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Premorbid Cognitive Deficits in Young Relatives of Schizophrenia Patients

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Abstract

Neurocognitive deficits in schizophrenia are thought to be stable trait markers that predate the illness and manifest in relatives of patients. Adolescence is the age of maximum vulnerability to the onset of schizophrenia and may be an opportune "window" to observe neurocognitive impairments close to but prior to the onset of psychosis. We reviewed the extant studies assessing neurocognitive deficits in young relatives at high risk (HR) for schizophrenia and their relation to brain structural alterations. We also provide some additional data pertaining to the relation of these deficits to psychopathology and brain structural alterations from the *Pittsburgh Risk Evaluation Program* (PREP). Cognitive deficits are noted in the HR population, which are more severe in first-degree relatives compared to second-degree relatives and primarily involve psychomotor speed, memory, attention, reasoning, and social-cognition. Reduced general intelligence is also noted, although its relationship to these specific domains is underexplored. Premorbid cognitive deficits may be related to brain structural and functional abnormalities, underlining the neurobiological basis of this illness. Cognitive impairments might predict later emergence of psychopathology in at-risk subjects and may be targets of early remediation and preventive strategies. Although evidence for neurocognitive deficits in young relatives abounds, further studies on their structural underpinnings and on their candidate status as endophenotypes are needed.

Keywords:

1. Introduction
Schizophrenia (SZ) was originally described over a century ago with the earlier name "dementia praecox," which literally means "cognitive decline with onset in youth." Cognitive impairment is *highly prevalent* in patients with SZ as determined by the majority of patients who show cognitive decrement relative to parental education [1] or to their own estimate of premorbid intelligence measured by single word identification [2]. Meta-analyses show that cognitive impairment distinguishes patients with SZ from healthy comparison subjects to a *robust* degree (i.e., an effect size of approximately 1 with approximately 1 standard deviation); these deficits are apparent at the first episode and roughly are equal to those observed in chronic cases [3]. Average effect sizes for cognitive impairments in SZ are about twice as large as those obtained in structured magnetic resonance imaging studies[4]. Cognitive impairment is a *stable, trait-related* aspect of schizophrenia, being present in the early phase of the illness and persisting during the long-term course [5]. Cognitive impairment is a *predictor* of social and vocational outcome as evaluated longitudinally [6]. Recent studies suggest that social cognition may have a particularly strong relation to functional outcome [6]. Finally, cognitive impairment may differ to some extent between SZ and other psychiatric disorders [7]. Cognitive deficits in patients with SZ are generally more severe and pervasive compared to patients with psychotic and non-psychotic affective disorders [8, 9]. All of the above observations firmly point to cognitive deficits being a core feature of SZ and clearly a key path toward understanding the etiopathology of this illness.

Genetic factors are the best established etiological determinants of schizophrenia [10] as suggested by a heritability of 0.41 to 0.87 [11]. The risk of SZ is proportional to genetic dose (number of affected relatives and relatedness with the proband). This suggests that studies of relatives at genetic high-risk (GHR) are a very valuable approach to elucidate the genetic underpinnings of this illness. Offspring of patients have a ten- to fifteen-fold increase in risk of developing the illness. Having two parents with schizophrenia increases the risk to about 40% [12]. While studies of unaffected relatives of schizophrenia patients help us understand the genetic underpinnings of this illness, all such relatives may not necessarily be at high-risk; studies of young relatives who are within, or younger than the age range of risk for schizophrenia are more likely to illuminate neurocognitive indicators of risk. The view that SZ is a neurodevelopmental disorder [13-16] suggests that neurocognitive and neurobiological alterations may be detectable in the *premorbid* phase before the typical onset of the features of the illness (e.g., psychosis) during childhood, adolescence, or early adulthood. These alterations may also represent endophenotypes (i.e. markers intermediate between phenotypic manifestations of the disease and the genotype) [17].

In this paper, we review studies that have examined various cognitive domains including attention, learning and memory, general intelligence, social-cognition, speed of processing and executive-function[18] in unaffected young relatives presumed to be at high genetic risk. We did an extensive PubMed search using keywords "schizophrenia", "relatives" and "cognition." In particular, several high-risk studies conducted over the last three decades were reviewed (Table 1). We also summarize findings from our ongoing studies related to neurocognition, as well as provide some additional data on the nature of cognitive deficits and their relation to neurobiological alterations as well as the dose of familial risk (first vs. second-degree relatives) in young relatives at risk for schizophrenia.

