (30 to 70 Hz), which is also the frequency of neural activity oscillation in the cortex thought to be involved in feature binding and visual attention (Alais, Blake, & Lee, 1998; Singer, 1993; Traub, Whittington, Stanford, & Jefferys, 1996). Several investigators have reported that while

controls demonstrated a distinct increase in performance during gamma range stimulus presentation, persons with schizophrenia and their healthy relatives failed to show this performance improvement (Cadenhead et al., 1998; Green et al., 1997). Green et al (1999) hypothesized that this lack of performance improvement at gamma range stimulus presentation was an indication that persons with schizophrenia genes fail to establish cortical oscillations in the visual cortex. While this theory has yet to be supported with physiological measures, the data in the present study are consistent with the notion that relatives of persons with schizophrenia experience an age-related decline in the ability of the visual cortex to establish cortical oscillation in the gamma range.

Performance at the four ISIs in the location condition was further examined with linear regression. Only the longest ISI (80 ms) approached statistical significance for accelerated age-related decline in the relatives, $F(1,57) = 3.25$, $p = .08$. Thus, similar to performance in the identification condition, the relatives display increasing difficulty with age in escaping the masking effect at the longest time interval. Main effect analyses for group membership revealed no statistically significant difference in performance for the remaining three ISIs.

Performance on the degraded condition of the Continuous Performance Test (CPT) also displayed evidence of accelerated age-related decline in the relatives, but changes in performance on this measure only approached statistical significance, $F(1,54) = 3.61$, $p = .06$. The A' measure of performance accuracy did not follow a normal distribution and failed to show homogeneity of variance across groups, violating several statistical assumptions of linear regression and reducing confidence in the related results. In addition, it is possible that the relatively brief duration of the task (2.5 minutes)

reduced the opportunity for errors, which may account for the ceiling effect found in performance scores. However, performance on this test contributed to the accelerated age-related decline found in the VPSS, which likely reflects the visual processing required to adequately detect the target letters against the noise background. This is consistent with research finding performance deficits with persons sharing schizophrenia genes on conditions of the CPT that place an emphasis on visual processing (Chen & Faraone, 2000; Chen et al., 1998; Finkelstein et al., 1997; Franke et al., 1994; Laurent et al., 1999; Maier et al., 1992; Mirsky, Ingraham et al., 1995; Mirsky, Yardley et al., 1995; Nuechterlein, 1983; Rutschmann et al., 1977).

As schizophrenia is thought to be influenced by multiple genes of small effect (Risch, 1990a; Tsuang, 1993) and first-degree relatives share half of their genes with the affected proband, it is likely that a subset of the relatives have genetic loading for schizophrenia, but never express the clinical phenotype. Similarly, it follows that another subset of relatives likely have no genetic loading for schizophrenia. As a result, considerable heterogeneity of performance is expected on tasks that are sensitive to the effects of genes related to schizophrenia. Thus, the relatively strong effect size found with accelerated age-related decline in the relatives' VPSS score, $F(1,57) = 9.58$, $p = .003$) may represent a particularly strong link to the genes, as the effect was greater than the increased variance due to probable inclusion of relatives who lack genes related to schizophrenia.

The interpretation of the results is limited by the use of cross-sectional design. Examination of age-related changes within individuals was not possible, which allows for the possibility that selection biases created a false impression of age-related decline (e.g.,

it is possible that the older relatives had greater visual processing difficulty by chance). However, it is improbable that selection biases influenced the results in this study, as there were no outlying data points influencing the results and it is unlikely that the majority of the older relatives participating in the study had visual processing difficulty beyond that found in the larger population of older relatives of persons with schizophrenia. Yet, a prospective longitudinal design may provide more definitive support of accelerated age-related decline in relatives and would allow for a more valid assessment of the detailed process involved in such a decline.

In summary, this study used a cross-sectional design to examine the effect of aging on visual perception, IQ, and sustained attention in healthy first-degree relatives of persons with schizophrenia and healthy controls. Results demonstrated evidence for an accelerated age-related decline in the relatives for measures of visual perception and IQ, but not sustained attention. It is hypothesized that these changes reflect specific changes in the brain that occur roughly in the middle age range in healthy relatives sharing genes for schizophrenia in the absence of the disorder. Further research is planned to test this hypothesis using cross-sectional design and functional magnetic resonance imaging.

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APPENDIX A

DEMOGRAPHIC QUESTIONNAIRE

Demographic Questionnaire (adapted from computer version – Microsoft Access 2000)

Variable List:

- Study code
- Full name
- Date of participation
- Phone number
- Study group (controls, relatives, neither)
- Date of birth
- Born in USA?
- State of birth
- Race (Caucasian, African-American, American Indian/Alaskan, Asian, Hispanic, Mixed, Other)
- Marital Status
- Gender
- Currently employed?
- Type of current employment
- Current living status (independently, spouse, family members, friend, nursing home, assisted living)
- Highest education attained (graduate, bachelor, associate, high school diploma, 11^{th} grade, 7^{th} grade, less than 7^{th} grade)
- Native language
- Dominant hand (right, left)
- Current medications

- Current address
- Proband ID # (if relative)
- Have you ever been diagnosed with:
    - Head injury?
    - Stroke?
    - Neurological condition?
    - Psychiatric condition?
    - Learning disability/dyslexia
- Have you ever been hospitalized for psychiatric care?
- Do you have any family members with schizophrenia?
    - If so, what is the relation to you?
- Proband schizophrenia type (undifferentiated, paranoid, disorganized, catatonic, schizoaffective)
- May we contact again for a future study?
- Do we have a structural MRI on this participant?

APPENDIX B

TABLES AND FIGURES

Table 1. Descriptive Factors for Study Participants

	Controls (N=34)	**Relatives (N=28)** [5]	**Test Statistic**	**P**
Age	53.0±16.1 (range:19-82)	49.1±13.5 (range:21-72)	t=1.02	ns
Visual Acuity[1]	0.91±0.30	0.82±0.28	U=419.0	ns
IQ Estimate[2]	115.3±17.1	93.6±16.2	t=5.08	<0.001
State Anxiety Estimate[3]	27.3±5.4	27.5±6.0	t=0.18	ns
Socioeconomic Status[4]	3.0±1.13	4.0±0.74	U=234.5	<0.001
Race	85% Caucasian	36% Caucasian	X^2=16.18	<0.001
Gender	62% female	79% female	X^2=2.04	ns

[1] Based on the Snellen Visual Acuity Chart. In order to make statistical comparisons with resulting scores, each ratio was changed into a number by dividing the top number by the bottom (e.g,. 20/40 was converted to 0.50). The higher the resulting number, the better the visual acuity. A score of 1 represents average visual acuity (e.g, 20/20).

[2] Based on the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999)

[3] Based on the total from the State-Trait Anxiety Questionnaire (Form Y-1)

[4] Hollingshead Social Class based on education and occupation (Hollingshead, 1965)

[5] From the participants comprising the relatives group: 15 were a full-sibling, 5 were a biological parent, and 5 were a biological child of a person with schizophrenia. Three relatives were a full-sibling of a person with schizoaffective disorder.

