THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
2022, VOL. 23, NO. 9, 677–688
https://doi.org/10.1080/15622975.2021.2023758

ORIGINAL INVESTIGATION

Neurocognitive profile of adolescents with early-onset schizophrenia and their unaffected siblings

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ABSTRACT

Background: We investigated the neurocognitive profiles of Early-Onset Schizophrenia (EOS; onset before age 18) and paired unaffected siblings and the little-studied effect of age-of-onset and duration of illness on cognitive performance.

Methods: 31 EOS probands, and 31 of their siblings, had four cognitive domains assessed: (a) Memory: California Verbal Learning Test, and the Wechsler Memory Scale-Revised; (b) Working memory: Digit Span; (c) Attention: Degraded-Stimulus Continuous Performance Test, Span of Apprehension (SPAN), and Trail Making Test (TMT) part A; (d) Executive function: Wisconsin card sorting task, and TMT part B. Diagnosis was confirmed using the structured clinical interview for DSM-IV.

Results: While EOS showed a generalised neurocognitive deficit (0.25–0.50 effect size) compared with siblings, across all cognitive domains, significantly greater patient deficits were observed with, working memory, attention, and executive function and minimal differences for digit span forward, block design and false alarms on the SPAN-12 confirmed by repeated measures MANOVA. Patients with earlier onset (12–15) showed greater deficits on false alarm and digits backward scores. Siblings showed individual cognitive task profiles similar to patients, confirming familial effects. EOS showed much more variable scores than siblings with more individual tasks showing 2 SD deficits than siblings. Long duration patients had greater z-score variability across tasks.

Conclusions: Duration of illness was a more important characteristic in patients with onset 16 and over than in younger onset patients with comparable durations. Both the similarity of sibling pair profiles and greater patient variability across task provide further support for neurobiological heterogeneity in schizophrenia.

ARTICLE HISTORY
Received 11 March 2021
Revised 20 December 2021
Accepted 23 December 2021

KEYWORDS
Adolescent; attention; cognition; early onset; executive function; memory; schizophrenia

Introduction

Early onset schizophrenia

Early onset schizophrenia (EOS) is an insidious, severe, and chronic form, although many features are neurobiologically and clinically continuous with the adult-onset counterpart (see review, Vyas et al. 2011). About 75% of patients with schizophrenia have onset over 21 years of age and approximately 25% have onset ages 14–20 (Shimizu et al. 1988; Vyas et al. 2010; Driver et al. 2013). Studying EOS and unaffected siblings provides a unique opportunity in understanding cognitive functioning in schizophrenia since this enriched group is treated for long intervals with psychoactive drugs, typically share life-time environments with their siblings, and have not been exposed to homelessness and associated injury and illness as have older patients (Vyas and Gogtay 2012). Since they are still living at home, multiple sources of illness onset information are also available.

Cognitive trajectory

The ongoing development of the brain during adolescence, especially prefrontal regions, suggests different cognitive deficit trajectory with each later year of

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Supplemental data for this article can be accessed at https://doi.org/10.1080/15622975.2021.2023758.

onset, age 12–18, as the prefrontal and other brain regions mature (Gogtay et al. 2011). Greater cognitive impairment, as assessed by the cognitive component of the PANSS, was associated with age-of-onset under age 17 in a sample of 104 patients including childhood and adult-onset schizophrenia (Kao and Liu 2010). In a valuable meta-analysis comparing adolescent onset (age 13) and first-episode (age 23) patients (Rajji et al. 2009), the tasks with the greater deficit in adolescent than first-onset cases included the Wisconsin Card Sorting Test (WCST) (deficit against healthy effect sizes 2.00 vs 0.77), Trail Making Test (TMT) A and B, and full-scale IQ (deficit effect sizes 1.77 vs 0.89) while the Continuous Performance Test (CPT), visuospatial construction, and memory tests showed approximately equal deficits in both groups (generally 0.8 effect sizes). Younger adolescent male patients (ages 13–16) showed significantly greater overall neuropsychological test performance than older patients (17–21) (diagnosis by age by sex interaction) (Brickman et al. 2004). These results could be taken as showing frontal lobe deficits appear stronger with earlier onset as suggested by the WCST result or that broad general deficits appear stronger with earlier onset as suggested by the full-scale IQ result. However, this meta-analysis combined some neuropsychological tasks and task scores, and combined scores from studies with a variety of population ages and indicates the need for a more exact age group contrast. It is also limited by grouping together all patients with onset in ages 12–23 rather than examining periods of brain development within the adolescent period. The neurodevelopmental model (Rapoport et al. 2012) may thus be subject to heterogeneity in anatomical focus.

A study on first-episode adolescent patients (age = 15.3, sd = 1.7) and matched healthy controls, reported the largest difference in the TMT-B with Buschke Selective Reminding and CANTAB rapid visual information processing scores was next ranked (Fagerlund et al. 2006). Minimal group differences were seen for the CANTAB Intra-Extra dimensional set shifting task, and Stockings of Cambridge score. Thus, a clear differential frontal versus global versus temporal lobe was not fully apparent.