Study / Author	Design	Groups and sample Size	Major Findings
Speed of Processing			
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Impaired speed of processing
NCPP	0, 4, 8 m, 1, 4, 7 y. f/u	S = 32, HR = 25, HC = 201	Deficits in coding subtest (p=0.03)
Memory			
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Deficits in spatial memory capacity
PREP	3 y. f/u	HR = 81, C = 80	Reduced spatial working memory
HHAHRS	Cross sectional	HR SZ = 73, HR Aff =18, C = 84	Reduced verbal, visual-spatial and working memory
Delawalla et al. 2006	Cross sectional	S= 27, HR = 31, HC = 39, HC.sib = 42	Deficits in working memory
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Deficits in verbal memory predicted future schizophrenia
NYHRP	6 assessments, first 9 y, latest 30 y. f/u	Phase A: HR = 84, HRaff = 67, C =136 Phase B: HR= 46, HRaff = 39, C=65	Verbal short-term memory predicted schizophrenia
NCPP	0, 4, 8 m, 1, 4, 7 y. f/u	HR = 54, HC = 72	Verbal memory deficits with significant gender interaction
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Deficits in visual memory
Attention			
IHRS	8– 15, 14–21, 23– 30, 31– 40 y. f/u	HR= 50, C= 50	Poor attentional skills predicted later SZ.
JIDS	0, 3, 14 d, 4, 8, 12 m, 7– 14, 14– 21 y. f/u	HR= 29, other = 30, C=27	Attentional dysfunction, measured as part of global neurobehavioral functioning.
NYHRP	6 assessments, first 9 y, latest 30 y. f/u	Phase A: HR = 84, HRaff = 67, C =136 Phase B: HR= 46, HRaff = 39, C=65	Attention deficits predicted social outcome and later SZ.
SBHRP	7– 15, 10– 18, >18 y. f/u	HR= 80, HRmdd = 154, HRbp = 134, C = 176	Impaired perceptual sensitivity (d')
PREP	3 y. f/u	HR = 81, C = 80	Impaired sustained attention

Reasoning and Executive Function			
Franke et al 1992	Cross sectional	S=73, HR=61, HC=35	More perseverative errors and relatively normal non-

			perseverative errors
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Deficits in response inhibition
Ma et al	Cross sectional	S=207, HR=322, C= 133	Poor performance on perseverative errors
Klemm et al	Cross sectional	HR=32, HC=32	Poor performance on completed categories and perseverative errors
Tact or Social Cognition			
JIDS	0, 3, 14 d, 4, 8, 12 m, 7– 14, 14– 21 y. f/u	HR= 29, other = 30, C=27	Impaired social competence
NYHRP	6 assessments, First 9 y, latest 30 y. f/u	Phase A: HR = 84, HRaff = 67, C =136 Phase B: HR= 46, HRaff = 39, C=65	Impaired social competence
EUP	0– 5,1– 6, 2– 7 y, studied three times 1 y. apart f/u	HR SZ = 61, HRmdd = 33, C=33	Impaired social competence
Eack et al 2009	Cross sectional	HR = 70, HC = 63	Emotion recognition deficits associated with prodromal symptoms
Bediou et al 2007	Cross sectional	S=40, HR =30, HC =26	Impaired emotion recognition
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Deficits in theory of mind tasks
General Intelligence			
EHRS	18-m. intervals for 5y. f/u	HR = 163, C = 36	Deficits in all measures of IQ (full scale, verbal and performance IQ) and poor IQ predicted future schizophrenia
NCPP-B and NCPP-P	0, 4, 8 m, 1, 4, 7 y. f/u	HR SZ = 118,HRaff = 126, C = 165	Deficits in IQ, lower premorbid IQ associated with genetic vulnerability to SZ
RLS	0, 4 m, 1, 2.5, 4 y. f/u	HR SZ = 29, HR other = 98, C=57	No significant IQ deficits
HHAHRS	Cross sectional	HR Sz = 73, HR Aff =18, C = 84	Reduced verbal ability (d=0.73)
SLRRP	7, 10, 13, 16, 19, 22, > 25 y. f/u	HR = 100, HRaff = 60, C = 130	Temporal progression in IQ deficits and a time by parental diagnosis interaction on verbal IQ
NYHRP	6 assessments,	Phase A: HR = 84,	No temporal progression in

	first 9 y, latest 30 y.	HRaff = 67, C =136 Phase B: HR= 46, HRaff = 39, C=65	IQ deficits and could not predict schizophrenia

Table 1: Findings in Cognitive Domains in High-Risk Relatives. d = days, m = months, y = years, f/u = follow up, aff = affective psychosis, C = control group, de = depression, HR = High-Risk group, HC sib = siblings of healthy controls, mdd = major depressive disorder, other = other mental disorder, HR other = high risk for other disorders pd = personality disorder, S = schizophrenia, HR.BP = High risk for bipolar disorder, HR SZ = high risk for schizophrenia, HR aff = high risk for affective psychoses EHRS = Edinburgh High Risk Study [19-28], PREP = Pittsburgh Risk Evaluation Program [29], HHAHRS = Harvard and Hillside Adolescent High Risk Study [30, 31], NCPP = National Collaborative Perinatal Project (P-Providence, B-Boston) [31-33], NYHRP = New York High Risk Project [34-36] JIDS = Jerusalem Infant Development Study [37, 38], IHRS = Israeli High Risk Study [38, 39], EUP = Emory University Project [40], SLRRP = St. Louis Risk Research Project) [41], RLS = The Rochester Longitudinal Study [42], SBHRP = Stony Brook High Risk Project [43], Delawalla et al. 2006[44], Franke et al 1992[45], Klemm et al 2006[46], Eack et al 2009[47], Bediou et al 2007[48], Ma et al [49]

