Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorder - the Danish high risk and resilience study VIA 7

Anna Hester Ver Loren van Themaat [a,*], Md Jamal Uddin [b,c,d], Camilla Jerlang Christiani [b,c], Nicoline Hemager [a,b,c], Ditte Ellersgaard [b,c], Birgitte Klee Burton [a,c], Katrine Søborg Spang [a,c], Aja Greve [c,e], Ditte Gantriis [c,e], Ole Mors [c,e], Anne Amalie Elgaard Thorup [b,c,f], Kerstin Jessica Plessen [a,c,g], Merete Nordentoft [b,c,f], Jens Richardt Møllegaard Jepsen [a,b,c,h,i]

[a] Child and Adolescent Mental Health Centre, Mental Health Services, Gentofte Hospitalsvej, Entrance 15, 4th Floor, DK-2900, Hellerup, Copenhagen, Capital Region of Denmark, Denmark
[b] Copenhagen Research Centre for Mental Health – CORE, Mental Health Centre Copenhagen, Mental Health Services, Copenhagen Gentofte Hospitalsvej 15, 4th Floor, Hellerup, DK-2900 Copenhagen, Capital Region of Denmark, Denmark
[c] The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Fuglesangs Allé 26, DK-8210 Aarhus, Denmark
[d] Section of Biostatistics, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, DK-10104 Copenhagen, Denmark
[e] Psychosis Research Unit, Aarhus University Hospital, Palle Juul-Jensens Boulevard 175, DK-8200 Aarhus, Denmark
[f] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen, Denmark
[g] Service of Child and Adolescent Psychiatry, Department of Psychiatry, University Medical Center, University of Lausanne, Avenue d'Echallens 9, CH-1004 Lausanne, Switzerland
[h] Center for Neuropsychiatric Schizophrenia Research, Mental Health Services, Glostrup, Ndr. Ringvej 29-67, Copenhagen DK-2600, Capital Region of Denmark, Denmark
[i] Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Services, Nordstjernevej 41, Glostrup, Copenhagen DK-2600, Capital Region of Denmark, Denmark

ARTICLE INFO

Article history:
Received 1 November 2019
Received in revised form 20 December 2019
Accepted 20 December 2019
Available online xxxx

Keywords:
Neurodevelopment
Offspring
Endophenotype
Olfactory functioning

ABSTRACT

Background: Odor identification deficits occur in individuals with schizophrenia and their unaffected first-degree relatives, while deficits are less pronounced in individuals with bipolar disorder. We hypothesized that children at familial high-risk for schizophrenia (FHR-SZ) show odor identification deficits compared to population-based controls and that children at familial high-risk for bipolar disorder (FHR-BP) perform intermediate.
Methods: Odor identification was assessed at age 7 in 184 children with FHR-SZ, 106 children with FHR-BP, and 186 population-based controls with the Brief Smell Identification Test. Dimensional and predefined categorical outcomes were used in the analyses. Potential relationships with psychopathological, cognitive, and home environmental variables were conducted using hierarchical and logistic multiple regression analyses.
Results: ANOVA revealed no between-group differences in odor identification. Using the recommended cut-off (below 5), we found a significantly greater proportion of boys at FHR-SZ than population-based boys with an abnormal odor identification ($p = .013$). However, a supplementary analysis using a Danish-based cut-off (below 4) did not support this. All children showed significant, positive associations of odor identification with female gender, social responsiveness, and verbal working memory. Lower social responsiveness predicted abnormal odor identification in boys at FHR-SZ, only using the recommended cut-off.
Conclusions: Odor identification efficacy and risk status appear independent in this early developmental phase. Using the recommended threshold, abnormal odor identification is more frequent in young boys at FHR-SZ than in population-based boys and is linked to lower social responsiveness. The validity of these results is questioned by non-significant differences in the rates when using an exploratory Danish-based threshold.

1. Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are severe mental disorders that are intricately connected partially through shared genetic risk factors (Brainstorm et al., 2018). Both are considered as neurodevelopmental disorders, with social, emotional, and cognitive deficits that start long before the onset of the illness (Insel, 2010), although some of the findings regarding the neurodevelopmental

* Corresponding author at: Gentofte Hospitalsvej 15, 4th floor, DK-2900 Hellerup, Denmark.
E-mail address: anna.hester.ver.loren.van.themaat.01@regionh.dk (A.H. Ver Loren van Themaat).

https://doi.org/10.1016/j.schres.2019.12.028
0920-9964/

nature of BP are still contradictory (Sanches et al., 2008). To study the developmental trajectories prior to illness onset, one can examine children of patients with SZ or BP. Children of a parent with SZ or BP carry the genetic liability for these disorders and are therefore at familial high-risk (FHR) to develop such illnesses themselves (SZ: 12% and BP: 6%) (Rasic et al., 2014). By investigating relatively young children at FHR for SZ (FHR-SZ) and BP (FHR-BP), we can provide evidence of distinct or shared developmental pathways of two severe mental disorders at an early phase, without the consequences of having the illness.

Impairments of olfaction is a likely endophenotype for SZ (Moberg et al., 2014; Turetsky et al., 2008). A recent meta-analysis comparing olfaction in patients with chronic SZ to that in healthy controls found a medium-large effect size for odor identification deficits in patients with SZ, the highest effect size among other aspects of olfaction (e.g. odor detection threshold and odor discrimination) (Moberg et al., 2014). Unaffected FDR of patients with SZ primarily show deficits in odor identification (Cohen's d: 0.25–0.69) (Compton et al., 2006; Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008) while individuals with first-episode psychosis (Kamath et al., 2018) and individuals at clinical high-risk (CHR) for psychosis (Turetsky et al., 2018) also show deficits in odor discrimination. This may underline that identification deficits precede further deterioration of olfactory functioning once the illness has commenced. Despite olfactory studies in other neurodevelopmental disorders (Kronenbuerger et al., 2018; Muratori et al., 2017), little is known about odor identification in patients with BP. One study found odor deficits in both psychiatric groups, however, deficits were more pronounced in patients with SZ than in those with BP (Cumming et al., 2011).

Odor identification deficits in SZ are consistently present irrespective of illness phase, age, smoking status, task complexity, or medication status (Kopala et al., 1995; Moberg et al., 2014). Despite observations of odor identification deficits in both males and females with SZ, some found more pronounced deficits in male patients with SZ (Malaspina et al., 2012; Seidman et al., 1997). Also, odor identification deficits are correlated with negative symptoms (Pearson's *r*: 0.43–0.47) (Brewer et al., 1996; Corcoran et al., 2005; Goudsmit et al., 2003), but not with positive symptoms (Corcoran et al., 2005; Malaspina and Coleman, 2003; Malaspina et al., 2012; Seidman et al., 1997). In individuals with CHR of psychosis, odor identification deficits are suggested to predict transition to psychosis (Brewer et al., 2003) and in individuals with first-episode psychosis, deficits predict the persistence of negative and cognitive/disorganized symptoms after 1 year (Good et al., 2006).

In addition, cognitive links to olfaction exist because successful identification of odors partially relies on semantic and olfactory knowledge obtained through prior experience with these odors. Accordingly, odor identification is associated with intelligence, verbal memory, and conceptualization (the ability to form abstract concepts) (Pearson's *r*: 0.28–0.58) (Brewer et al., 1996; Compton et al., 2006; Corcoran et al., 2005). Moreover, lower social drive (defined as less interest in and initiation of social interaction) accounts for 23% of the variance of odor identification in SZ and explains the relationship between odor identification deficits and negative symptoms (Malaspina and Coleman, 2003). This suggests common pathophysiology and perhaps shared neurobiological mechanisms that underlie olfaction and social functioning in SZ.

Finally, the olfactory bulbs, important for their direct connections to the primary olfactory cortex, have been implicated in the psychopathology of SZ; patients with SZ show reduced volumes of the olfactory bulbs (Turetsky et al., 2000). Notably, smaller olfactory bulb volumes are reported in their unaffected first-degree relatives (FDR) (Turetsky et al., 2003) and also in male adolescents, but not female, with CHR for psychosis whose reduced volumes correlate with negative symptoms (Turetsky et al., 2018). Therefore, the smaller olfactory bulb volume observed both in patients with SZ as well as their unaffected FDR might represent a risk indicator for SZ.