Recent studies have emphasised heterogeneity in clinical trajectory from premorbid risk factors to schizophrenia caseness (Dickinson et al. 2004), but data on how specific cognitive deficits appear chronologically during the period of rapid frontal lobe development is understudied. One study found that academic skills in school were not associated with adult onset of schizophrenia and only sports and handcraft performance indicative of a motor deficit predicted schizophrenia (Cannon et al. 1999) and this was consistent with the early onset association with motor control found in adults (Manschreck et al. 2004). Adolescent onset may presage a deteriorating course with similarity with adult-onset illness (Remschmidt 2002). Age-of-onset was unrelated to general cognitive performance but statistical tests of differences in performance across cognitive domains were not considered possible in a meta-analysis (Schaefer et al. 2013). Neither age-of-onset or duration of illness was significantly associated with neuropsychological domain scores in a sample of adolescent patients (Rhinewine et al. 2005).

None of the authors we located report age vs. neuropsychological task score correlations within the key 13–18 age range despite the importance of frontal lobe development during this period.

Generalised vs specific cognitive deficits in schizophrenia

While some authors have argued that the cognitive deficits in schizophrenia are general rather than specific (Dickinson et al. 2004) others specifically testing the patient vs. healthy group by task interaction found greater executive function and memory deficits than language deficits (Bilder et al. 2000; Rhinewine et al. 2005). Separate frontal executive and left temporal patient groups were discriminated in an adult sample (Kremen et al. 2004). Specific deficits would tend to be obscured in meta-analysis of studies which used different neuropsychological tasks to represent different cognitive dimensions.

The siblings of adolescent patients (mean age 19.3, sd = 7) were compared to community volunteers and a deficit on TMT B ($Z = -0.45$) was found but TMT A, digit span, and vocabulary did not differ (Gochman et al. 2004). Adolescent patients with schizophrenia (mean age = 19.2, sd = 1.7) and their siblings (mean age = 17.5, sd = 2.18) were compared (Groom et al. 2008) but IQ was not different (our *t*-test 89.3 vs 94.2, $t = 1.44$, $p = 0.15$) and other tests such as the Continuous Performance test similarly were not significantly different (our *t*-test on data of Groom et al. 2008, 1.36 vs 1.51, $t = 0.73$, $df = 64$. $p = 0.47$).

Cognitive impairments are strong candidates for the endophenotypes of schizophrenia (Gottesman and Gould 2003). The evidence that indicates that the cognitive impairments in schizophrenia are specific or shaped by age-of-onset is less clear. The analysis of

Table 1. Sample demographics of EOS probands and their unaffected siblings.

	EOS probands ($n = 31$)	Unaffected siblings ($n = 31$)
Age	17.34 ± 1.3	19.25 ± 3.97
Gender (M/F)	14/17	20/11
Global Assessment of Functioning GAF	56.13 ± 13.39	81.6 ± 6.9
No. of hospital admissions	1.1 ± 0.95	N/A
Illness duration (months)	23.5 ± 18.5	N/A
Verbal IQ	95.34 ± 19.51	99.87 ± 21.63
Performance IQ	97.07 ± 22.46	96.73 ± 22.05
Full scale IQ	95.56 ± 18.75	99 ± 22.66

both patients with early onset and their relatives can assist in the evaluation of the confounding effects of illness duration and underlines the need to explore whether cognitive impairments found in patients with EOS and also observed in non-psychotic siblings.

This study is the first to statistically compare neuropsychological performance profiles in early (12–15) and late (16–19) adolescence in groups with long and short duration of illness. We hypothesised that: (a) patients with EOS will perform significantly poorly on all cognitive domains compared with healthy controls but that tasks will still be differentially affected by the illness; (b) siblings of EOS patients will show an attenuated but correlated pattern of task change similar to their ill siblings; (c) age-of-onset will alter the cognitive profile more than illness duration. For this hypothesis we posit three possibilities: early onset will be generally devastating on both executive function (frontal) and memory (temporal deficits) and early onset will affect temporal lobe memory functions vs. late onset and frontal deficits in parallel with brain development trajectories; (d) patients will show heterogeneous deficits consistent with the concept of schizophrenia as a heterogeneous disease.

Methods

Participants

Thirty-one patients (14 boys and 17 girls) with EOS, diagnosed by a Consultant Child Psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al. 2002a) were recruited through clinicians' referrals in adolescent psychiatry services in London (Table 1). Thirty-one biological siblings of the patients with no Axis I diagnosis, confirmed by the non-patient SCID interview (First et al. 2002b), also participated in the Vulnerability to Psychosis Studies. The study was approved by the Joint South London and Maudsley and Institute of Psychiatry NHS Research Ethics Committee. The sample in this study overlapped with our previous studies (Kumar et al. 2010; Vyas et al. 2012; Vyas and Puri 2012; Vyas et al. 2014).

Cognitive assessment

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981) or child equivalent, Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) (Wechsler 1991) was used to measure intelligence quotient. To enable comparability across all age groups in the child and adult scale in this study, the WISC-III scores were converted into WAIS-R equivalents based on Tables 5.12 and 5.13 of the WISC-III manual recommendations (Wechsler 1991, p. 92–93). Verbal memory was measured using the California Verbal Learning Test (Delis et al. 1987). The Wechsler Memory Scale-Revised (WMS-R; Wechsler 1987) was used to assess forward and backward digit span, verbal memory, visual memory, general memory, attention, and delayed recall indices. The degraded-stimulus CPT (Nuechterlein et al. 1983) measured vigilance and sustained attention. Selective attention and processing speed was measured using the Span of Apprehension test (SPAN) (Asarnow et al. 1991) and the TMT-A (Reitan 1958), respectively. The WCST (Heaton et al. 1993) and TMT-B measured executive function.