2. Nature of neurocognitive deficits in young relatives at risk for SZ
There are prominent impairments in schizophrenia in several domains of cognition, including psychomotor speed, memory, attention, reasoning, and social cognition (Table 1). These may be easily remembered by the mnemonic *SMART* [Speed of processing, Memory, Attention, Reasoning and Tact (or social cognition)]. Studies have suggested some inter-correlation between cognitive performance on these domains, although there is no clear consensus regards the degree of shared variance of across domains. Studies have shown both significant [50] and non-significant correlations between these domains [51] in patients with schizophrenia. A common 'general intelligence' factor, correlating with all domains may explain the lack of independence of cognitive performance on these domains. Evidence suggests correlation of IQ (an index of general intelligence) with performance across domains in schizophrenia patients [52-56] and may represent this common general intelligence factor. Alternatively, the inter-dependence of specific cognitive domains could be due to similarities across the different neuropsychological tests used to assess different domains [57]. Although IQ deficits generally share variance with specific cognitive deficits, deficits in some domains such as speed of processing and verbal memory have been found to be independent of the IQ deficits. It is therefore unclear if domain-specific deficits can be fully accounted for by a super-ordinate factor like general intelligence.

2.1. Speed of Processing
This domain measures cognitive efficiency and involves the ability to automatically and fluently perform relatively easy or repetitive cognitive tasks. Shakow [58]originally described this deficit in schizophrenia studying reaction time slowing. Speed of processing has been posited as a predictor of global functioning, autonomy, self care and hence of illness outcome and quality of living [59]. Reaction time, an indicator of speed of processing, is increased in relatives of patients [60]. Young relatives at risk for schizophrenia have reduced processing speed even after controlling for IQ as shown by the Edinburgh High-Risk Study (EHRS) (p=0.044) [61], [62],

[63], as well as our studies which will be described later. These deficits might be state-independent given that psychotic symptoms do not alter the severity of speed of processing deficits in patients [20]. Evidence suggests that processing speed may depend on testing conditions. In a study with varying cognitive processing loads, while the fastest reaction times (that happen during low-cognitive load tasks) were not increased in relatives [64], mean reaction time was slower, suggesting slower reaction times during high-cognitive-load tasks. Slowed performance on the various psychomotor measures has been shown to be independent of medication [65]. Speed of processing has also been found to predict negative symptoms and impaired functional outcomes [65, 66].

A genetic-load effect is noted with performance of relatives being intermediate between that of healthy controls and patients on this domain [64, 67, 68]. Reaction time has been proposed as a putative endophenotype of the illness [69]. However, a study showed that both patients with and without reaction time deficits on the CPT have relatives showing these deficits [64]. Thus, the candidacy of reaction time deficits as an endophenotype, as well as their role as premorbid vulnerability indicators deserve further consideration.

2.2. Memory
Working memory (WM) involves holding information online for brief periods of time, and typically involves processes like information manipulation, maintenance and monitoring in verbal, visual and spatial domains [70]. Maintenance involves retaining information in a sequential manner, manipulation deals with rearrangement of the information sequence while monitoring checks and updates the contents of working memory to determine the next step in a sequential task. Working memory in all subsystems is impaired in first episode patients [71] and unaffected first degree relatives [72-74]. Relatives of SZ patients perform poorly on spatial working memory [75], [76] and spatial memory capacity [62]. Several studies report impairments in verbal, spatial and object WM domains with a graded pattern of impairment; deficits in patients > relatives > controls are observed for verbal WM [32, 74]. Deficits in WM to appear to correlate with negative symptoms [77]. Impaired working memory has been proposed as a putative endophenotype for schizophrenia [32].

Verbal declarative or long-term memory is significantly reduced in patients [77], is associated with earlier disease onset, is related to social functioning and negative symptoms [66] and is proposed to be a predictor of later SZ in high-risk individuals [78, 79] (Table 1). However, a study reported no verbal-memory deficits in high-risk offspring after controlling for education [77]. In the *Edinburgh High-Risk Study* (EHRS), deficits in Rey's auditory verbal learning test predicted later schizophrenia but deficits in Rivermead Behavioral Memory Test did not [80], [61], [81], [82], [83], [84], [85]. The New York High-Risk Project (NYHRP) reported that verbal memory deficits predict 83% of high-risk subjects who subsequently received a diagnosis of schizophrenia. The Harvard and Hillside adolescent high-risk study [86] showed that verbal memory impairment may have promise as a premorbid predictive marker in those at genetic risk for the illness, but further investigation is needed into confounding mediator factors such as affective symptomatology, education and environmental factors in these deficits. Another multi-site study (The Consortium on the Genetics of Schizophrenia) has proposed verbal working memory deficits to be putative inherited endophenotypes of schizophrenia [87, 88]. In general, verbal memory has been shown to be one of the most robust deficits in studies of relatives.