Table 2. Intercorrelations between Demographic Variables and Dependent Variables Within Each Experimental Group (white cells represent the control group (N=34); gray cells represent the relatives group (N=28))

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Age		.193	-.214	.012 [s]	-.186	-.410 [s]	-.671*	.204	-.023	.080
2. Gender[1]	.091		-.015	.416 [s]	.087	-.397 [s]	-.328	.244	-.171	-.302
3. Race[2]	.292	.156		.279 [s]	-.196	-.004 [s]	-.266	.053	-.085	-.564*
4. SES[3]	.159 [s]	-.099 [s]	.234 [s]		-.150 [s]	-.045 [s]	-.239 [s]	.119 [s]	-.377 [s]	-.654 [s]*
5. State Anxiety[4]	-.102	-.059	.055	.331 [s]		-.150 [s]	.117	.065	.029	.236
6. Visual Acuity[6]	-.353[s]	-.281 [s]	-.255 [s]	-.265 [s]	.182 [s]		.546 [s]*	-.154 [s]	-.001 [s]	-.070 [s]
7. VPSS[7]	-.745*	-.240	-.498	-.454 [s]	-.274	.567 [s]		-.459	.164	.266
8. SASS-SOA[8]	-.019	-.102	-.450	.023 [s]	-.277	-.072 [s]	.208		.086	-.292
9. SASS-CPT[9]	.187	.045	-.080	.186 [s]	.155	.124 [s]	-.052	.391		.564*
10. IQ Estimate[5]	-.471	-.012	-.522	-.624 [s]*	-.222	.511 [s]	.707*	-.058	-.266	

* Statistically significant at the Bonferroni corrected alpha of <.002

[s] Spearman correlation. All others values are Pearson correlations.

[1] Coded: 1=male, 2=female

[2] Coded: 1=Caucasian, 2=minority

[3] Hollingshead Social Class based on education and occupation (1=highest social class; 5=lowest) (Hollingshead, 1965)

[4] Based on the total from the State-Trait Anxiety Questionnaire (Form Y-1)

[5] Based on the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999)

[6] Based on the Snellen Visual Acuity Chart. In order to make statistical comparisons with resulting scores, each ratio was changed into a number by dividing the top number by the bottom (e.g,. 20/40 was converted to 0.50). The higher the resulting number, the better the visual acuity. A score of 1 represents average visual acuity (e.g, 20/20).

[7] Visual Perception Summary Score

[8] Sustained Attention Summary Score from the Span of Apprehension Test

[9] Sustained Attention Summary Score from the Continuous Performance Test

Table 3a. Primary Interaction Regression Analyses[1]

Dependent Variable	Controls (N=34) Model (intercept + slope)	Relatives (N=28) Model (slope + intercept)	F (interaction)	P (interaction)
Visual Perception Summary Score	1.82 - 0.026*age t = 3.28, p = .002 †	3.22 – 0.064*age t = 6.31, p < .001 †	9.58	.003 †
Sustained Attention Summary Score-CPT	0.04 + 0.003*age t = 0.21, *ns*	-0.88 + 0.021*age t = 1.31, *ns*	0.89	.35
Sustained Attention Summary Score-SOA	-0.26 + 0.003*age t = 0.25, *ns*	0.57 – 0.011*age t = 0.79, *ns*	0.65	.42
Full Scale IQ	-0.25 + 0.009*age t = 0.88, *ns*	0.36 – 0.029*age t = 2.10, p = .04	5.09	.03

Table 3b. Primary Interaction Regression Analyses, Excluding Relatives With Current Psychiatric Medication or Taking Psychoactive Medications (N=7) [1]

Dependent Variable	Controls (N=34) Model (intercept + slope)	Relatives (N=21) Model (intercept + slope)	F (interaction)	P (interaction)
Visual Perception Summary Score	1.82 – 0.027*age t = 3.41, p = .001 †	2.96 – 0.062*age t = 5.55, p < .001 †	7.13	.01 †
Sustained Attention Summary Score-CPT	0.04 + 0.001*age t = 0.08, *ns*	-0.91 + 0.022*age t = 1.21, *ns*	0.96	.33
Sustained Attention Summary Score-SOA	-0.26 + 0.002*age t = 0.13, *ns*	0.55 - 0.012*age t = 0.71, *ns*	0.46	.50
Full Scale IQ	-0.25 + 0.009*age t = 0.87, *ns*	-0.05 – 0.021*age t = 1.39, *ns*	2.81	.10

† Statistically significant at the Bonferroni corrected alpha of <.013

[1] All regression models consisted of (in order of entry into model): Visual acuity, group, age, group*age (interaction)

Table 4. Johnson-Neyman Procedure[1] Analyses on Statistically Significant Age by Group Regression Interactions

Measure	A	B	C	xlower	xupper
Visual Perception Summary Score	0.0010	-0.0292	0.6481	14.69	45.58
SOA – 6 letter condition	0.0011	-0.0308	0.4820	9.50	44.74
SOA – 12 letter condition	0.0023	-0.0808	2.6075	24.97	45.56
Backward Masking – Identification (all)	0.0011	-0.0424	1.4167	23.99	55.01
Backward Masking – 93 ms Identification	0.0027	-0.1226	5.4441	37.65	54.10
Full Scale IQ	0.0006	0.0208	-2.0310	-106.17	33.41

[1] The Johnson-Neyman procedure (Johnson & Neyman, 1936; Potthoff, 1964) identifies points on the dimension of age where the difference between the groups become statistically significant. The values of A, B, and C are used to derive the lower limit of statistical significance (xlower) and the upper limit (xupper). Estimated age values that are outside of the range examined by this study (19-82) are not regarded as valid estimates.

Table 5. Main Effect of Group Membership[1] for Regression Analyses of Age by Group Interaction that Failed to Approach Statistical Significance

Measure	Controls (N=34) Mean±Standard Deviation	Relatives (N=28) Mean±Standard Deviation	F	p
Sustained Attention Summary Score-CPT	-0.0321 ± 0.94	-0.0272 ± 1.09	0.10	.75
Sustained Attention Summary Score-SOA	-0.0028±1.00	0.0581 ± 1.00	0.06	.81
Backward masking (location condition)	-0.0011 ± 1.00	-0.1290 ± 1.20	0.64	.43
Backward masking (l3 ms identification)	-0.0018 ± 1.00	-0.1421 ± 0.83	0.002	.96
Backward masking (40 ms identification)	-0.0002 ± 1.00	0.0659 ± 1.41	0.14	.71
Backward masking (80 ms identification)	0.0000 ± 1.00	0.1013 ± 1.22	0.05	.83
Backward masking (13 ms location)	0.0000 ± 1.00	-0.0914 ± 1.22	0.57	.45
Backward masking (27 ms location)	0.0000 ± 1.00	0.0953 ± 1.01	0.03	.86
Backward masking (40 ms location)	0.0000 ± 1.00	-0.0993 ± 1.04	0.54	.47

† Statistically significant at the Bonferroni corrected alpha of <.006

[1] All analyses are ANCOVAs examining the effect of group membership on the dependent measure after controlling for the influence of visual acuity and age.