Statistical analysis

Statistical analyses were implemented using SPSS (Statistical Package for the Social Sciences) version 26, Statistica (StatSoft 2003), and R language programs (Smyth 2020). We have conducted our analysis in two steps. First, we converted the raw scores of the measured cognitive performance into standardised scores with a mean and standard deviation of the patients and siblings. Such a standardisation offers a quick assessment of patients' and their siblings' cognitive performance relative to each other and allows clearer interpretation of repeated measures analysis of task profile differences between groups. In addition, such a procedure allows us to compare directly the results with prior research applying identical strategy. The only exceptions to the standardisation procedure for IQ (with well-known population parameters: $\mu = 100$ and $\sigma = 15$). All variable Z scores for which a high

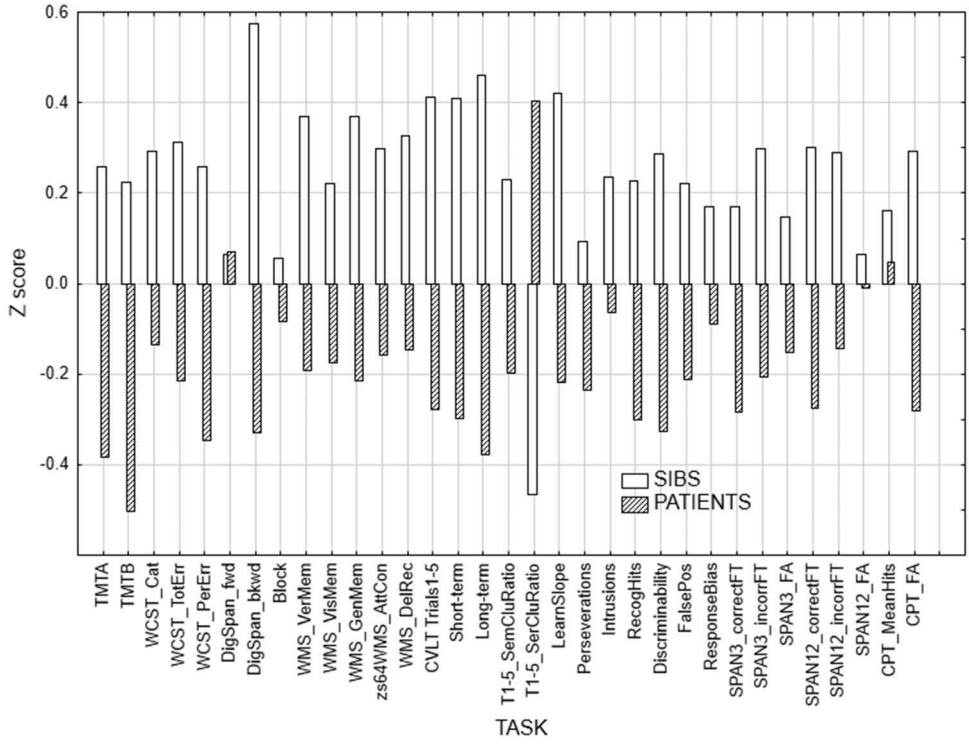

Figure 1. Task Z scores for patients with schizophrenia and their paired sibling. Task by patient group ANOVA interaction ($F = 1.82$, $df = 32{,}864$, $p = 0.0039$).

score indicated poor performance were multiplied by −1 to that all high scores indicate better performance.

Second, to identify the cognitive performance differences between the patients. We used the GLM ANOVA and MANOVA method in Statistica because of the non-independence of the data, namely the nested structure of the data (patients and their paired siblings). Significant omnibus effect was followed up by post-hoc tests identifying differences between the pair of groups (we reported means and standard deviations). This was extended by including age-of-onset and duration of illness as additional group effects.

Third, to examine the profile of cognitive dysfunction with paired 31 patients and 31 siblings, we standardised the data within the 31 patients for a patient-only analysis and within the group of 31 patients and their 31 siblings (62 persons) for comparison of patients with siblings.

Age-of-onset (patient history) and duration of illness to time of testing was coded, for onset (12–15 years and 16+) and for duration (1 year vs. 2 years+). This yielded 13 young and 9 old for short duration and 4 young and 5 old for long duration. The sample of groups was unbiased in category (Fisher exact $p = 0.69$). Repeated measures ANOVA and MANOVA was performed across all 33 task scores and for groupings of scores within tasks (e. g. TMT-A&B as repeated measures). Since the main group ANOVA were almost uniformly significant, we also report individual task t-tests treating patients and siblings as independent groups and treating them as siblings for paired t were done. Because the patients were paired with their siblings and thus shared common environment and were close in age, we conducted analysis using the patient and sibling pairs as repeated measures. However, to account for concerns about violating the assumptions of independence we also tested the patient-sibling differences treating them as independent groups.