The current study assessed whether two FHR groups for SZ or BP show common impairment in odor identification. Therefore, we compared children at FHR-SZ, children at FHR-BP, and population-based controls (PBCs) on a test of odor identification (Doty, 2001). We hypothesized that both FHR groups would demonstrate significant odor identification deficits compared to the controls, with more pronounced deficits for children at FHR-SZ than for children at FHR-BP. Additionally, we exploratively analyzed whether odor identification is differentially associated with other cognitive functions in the three groups. The choice of cognitive functions was based on previously observed associations between odor identification and cognition (Compton et al., 2006; Larsson et al., 2004) as well as on earlier studies of cognitive deficits in children at FHR-SZ or FHR-BP (Burton et al., 2018; Christiani et al., 2019; Hemager et al., 2018). Cognitive functions were expected to relate positively with olfaction. Exploratively, this study also included demographic, psychopathological, and home environmental characteristics to provide a comprehensive identification of potential cross-sectional relations to the child's odor identification. We expected less symptomatology and a more stimulating and stable home environment to be positively associated with olfaction.

2. Methods

2.1. Study design and participants

This study is part of the Danish High Risk and Resilience Study - VIA 7 which is a nationwide population-based cohort study of 522 children. The cohort was collected from the national population of 7-year-old children with a parent diagnosed with schizophrenia spectrum psychosis, defined as schizophrenia, delusional disorder or schizoaffective disorder (ICD 10-codes: F20, F22, F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99), or bipolar disorder (ICD 10-codes F30 or F31 or ICD 8-codes 296.19 or 296.39), and a control group with none of these two disorders (other diagnoses were allowed). The VIA 7 study design is described elsewhere (Thorup et al., 2015). The project was approved by The Danish Data Protection Agency. The study procedures were aligned with the guidelines of the National Committee for Health Research Ethics, although formal ethical approval was not required due to its observational design. With the help of the Danish Civil Registration System (Pedersen et al., 2006) and The Danish Psychiatric Central Research Register (Mors et al., 2011), data from 202 children at FHR-SZ, 120 children at FHR-BP, and 200 PBC children were collected; controls were matched on age, sex, and municipality to the children at FHR-SZ. Controls were not matched to children at FHR-BP, however, the groups were comparable on the parameters in question. Data were collected between January 1st, 2013 and January 31st, 2016. Legal guardians of the children gave written informed consent to participate after receiving a thorough oral and written explanation of the study. Participants were required to have Danish as their first language. <2% of the participants decided to stop study participation after giving written informed consent.

2.2. Procedures

Odor identification was assessed as part of a comprehensive assessment battery by trained psychologists, medical doctors, and nurses. While most of the assessments took place at the research sites in Copenhagen and Aarhus, Denmark, in few cases the test was performed in the child's homes (only if there was a quiet room with no distractions). Child assessors were blinded to the risk status of the children. Caregivers were asked about the child's health, for example, current nasal infections, allergies, sinus operations, or other complications that may have a negative impact on the child's olfaction.

Please cite this article as: A.H. Ver Loren van Themaat, M.J. Uddin, C.J. Christiani, et al., Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorde..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.12.028

2.3. Measures

2.3.1. Odor identification testing

To assess odor identification, we used the Brief Smell Identification Test (BSIT) (Version A, Danish version) which is a validated, standardized, non-invasive, and quantitative test for all ages above 5 years (Doty, 2001). With its 12 items (menthol, soap, gasoline, rose, cherry, cloves, leather, strawberry, lilac, pineapple, smoke, and lemon), BSIT is a shorter version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984) and contains items based upon world-wide reports (e.g. from France, Sweden, Russia, China, and Japan) to broader cross-cultural familiarity (Doty, 2001). Items were presented as micro-encapsulated odorant strips in a "scratch 'n sniff", forced multiple-choice format; each odor corresponds to one of four odors names. To avoid potential bias from differences in the reading ability of these young children, the assessor neutrally read out the four multiple-choice options to all children. After the assessor scratched and the child sniffed, the options were repeated and thereafter the child verbally reported her/his choice which was registered by the assessor. The assessor repeated the four multiple-choice options as many times as the child wanted.