Table 6. Secondary Interaction Regression Analyses[1]

Dependent Variable	Controls (N=34) Model (intercept + slope)	Relatives (N=28) Model (intercept + slope)	F (interaction)	p (interaction)
SOA (6 and 12 letter conditions)	2.04 – 0.031*age *t* = 3.57, *p* = .001 †	4.05 – 0.086*age *t* = 7.67, *p* < .001 †	16.21	<.001 †
SOA (6 letter condition)	2.07 – 0.031*age *t* = 3.46, *p* = .001 †	3.56 – 0.073*age *t* = 6.21, *p* < .001 †	8.41	.005 †
SOA (12 letter condition)	1.61 – 0.022*age *t* = 2.44, *p* = .02	3.69 – 0.076*age *t* = 6.49, *p* < .001 †	14.27	<.001 †
Backward masking (identification and location conditions)	1.82 – 0.026*age *t* = 2.85, *p* = .006 †	3.08 – 0.057*age *t* = 4.74, *p* < .001 †	4.32	.04
Backward masking (identification condition)	1.84 – 0.025*age *t* = 2.24, *p* = .02	3.85 – 0.070*age *t* = 4.82, *p* < .001 †	6.45	.01
Backward masking (location condition)	1.80 – 0.028*age *t* = 2.71 , *p* = .009	2.32 – 0.044*age *t* = 3.31, *p* = .002 †	0.98	.33
CPT (A' measure from degraded condition) [2]	1.38 – 0.018*age *t* = 1.26, *ns*	2.61 – 0.059*age *t* = 3.42, *p* = .001 †	3.61	.06

† Statistically significant at the Bonferroni corrected alpha of <.007

[1] All regression models consisted of (in order of entry into model): Visual acuity, group, age, group*age (interaction)

[2] Data were missing from the CPT degraded condition for two controls and one relative.

Table 7. Interaction Regression Analyses[1] of Individual Interstimulus Intervals in Identification Condition of Backward Masking

Interstimulus Interval	Controls (N=34) Model (slope + intercept)	Relatives (N=28) Model (slope + intercept)	F (interaction)	p (interaction)
13 ms	-1.00 + 0.025*age *t* = 2.41, *p* = .02	-0.14 + 0.006*age *t* = 0.42, *ns*	1.40	.24
27 ms	0.20 – 0.002*age *t* = 0.12, *ns*	1.84 – 0.039*age *t* = 2.50, *p* = .02	3.90	.05
40 ms	2.28 – 0.043*age *t* = 3.65, *p* = .001 †	2.38 - 0.047*age *t* = 3.11, *p* = .003 †	0.54	.82
80 ms	2.04 – 0.030*age *t* = 3.25, *p* = .002 †	3.01 – 0.051*age *t* = 4.26, *p* < .001 †	2.05	.16
93 ms	1.29 – 0.013*age *t* = 1.23, *ns*	4.06 – 0.072*age *t* = 5.41, *p* < .001 †	13.42	.001 †

† Statistically significant at the Bonferroni corrected alpha of < .01

[1] All regression models consisted of (in order of entry into model): visual acuity, group, age, group*age (interaction)

Table 8. Interaction Regression Analyses[1] of Individual Interstimulus Intervals in Location Condition of Backward Masking

Interstimulus Interval	Controls (N=34) Slope±Standard Error	Relatives (N=28) Slope±Standard Error	F (interaction)	p (interaction)
13 ms	1.61 – 0.023*age $t = 1.81$, *ns*	1.75 – 0.032*age $t = 2.00$, $p = .05$	0.24	.63
27 ms	1.37 – 0.024*age $t = 2.23$, $p = .03$	1.45 – 0.023*age $t = 1.65$, *ns*	0.004	.95
40 ms	1.82 – 0.028*age $t = 2.99$, $p = .004$ †	2.50 – 0.046*age $t = 3.88$, $p < .001$ †	1.66	.20
80 ms	1.39 – 0.022*age $t = 2.12$, $p = .04$	2.45 – 0.052*age $t = 3.84$, $p < .001$ †	3.25	.08

† Statistically significant at the Bonferroni corrected alpha of <.013

[1] All regression models consisted of (in order of entry into model): visual acuity, group, age, group*age (interaction)

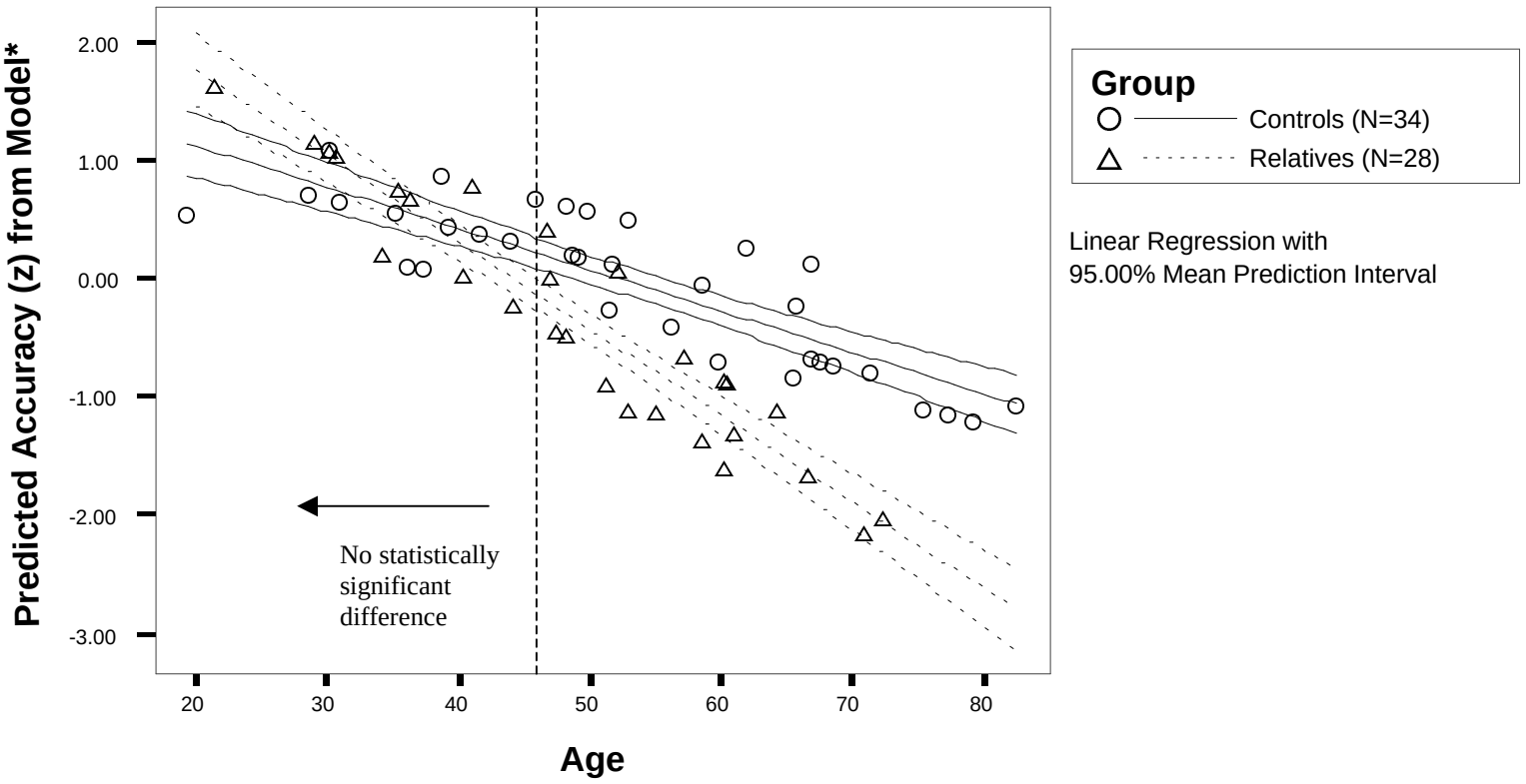

Figure 1a. Accelerated Age-Related Decline of Predicted* Visual Perception (z) in First-Degree Relatives of Persons with Schizophrenia