Results

Adolescent patients and matched sibling comparison

Patients had significantly lower *Z* scores across all 33 tasks (−0.19) than their siblings (0.24) and this was confirmed in the GLM (main effect of sibling/patient, $F = 19.8$, $df = 1,\ 27$, $p = 0.00013$, repeated measures ANOVA with sibling/patient and task as repeated measures and age-of-onset (12–15 vs 16+) as independent groups. TMT-B, WCST perseverations, digit

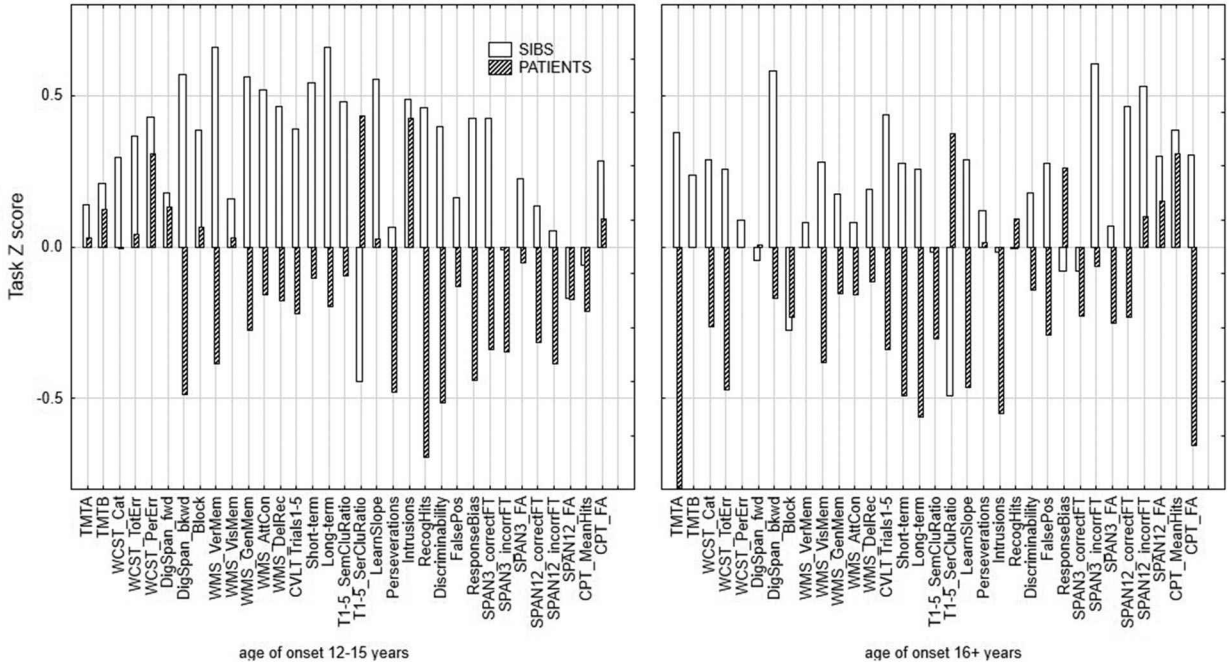

Figure 2. Task performance in early onset (12–15 years) and later onset (16+ years of age) schizophrenia.

span backwards, CVLT long and short-term memory, CVLT serial learning, and CPT false alarms had the larger effects (Figure 1 and Supplementary Table 1) while digit span forward and block design had small differences (sibling/patient by task interaction, $F = 1.82$, $df = 32, 864$, $p = 0.0039$, Huynh-Feldt corrected $df = 19.02, 513.4$, $p = 0.018$, effect size partial eta-squared (η_p^2) 0.063). IQ for Verbal, Performance and Full did not differ significantly between patients (95.3, sd = 20, 97.1, sd = 22.4, 95.6 sd = 18.8) and siblings (99.8 sd = 21.6, 96.7 sd = 22.0, 98.9, sd = 22.7) with t (−0.84, 0.06 and −0.63) respectively.

Age-of-onset and duration of illness

Older age onset patients showed greater deficits in comparison to siblings on WCST total error, SPAN False Alarms and on TMT-A. Younger age-of-onset patients showed greatest deficits on digit span backwards, CVLT recognition hits, and SPAN scores. This was confirmed by a sibling/patient by task by age-of-onset interaction ($F = 1.60$, $df = 32, 864$, $p = 0.019$, Huynh-Feldt corrected $df = 19.02, 513.4$, $p = 0.049$, $\eta_p^2 = 0.056$) is shown in Figure 2 in plots for siblings and patients and Supplementary Figure 1 for plots by age-of-onset.

Duration of illness was a more important characteristic in patients with onset 16 and over than in younger onset patients with comparable durations. In the analysis of patients alone, the task by age-of-onset interaction also significant ($F = 1.95$, $df = 32, 864$, $p = 0.0013$, Huynh-Feldt corrected $df = 10.1, 274$, $p = 0.039$, $\eta_p^2 = 0.067$) and the age-of-onset by duration by task interaction was significant (Figure 3) ($F = 1.80$, $df = 32, 864$, $p = 0.0045$. Huynh-Feldt corrected $df = 18.5, 499.4$, $p = 0.021$, effect size = 0.063). The task by duration and main effect of duration were not significant.

Executive function vs. memory

On the WCST, the older age-of-onset patients showed greater deficits (Figure 4) while on the memory tasks, the older patients showed slightly higher performance than younger patients (three-way sibling/patient by age-of-onset by WCST/Memory interaction, $F = 4.57$, $df = 1, 27$, $p = 0.042$, from four-way ANOVA sibling/patient, WCST (Categories, Total errors, perseverations) and WMS (Verbal, Visual, General Memory)). This indicated executive performance (across all three WCST scores) was more disturbed in patients with onset after age 16 than early onset patients while memory was more disturbed in patients with onset 12–15 years across all three memory scores.

