Schizophrenia Research 240 (2022) 186–192

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Altered working memory-related brain activity in children at familial high risk for psychosis: A preliminary study

Kevin C.A. van Gool [a,*], Guusje Collin [a,b,*], Clemens C.C. Bauer [b,c], Elena Molokotos [d], Raquelle I. Mesholam-Gately [e], Heidi W. Thermenos [e], Larry J. Seidman [e], John D.E. Gabrieli [b], Susan Whitfield-Gabrieli [b,c], Matcheri S. Keshavan [e,f]

[a] Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht, the Netherlands
[b] Department of Brain and Cognitive Sciences, McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA, USA
[c] Department of Psychology, Northeastern University, Boston, MA, USA
[d] Department of Psychology, Suffolk University, Boston, MA, USA
[e] Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[f] Department of Mental Health, Massachusetts Mental Health Center, Boston, MA, USA

ARTICLE INFO

Keywords:
Schizophrenia
Psychosis
Familial high-risk
Working memory
N-back
fMRI

ABSTRACT

Background: Schizophrenia spectrum disorders are heritable illnesses that usually manifest in early adulthood but are increasingly viewed as neurodevelopmental disorders. Functional magnetic resonance imaging (fMRI) studies show altered brain activity during performance of working memory (WM) tasks in both individuals with schizophrenia and their first-degree relatives as compared to healthy controls (HC). This study examined whether similar changes are already present in pre-adolescent children at familial high-risk (FHR) for psychosis.

Methods: 37 children (17 FHR, 20 HC) between 7 and 12 years old participated in this study. WM performance was assessed using the Wechsler Intelligence Scale for Children-IV (WISC-IV). To assess brain activation during WM performance, participants completed a visual block-designed n-back task with 2 conditions (2-back and 0-back) during scanning. fMRI data was preprocessed and analyzed using FSL Feat.

Results: Compared to HC, FHR children showed significantly lower WISC-IV WM scores. In addition, FHR children exhibited hypoactivation in the 2-back (versus 0-back) condition in a cluster encompassing bilateral precuneus and cuneus and right posterior cingulate cortex. There were no significant group-differences in n-back task performance and brain activation. The precuneus cluster was not correlated with n-back performance or WISC WM scores.

Conclusions: The current results provide preliminary evidence of impaired WM function and altered brain activity during WM performance in children with a familial predisposition for psychosis. Longitudinal studies are needed to determine whether these findings are related to abnormal brain development and predictive of cognitive deficits and psychosis later in life.

1. Introduction

Schizophrenia and related psychotic disorders are heritable neurodevelopmental disorders (Murray et al., 1987; Owen et al., 2011; Weinberger, 1986). Due to a combination of genetic and environmental risk factors, first-degree relatives of individuals with schizophrenia are at increased risk for altered neurodevelopment and at familial high-risk (FHR) for mental illness (Paus et al., 2008; Rasic et al., 2014). Although psychosis tends to manifest in adolescence or early adulthood, other characteristics of schizophrenia spectrum disorders such as cognitive deficits and behavioral disturbances are observed years before illness onset (Liu et al., 2015; Tarbox and Pogue-Geile, 2008; Welham et al., 2009; Woodberry et al., 2013). Cognitive impairments in schizophrenia have been reported particularly in domains related to fronto-striatal function, including working memory (WM) and attention (Diwadkar et al., 2012; Jiang et al., 2015). Neuropsychological studies have demonstrated WM deficits in FHR children and youth that are often accompanied by behavioral problems (Aronen et al., 2005; Hemager

* Corresponding authors at: Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht, the Netherlands (G. Collin).
E-mail addresses: k.c.a.vangool@students.uu.nl (K.C.A. van Gool), g.collin@umcutrecht.nl, gcollin@mit.edu (G. Collin).

https://doi.org/10.1016/j.schres.2021.12.030
Received 6 May 2021; Received in revised form 3 October 2021; Accepted 22 December 2021
Available online 12 January 2022

et al., 2018; Seidman et al., 2006). Moreover, WM deficits have been proposed to be a central feature of the schizophrenia prodrome that may be predictive of subsequent transition to psychosis (Niendam et al., 2003; Pukrop et al., 2007; Seidman et al., 2006). Investigating WM function in FHR children prior to the age of highest risk for onset of psychosis allows us to examine putative neurocognitive precursors of psychosis and their neural correlates.

WM refers to a cognitive system for the temporary holding and manipulation of information (Baddeley, 1992; Goldman-Rakic, 1999). Important brain regions related to WM include the prefrontal cortex, parietal cortex, and basal ganglia (Petrides, 2000; Wager and Smith, 2003). A recent review of 52 WM studies in individuals with schizophrenia yielded strong evidence for hypoactivation of the dorsolateral prefrontal cortex (DLPFC) (Brodmann Area 9; BA) during WM task performance (Wu and Jiang, 2019). In addition, individuals with schizophrenia have been found to show hypoactivation of inferior regions of the prefrontal lobe (BA 9 & 44) and hyperactivation of the left inferior parietal lobe (BA 40) during WM performance (Wu and Jiang, 2019). Similar findings were reported in a review of 15 WM studies in unaffected relatives of individuals with schizophrenia (Zhang et al., 2016). These alterations in WM-related brain activity may constitute biomarkers of schizophrenia risk (Wu and Jiang, 2019; Zhang et al., 2016), but it is unknown whether these changes are already present in childhood. Children at FHR for schizophrenia are a valuable population for studying putative brain changes that precede and may contribute to the development of psychosis.

To date, few studies have assessed WM-related brain activation in FHR children and those studies involved mainly FHR youth in the adolescent to young adult age range. One study examining youth at FHR for schizophrenia and schizoaffective disorder (ages 8–20 years) reported hypoactivation of the parietal cortex (BA 7 & 40) during high (2-back) versus low (0-back) WM demand as compared to HC (Bakshi et al., 2011). Another study in youth at FHR for schizophrenia (ages 9–20 years) utilized a visual n-back task with faces and noted hyperactivation of the DLPFC and left head of the caudate nucleus in FHR (Diwadkar et al., 2012). Finally, a study in youth at FHR for psychotic bipolar disorder (ages 13–24 years) found hypoactivation of left cerebellum, bilateral insula, right brainstem and right parahippocampal gyrus as well as hyperactivation of the left frontopolar cortex during 2-back versus 0-back WM demand (Thermenos et al., 2011).