* Model = Visual acuity + age + group + age*group; **Interaction: F(1, 57)=9.58, p=.003**

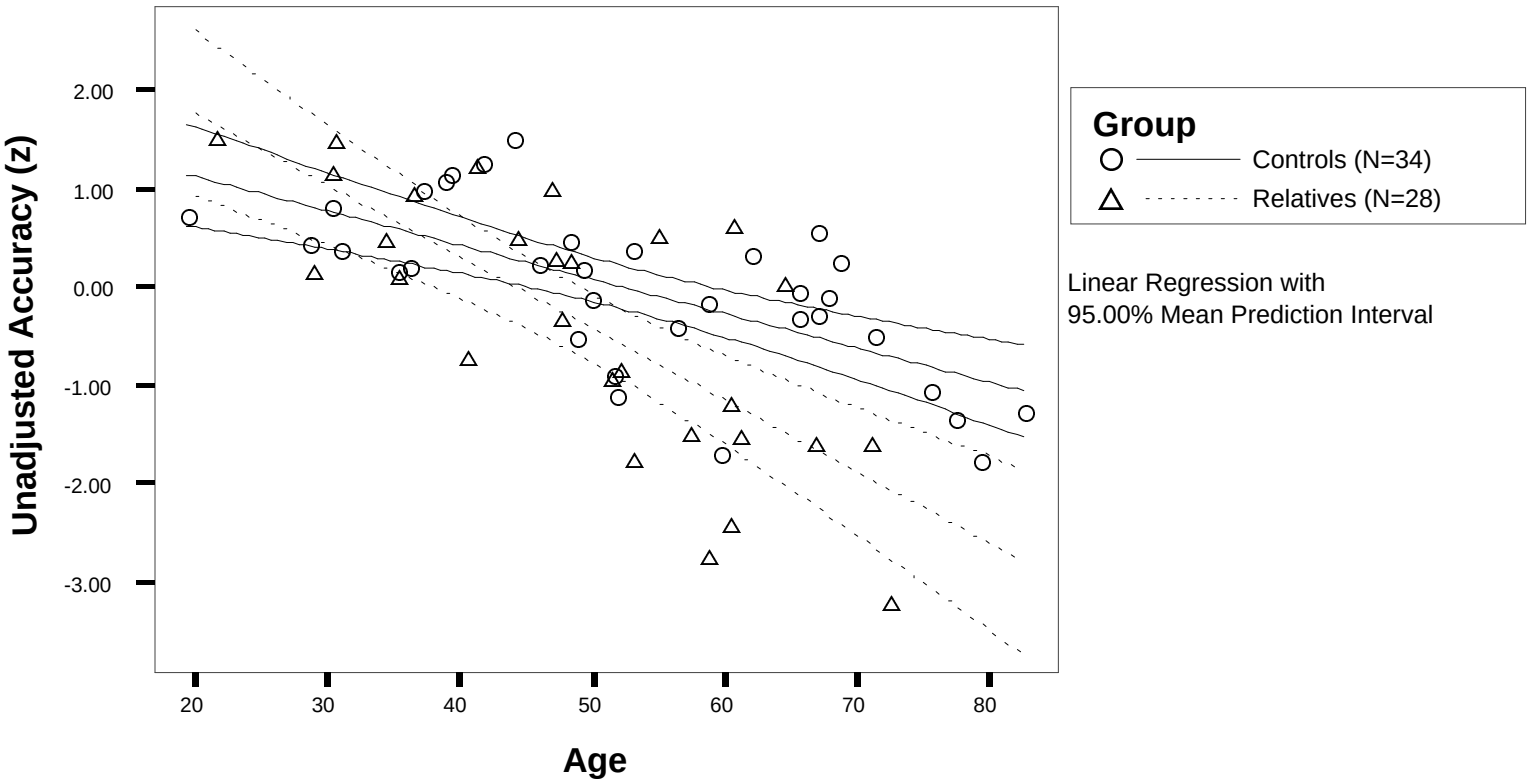

Figure 1b. Accelerated Age-Related Decline of Unadjusted Visual Perception (z) in First-Degree Relatives of Persons with Schizophrenia

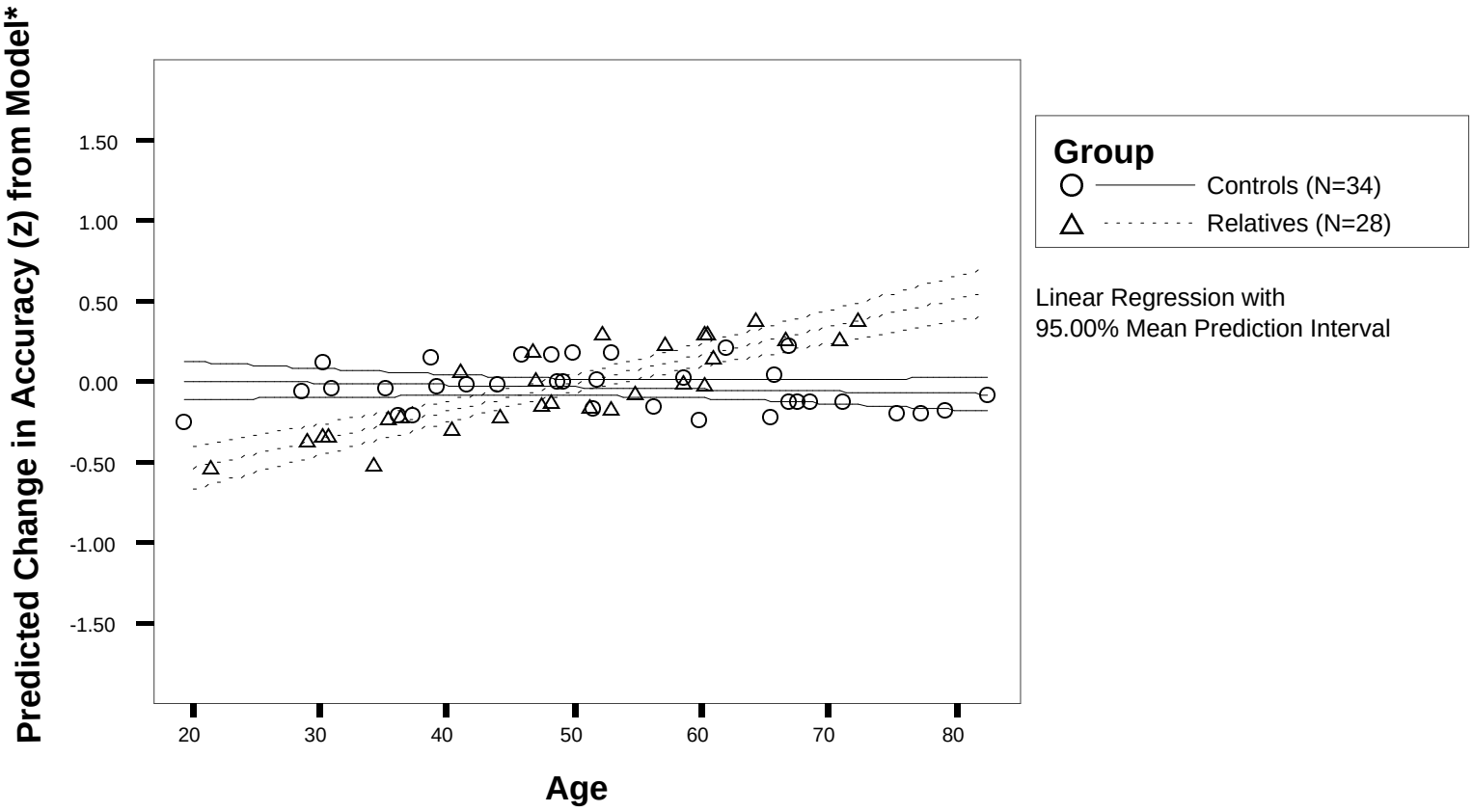

Figure 2a. Relation of Age With Predicted* Sustained Attention Summary Score (z) from the Continuous Performance Test