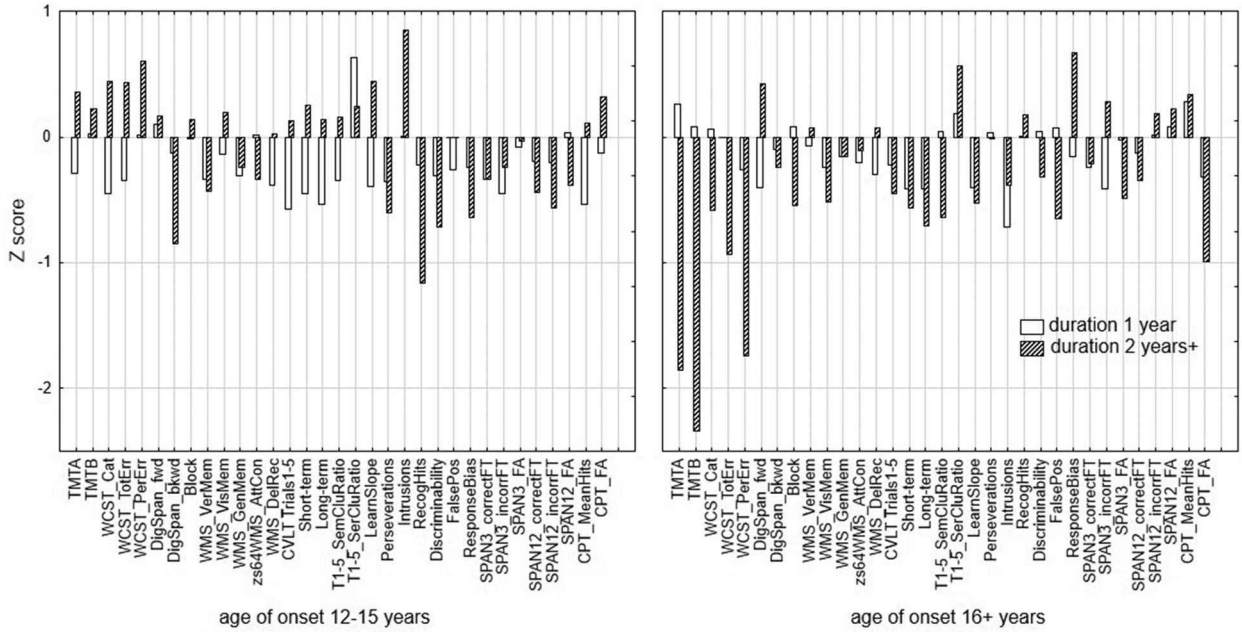

Figure 3. Age-of-onset and duration in patient group t.

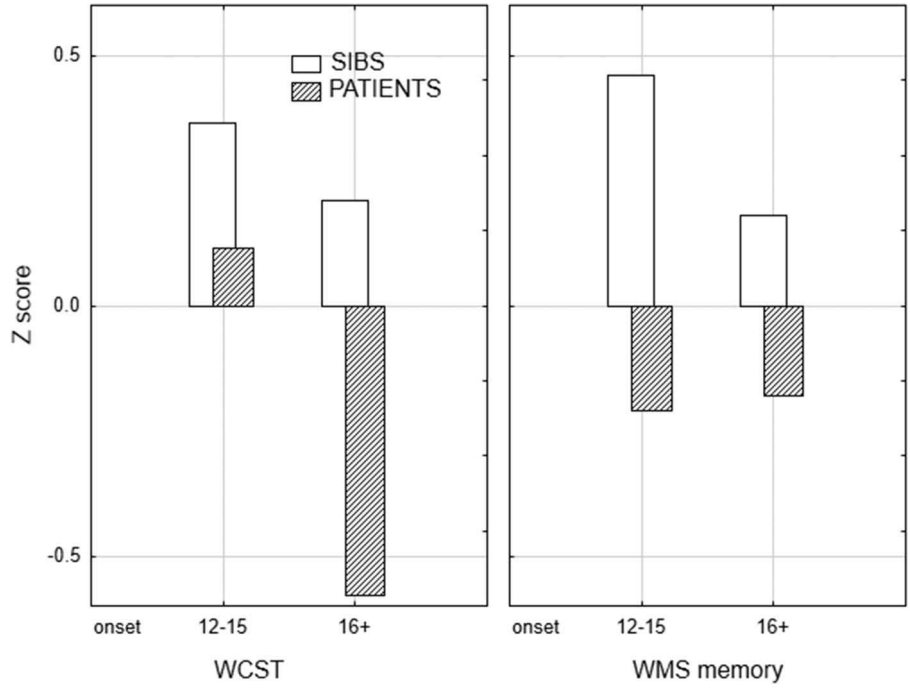

Figure 4. Executive function vs. memory and age-of-onset. Wisconsin card sort test compared with WMS-R memory indices.

Independent group comparisons

The independent group four-way ANOVA analysis (sibling/patient, task, early/late onset, short/long duration) was similar to the repeated measures analysis (patient and sibling as repeated measures) with a significant sibling/patient main effect ($F = 10.4$, $df = 1, 54$, $p = 0.0021$, effect size 0.16), sibling/patient by task interaction ($F = 1.52$, $df = 32, 1728$, $p = 0.031$, $\eta_p^2 = 0.027$). The effect size was smaller than the 0.063 observed with treating patient/sibling dimension as a repeated measure, indicating the importance of familial effect. However, the higher-order interactions (sibling/patient by age-of-onset by task and sibling/patient by age-of-onset by duration by task) were not confirmed by ANOVA although the sibling/patient by duration by task interaction was found with MANOVA ($F = 2.12$, $df = 32, 23$, $p = 0.032$, Wilks lambda = 0.25). Instead, the interactions without subject group were significant (age-of-onset by task, $F = 1.69$, $df = 32, 1728$, $p = 0.0093$, $F = 2.54$) and age-of-onset by duration by task ($F = 1.57$, $df = 32, 1728$, $p = 0.023$, $\eta_p^2 = 0.028$).