It remains to be determined if results in unaffected adult relatives and FHR youth generalize to children in younger age ranges. Studies comparing WM-related brain activity between healthy adults and children have demonstrated that parietal brain regions appear to be similarly activated during WM performance in children and adults, while prefrontal regions are more strongly activated in adults as compared to children (Owen et al., 2005; Yaple and Arsalidou, 2018). This may relate to parietal brain regions maturing earlier in neurodevelopment than the prefrontal cortex, which shows a protracted maturation throughout adolescence in concert with increasing WM competence (Gogtay et al., 2004; Honey and Fletcher, 2006; Niendam et al., 2003). To understand the trajectory of brain changes in schizophrenia, it is important to examine whether FHR children show changes in WM-related brain activity, and if these changes are similar in pattern to those observed in older high-risk samples.

In sum, studies suggest that FHR children show impairments in WM function and altered brain activity during WM performance as compared to children without a family history of psychotic illness (Bakshi et al., 2011; Diwadkar et al., 2012; Hemager et al., 2018; Seidman et al., 2006; Thermenos et al., 2011). However, due to the paucity of research in children under the age of 13 years, it is unknown whether similar alterations are present at a younger age. As a result, it remains unclear whether these changes arise during or before adolescence, a developmental window associated with brain changes relevant to psychosis (i.e., large-scale synaptic pruning, white matter maturation, and modifications in GABAergic, glutamatergic, and dopaminergic neurotransmission). Therefore, the main aim of this study was to determine whether pre-adolescent children at FHR for psychosis show differences in brain activity during WM task performance as compared to HC children. In addition, we aimed to assess whether the current cohort of FHR children showed deficits in WM function and whether such deficits were related to putative changes in WM-related brain activation.

2. Materials and methods

2.1. Participants

This study included 37 participants (17 FHR, 20 HC) between the ages of 7 and 12 years old. FHR children had a first-degree relative (parent or sibling) diagnosed with psychotic illness (schizophrenia, schizoaffective disorder or affective psychosis). Children at FHR for both affective and non-affective psychosis were included because neuropsychological impairments in non-psychotic relatives tend to overlap across the schizophrenia – psychotic bipolar disorder spectrum (Hill et al., 2013). The FHR sample originated from 11 separate families and included two sibling pairs and two sets of three siblings. HC children originated from a total of 16 families and included two sibling pairs and one set of three siblings. Exclusion criteria for HC included a family history of a major mental disorder and a lifetime history of anti-psychotic medication. Exclusion criteria for FHR included current or recent use (within the last 30 days) of anti-psychotic medication. Exclusion criteria for all participants were age above 12 years, IQ below 70, any life-time diagnosis of psychotic illness, contraindications for MRI use, and current or recent use of any other psychotropic medication (defined as within four half-life of the concerned medication). Participants were recruited between October 2012 and June 2016 at the Department of Psychiatry of Beth Israel Deaconess Medical Center (BIDMC) in Boston. Parents provided informed consent and all children gave assent to participate in the study.

2.2. Data collection

2.2.1. Demographic, clinical and (neuro)psychological evaluation

Clinical diagnoses of family members were confirmed using the Structured Clinical Interview for DSM-IV (SCID) combined with an assessment of their medical history and by interviewing at least one informant using the Family Interview for Genetic Studies (FIGS) (First et al., 2002). Clinical diagnoses were determined by consensus in meetings attended by senior clinicians (LJS, MSK, RMG). The SCID for Childhood Diagnoses (Kid-SCID) was used to assess any current psychiatric diagnoses of the participants (Hien et al., 1994). IQ was estimated for each participant using the four index scores of the WISC-IV (Wechsler, 2003). WM performance was computed by combining scores of three subtests of the WISC-IV (forward and backward digit span and letter-number sequencing) (Wechsler, 2003). WM ability in daily life was assessed with the WM subscale of the Behavior Rating Inventory of Executive Function (BRIEF). This questionnaire was filled out by one of the participants' parents. Examples of items are: 'forgets what he/she is doing' and 'needs help from an adult to stay on task' (Gioia et al., 2010). The Child Behavior Checklist (CBCL) was used to measure problem behavior including attention problems, attention deficit hyperactivity disorder problems, internalizing problems, and externalizing problems (Achenbach and Rescorla, 2001). Socioeconomic status (SES) was assessed using the Hollingshead scale. Using this instrument, participants were assigned to one of five classes based on their parent's employment status, educational attainment, and occupational prestige, with class one reflecting high-SES and class five reflecting low-SES (Hollingshead, 1975).

2.2.2. N-back Task

All participants performed two runs of a visual block-designed n-

back task, adjusted to meet the developmental level of children in this age range (Casey et al., 1995). Each run consisted of 6 blocks with 10 stimuli, alternating between a 0-back and a 2-back condition (further details in supplementary material). Participants held an MR-safe button box in their dominant hand and a stuffed animal in their non-dominant hand for comfort. In the 0-back condition, participants were instructed to press the button when the letter ''W'' was presented and not to press the button when another (i.e., non-target) letter was presented. In the 2-back condition, participants were instructed to press the button when the presented letter was identical to the letter presented two trials back. The ratio of target to non-target letters was 3:10.

2.2.3. Behavioral analysis

Scores for both runs of the n-back task were combined. Performance (accuracy) was defined as the percentage of correct responses and was computed for the 0-back and 2-back condition separately. Participants with an average accuracy below 70% or more were excluded from fMRI data-analysis to ensure that final analysis included only participants who understood and were engaged in the task. Reaction time (RT) for both conditions was measured as the sum of all RTs when the given answer was correct, divided by the sum of correct answers. When participants responded to a non-target letter, this was recorded as a false positive response. Participants with a false positive rate greater than 10% for the 0-back condition were removed from analysis to ensure that correct answers were not achieved by chance. In total, four participants were removed from analysis because of accuracy below 70% ($N = 3$) or false positive rate above 10% in the 0-back condition ($N = 1$).