Visual memory has been studied less frequently than verbal memory in patients, and impairments in the visual domain among family members appear to be somewhat less severe than in the verbal domain [89]. A study reported verbal recall deficits over short and long delays in both patients and relatives of patients but visual recall deficits only in patients [90-92]. Visual recall deficits have been thought to be state dependent while verbal memory deficits may be heritable stable trait markers [93]. Visio-spatial memory deficits in relatives correlate with their proximity to probands (genetic loading) [94]. Also, visual recall deficits in delayed recognition tasks have been observed in high-risk relatives [80].

2.3. Attention

Attention involves the appropriate allocation of processing resources to relevant stimuli, and includes sub-processes like sustained attention and selective attention. A frequently used test to assess attention-performance is the *Continuous Performance Test* (CPT). Several CPT versions vary with regards to modality (auditory or visual), type of stimulus (letters, numbers, colors, or geometric forms), and nature of the task [95]. Attentional abnormalities have been well documented in schizophrenia; attentional deficits are associated with negative and disorganized symptoms and persist despite treatment. Impaired sustained attention indexed by perceptual sensitivity (d') in the CPT task strongly discriminates high-risk relatives from healthy controls [96]; attention deficits are consistent, temporally stable, and independent of environmental factors or onset of psychotic symptoms [96], [97], [98]. Attention deficits predicted more than half (58%) of the high-risk offspring who developed schizophrenia in their future [96]. Measures of attention deviance predicted social outcomes while poor neurobehavioral functioning predicted future schizophrenia spectrum disorders [96, 99] . Attention deficits have been observed in unaffected relatives in the prodromal as well as premorbid phases and have been considered as 'endophenotypes' for later emergence of schizophrenia [100], using poor attentional performance as a marker of vulnerability to schizophrenia could provide a valuable measure of genetic risk.

2.4. Reasoning and Executive Function

Executive functions refer to cognitive processes that bear specific tasks related to problem solving. Abstraction (extracting a common feature from various perceptions), reasoning, set shifting (ability to modify ongoing behavior in response to changing goals or environmental input), and error monitoring are critical aspects of executive function. Perseverative and non-perseverative errors on the *Wisconsin Card Sorting Test* (WCST) are indicators of deficits in cognitive set shifting and generalized reasoning, respectively [101, 102]. Relatives of SZ patients show higher perseverative errors but relatively normal non-perseverative errors than controls, suggesting cognitive set shifting to be a vulnerability marker of the illness. Additionally, patients have deficits in non-perseverative errors indicating these to be state dependent; poorer performance on reasoning and problem solving is associated with reduced global functioning [66]. By factor analysis in first degree relatives, perseverative errors, set-shifting difficulties, and idiosyncratic sorting were identified as orthogonal (uncorrelated) dimensions assessed by the WCST [103]. In young high-risk relatives of schizophrenia patients, EHRS found deficits in executive function [61],[81], while another study displayed poor performance on WCST in relatives of patients having a family history of schizophrenia compared to relatives of patients

without a family history of schizophrenia [104]. Some studies have been equivocal [105], suggesting further investigation.

2.5. Social Cognition

Social cognition involves faculties allowing tactful and socially appropriate behavior that involve affect perception, emotion regulation, and the ability to infer other people's mental states (Theory of Mind). These functions are reported to be compromised in individuals with schizophrenia [106, 107]. Impairments in social cognition are only partly correlated with and largely independent of neurocognitive dysfunction [108, 109], and may underlie symptoms of schizophrenia and disability [110, 111]. Studies have shown that many of these domains of cognitive impairment are stable over time and are present after the cessation of schizophrenic symptoms [112, 113].

Social cognitive deficits may have predictive value for later schizophrenia [114-116], [117-121], [121-127]. A large body of evidence shows social cognition aberrations to be the predominant cognitive deficit in the prodrome, a phase that often progresses to psychotic disorder [122, 125, 126, 128-131]. Social dysfunction is a predictor of future positive symptoms [125, 129-131] and influences prodromal morbidity and functioning more than other neurocognitive deficits [121, 123-127]. Structural alterations in regions mediating social cognition [68, 102, 132-138] might therefore be promising predictors of schizophrenia.

Unaffected relatives of patients show deficits in emotion recognition [139], [140], [141], and theory of mind tasks [142]. A study on siblings of SZ patients [143] demonstrated significant performance deficits in the recognition of facial anger. Recently, one study [144] found that individuals clinically at high risk for developing schizophrenia (i.e., those with prodromal symptoms) performed as poorly as first episode patients on an emotion identification task. Theory of mind deficits also have been shown to be compromised in relatives and together with emotion perception may predict functioning in the community [25, 145, 146]. As reviewed in Phillips (2008) [147], emotion perception deficits in relatives are consistently present, as well as social anhedonia and negative affect. Some studies have found high-risk offspring to have poor social competence [99], [148], [149].