Sibling vs. patient task score correlation

The correlations for each neuropsychological task in siblings and patients showed familial association (Supplementary Table 2). Of the 33 correlations, 16 were $p < 0.05$, 1-tailed and all but three were positive. We calculated the correlation between each patient and their paired siblings for all 33 tasks. For the 31 patients, 21 had positive profile correlations, and the mean correlation was $r = 0.125$, se = 0.043, (different from zero, $t = 2.92$, $p = 0.0025$). When the patients were randomly paired with another sibling, a permutation analysis (1000 iterations) yielded a mean pair correlation of $r = -0.016$, standard error 0.04, and showed the real data value of $r = 0.125$ to be at the $p = 0.0050$ level (995 correlations lower) and $t = 0.0052$ for 2.92 t-test value of different from zero for actual data. This large difference is consistent with a large family effect on the exact shape of the profile.

The actual data patient-sibling profile correlation for each subject was positively correlated with higher Z scores in patients for 31 of 33 tasks and significant $p < 0.05$ for WMS-R General Memory ($r = 0.37$), CVLT Trials 1–5 ($r = 0.45$), CVLT Discriminability, and CVLT false positives. Cognitive profiles in patients that were more similar to the paired sibling is thus associated with superior performance on nearly every task. However, the highest patient vs. sibling correlations for the patient-sibling correlation coefficient were IQ scores (0.50 ($p = 0.004$), 0.44 ($p = 0.012$), 0.62 ($p < 0.0001$) for verbal, performance, and full-scale IQ respectively).

Sibling vs. patient effects of age-of-onset on IQ

Age-of-onset in patients was correlated with verbal, performance and full-scale IQ $r = -0.12$, $r = -0.17$, and $r = -0.15$ respectively all n.s. while age-of-onset in patients was correlated with IQ in siblings $r = -0.37$ ($p = 0.038$), $r = -0.34$ ($p = 0.058$) and $r = -0.37$ ($p = 0.038$). This suggested that early onset in patients was associated with better IQ outcome in siblings. These correlation differences were not statistically significant. Patient age-of-onset was not correlated with sibling age at testing ($r = 0.25$, ns).

Task alone

Because of the importance of the question of whether patients with schizophrenia have a generalised cognitive deficit or specific areas of cognitive loss, we examined the task effect in the group of patients and siblings, patients alone, and siblings alone. The task effect size was 0.0072 for siblings and patients together, 0.036 for siblings only and 0.027 for patients alone. Thus, with heterogeneous clinical groups, only generalised effects are seen and are marked (main effect of sibling vs patients across 33 tasks, $F = 19.80$, $df = 1, 27$, $p = 0.00013$, $\eta_p^2 = 0.42$). However, when developmental features such as age-of-onset are considered, significant profile differences among task deficits between groups are observed. Analysis of siblings alone revealed no significant interactions with age or duration.

Age

Older age in patients was associated with poorer performance on TMT-B ($r = -0.46$, $p = 0.009$), WCST Percent Error ($r = -0.36$, $p = 0.043$) but no other task (16 of 32 correlations). Older age in siblings was associated with fewer recognition hits on the CVLT ($r = -0.36$, $p = 0.048$), worse response bias ($r = -0.42$, $p = 0.018$), SPAN-3 correct ($r = -0.42$, $p = 0.018$). The difference in age (range 3 to −4 years), sibling minus patient in the sibling group correlated only with digit span ($r = -0.37$, $p = 0.043$) and 16 of 32 correlations were negative. Thus, age was not a strong associate of performance in this somewhat restricted age range. Similarly, illness duration was not a significant correlate of either patient or sib neuropsychological

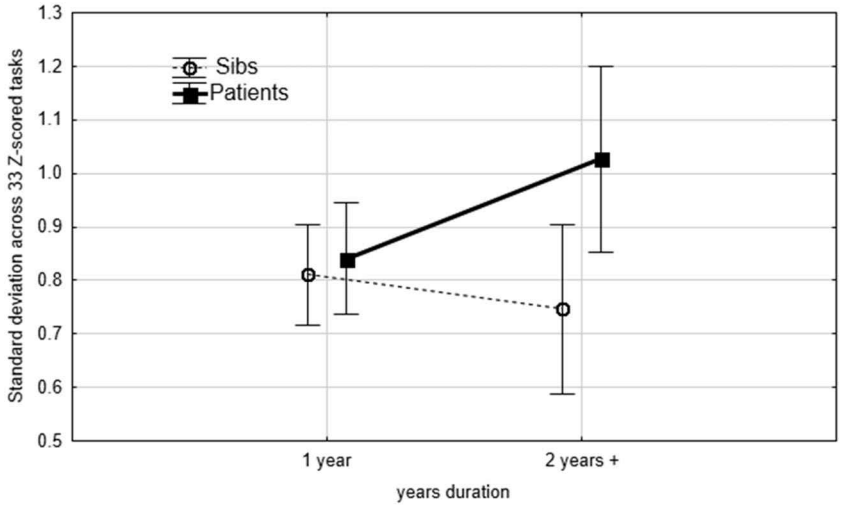

Figure 5. Variability across profile of 33 tasks in short vs long duration of illness.

performance (except for the single unexpected positive correlation for CVLT intrusions, $r = 0.39$, $p = 0.028$).