2.2.4. Image acquisition and preprocessing

MRI scans were acquired on a 3 T Siemens, Magnetom Trio scanner at Beth Israel Deaconess Medical Center and included two fMRI scans (one for each run of the task) and one anatomical T1-weighted scan for anatomical reference (acquisition details in supplementary material). fMRI preprocessing was carried out using FMRIB's Software Library (FSL) version 5.0.9 (Jenkinson et al., 2002; Jenkinson and Smith, 2001; Smith, 2002; Smith et al., 2004) and included realignment, spatial normalization, motion correction, spatial smoothing, and band pass filtering (details in supplement).

2.2.5. fMRI whole brain analysis

Analysis of task-fMRI data performed using FSL FEAT (FMRI Expert Analysis Tool) Version 6.00 (Woolrich et al., 2004) (details in supplement). Between-group analysis comparing WM-related brain activation between FHR and HC was performed using a mixed effects model with age and sex as covariates. MNI coordinates of statistically significant activation clusters exceeding a threshold of $Z > 2.3$ and (corrected) cluster significance level of $p < 0.05$ are reported. Corresponding brain regions and Brodmann areas were retrieved from FSL using Talairach Daemon Atlas (Talairach and Tournoux, 1988).

2.3. Statistical analysis

2.3.1. Demographic, clinical and (neuro)psychological data

Demographic, clinical (CBCL), and neuropsychological (WISC and BRIEF) data of both groups were compared and analyzed with independent sample t-tests for continuous data and chi-square (χ^2) tests for categorical data (Table 1). Between-group differences in n-back performance were analyzed using independent sample t-tests on accuracy, RT, and false positive rates (Table 2). Pearson's correlation analyses between 2-back RT and accuracy and age as well as behavioral problems were conducted for both groups individually. A Bonferroni-corrected alpha of $p < 0.005$ was used to correct for multiple comparisons. Findings at uncorrected $p < 0.05$ are reported as trend-level results.

2.3.2. Brain-behavioral correlations

Mean activation levels of clusters showing significant group-differences in the 2-back > 0-back contrast were tested for associations with 2-back RT and accuracy, age, WISC and BRIEF WM scores, and internalizing and externalizing symptoms using Pearson's

Table 1
Demographic, clinical and (neuro)psychological characteristics.

	FHR ($N = 15$)	HC ($N = 18$)	*Statistics*
Age in years, mean (SD) [range]	9.6 (2.1) [7.02–12.4]	9.3 (1.7) [7.2–12.2]	$t_{(31)} = -0.49$, $p = 0.630$
Sex (male/female)	6/9	8/10	$\chi^2 = 0.07$, $p = 0.797$
IQ, mean (SD)[a]	103.1 (13.9)	111.3 (17.7)	$t_{(31)} = 1.47$, $p = 0.152$
Parental SES, mean (SD)[b]	3.5 (1.6)	1.6 (0.86)	$t_{(20.2)} = -4.07$, $p = 0.001$
DSM diagnosis participant, *n* (%)[c]	7 (46.7)	0 (0)	$\chi^2 = 9.88$, $p < 0.002$
Relationship affected proband (mother/father/sibling)	8/2/5	-	
Diagnosis affected proband (SZ/SA/AP)	7/6/2	-	
WISC-IV WM, mean (SD)[d]	97.2 (12.3)	107.5 (12.8)	$t_{(31)} = 2.34$, $p = 0.026$
BRIEF WM, mean (SD)[e]	54.9 (12.6)	44.8 (7.3)	$t_{(21.6)} = -2.7$, $p = 0.012$
Attention problems, mean (SD)[f]	58.4 (10.7)	51.3 (2.3)	$t_{(13.9)} = -2.42$, $p = 0.030$
ADHD problems, mean (SD)[f]	57.8 (11.2)	50.6 (1.7)	$t_{(13.5)} = -2.40$, $p = 0.031$
Internalizing problems, mean (SD)[f]	50.4 (11.0)	40.4 (6.9)	$t_{(30)} = -3.14$, $p = 0.004$
Externalizing problems, mean (SD)[f]	51.6 (12.3)	37.2 (5.2)	$t_{(16.6)} = -4.10$, $p = 0.001$

Demographic, clinical, and neuropsychological characteristics of FHR and HC groups in final analysis.
[a] IQ based on four WISC-IV index scores. [b] From Hollingshead; 1 highest, 5 lowest. [c] DSM diagnosis missing for 9 participants (3 FHR, 6 HC). [d] WM standard scores based on three subtests of WISC-IV (forward/backwards digit span, letter-number sequencing) [e] BRIEF T-scores, higher scores reflect more WM problems [f] CBCL T-scores, missing for 1 FHR participant. See supplementary material Table S1 for demographic characteristics of the total baseline sample (i.e., prior to exclusion for low task accuracy). SZ = schizophrenia; SA = schizoaffective disorder; AP = affective psychosis.

Table 2
N-back task performance.

	FHR ($N = 15$)	HC ($N = 18$)	*Statistics*
Accuracy, % correct (SD)			
0-back	97.78 (4.6)	94.75 (7.7)	$t_{(31)} = -1.33$, $p = 0.193$
2-back	75.93 (22.5)	82.4 (16.0)	$t_{(31)} = 0.97$, $p = 0.341$
Reaction time, msec (SD)			
0-back	0.62 (0.1)	0.60 (0.1)	$t_{(31)} = -0.71$, $p = 0.484$
2-back	0.74 (0.2)	0.73 (0.2)	$t_{(31)} = -0.07$, $p = 0.943$
False positives, % correct (SD)			
0-back	2.70 (2.5)	2.65 (2.4)	$t_{(31)} = -0.06$, $p = 0.952$
2-back	6.67 (5.2)	6.35 (4.0)	$t_{(31)} = -0.20$, $p = 0.844$

Results of n-back working memory task for both FHR and HC children ($N = 33$). Additional analyses with total baseline sample also showed no between-group differences in WM task performance.

correlation analysis. A Bonferroni-corrected alpha of $p < 0.007$ was used to correct for multiple comparisons.