The primary outcome is the sum of correctly identified odors, providing a total score ranging from 0 up to 12. Thus, a higher BSIT total score reflects better odor identification. The secondary outcome is the recommended sex- and age-based cut-off scores to distinguish individuals with normosmia (normal olfaction) from those with microsmia, defined as a significant impairment in odor identification which interferes with functioning. The cut-off score for microsmia is a BSIT total score below 5 for boys at ages 5–9 and a BIST total score below 4 for girls at ages 5–9 (Doty, 2001).

2.3.2. Psychopathological measures

The Child Behavior Checklist (CBCL) (Achembach and Rescorla, 2001) and the Attention Deficit/Hyperactivity Disorder – Rating Scale (ADHD-RS) (Makransky and Bilenberg, 2014) assessed the severity of dimensions of psychopathology. These questionnaires were accomplished by the primary caregiver. The child's teacher filled in the Social Responsiveness Scale (SRS), providing an index of social reciprocity reflective of the severity of potential autistic traits (Constantino and Gruber, 2005). (The study cohort's dimensional psychopathology is described elsewhere (Christiani et al., 2019; Ellersgaard et al., 2018).

2.3.3. Cognitive functioning

The Reynold's Intellectual Screening Test (RIST) (Reynolds and Kamphaus, 2003) assessed intelligence. Verbal memory was assessed with two subtests of Test of Memory and Learning, 2nd version (TOMAL-2) (Reynolds and Voress, 2007), Memory for Stories (MFS) and Word Selective Reminding (WSR; the immediate and delayed conditions in both). MFS measures a verbal free-recall of orally presented stories while WSR is a verbal learning test requiring participants to recall an orally presented list of words. MFS and WSR assess different aspects of verbal memory; semantic recall (MFS) and learning and immediate recall functions (WSR), and these test scores were kept separate in the analyses (Reynolds and Bigler, 1996). Processing speed was assessed with the subtests Coding and Symbol Search from the Wechsler Intelligence Scale for Children – fourth edition (WISC-IV) (Wechsler, 2003); the subtest Letter-Number Sequencing was used to assess verbal working memory. The Rapid Visual Information Processing (RVP) A' (A prime) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) assessed sustained attention (Sahakian and Owen, 1992). (The study cohort's neurocognitive functioning is described elsewhere (Hemager et al., 2018).)

2.3.4. Environmental exposure

To evaluate the child's home environment of potential relevance for olfaction we choose one subscale ("Active Stimulation") of the Middle Childhood – Home Observation for Measurement of the Environment (MC-HOME) (Bradley et al., 1988). The Active Stimulation Subscale evaluates whether the family actively stimulates the child broadly. To illustrate, one item asked whether the child is taken on trips outside their home, village, or city, which would potentially increase the chance of smelling new odors. The primary caregivers social functioning was assessed with the Personal and Social Performance scale (PSP) (Morosini et al., 2000).

2.4. Statistical analyses

To compare the demographic, psychopathological, cognitive, and home environmental characteristics of the three study groups (FHR-SZ, FHR-BP, and PBC), we used parametric and non-parametric statistical methods as appropriate. We compared continuous variables across the risk groups using univariate analysis of variance (ANOVA) or Welch's ANOVA in case of heterogeneity of variance. We performed post-hoc multiple comparisons by means of Bonferroni corrections and Games-Howell (following the Welch's ANOVA). We compared the binary variable and the categorical outcome measure across the risk groups using chi-square tests for independence.

All test scores were standardized into z-scores with the mean and standard deviation of the PBCs as reference. A negative z-score reflect poorer performance. Two composite verbal memory z-scores were constructed (the MFS immediate and delayed scores as well as the WSR immediate and delayed scores) and one composite z-score for processing speed (the WISC-IV subtests Coding and Symbol Search scores). Composite z-scores were re-standardized.