Task profile and variability

We calculated the standard deviation across the *Z* scores of the 33 tasks for each patient and sibling. Patients had a greater variation in Z score across the 33 tasks (SD = 0.93) than siblings (SD = 0.77) ($F = 6.95$, $df = 1, 27$, $p = 0.014$, effect size = 0.20) This was more marked in the long duration patients (Figure 5) ($F = 4.56$, $df = 1, 27$, $p = 0.042$, effect size 0.14). Patients showed a significant correlation between standard deviation of their Z-scores across the 33 tasks and age ($r = 0.36$, $p = 0.041$), Full scale IQ ($r = -0.48$, $p = 0.01$), performance IQ ($r = -0.54$, $p = 0.01$) but this was not found in siblings ($r = -0.090$, $p = 0.11$). Correlations with GAF, age-of-onset, and duration were not significant.

Patients were more likely to show more z-scores below −2.00 than siblings (see Supplementary Figure 2).

Sibling-patient age difference and task performance

We hypothesised that siblings who were older than patients were more likely to have passed through the age of risk for schizophrenia and therefore had less deficit on tasks. This was confirmed in the −2SD task result, with a correlation of −0.48 ($p = 0.0078$) between sibling minus patient age scores and the number of −2 *Z* tasks in the siblings. However, correlations with IQ scores were not significant and the correlations with task were also non-significant (17 of 33 negative).

Discussion

Differential task deficits, age-of-onset, and temporal lobe dysfunction

Adolescent patients with schizophrenia did not have a completely uniform cognitive deficit across tests of executive function, memory and attention, and these deficits varied with age-of-onset (see Figure 3 and Supplementary Figure 1). These results are consistent with the hypothesis that it is the peri-onset period that may be most important disturbing regional brain development. Executive function deficits were associated with later onset of the illness while memory deficits were more pronounced in early onset patients. This suggests that temporal lobe areas which may develop earlier than frontal cortex are more impaired if the illness develops in ages 12–15 while frontal lobe area which develops later are more impaired if the illness develops in the 16–19 year period. A similar age pattern in adults was found with patients having left temporal neuropsychological deficits being younger than patients with frontal executive deficits (Kremen et al. 2004). Young age-of-onset has been associated with poorer social/occupational function (Vyas et al. 2007; Immonen et al. 2017). We have found temporal lobe volume deficits more associated with poor outcome than frontal lobe deficits, again consistent with an earlier onset, temporal lobe dysfunction pattern (Mitelman et al. 2003). Late adolescence rather than early adolescence frontal lobe disruption was also

found within a group of adolescent onset patients with schizophrenia; frontal white matter anisotropy was higher (more normal) (Kyriakopoulos et al. 2009) in younger than in older patients (patient group mean age = 16.7, SD = 1.3, mean age of onset 14.8, SD = 2.4). An analysis of ventricular volumes comparing patients with onset age 7–14 with later onset failed to show significant differences (Lim et al. 1996), but specific cortical areas were not assessed.

Patient-sibling similarity

The profile across the 33 tasks was correlated between each patient and paired sibling, yielding a significant measure of profile similarity. Sixteen of the 33 tasks showed significant patient-sibling correlations, a greater proportion than observed in a similar adolescent cohort (Bigdeli et al. 2020). Greater similarity in profile between patient and siblings was associated with superior cognitive performance by the patient, consistent with the punctate marked deficits in individual test scores < -2 Z cognitive profiles seen in many of the patients. It is of interest that of the 33 tasks, no task had more than three patients who were -2 Z scores (see Supplementary Figure 2): each patient had cognitive deficits nearly unique to themselves. This is consistent with cognitive heterogeneity in patients and this measure increased with age. A similar cross-task variability measure also showed increase with age from age 13–21 similar with our data although the age effect was more marked for tasks involving speed of response than accuracy (Roalf et al. 2014).

In our data, 22 of the 33 tasks had higher SD in the patient than sibling group.

We searched for mean and standard deviation scores on a neurocognitive battery in genetic isolate populations to learn whether there was a smaller variation in task performance in patients. Torniainen et al. (2013) compare a genetic isolate sample of patients with schizophrenia with patients from the rest of Finland, and they observe (their Table 3) that smaller SD are seen in the isolate for Block Design, digit span forward, digit span backward, and immediate, short and long delay on the CVLT although TMT A and B have larger SD in the isolate; no variance differences reach statistical significance.

Although within groups IQ was correlated with task performance on many tasks, group differences in full scale IQ between patients and siblings were not confirmed. This may be methodologically advantageous for comparing differences in group profiles since profile differences could not be attributed to IQ differences. The standard deviations for full-scale IQ within groups was larger than the normative 15 points consistent with the larger than expected variation from task to task in patients.