3. Results

3.1. Demographic and behavioral data

Thirty-three participants were included in final analysis (15 FHR, 18 HC). Groups were well-matched for age and sex (Table 1). Mean IQ was around 8 points lower in FHR compared to HC children, but this difference was not statistically significant. Parental SES was significantly lower in FHR relative to HC children. DSM diagnoses, including mainly ADHD, were significantly more common in FHR than HC. FHR children had significantly lower WISC-IV WM scores compared to HC children and parents reported significantly more WM problems on the BRIEF. Also, FHR children scored significantly higher on CBCL attention, ADHD, internalizing, and externalizing problems (Table 1).

3.2. N-back Task

Both FHR and HC children had better accuracy scores and responded faster in the 0-back condition compared to the 2-back condition (Table 2). There were no significant group-differences in accuracy, RT, and false positive rate in either condition.

The FHR group showed a trend-level negative correlation between 2-back accuracy and externalizing problems ($r = -0.54$, $p = 0.045$). Within the HC group, age showed a strong negative correlation with 2-back RT ($r = -0.73$, $p < 0.001$). This association was not observed in the FHR group ($r = -0.46$, $p = 0.084$).

3.3. Whole brain analysis

3.3.1. Within-group effects

Fig. 1 shows mean within-group activation for the 2-back > 0-back condition. Both FHR and HC groups showed activation in brain areas commonly associated with WM function including the bilateral DLPFC (BA 6 & 9), bilateral parietal cortex (BA 7 & 40), and anterior cingulate cortex (including the medial prefrontal cortex; BA 8 & 32).

3.3.2. Between-group effects

Between-group analysis showed hypoactivation in FHR as compared to HC in a cluster encompassing bilateral precuneus (BA 7) and cuneus (BA 18/19), and right posterior cingulate cortex (PCC, BA 23) for the 2-back > 0-back contrast (Fig. 2, Table 3). There were no brain areas with significantly greater activation in FHR children relative to HC children.

3.3.3. Validation analyses

Validation analyses confirmed that the current results were not driven by heterogeneity of the FHR sample ($p = 0.004$) or the preponderance of ADHD diagnoses in the FHR group ($p < 0.001$) (details in supplementary material, including Figure S1).

3.3.4. Brain-behavioral correlations

There were no significant associations between activation of the bilateral parietal/occipital cluster and n-back RT and accuracy, age, WISC or BRIEF WM scores, and internalizing or externalizing scores in either the FHR or HC group.

4. Discussion

The aim of this study was to investigate whether pre-adolescent FHR children show abnormalities in WM performance and WM-related brain activity as compared to children without a family history of psychosis. We hypothesized that FHR children would show impairments in WM performance (1) and abnormalities in WM-related brain activity (2) as compared to HC children and that putative alterations in brain activity in FHR children would be associated with impairments in WM performance (3). In line with our first two hypotheses, our results showed that pre-adolescent FHR children exhibit impairments in WM performance as assessed with WISC-IV and WM abilities in daily life as assessed with the BRIEF. In addition, as compared to HC, FHR children exhibited hypoactivation in a cluster encompassing bilateral precuneus and cuneus and right PCC during n-back task performance. However, in contrast with our third hypothesis, group-differences in WM-related brain activation were not related to WISC WM scores or n-back task performance.

WM-related hypoactivation of bilateral precuneus and cuneus and right PCC in the FHR group was observed in the context of comparable n-back performance. Similar findings have been documented in FHR adolescents and adults (Jiang et al., 2015; Karch et al., 2009) and first-episode individuals with schizophrenia (Schneider et al., 2007). Among adolescent FHR samples, Bakshi et al., (2011) reported WM-related hypoactivation of a cluster in the left parietal lobe including the precuneus during high WM load with intact WM performance. Discrepancies in the regional localization of WM-related abnormalities in brain activation between previous studies and our current results may be due, in part, to the older age range of earlier investigations. Putatively, WM-related abnormalities in brain activity may show up first in those regions that mature first (e.g., precuneus and larger parietal cortex) and manifest later in brain regions that take longer to mature (e.g., prefrontal cortex). Indeed, WM-related brain areas are known to mature throughout adolescence, in association with developmental improvements in WM performance (Conklin et al., 2007; Gogtay et al., 2004; Honey and Fletcher, 2006; Niendam et al., 2003). Our current results show that abnormalities in WM-related brain activation exist before adolescence in children with a (familial) risk for schizophrenia, suggesting that these abnormalities may stem from alterations in the (pre-adolescent) development of WM-related brain areas. Abnormalities in WM-related brain activation could be caused by reduced neuropil in these brain areas. It is hypothesized that individuals with schizophrenia have hypoactive dopaminergic modulation of pyramidal cell activity

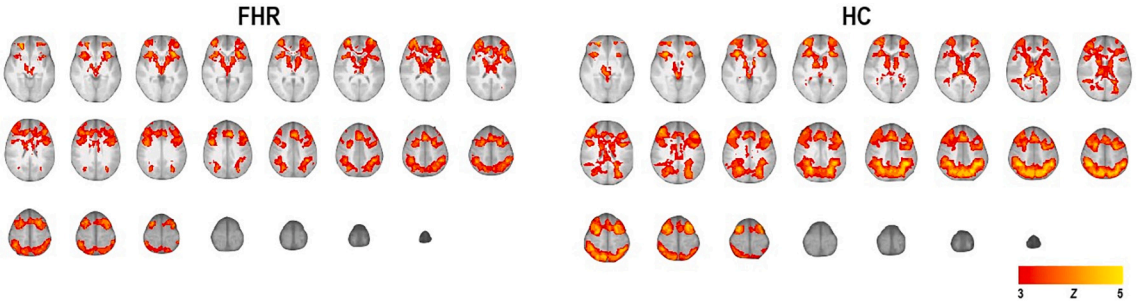

Fig. 1. Mean activation in both groups in the 2-back > 0-back contrast. *Brain slices showing similar activation in 2-back > 0-back condition in brain areas associated with WM function in FHR and HC groups, including bilateral DLPFC (BA 6 & 9), bilateral parietal cortex (BA 7 & 40), and anterior cingulate cortex. Scale on color bar represents Z-scores.*