2.6. Verbal fluency

Language related cognitive deficits, verbal memory [150, 151], verbal fluency [150, 151], semantic memory [152], comprehension [153], and receptive language [153] are found to be deficient in patients with schizophrenia and are also present in at-risk children [154, 155], [156]. Category verbal fluency indexes semantic memory, lexical access, and executive function while letter fluency may index psychomotor speed [157]. Although verbal fluency is shown to be altered in relatives of SZ patients [158], few studies have assessed young relatives [159]. A recent meta-analysis revealed a large effect size (0.68) in category fluency [89]. Verbal fluency may be significantly correlated with intelligence[160]; another study reported deficits in verbal fluency and executive function among relatives of schizophrenia patients. [161] The possibility of verbal fluency deficits in young relatives was assessed by the *Pittsburgh High-Risk Study* (see below) which found significant deficits at the baseline assessment.

2.7. General Intelligence

Intelligence deficits in relatives at risk for SZ are equivocal with studies both showing [148, 162-165] and not showing significant IQ deficits [166]. IQ deficits tend to progress with time as evidenced by some studies [167] while others did not find such a pattern [148, 149]. Some studies with HR offspring bearing IQ deficits predicted adult schizophrenia [82] while others could not [148]. A study reported low social status and severity of maternal illness to be strong predictors of low IQ in offspring of patients [168]. Worland et al., reported a time by parental diagnosis interaction on verbal IQ among high risk offspring, children of mothers with schizophrenia showed more deficits than children of fathers with schizophrenia during a 16 year follow-up, and also children of schizophrenia parents had the lowest stability on IQ scores [167]. The question of whether the liability to schizophrenia is mainly related to a generalized intellectual defect or whether there exists unique cognitive domains with selectively more prominent impairments remains unclear [169].

3. Neurobiology of Cognitive Deficits in HR relatives

Schizophrenia patients show enduring structural gray matter volumetric deficits of the subcortical regions [170], medial-temporal, cingulate, prefrontal temporal, and parietal cortices [171]. These alterations may be heritable and have been posited as stable trait markers or endophenotypes of schizophrenia [134, 135]. As structural alterations may reflect genetic liability to schizophrenia, brain regions altered in patients may also be altered in their relatives [134, 135]. High-risk relatives show alterations of amygdalae, hippocampus [172-177], thalami [178], basal ganglia [178-180], anterior cingulate gyros [119, 181], and ventricular enlargement [176, 177]. HR subjects have been reported to show structural alterations in white matter: reduced levels of FA (Fractional Anisotropy – an indicator of white matter integrity) [182] in anterior limb of internal capsule [183] and in bilateral cingulate and angular gyri [182] but relatively increased orbitofrontal white matter volumes [184]. Deficits in left posterior cingulate, right inferior parietal, orbitofrontal cortex, and right middle frontal agree with results from the Edinburgh High-Risk Study [185] which found an exaggerated longitudinal volume decline in these regions in relatives using voxel based approaches. A left > right decrement of the hippocampal amygdalar complex [172, 186] in relatives of patients is also reported [187]. The left parahippocampal gyrus is noted to be altered in those at genetic risk [188]. As reviewed earlier, studies in young relatives of schizophrenia patients have found deficits [102, 189-191] in executive-function [192], working-memory, attention [86, 193-196], language [22, 24, 193, 197, 198], speed of processing [199] and social cognition [102] [145, 200, 201]. It is proposed that speed of processing (reaction time) depends on nerve conduction velocity which is in turn based on the myelination of white matter fibers [202]. Subjects at risk for schizophrenia have altered white matter volumes, and may lead to slower reaction time [199]. Preliminary studies show that presence of genetic polymorphisms affecting the integrity of white-matter tracts may correlate with reaction-time deficits [203].

The amygdalae, hippocampi, and orbito and medial prefrontal regions mediate social-cognition [204-206]. The inferior parietal lobule [207], and the inferior frontal cortex [208-210] perform language processing while the thalamus, caudate-nucleus [211, 212], middle frontal gyrus, and superior parietal cortex [213] have been shown to mediate attention, working-memory, and executive function [214-217]. Frontal release signs, indices of prefrontal pathology are correlated with executive function and attention [218].

Premorbid cognitive deficits may map onto observed structural deficits in brain regions mediating corresponding cognitions. Relations between cognitive deficits and brain structural alterations in high-risk relatives have not been systematically examined. If such relations are established, cognitive and brain structural deficits, both considered to be endophenotypes of schizophrenia, might be more parsimoniously explained by the "extended endophenotype" concept [219].

4. Neurocognitive Deficits in young HR relatives: Findings from the *Pittsburgh High-Risk Study*

In an ongoing longitudinal study, the Pittsburgh Risk Evaluation Program (PREP), we assess young (10 to 25 years) first- and second-degree relatives of schizophrenia probands and healthy controls. The participants were identified at the Western Psychiatric Institute and Clinic (WPIC), Pittsburgh or related clinical sites. Young HR relatives were recruited by first approaching patients with schizophrenia with eligible relatives in our outpatient clinical services and via advertisements in community locations. Participants were included if they had a first or second degree relative with schizophrenia or schizoaffective disorder, had an IQ $\geq$ 80, did not have any lifetime evidence of psychotic disorders, antipsychotic medication exposure, history of substance use, and neurological or medical condition. Age and gender matched healthy controls were recruited from the same community neighborhoods as HR subjects. The study design, demographic, and clinical characteristics of these subjects have been described elsewhere [220]. We report herein summary observations in key neurocognitive domains and their neuroimaging correlates.