Odor identification was analyzed 1) using the primary dimensional outcome (BSIT total score) with a two-way ANOVA with group and sex as fixed factors to examine the potential between-group differences and 2) using the secondary categorical outcome with a chi-square test of independence to examine the distribution of normosmic versus microsmic. We also performed separate one-way ANOVA's stratified for sex. Exploratively, we used the psychopathological, cognitive, and home environmental variables as predictors in the hierarchical multiple regression analysis on the dimensional outcome, including their interaction with group. Additionally, we conducted a sex-specific multiple logistic regression analysis. All basic assumptions of regressions analyses were checked. The hierarchical multiple regression analysis was conducted with risk status, sex, and age entered in the first step (Model 1), psychopathological and cognitive variables in the second step (Model 2), and home environmental variables in the third step (Model 3) (Table 4). Interaction terms with FHR*variables were included but did not reach statistical significance (data not shown). The sex-specific multiple logistic regression analysis on the categorical outcome was conducted with "normosmic" and "microsmic" as dependent variable. Due to lack of power, three predictors that were theoretically most relevant were selected: verbal memory, social reciprocity, and verbal working memory. As the means of the Danish PBC boys (Cohen's $d = 1.07$) and girls (Cohen's $d = 0.78$) were unexpectedly low compared to the normative data of the American boys and girls, we exploratively defined microsmia as a score <1.5 SD below the mean of the Danish PBC boys and girls. Using this definition, both boys and girls who scored below 4 were identified as microsmic, i.e. no change in the threshold for girls compared to the American threshold. We did all analyses in SPSS Statistics software (version 22.0).

3. Results

3.1. Cohort and demographic characteristics

The entire VIA 7 study cohort included 522 children (202 (39%) children at FHR-SZ, 120 (23%) at FHR-BP, and 200 (38%) PBC). BSIT data of 46 children (non-significantly differently distributed across the groups) were not analyzed due to either missing data (3 FHR-SZ, 4 FHR-BP, and 3 PBC) or excluded because sickness may have influenced olfaction (15

Please cite this article as: A.H. Ver Loren van Themaat, M.J. Uddin, C.J. Christiani, et al., Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorde..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.12.028

FHR-SZ, 10 FHR-BP, and 11 PBC). Thus, data from 476 children were analyzed and there were no significant group differences on age or sex (Table 1).

3.2. Odor identification

The main effect of group in the two-way ANOVA conducted on the primary dimensional outcome (the BSIT total score) showed no significant difference ($F = 0.94$, $p = .390$) while the main effect of sex showed a significant difference ($F = 25.00$, $p < .001$) (Table 2). The interaction effect was not significant ($F = 0.962$, $p = .383$) (supplementary material: Sex-stratified ANOVA's on BSIT total score). The secondary categorical outcome showed no significantly different distribution of normosmic versus microsmic across the groups including both sexes ($\chi^2 = 2.05$, $p = .36$). However, a significantly greater proportion of boys at FHR-SZ (27 out of 98; 28%) than PBC boys (13 out of 100; 13%) was classified as microsmic ($\chi^2 = 6.48$, $p < .05$) (Table 3). The proportion of boys at FHR-BP that fell into the microsmic group (21%) was in between boys at FHR-SZ and PBC boys but these differences were non-significant in both directions (see Fig. 1). We found no significant differences in distributions across groups for girls ($\chi^2 = 3.10$, $p = .21$). Using the microsmic threshold based on the Danish PBC boys´ mean and SD, there was no significant between-group difference in the proportion rates for boys, with 11% of the boys at FHR-SZ, 8% of boys at FHR-BP, and 7% of PBC boys having microsmia ($p = .571$). The distribution of the test scores can be found in the supplementary material (Box-and-whisker plots of test scores of total group, boys, and girls).

3.3. Psychopathological, cognitive, and home environmental characteristics

The ANOVA showed significant differences in psychopathological, cognitive, and home environmental measures across the three groups (Table 1). Results on the full cohort are published elsewhere (Christiani et al., 2019; Ellersgaard et al., 2018; Hemager et al., 2018) and thus not replicated here (supplementary material: Results on psychopathological, cognitive, and environmental exposure variables).

Table 2
Two-way ANOVA on a dimensional score of odor identification in 7-year-old children with familial high-risk group and sex as fixed factors.