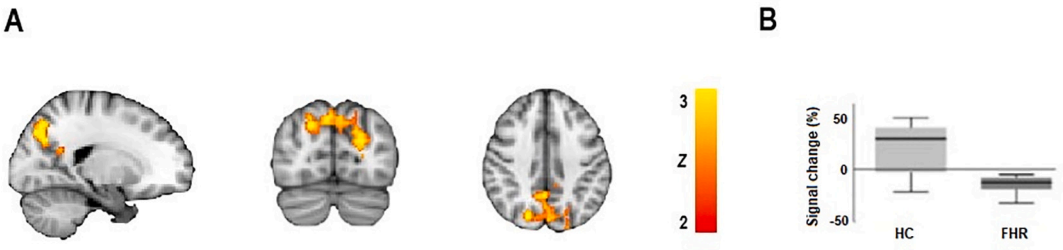

Fig. 2. Cluster of significant HC > FHR brain activation in 2-back > 0-back condition. *A. Sagittal, coronal and horizontal slices showing significant brain activation (HC > FHR) in bilateral precuneus and cuneus (right posterior cingulate gyrus is part of cluster, but not displayed here). MNI coordinates of peak activation were 20, −76, 38. Scale on color bar represents the Z-score. B. Boxplot shows the amount of signal change in the bilateral precuneus/cuneus cluster in the 2-back > 0-back contrast. Mean (sd) signal change in HC children was 27,6% (44.5) compared to −13.2% (16.4) in the FHR children, illustrating that HC children showed increased activation in this cluster during the 2-back (versus 0-back) condition, whereas FHR children showed decreased activation during the 2-back condition. The group-difference in mean activation was statistically significant (p = 0.002).*

Table 3
Group-differences in neural activation during WM task.

Included areas in cluster (R/L)	BA	MNI coordinates (mm)			*Z*-value
		x	y	z	
R precuneus	7	20	−76	38	3.54
L precuneus	7	0	−52	40	2.94
R cuneus	18	14	−76	34	2.48
	19	18	−70	30	3.45
L cuneus	19	−24	−74	22	3.13
R posterior cingulate cortex	23	14	−48	10	3.36

Significant HC > FHR activation response in 2-back > 0-back condition in the bilateral parieto-occipital cluster. Areas showing significant HC > FHR activation response in the 2-back > 0-back condition are reported in MNI coordinates. Peak activation was found in the right precuneus (20, −76, 38). R = right; L = left; BA = Brodmann Area. MNI = Montreal Neurologic Institute; HC = healthy control; FHR = familial high risk, x = sagittal plane; y = coronal plane; z = axial plane.

due to reduced interneuronal neuropil, especially in the DLPFC. It is thought that this is a substrate for schizophrenia pathophysiology, including cognitive impairments (Glantz and Lewis, 1997; Selemon and Goldman-Rakic, 1999). It is possible that other WM-related brain areas share a similar mechanism. However, more research is needed to determine whether reduced neuropil in WM-related areas can also be found in FHR children. Furthermore, the issue of whether or not schizophrenia and related psychotic disorders should be viewed as neurodevelopmental disorders remains topic of debate. Indeed, first psychotic symptoms manifest during adolescence. However, a decline in neurocognitive development precedes the onset of psychosis with many years (Welham et al., 2009) and reduced intracranial volume in individuals with schizophrenia is suggestive for abnormalities in brain development before adolescence (Giedd et al., 1996; Woods et al., 2005).

Meta-analytic data show that the precuneus is consistently activated during WM performance in healthy participants, regardless of age, sex, and memory load (Wang et al., 2019). The precuneus is also reliably activated during self-referential processing (Northoff et al., 2006). In line with these findings, the precuneus exhibits state-dependent differences in its functional connectivity profile, such that it is connected with the frontoparietal network (FPN) during (cognitive) task performance, while it is connected with the default mode network (DMN) during rest and internally focused or self-referential tasks (Li et al., 2019; Utevsky et al., 2014). This is of interest in light of observations that the precuneus and PCC show hyperactivation during self-referential processing in individuals with schizophrenia (Holt et al., 2011; Shad and Keshavan, 2015; Tan et al., 2015) and their unaffected relatives (van Buuren et al., 2012). Moreover, a recent study by our group showed precuneus/PCC hyperactivation during self-referential processing in the current FHR sample (Collin et al., 2021). Taken together, these previous findings and our current results suggest that schizophrenia spectrum disorders may involve precuneus hyperactivation during DMN-related internally focused tasks (and rest) and hypoactivation during FPN-associated externally focused tasks including WM performance.

Precuneus activation has been found to show a positive linear relationship with increasing WM load in healthy participants (Vogan et al., 2016). Moreover, hypoactivation of the precuneus has been associated with poorer WM performance in individuals with schizophrenia (Schneider et al., 2007). Our current finding of precuneus hypoactivation during WM performance in FHR children is thus a tentative indication that aberrant precuneus function may be part of the neurobiological mechanisms driving the development of WM deficits in at-risk children. Although we found no group-differences in n-back performance and no associations between precuneus hypoactivation and metrics of WM performance, FHR children did score lower on WM subtests of the WISC-IV. In addition, their parents reported more WM-related problems in daily life on the BRIEF and FHR children showed more behavioral problems related to WM impairment on the CBCL (Aronen et al., 2005). These findings are in line with literature showing that FHR children, as a group, show impairments in WM function (Hemager et al., 2018; Seidman et al., 2006). However, it remains to be determined whether, and if so how, the observed alterations in precuneus function underlie impairments in WM performance in FHR children. One possible explanation for the lack of direct association in the current data may be that the n-back task lacks sensitivity to pick up more subtle changes in WM performance. Increasing n-back load may have revealed more subtle changes associated with brain functional alterations. Another possibility is that deficits in n-back performance become more evident as WM-related brain structures, including the prefrontal cortex mature (Conklin et al., 2007; Honey and Fletcher, 2006) or emerge in adolescence as a result of subsequent abnormalities in the maturation of the frontal cortex (Gómez et al., 2017; Paus et al., 2008). Tentative support for this hypothesis comes from our observation that older HC children showed improved WM performance (i.e., shorter 2-back reaction times) as compared to younger HC children, which was not observed in the FHR children and may be indicative of a failure to improve WM performance with age in this group.