Well siblings of patients have a general cognitive advantage over their ill siblings. No significant interaction appeared when well siblings alone were compared on the age-of-onset and illness duration of their ill siblings. This may suggest that the significant correlations between scores for well and ill siblings for each task may reflect genetic and environmental factors unrelated to the variations in schizophrenia symptom trajectory. However, it should be noted that the correlations, although significant, and nearly uniformly positive (Supplementary Table 2) explained only a small share of the variance. This table also reports strong evidence for heterogeneity: when the sibling pairs were randomised in a simulation, the patient-sibling profile correlations were lost. If only one schizophrenia taxon was present, and siblings were a less severe group than patients, then the schizophrenia neuropsychological profile would be present in all pairs and relatively little reduction in patient-sibling pairs have resulted from randomisation. In addition, we found the surprising effect that early age-of-onset in patients was positively correlated with IQ scores in siblings. Could siblings first exposed to an ill sibling at an early age be less affected than siblings exposed at a more insightful age? Could early onset in a sibling be associated with higher neuropsychological test scores in an older sibling since they had already passed through the age of risk for that family and therefore more likely to have avoided having a deficit?

Task profiles

Figures 1–5 and the associated ANOVA task interaction terms confirm that the neurocognitive profiles of patients and siblings show different task deficits. Patients and siblings differed greatly on TMT-B, digits backward, CVLT serial ordering and were little different on digits forward and block design. Figure 2 demonstrates task differences and is consistent with a familial effect of age-of-onset on the task performance profile. However, the effects shown with sibling-patient similarity correlations across the 33 tasks indicated that each sibling-patient pair had a different profile. This is consistent with a large familial effect. It is also consistent with heterogeneity in schizophrenia. If schizophrenia had a uniform cognitive profile effect (even if attenuated in siblings) then the random pairing of

siblings and patients should not have removed the pair correlation. While the paired data correlation might be contributed to by a degree of age matching, we found only restricted effects of age as a main effect, minimising the age contribution to the patient-sibling correlation coefficients. It is also of interest that the more similar the patient and sibling cognitive profiles were, the better their IQ and general cognitive abilities.

Age

Age did not appear to be a strong determinant of neuropsychological performance in these groups. One might have expected that if siblings were younger than patients that this gave the sibling a greater chance of not having passed through the age of risk and therefore more likely to be a case in the future and have greater neuropsychological deficit but this hypothesis was not supported in this small sample One possible explanation for the minimal age correlations is that the disease onset is recognised by a threshold of cognitive severity, thus confounding the association between age-of-onset, age, and neuropsychological deficit. Onset may also be associated with fixed societal changes in cognitive challenge at particular age thresholds. This might lump together the illness onset of individuals in different points of their age trajectory, minimising linear age correlations.

This suggests support of the peri-onset cognitive decline concept as these frontal executive scores decline in the period of rapid frontal development but a duration effect on temporal memory scores was not seen in the early onset group. The minimal effects of age and duration are consistent with the concept of neuropsychological deficits as endophenotypes of schizophrenia (Gottesman and Gould 2003) and our observed variability across tasks consistent with the concept that there may be many endophenotypes.

Comparison with other samples

Our sample was similar to Groom (Groom et al. 2008) in finding no IQ difference between patients and siblings and in finding the mean IQ in both groups below 100. While the tasks used were different, the sibling scores generally fell half-way between the patient and healthy values and three group differences were confirmed with ANOVA; pairwise sibling vs patient data were not presented. Our sample was only somewhat similar to that of Ueland and colleagues (Ueland et al. 2004) in finding large deficits in adolescents in executive function, but we found Span 12 hits score deficits (see Figure 1) while their sample had scores identical to healthy subjects.

Limitations

This study has several limitations which should be considered when interpreting the findings. Our sample size is not large, but the availability of a sample of paired siblings is not extensive. We have reported effect sizes and where available power estimates. A larger sample would have allowed a greater exploration of the age-of-onset vs duration of illness interaction. Our univariate correlations were in the 0.35–0.45 range, power 72% for our sample size (Cohen, 1988). A healthy volunteer group could also have contributed to generalise the study findings, but recruiting an age, parental education level, and socioeconomic level matched sample poses additional problems. The non-patient siblings had the advantages of matching on many variables and answering questions not already more studied about schizophrenia versus healthy comparisons.

Clinical significance

The study findings reporting cognitive deficits across a wide range of cognitive dimensions may provide useful clues into the treatment of cognitive deficits in adolescent onset psychosis. Previous studies have reported the efficacy of cognitive remediation therapy interventions in adolescents with EOS (Ueland and Rund 2005; Puig et al. 2014) and individuals at ultra-high risk psychosis (Glenthøj et al. 2017). A systematic evaluation of cognitive impairments in EOS may enable a more optimised treatment strategy to alleviate cognitive dysfunction in this enriched population, which will lead to improvements in functional outcome.

Summary

These results are consistent with earlier reports of cognitive deficits in the relatives of patients with schizophrenia. They support a general cognitive deficit but also support marked individual differences in task deficits with punctate single task deficits on different tasks characterising the patient but not sibling group. Familial effects on the shape of the task profile were observed, and less severe patients had profile shapes more resembling their well sibling. Our new findings on age-of-onset also shaped the profile with early

onset being more associated with memory deficits and later onset being associated with executive deficits.

Acknowledgments

We are grateful to the participants who took part in the VIPS study. Nora S. Vyas, Ph.D. is supported by the Winston Churchill Memorial Trust Fellowship. Bradley R. Buchsbaum, Ph.D. provided programming consultation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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