Previously published findings from the PREP study involve deficits in memory, attention, verbal fluency, executive function, social cognition, and general intelligence. High-risk offspring performed poorer compared to controls on spatial working memory, sustained attention, category verbal fluency [221], executive function [29, 221, 222], and general intelligence [221]. Social cognition deficits in facial emotion recognition were also noted [139]. Relatives were found to over-attribute negative valence to neutral faces and took longer to identify neutral faces. These deficits were independent of other neurocognitive dysfunction and correlated with positive symptoms and general psychopathology scores [222]. Compared to healthy controls, relatives of schizophrenia patients were more prone to develop attention deficit hyperkinetic disorder (ADHD) [223] and schizotypal personality traits. Using a multivariate psychobiological prediction model comprised of neuroimaging, neurocognitive, and psychosis proneness measures, these variables together predicted 71% chance to develop psychopathology, in contrast to individuals not identified to develop psychopathology by the model who only had a 17% chance of developing psychopathology [221]. In this review, we provide additional data on a) neurocognitive findings and their familial dose effects and b) brain structural correlates of neurocognitive deficits in young relatives at risk for schizophrenia.

4.1. Neurocognitive Deficits and genetic dose effects

Neurocognitive scores (measured in parentheses) were collected from a neuropsychological battery including IQ (Wechsler Abbreviated Scale of Intelligence) [224]; working memory (Cogtest Spatial Working Memory Test; distance median after a 12 s delay) [225]; executive functioning (Wisconsin Card Sorting Test perseverative error scores) [226]; attention

(Continuous Performance Test, IP version visual *d prime)* [227]; and verbal fluency (Benton and Hamschler total correct from the category/letter fluency task) [157].

Table 2 denotes deficits seen in first- and second-degree relatives (HR) compared to HC controlling for age at baseline assessment of the PREP study. Significant deficits were noted in HR in IQ (p<0.000). Higher order cognitive domains like executive function and spatial-working memory [228] were not as prominently affected in HR as were simpler domains such as psychomotor speed, sustained attention, and verbal fluency. Deficits in both attention and spatial working memory were attenuated and those in verbal fluency lost significance after controlling for psychomotor speed, suggesting that higher order cognitive deficits may be mediated by deficits in hierarchically more basic cognitive processes such as speed of processing [229]. We assessed familial-loading effects by comparing groups of first-degree relatives (n=122), second-degree relatives (n=23) and healthy controls (n=109) using ANCOVA models. Familial-loading effects were seen at p<.05 for psychomotor speed [F= 5.89, p=.043], executive-function [F=4.56, p=.05] and at [F=3.91 p=.078] for verbal-fluency with first-degree relatives performing poorer than second-degree relatives on all domains except working memory. Figure 1 shows that first-degree relatives have the more prominent deficits, while second-degree relatives have impairment intermediate to that of first-degree relatives and healthy controls in all domains except working memory. No moderating effects of gender on the main effect of study group (HR versus HC) were noted.

Cognitive domain	Test	Sample size	Healthy controls, mean, S.D.	HR subjects, mean, S.D.	Controls vs. HR subjects, F, (p)	Effect size, partial eta square
Psychomotor speed	Go reaction time (Go-no-go test)	HC= 56 HR= 86	426.8, 0.82	488.9, 0.94	18.25, (0.000)	0.12
Sustained attention	CPT-IP visual d'	HC= 85 HR= 118	1.63, 0.82	1.17, 0.94	9.76, (0.002)	0.05
Verbal fluency	Letter and category	HC= 47 HR= 69	83.2, 20.7	69.1, 18.4	11.67, (0.001)	0.09
Spatial working memory	Delayed recognition task (12s delay)	HC= 58 HR= 66	55.8, 22.3	67.0, 30.1	3.46, (0.065)	0.03
Executive Function	Wisconsin Card Sort Test, perseverative errors	HC= 96 HR= 122	11.94, 5.4	12.0, 6.15	6.18, (0.433)	0.00