A number of limitations should be considered when interpreting the current results. First, our findings should be viewed as preliminary due to our small sample size. This likely limited our ability to show more subtle changes in WM-related activation of other brain regions and establish brain-behavior relationships, although these can be difficult to show even in larger samples. We note that it is challenging to collect (large) samples of young FHR children as individuals with a psychotic disorder tend to have fewer offspring (Laursen and Munk-Olsen, 2010; MacCabe et al., 2009). Given these challenges, we believe that the current findings represent a valuable addition to current literature, despite our modest sample size. Moreover, the FHR and HC group were

significantly different in terms of SES and, not surprisingly, in the frequency of DSM diagnoses (mostly ADHD). Putatively, future studies with better matching groups may be able to link WM-related brain activation differences more closely to psychosis risk, although validation analyses showed no differences in cluster activation between FHR children with and without ADHD. Moreover, ADHD and other developmental disorders are known to be more common in high-risk families and may be an expression of underlying risk factors (Keshavan et al., 2003). Similarly, familial risk for psychosis is associated with lower SES (Keshavan et al., 2003). Including only FHR children without developmental disorders and with high SES could thus lead to an overly healthy subset of high-risk individuals that may omit much of the important risk signal.

Future studies may focus more specifically on the precuneus and its connections with related networks, including DMN and FPN. This may provide more insight in the role of the precuneus in WM impairments in FHR children and youth. Also, higher n-back task load may show whether more subtle differences in n-back performance exist between FHR and HC in this age range and whether such changes are associated with abnormal WM-related brain activation. Moreover, future studies should include FHR children with either affected parents or siblings and should strive for not having multiple participants from one family to obtain more independent data. Lastly, a longitudinal prospective design is needed to examine how alterations in WM-related brain activation and WM performance develop over time and whether the currently observed patterns are predictive of subsequent WM deficits and the development of psychosis later in life.

In conclusion, our results provide preliminary evidence for an abnormal role of the precuneus in WM-related processes in children with a familial predisposition to psychosis. In addition, our findings of impairments in WM function and WM abilities in daily life in FHR children replicate previous results of WM impairments as a premorbid indicator of schizophrenia risk, but we were unable to relate the impairments to observed alterations in WM-related brain activation. These findings are of interest to efforts to develop early psychosocial and cognitive interventions in the premorbid phase of psychotic disorders and to identify individuals who may be at-risk for future cognitive impairments.

Ethics statement

This study involved human participants and was reviewed and approved by the Institutional Review Board (IRB) of Beth Israel Deaconess Medical Center (BIDMC), Boston, MA, USA. Written informed consent to participate in this study was provided by the participants' parents/legal guardians and participants provided assent to participate in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the National Institute of Mental Health grant MH092840 (LS, JG, MK) and by the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No. 749201 (GC).

The authors declare no competing interests.

LS, MK, JG, HT, and SW-G contributed to the conception and design of the study and the acquisition of funding. EM, RM-G, and HT contributed to data acquisition. LS, RM-G, and MK led clinical consensus meetings to ascertain clinical diagnosis. KG performed statistical analyses and wrote the first draft of the manuscript. KG, GC and CB contributed to data analysis and interpretation. All authors contributed to manuscript revision, and read and approved the final submitted manuscript.

The National Institute of Mental Health and the European Union's Horizon research and innovation program had no further role in study design; in the collection, analysis and interpretation of data; in writing of the report; and in the decision to submit the paper for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.12.030.

References

Achenbach, T.M, Rescorla, L.A, 2001. Manual for ASEBA school-age forms and profiles. University of Vermont, Research Center for Children, Youth, and Families, Burlington, VT.

Aronen, E.T., Vuontela, V., Steenari, M.-R., Salmi, J., Carlson, S., 2005. Working memory, psychiatric symptoms, and academic performance at school. Neurobiol. Learn. Mem. 83 (1), 33–42.

Baddeley, A., 1992. Working memory. Science 255 (5044), 556–559.

Bakshi, N., Pruitt, P., Radwan, J., Keshavan, M.S., Rajan, U., Zajac-Benitez, C., Diwadkar, V.A., 2011. Inefficiently increased anterior cingulate modulation of cortical systems during working memory in young offspring of schizophrenia patients. J. Psychiatr. Res. 45 (8), 1067–1076.

Casey, B.J., Cohen, J.D., Jezzard, P., Turner, R., Noll, D.C., Trainor, R.J., Giedd, J., Kaysen, D., Hertz-Pannier, L., Rapoport, J.L., 1995. Activation of prefrontal cortex in children during a nonspatial working memory task with functional mri. Neuroimage 2 (3), 221–229.

Collin, G., Bauer, C.C.C., Anteraper, S.A., Gabrieli, J.D.E., Molokotos, E., Mesholam-Gately, R., Thermenos, H.W., Seidman, L.J., Keshavan, M.S., Shenton, M.E., Whitfield-Gabrieli, S., 2021. Hyperactivation of Posterior Default Mode Network During Self-Referential Processing in Children at Familial High-Risk for Psychosis. Front. Psychiatry 12, 613142.

Conklin, H.M., Luciana, M., Hooper, C.J., Yarger, R.S., 2007. Working Memory Performance in Typically Developing Children and Adolescents: Behavioral Evidence of Protracted Frontal Lobe Development. Dev. Neuropsychol. 31 (1), 103–128.