* Model = Visual acuity + age + group + age*group; **Interaction: F(1,57)=0.89, ns**

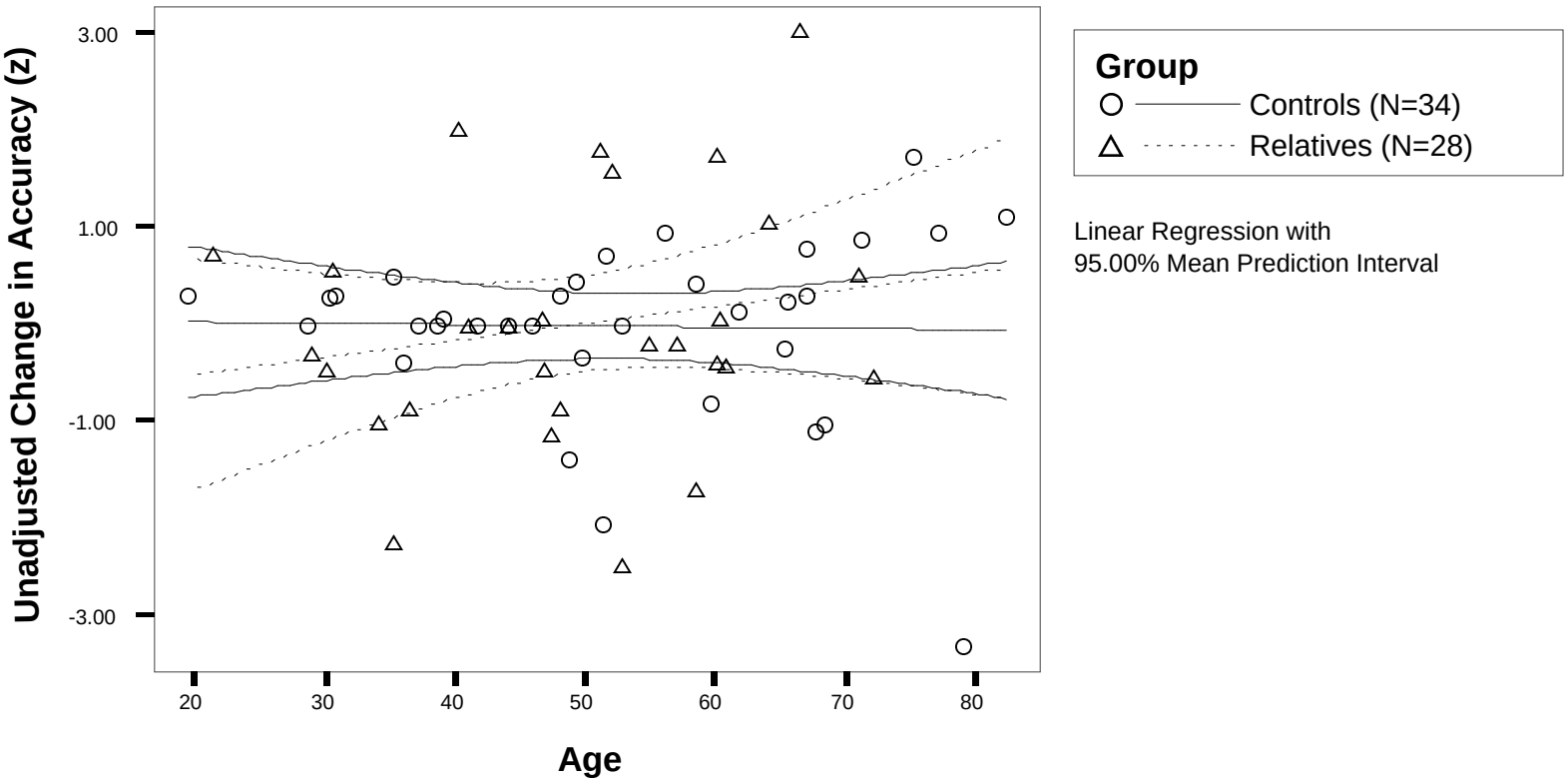

Figure 2b. Relation of Age With Unadjusted Sustained Attention Summary Score (z) from the Continuous Performance Test