	Parameter estimate (B)	Confidence interval (95%)	p-value
Intercept	6.250	5.930–6.570	<0.001
FHR-SZ versus PBC	−0.274	−0.667–0.118	0.170
FHR-BP versus PBC	−0.129	−0.588–0.331	0.583
Female versus male	0.958	0.611–1.306	<0.001

Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls.

3.4. Potential relationships between odor identification and aspects of psychopathology, cognitive functioning, and the home environment

The exploratory hierarchical regression analysis on potential associations between variables on psychopathology, cognition, and the home environment and odor identification revealed that BSIT total score was only significantly associated with sex, efficacy of social responsiveness, and verbal working memory functioning ($R^2 = 0.17$, $p < .001$) (Table 4). The likelihood of falling into the American-based microsmic group was, for boys at FHR-SZ, significantly associated with less social reciprocity (pseudo $R^2 = 0.10$, $p = .023$) whereas there was no significant association for verbal working memory or verbal memory (Table 5). A supplementary analysis was performed using the Danish-based threshold for microsmia, which showed no significant association between social reciprocity and microsmia ($p = .984$) (supplementary

Table 1
Demographic, psychopathological, cognitive, and home environmental characteristics of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based control (PBC) presented in raw scores and pairwise comparisons between groups.

Variables, mean (SD)	Assessed function	N	FHR-SZ	N	FHR-BP	N	PBC	*P*-value	Pairwise Comparisons (*P* value)		
									FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Demographics											
Children		184		106		186					
Female %			46.7		43.4		46.2	0.067[a]			
Age - years at inclusion			7.8 (0.2)		7.8 (0.2)		7.8 (0.2)	0.850			
Dimensions of psychopathology											
CBCL Internalizing subscale	Internalizing problem behavior	179	6.5 (6.0)	99	6.4 (6.4)	180	4.9 (4.5)	0.007[b]	0.010	0.104	0.983
CBCL Externalizing subscale	Externalizing problem behavior	178	7.7 (7.3)	100	6.2 (6.8)	180	4.1 (4.8)	<0.001[b]	<0.001	0.022	0.182
ADHD-RS Inattention subscale	Inattentive symptoms	179	6.8 (5.3)	102	6.6 (5.5)	180	4.8 (4.2)	<0.001[b]	<0.001	0.016	0.933
ADHD-RS Hyperactive-impulsive subscale	Hyperactive-Impulsive symptoms	179	7.0 (5.7)	102	6.4 (5.2)	180	5.4 (4.5)	0.016[b]	0.014	0.271	0.669
SRS	Social Responsiveness	157	37.3 (26.1)	93	33.7 (32.3)	159	24.9 (20.6)	<0.001[b]	<0.001	0.052	0.640
Cognition											
RIST	Intelligence	184	102.5 (11.5)	106	104.1 (9.0)	184	105.1 (10.0)	0.067[b]	0.053	0.715	0.335
MFS Immediate	Verbal memory (immediate)	183	19.3 (10.1)	106	20.7 (10.0)	185	19.8 (9.4)	0.534	1.00	1.00	0.790
MFS Delayed	Verbal memory (delayed)	183	14.9 (9.1)	106	17.0 (9.3)	185	15.4 (8.4)	0.149	1.00	0.425	0.163
WSR Immediate	Verbal memory (immediate)	177	38.6 (5.7)	105	39.7 (4.7)	185	39.0 (5.0)	0.246	1.00	0.944	0.283
WSR Delayed	Verbal memory (delayed)	176	6.1 (2.0)	104	6.4 (1.5)	182	6.2 (1.6)	0.326	1.00	0.913	0.407
Coding	Processing speed	183	26.6 (7.7)	104	28.9 (7.3)	186	29.4 (7.1)	0.001	0.001	1.00	0.037
Symbol Search	Processing speed	179	15.5 (5.3)	104	17.4 (4.9)	181	17.2 (5.3)	0.001	0.005	1.00	0.008
Letter-Number Sequencing	Verbal working memory	181	12.5 (4.1)	105	13.8 (3.9)	186	13.8 (3.5)	0.001	0.003	1.00	0.014
RVP A′	Attention	173	0.89 (0.06)	104	0.90 (0.06)	180	0.90 (0.05)	0.038	0.032	1.00	0.557
Home environment											
Active Stimulation	Stimulating home environment	179	5.6 (1.5)	105	5.6 (1.4)	185	5.9 (1.5)	0.061	0.078	0.293	1.00
PSP	Parental personal and social functioning	182	73.4 (14.3)	106	74.9 (14.1)	185	84.3 (9.2)	<0.001	<0.001	<0.001	0.989