Diwadkar, V.A., Pruitt, P., Zhang, A., Radwan, J., Keshavan, M.S., Murphy, E., Rajan, U., Zajac-Benitez, C., 2012. The neural correlates of performance in adolescents at risk for schizophrenia: Inefficiently increased cortico-striatal responses measured with fMRI. J. Psychiatr. Res. 46 (1), 12–21.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP). Biometrics Research. New York State Psychiatric Institute, New York.

Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A. C., Vauss, Y.C., Hamburger, S.D., Kaysen, D., Rapoport, J.L., 1996. Quantitative Magnetic Resonance Imaging of Human Brain Development: Ages 4–18. Cereb. Cortex 6 (4), 551–559.

Gioia, G.A., Isquith, P.K., Guy, S.C., Kenworthy, L., 2010. Behavior Rating Inventory of Executive Function. Child Neuropsychol 6, 235–238.

Glantz, L.A., Lewis, D.A., 1997. Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia regional and diagnostic specificity. Arch. Gen. Psychiatry 54, 943–952.

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T. F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. PNAS 101 (21), 8174–8179.

Goldman-Rakic, P.S., 1999. The physiological approach: Functional architecture of working memory and disordered cognition in schizophrenia. In: Biological Psychiatry. Elsevier, pp. 650–661.

Gómez, C.M., Barriga-Paulino, C.I., Rodríguez-Martínez, E.I., Rojas-Benjumea, M.Á., Arjona, A., Gómez-González, J., 2017. The neurophysiology of working memory development: From childhood to adolescence and young adulthood. Rev. Neurosci. 29, 261–282.

Hemager, N., Plessen, K.J., Thorup, A., Christiani, C., Ellersgaard, D., Spang, K.S., Burton, B.K., Gregersen, M., Søndergaard, A., Greve, A.N., Gantriis, D.L., Poulsen, G., Seidman, L.J., Mors, O., Nordentoft, M., Jepsen, J.R.M., 2018. Assessment of neurocognitive functions in 7-year-old children at familial high risk for schizophrenia or bipolar disorder the danish high risk and resilience study VIA 7. JAMA Psychiatry 75 (8), 844. https://doi.org/10.1001/jamapsychiatry.2018.1415.

Hien, D., Matzner, F.J., First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1994. Structured Clinical Interview for DSM-IV-Child Edition (Version 1.0). Columbia University, New York, NY.

Hill, S.K., Reilly, J.L., Keefe, R.S.E., Gold, J.M., Bishop, J.R., Gershon, E.S., Tamminga, C. A., Pearlson, G.D., Keshavan, M.S., Sweeney, J.A., 2013. Neuropsychological impairments in schizophrenia and psychotic Bipolar disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Am. J. Psychiatry 170 (11), 1275–1284.

Hollingshead, A.B., 1975. Four factor index of social status. Yale University Department of Sociology, New Haven, CT.