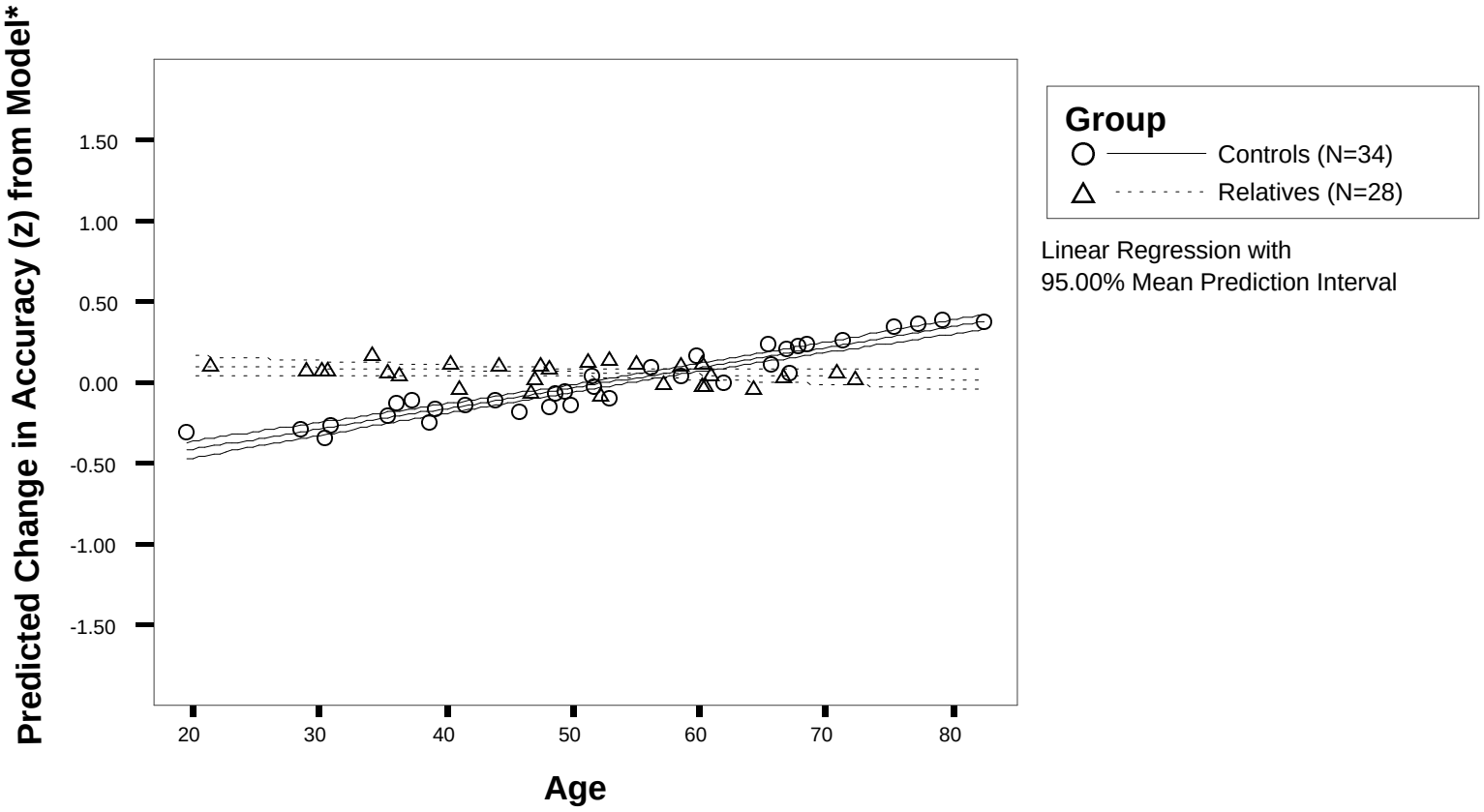

Figure 3a. Relation of Age With Predicted* Sustained Attention Summary Score (z) from the Span of Apprehension Task

* Model = Visual acuity + age + group + age*group; **Interaction: F(1,57)=0.60, ns**

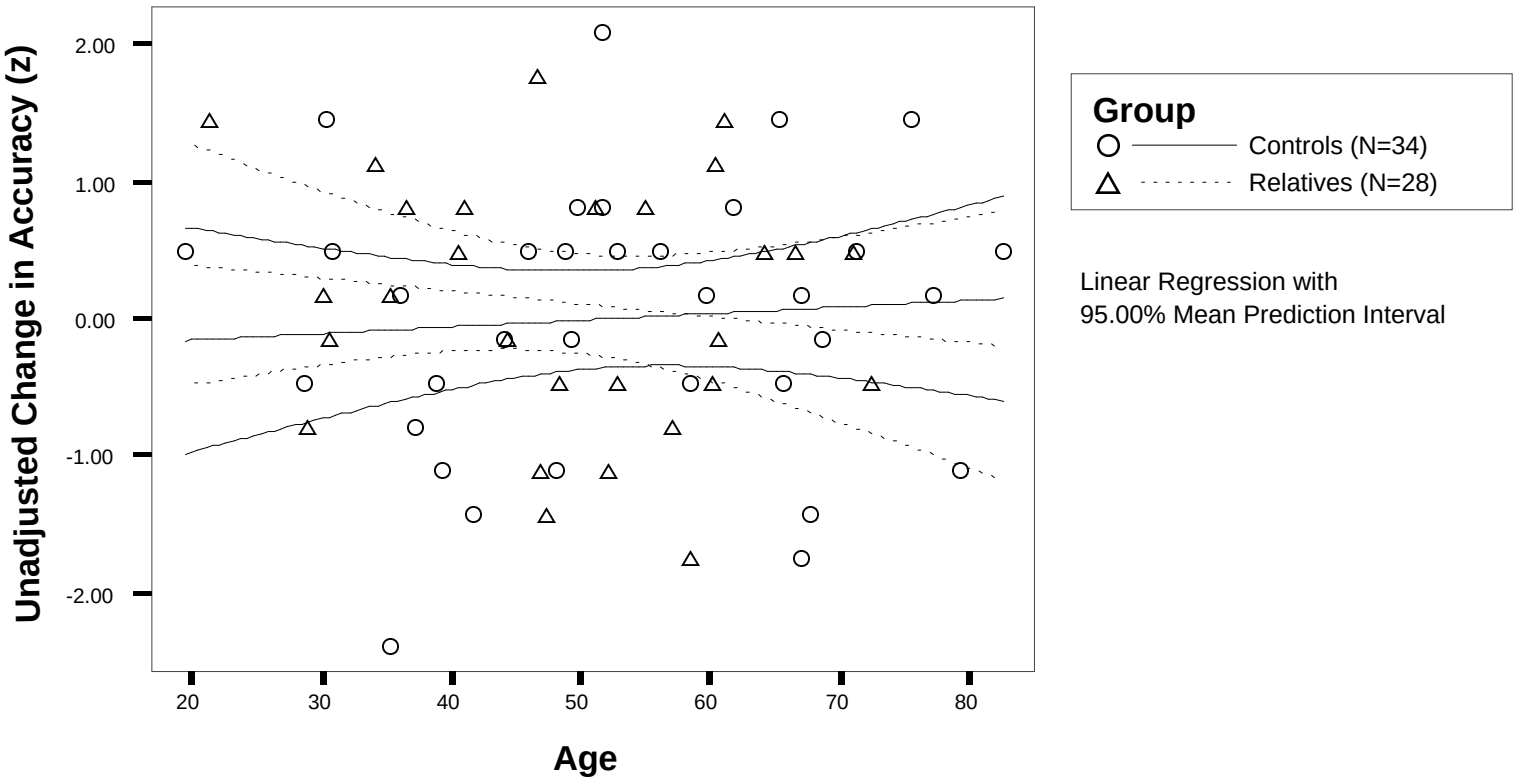

Figure 3b. Relation of Age With Unadjusted Sustained Attention Summary Score (z) from the Span of Apprehension Task