[a] Pearson chi-square.
[b] No homogeneity of variance thus Welch's ANOVA and multiple comparisons with Games-Howell. Abbreviations: A′, A prime; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale; CBCL, Child Behavior Checklist; FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; MFS, Memory for Stories; PSP, Personal and Social Performance; PBC, Population-Based Controls; RIST, Reynold's Intellectual Screening Test; RVP, Rapid Visual Information Processing; SRS, Social Responsiveness Scale; SD, standard deviation; WSR, Word Selective Reminding. See (Christiani et al., 2019; Ellersgaard et al., 2018; Hemager et al., 2018) for results on the full cohort.

Please cite this article as: A.H. Ver Loren van Themaat, M.J. Uddin, C.J. Christiani, et al., Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorde..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.12.028

Table 3
Categories of normal and abnormal olfaction of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based control (PBC).

Categorical, abnormal odor identification[a]	N	FHR-SZ	N	FHR-BP	N	PBC	P-value	Chi-square tests (*P* value)		
								FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
All children, %	29	15.8	15	14.2	20	10.8	0.358[b]			
Boys, %	27	27.6	13	21.7	13	13.0	0.039[b]	0.013	0.185	0.455
Girls, %	2	2.3	2	4.3	7	8.1	0.213[b]			

[a] Abnormal odor identification boys, BSIT total score < 5; girls, BSIT total score < 4 (Doty, 2001).
[b] Pearson chi-square test; Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls.

material: Univariate Logistic Regression Analysis of social responsiveness on odor identification of boys at FHR-SZ).

4. Discussion

The current study investigated odor identification in 7-year-old children at FHR-SZ or FHR-BP, and PBCs (their parents may have other diagnoses than SZ or BP). The three groups including both sexes did not differ significantly in odor identification efficacy (dimensional data). Analyses of the rates of normosmic versus microsmic (using recommended thresholds) of children in the risk groups showed that a significant higher percentage of boys at FHR-SZ (28%) were classified as microsmic compared to population-based boys (13%). The proportion of microsmic boys at FHR-BP was not significantly different from that of boys at FHR-SZ nor to that of population-based boys (Fig. 1). However, we did not find significant group differences in the rates of normosmic versus microsmic boys using a threshold of 1.5 SD below the Danish population-based boys´ mean. No significant differences were found in the proportions of microsmic girls across the groups. The exploratory regression models indicated that better odor identification was positively related to being female, better social reciprocity (fewer autistic traits), and better verbal working memory, whereas we found no significant relationships with the other cognitive, psychopathological, and home environmental factors. Additionally, boys at FHR-SZ with higher levels of autistic traits were more likely to be classified as microsmic than those with lower levels of autistic traits whereas verbal working memory and verbal memory were both unrelated to microsmia in this group. However, this association was only observed using the American-based threshold and not when using the Danish-based threshold for microsmia.

The results indicate that 7-year-old children at FHR-SZ or FHR-BP do not show odor identification deficits. Despite the results from the American-based threshold suggested that boys at FHR-SZ are more likely of having microsmia than population-based boys, this was not supported by findings based on a Danish-based threshold and it was not in line with the result of the dimensional analysis. The large difference (Cohen's $d = 1.07$) between means of odor identification of American boys and Danish population-based boys may question the cross-cultural validity of the BSIT.