Table 2: Neurocognitive Findings in Young Relatives of Schizophrenia Patients in the Pittsburgh High-Risk Study. HR = First-degree relatives of patients, HC = Healthy controls, CPT-IP Continuous Performance Test, Identical Pairs version.
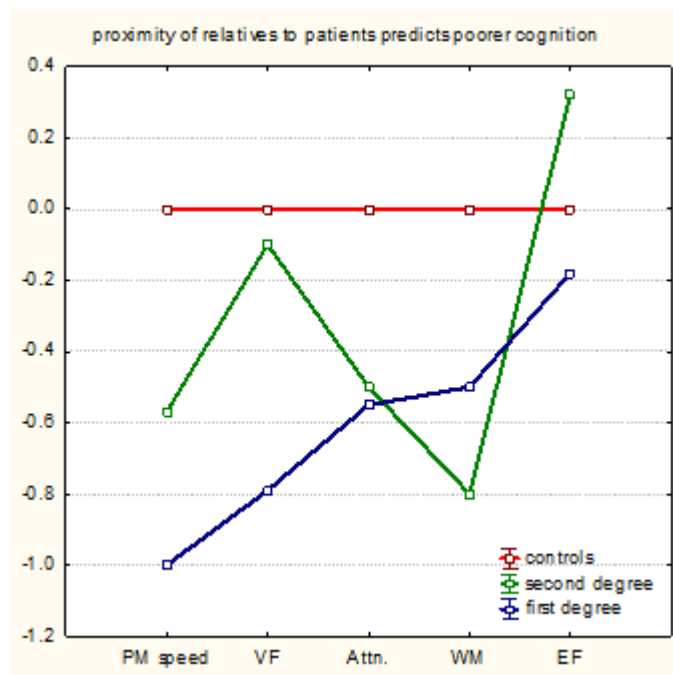
Figure 1: Proximity of relatives to patients predicts poorer cognition. Cognitive scores for each group were z-transformed to the control mean. Group-means of the z-scores are plotted on the y-axis. PM = psychomotor, VF = verbal fluency, EF = executive function, Attn = attention, WM = working memory.

As the exact relation of IQ deficits with domain specific deficits is unclear, we conducted parallel analyses controlling, as well as not controlling for IQ. Deficits in sustained attention [F=5.1, p=0.025], speed of processing [F=5.2, p=0.023] and verbal fluency [6.2, p=0.011] in relatives survived controlling for I.Q. All neurocognitive scores were significantly correlated with IQ (r ranging from 0.30 to 0.43). Studies in patients have shown most neurocognitive deficits, except for psychomotor speed and verbal memory, to be mediated by a latent "cognitive ability factor" [230, 231]. This agrees with findings of attention and verbal fluency deficits but not psychomotor speed deficits losing significance after controlling for IQ in the PREP study. A latent cognitive ability factor as underpinning all neurocognitive deficits is debatable as the latent factor was revealed using a correlation method in a cross-sectional design [50, 55, 231-235]. Longitudinal studies have shown cognitive deficits to precede generalized cognitive deficits like IQ [230]. Controlling for IQ when assessing cognitive deficits may be unnecessarily conservative, especially given the equivocal evidence about the role of IQ in cognitive deficits [231]. IQ deficit may be an inherent, natural property of subjects at genetic risk instead of a confound and hence controlling it may have the effect of throwing the baby out with the bathwater [236]. Also, correlations between a dependent variable and a putative confound argue against controlling for that confound as it may obscure real group differences of the dependent variables [236].

The spatial-working-memory deficits noted at the 12-second delay were absent for a 2-second delay. This supports previous evidence suggesting a task difficulty by group interaction when

comparing schizophrenia patients with healthy controls where memory deficits in patients are evident only at high difficulty levels. Disproportionately high BOLD response in the DLPFC during low difficulty level working memory tasks may interfere with the capacity of patients to increase DLPFC activity compared to baseline when presented with high difficulty tasks [237-239]. Longitudinal neurocognitive assessments are needed to explore further temporal decline in attention, verbal fluency, and psychomotor to detect a possible emergence of executive function and spatial working memory deficits.

4.2. Brain Structural Correlates of Neurocognitive Deficits

The Pittsburgh High-Risk Study also involved a structural brain-imaging component. Relatives were categorized into low cognitive scoring and high cognitive scoring groups based on verbal fluency, attention, psychomotor speed, and executive-function scores using K-means cluster analysis. This method is an iterative procedure, which clusters cases into two groups. The iterations seek to minimize within cluster variance and maximize variability between clusters in an ANOVA-like fashion. Brain regions involved in these cognitions and implicated in schizophrenia were compared across low and high scoring clusters of relatives.