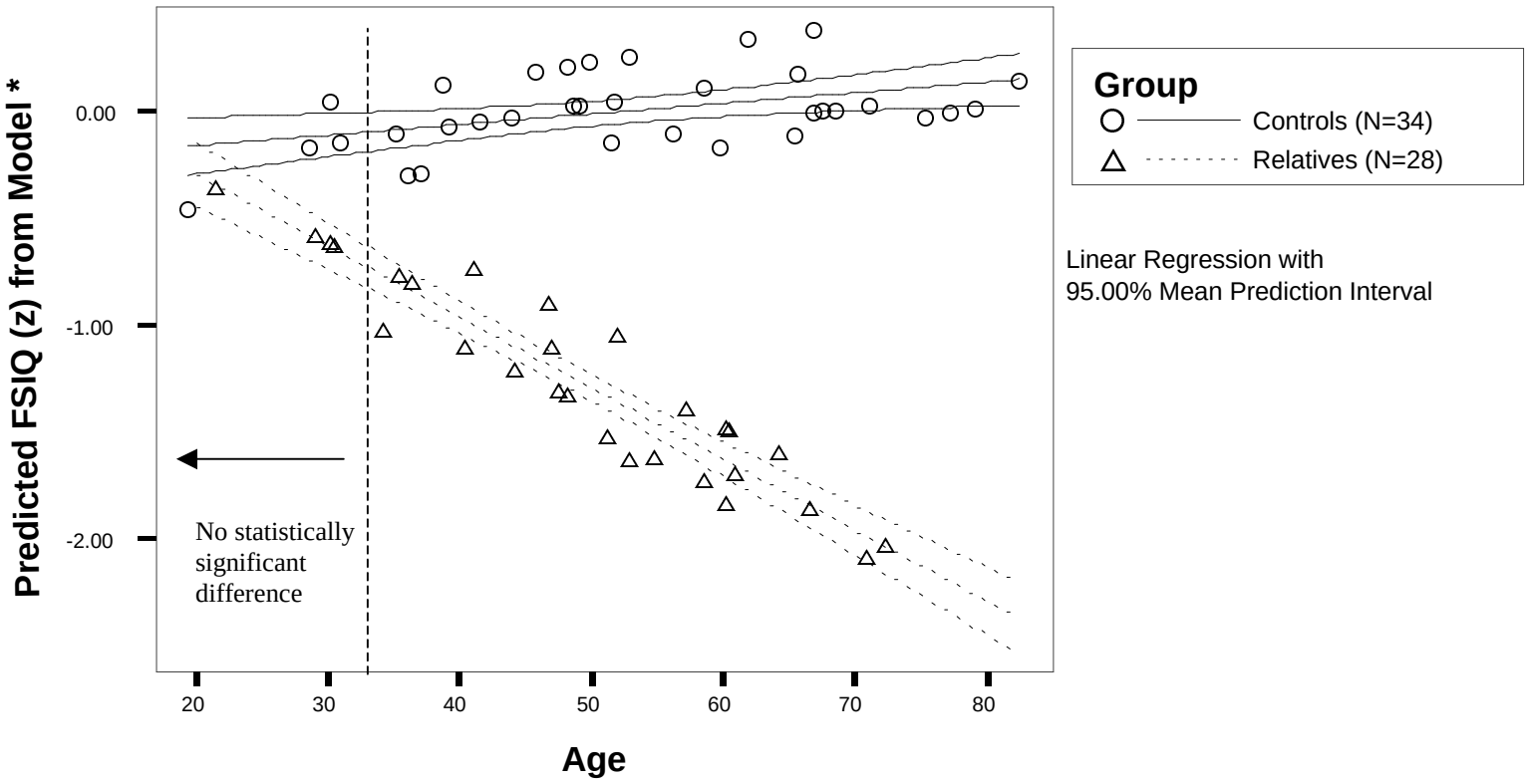

Figure 4a. Accelerated Age-Related Decline in Predicted* Full Scale IQ (z) in First-Degree Relatives of Persons with Schizophrenia.

* Model = Visual acuity+age+group+age*group; **Interaction: F(1,57)=5.19, p<.05**

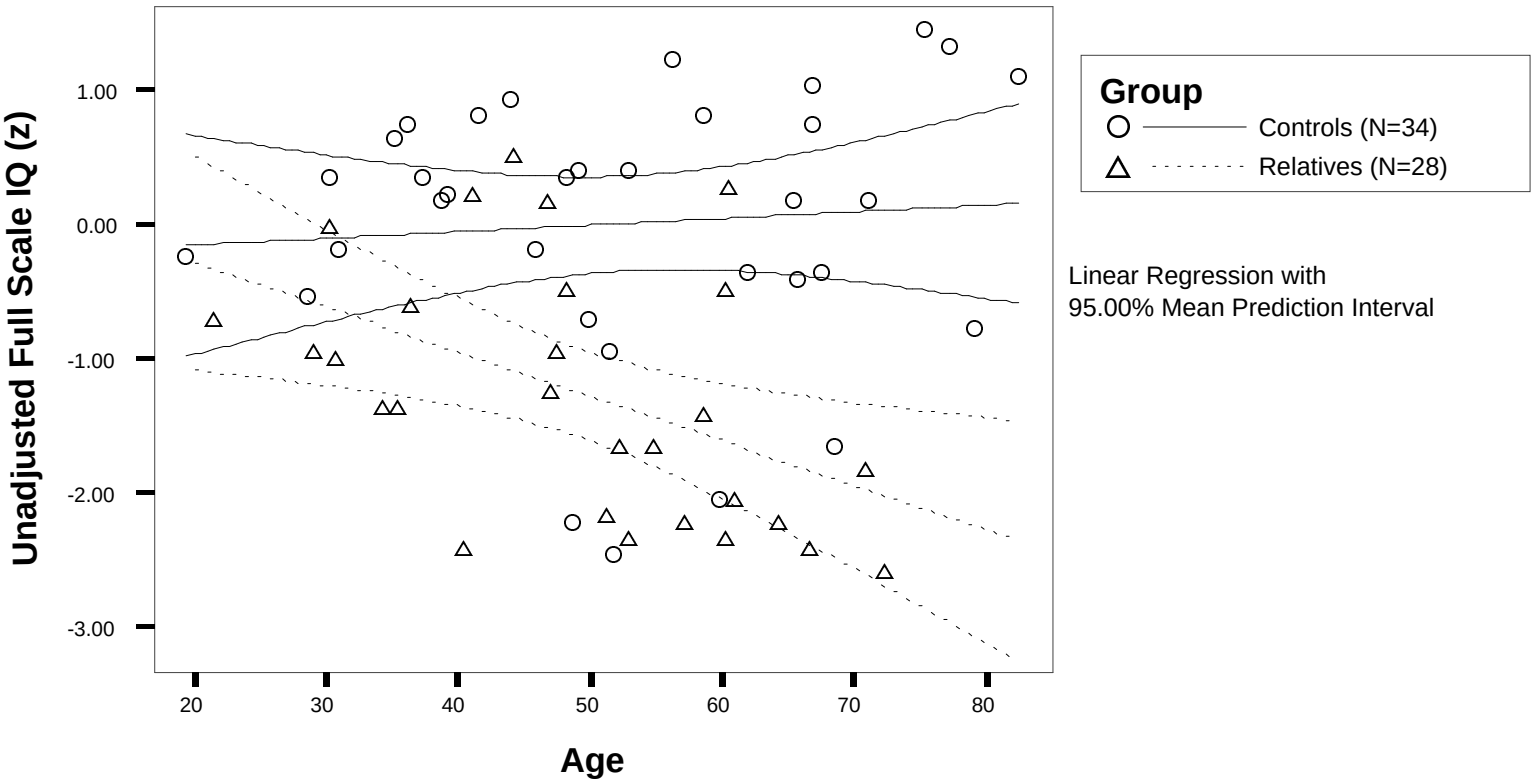

Figure 4b. Accelerated Age-Related Decline in Unadjusted Full Scale IQ (z) in First-Degree Relatives of Persons with Schizophrenia.