Holt, D.J., Cassidy, B.S., Andrews-Hanna, J.R., Lee, S.M., Coombs, G., Goff, D.C., Gabrieli, J.D., Moran, J.M., 2011. An anterior-to-posterior shift in midline cortical activity in schizophrenia during self-reflection. Biol. Psychiatry 69 (5), 415–423.
Honey, G.D., Fletcher, P.C., 2006. Investigating principles of human brain function underlying working memory: What insights from schizophrenia? Neuroscience 139 (1), 59–71.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. Neuroimage 17 (2), 825–841.
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5 (2), 143–156.
Jiang, S., Yan, H., Chen, Q., Tian, L., Lu, T., Tan, H.-Y., Yan, J., Zhang, D., Stamatakis, E. A., 2015. Cerebral Inefficient Activation in Schizophrenia Patients and Their Unaffected Parents during the N-Back Working Memory Task: A Family fMRI Study. PLoS One 10 (8), e0135468.
Karch, S., Leicht, G., Giegling, I., Lutz, J., Kunz, J., Buselmeier, M., Hey, P., Spörl, A., Jäger, L., Meindl, T., Pogarell, O., Möller, H.-J., Hegerl, U., Rujescu, D., Mulert, C., 2009. Inefficient neural activity in patients with schizophrenia and nonpsychotic relatives of schizophrenic patients: Evidence from a working memory task. J. Psychiatr. Res. 43 (15), 1185–1194.
Keshavan, M.S., Sujata, M., Mehra, A., Montrose, D.M., Sweeney, J.A., 2003. Psychosis proneness and ADHD in young relatives of schizophrenia patients. Schizophr. Res. 59 (1), 85–92.
Laursen, T.M., Munk-Olsen, T., 2010. Reproductive patterns in psychotic patients. Schizophr. Res. 121 (1-3), 234–240.
Li, R., Utevsky, A.V., Huettel, S.A., Braams, B.R., Peters, S., Crone, E.A., van Duijvenvoorde, A.C.K., 2019. Developmental maturation of the precuneus as a functional core of the default mode network. J. Cogn. Neurosci. 31 (10), 1506–1519.
Liu, C.H., Keshavan, M.S., Tronick, E.d., Seidman, L.J., 2015. Perinatal Risks and Childhood Premorbid Indicators of Later Psychosis: Next Steps for Early Psychosocial Interventions. Schizophr. Bull. 41 (4), 801–816.
MacCabe, J.H., Koupil, I., Leon, D.A., 2009. Lifetime reproductive output over two generations in patients with psychosis and their unaffected siblings: The Uppsala 1915–1929 birth cohort multigenerational study. Psychol. Med. 39 (10), 1667. https://doi.org/10.1017/S0033291709005431.
Murray, R.M., Lewis, S.W., Lecturer, L., 1987. Is schizophrenia a neurodevelopmental disorder? Br. Med. J. (Clin. Res. Ed). 295, 681–682.
Niendam, T.A., Bearden, C.E., Rosso, I.M., Sanchez, L.E., Hadley, T., Nuechterlein, K.H., Cannon, T.D., 2003. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. Am. J. Psychiatry 160 (11), 2060–2062.
Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain: A meta-analysis of imaging studies on the self. Neuroimage 31 (1), 440–457.
Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E.d., 2005. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25 (1), 46–59.
Owen, M.J., O'Donovan, M.C., Thapar, A., Craddock, N., 2011. Neurodevelopmental hypothesis of schizophrenia. Br. J. Psychiatry 198 (3), 173–175.
Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9 (12), 947–957.
Petrides, M., 2000. Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex visual working memory. J. Neurosci. 20, 7496–7503.
Pukrop, R., Ruhrmann, S., Schultze-Lutter, F., Bechdolf, A., Brockhaus-Dumke, A., Klosterkötter, J., 2007. Neurocognitive indicators for a conversion to psychosis: Comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. Schizophr. Res. 92 (1-3), 116–125.
Rasic, D., Hajek, T., Alda, M., Uher, R., 2014. Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies. Schizophr. Bull. 40 (1), 28–38.
Schneider, F., Habel, U., Reske, M., Kellermann, T., Stöcker, T., Shah, N.J., Zilles, K., Braus, D.F., Schmitt, A., Schlösser, R., Wagner, M., Frommann, I., Kircher, T., Rapp, A., Meisenzahl, E., Ufer, S., Ruhrmann, S., Thienel, R., Sauer, H., Henn, F.A., Gaebel, W., 2007. Neural correlates of working memory dysfunction in first-episode schizophrenia patients: An fMRI multi-center study. Schizophr. Res. 89 (1-3), 198–210.
Seidman, L.J., Giuliano, A.J., Smith, C.W., Stone, W.S., Glatt, S.J., Meyer, E., Faraone, S. V., Tsuang, M.T., Cornblatt, B., 2006. Neuropsychological Functioning in Adolescents and Young Adults at Genetic Risk for Schizophrenia and Affective Psychoses: Results from the Harvard and Hillside Adolescent High Risk Studies. Schizophr. Bull. 32 (3), 507–524.
Selemon, L.D., Goldman-Rakic, P.S., 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol. Psychiatry 45 (1), 17–25.
Shad, M.U., Keshavan, M.S., 2015. Neurobiology of insight deficits in schizophrenia: An fMRI study. Schizophr. Res. 165 (2-3), 220–226.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23 (Suppl 1), S208–S219.
Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain 3-Dimensional Proportional System: An Approach to Cerebral Imaging. Georg Thieme Verlag, Stuttgart, New York.
Tan, S., Zhao, Y., Fan, F., Zou, Y., Jin, Z., Zen, Y., Zhu, X., Yang, F., Tan, Y., Zhou, D., Zuo, X.-N., 2015. Brain Correlates of Self-Evaluation Deficits in Schizophrenia: A Combined Functional and Structural MRI Study. PLoS One 10 (9), e0138737.
Tarbox, S.I., Pogue-Geile, M.F., 2008. Development of Social Functioning in Preschizophrenia Children and Adolescents: A Systematic Review. Psychol. Bull. 134 (4), 561–583.
Thermenos, H.W., Makris, N., Whitfield-Gabrieli, S., Brown, A.B., Giuliano, A.J., Lee, E. H., Faraone, S.V., Tsuang, M.T., Seidman, L.J., 2011. A functional MRI study of working memory in adolescents and young adults at genetic risk for bipolar disorder: preliminary findings. Bipolar Disord. 13 (3), 272–286.
Utevsky, A.V., Smith, D.V., Huettel, S.A., 2014. Precuneus is a functional core of the default-mode network. J. Neurosci. 34 (3), 932–940.
van Buuren, M., Vink, M., Kahn, R.S., 2012. Default-mode network dysfunction and self-referential processing in healthy siblings of schizophrenia patients. Schizophr. Res. 142 (1-3), 237–243.
Vogan, V.M., Morgan, B.R., Powell, T.L., Smith, M.L., Taylor, M.J., 2016. The neurodevelopmental differences of increasing verbal working memory demand in children and adults. Dev. Cogn. Neurosci. 17, 19–27.
Wager, T.D., Smith, E.E., 2003. Neuroimaging studies of working memory: A meta-analysis. Cogn. Affect. Behav. Neurosci. 3 (4), 255–274.
Wang, H., He, W., Wu, J., Zhang, J., Jin, Z., Li, L., 2019. A coordinate-based meta-analysis of the n-back working memory paradigm using activation likelihood estimation. Brain Cogn. 132, 1–12.
Wechsler, D., 2003. Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). The Psychological Corporation, San Antonio, TX.
Weinberger, D.R., 1986. The pathogenesis of schizophrenia: A neurodevelopmental theory. Edited by Nasrallah, H.A., Weinberger D.R. Neurol. Schizophr. Elsevier, Amsterdam, 397–406.
Welham, J., Isohanni, M., Jones, P., McGrath, J., 2009. The antecedents of Schizophrenia: A review of birth cohort studies. Schizophr. Bull. 35 (3), 603–623.
Woodberry, K.A., McFarlane, W.R., Giuliano, A.J., Verdi, M.B., Cook, W.L., Faraone, S.V., Seidman, L.J., 2013. Change in neuropsychological functioning over one year in youth at clinical high risk for psychosis. Schizophr. Res. 146 (1-3), 87–94.
Woods, B.T., Ward, K.E., Johnson, E.H., 2005. Meta-analysis of the time-course of brain volume reduction in schizophrenia: implications for pathogenesis and early treatment. Schizophr. Res. 73 (2-3), 221–228.
Woolrich, M.W., Behrens, T.E.J., Beckmann, C.F., Jenkinson, M., Smith, S.M., 2004. Multilevel linear modelling for FMRI group analysis using Bayesian inference. Neuroimage 21 (4), 1732–1747.
Wu, D., Jiang, T., 2020. Schizophrenia-related abnormalities in the triple network: a meta-analysis of working memory studies. Brain Imaging Behav. 14 (4), 971–980.
Yaple, Z., Arsalidou, M., 2018. N -back Working Memory Task: Meta-analysis of Normative fMRI Studies With Children. Child Dev. 89 (6), 2010–2022.
Zhang, R., Picchioni, M., Allen, P., Toulopoulou, T., 2016. Working Memory in Unaffected Relatives of Patients With Schizophrenia: A Meta-Analysis of Functional Magnetic Resonance Imaging Studies. Schizophr. Bull. 42 (4), 1068–1077.