As seen in Figure 2, the low scoring subset of relatives (n=59) had lower volumes in critical brain regions compared to the high scoring subset (n=35), with the exception of the middle frontal gyrus. Relatives of patients show cognitive deficits that co-occur with alterations of regions mediating these compromised cognitions. This association may tentatively suggest structural alterations to underpin cognitive deficits seen in relatives. Brain regional abnormalities with their "downstream" attendant cognitive deficits may together be considered as "extended endophenotypes", a parsimonious conceptualization of schizophrenia [134].
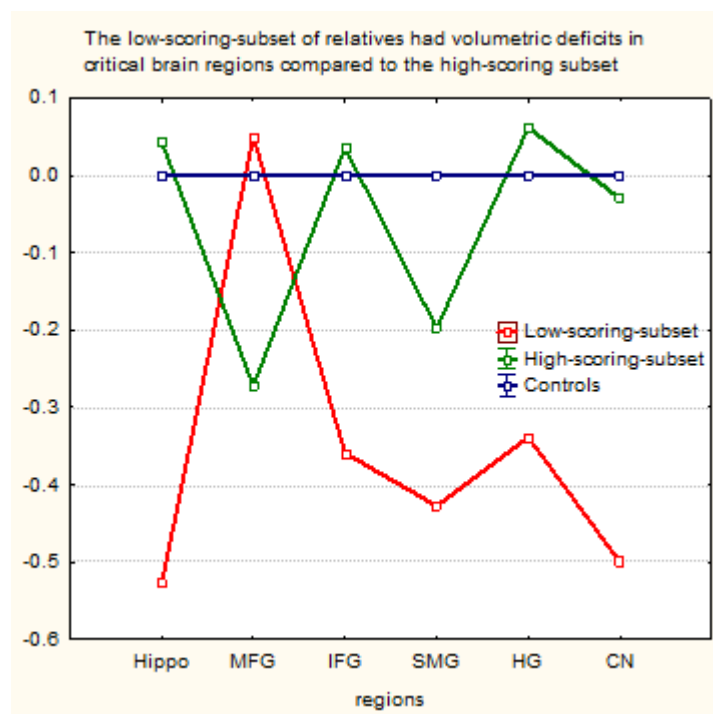
Figure 2: The low scoring subset of relatives had volumetric deficits in critical brain regions compared to the high scoring subset. Regional gray-matter-volumes (right and left combined) for each group were z-transformed to the control mean. Group-means of the z-scores are plotted on the y-axis in the low- scoring and the high-scoring groups (see text for description of approach to this classification). HG = Heschl's gyrus; SMG = Supramarginal gyrus; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; Hippo = Hippocampus; CN = caudate nucleus.

In summary, findings from the PREP study are consistent with previous reports of cognitive deficits in relatives of schizophrenia patients and suggest that these deficits may be related to neuroanatomical deficits of corresponding brain regions. The existence of distinct subgroups of low and high cognitive scoring subjects within the sample of relatives is a critical finding from the PREP study. The clustering of structural alterations within the low-scoring subgroup tentatively suggests a neuroanatomically and cognitively compromised 'hypervulnerable' subset within relatives with a familial diathesis for schizophrenia. The risk of schizophrenia and schizophrenia spectrum disorders in genetically liable relatives of patients is 11-15% and about 40% [181] respectively. This further suggests a heterogeneous risk-profile of the genetically vulnerable population for future psychotic illness and the occurrence of 'hypervulnerable' subgroups [181]. The latent genetic heterogeneity in schizophrenia explain the existence of these subgroups rather than a uniform vulnerability for schizophrenia within genetically predisposed populations [181, 240].

5. Conclusions

In summary, cognitive deficits are a core feature of the premorbid vulnerability to schizophrenia. Impairments are seen in several cognitive domains in unaffected relatives of patients including attention, working memory, verbal memory, visual memory, executive function, speed of information processing, social cognition, and general intelligence. In general, the abnormalities appear more severe in first-degree relatives, and are associated with more prominent brain structural alterations. These observations are of clinical as well as pathophysiological significance.

An important question of clinical relevance is whether premorbid cognitive deficits can predict the emergence of later schizophrenia in non-symptomatic at-risk subjects. As reviewed, the NYHRP and EHRS studies suggest that deficits in memory, attention, and social cognition in young relatives of schizophrenia patients may predict later psychosis. Attention deficits in young relatives of schizophrenia patients frequently have features of attention deficit disorder [220, 223]. This often leads to the clinical practice of treating such individuals with stimulant medications, which may have the undesirable effect of triggering psychosis in these vulnerable individuals. It is important to distinguish attentional impairments that are the precursors of a serious illness such as schizophrenia and treat them with the disease appropriate interventions. Thus, children and adolescents newly presenting with attentional impairments should not, as often happens, be automatically diagnosed as having attention deficit disorders, but should be assessed to rule out early features of schizophrenia (such as prodromal symptoms and schizotypy) or bipolar disorder (mood dysregulation). Inquiring for family histories of major psychiatric disorders is also important.

Investigating premorbid neurocognitive deficits is also of importance for early intervention.

Further research is needed to evaluate the efficacy of cognitive remediation approaches, shown to benefit early phases of schizophrenia [241], in at-risk individuals with cognitive deficits. Pharmacological interventions, including low dose atypical antipsychotics, have also been piloted in cognitively impaired relatives at risk for schizophrenia [242].

Cognitive deficits, being core impairments in the premorbid phase of schizophrenia, offer the best way to define the neurobiology of the vulnerability to this illness. As reviewed in this paper, cognitive deficits are robust, highly prevalent, stable, easily quantifiable, correlate with defined biological alterations in the illness, and are present in both those with the illness and those at risk. These features qualify cognitive impairments as endo- (or intermediate) phenotypes, which are beginning to pave the way to identification of the susceptibility gene(s) [243].

Disclosure/Conflict of Interest Statement

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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