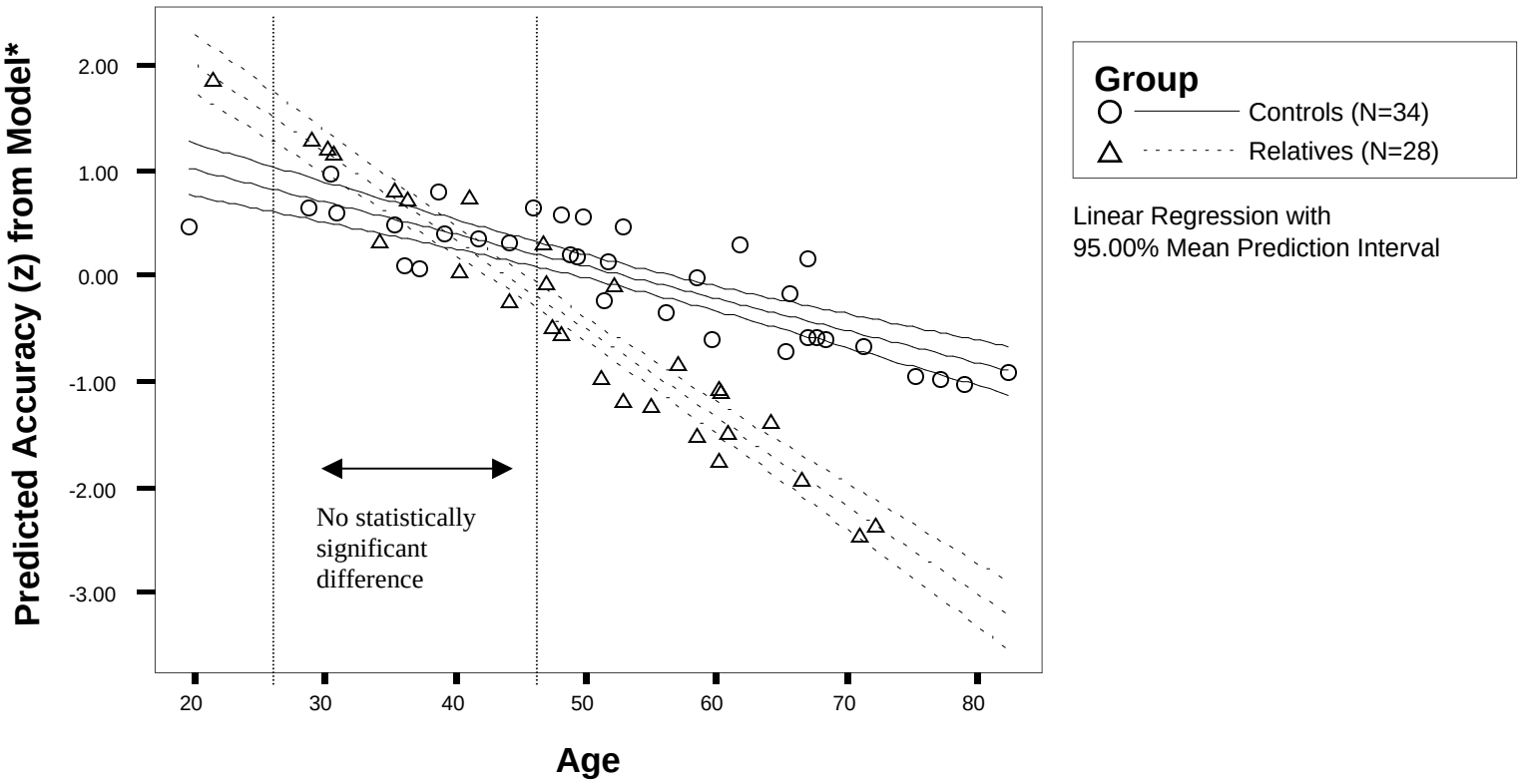

Figure 5. Accelerated Age-Related Decline in Predicted* Accuracy (z) on the 12-Letter Condition from the Span of Apprehension Task in First-Degree Relatives of Persons with Schizophrenia.

* Model = Visual acuity+age+group+age*group; **Interaction: F(1,57) = 14.27, p < .001**

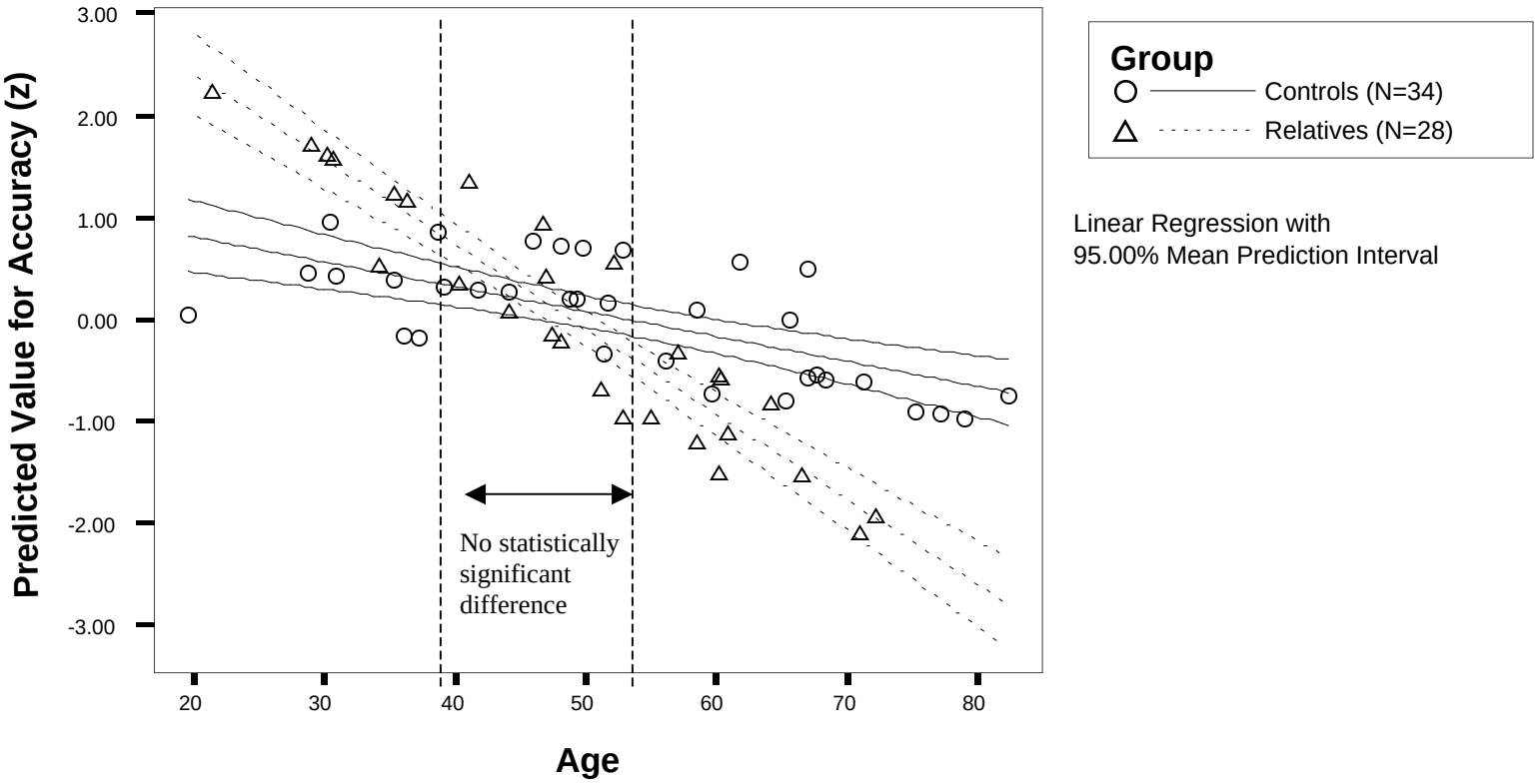

Figure 6. Accelerated Age-Related Decline in Predicted* Accuracy (z) on the 93 ms Interstimulus Interval from the Backward Masking Task in First-Degree Relatives of Persons with Schizophrenia.

* Model = Visual acuity+age+group+age*group; **Interaction: F(1,57) = 13.42, p = .001**