First, our findings in young children at FHR-SZ or FHR-BP expand on the literature of olfactory functioning in the prodromal phase of psychosis-related disorders and in patients with SZ. Previous studies observed impaired odor identification in youth with CHR for psychosis (Brewer et al., 2003; Kamath et al., 2014; Keshavan et al., 2009; Woodberry et al., 2013). Interestingly, our finding shows that odor identification is not significantly impaired in young children at FHR-SZ or FHR-BP, suggesting that olfactory deficits may arise in the prodromal phase, which may have implications for the underlying origin of these deficits. Second, across the three groups, the efficacy of olfaction identification was associated with severity of autistic traits and verbal working memory while there were no associations to other cognitive or home environmental factors. The link between olfaction and social cognition may glean from common brain structures underpinning both areas of functioning (Malaspina and Coleman, 2003). Third, several studies involving unaffected FDR (including both sexes) observed dimensional olfactory differences compared to healthy controls (Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008). The discrepancy

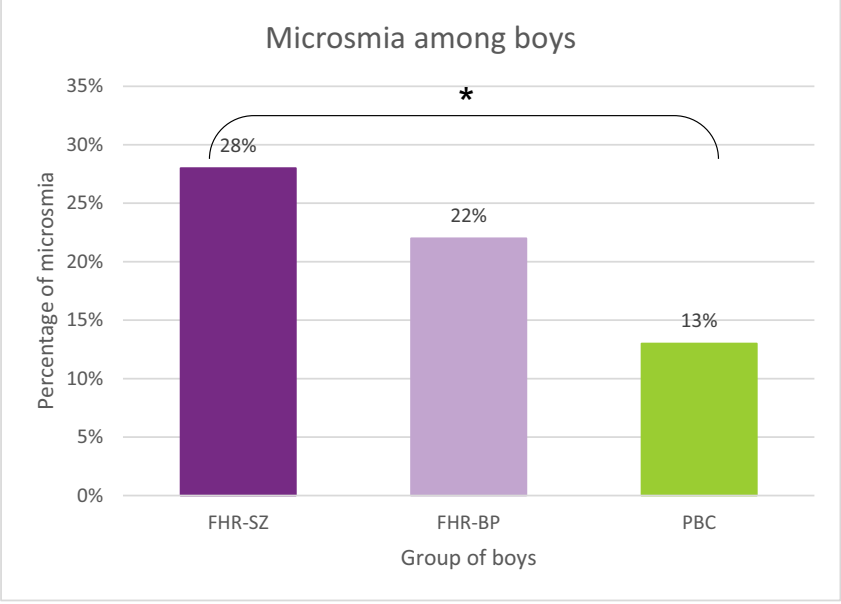

Fig. 1. Percentage of abnormal odor identification among boys at FHR-SZ, FHR-BP or PBC boys. Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls. * Significant at 0.05% level.

Please cite this article as: A.H. Ver Loren van Themaat, M.J. Uddin, C.J. Christiani, et al., Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorde..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.12.028

Table 4
Hierarchical Regression Analysis of demographical, psychopathological, cognitive, and home environmental predictors on odor identification of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based control (PBC).

Predictors	Assessed function	Model 1	95% CI	Model 2	95% CI	Model 3	95% CI
		Estimate		Estimate		Estimate	
Demographics							
High-risk status		0.06	−0.04; 0.18	0.02	−0.09; 0.14	0.01	−0.11; 0.13
Sex (boys)		−0.24*	−0.68; −0.29	−0.19*	−0.57; −0.18	−0.19*	−0.58; −0.18
Age		0.05	−0.24; 0.69	0.05	−0.22; 0.73	0.06	−0.21; 0.74
Dimensions of psychopathology							
CBCL Internalizing Subscale	Internalizing problem behavior			0.00	−0.10; 0.10	−0.01	−0.10; 0.09
CBCL Externalizing Subscale	Externalizing problem behavior			−0.12	−0.20; 0.02	−0.12	−0.20; 0.02
ADHD-RS Inattention Subscale	Inattentive symptoms			0.00	−0.10; 0.12	0.01	−0.10; 0.12
ADHD-RS Hyperactive-impulsive Subscale	Hyperactive- and impulsive symptoms			0.10	−0.03; 0.21	0.10	−0.03; 0.21
SRS	Social Responsiveness			0.18*	0.05;0.23	0.17*	0.04; 0.22
Cognition							
RIST	Intelligence			0.02	−0.09; 0.13	0.01	−0.10; 0.12
MFS (composite)	Verbal memory			0.11	0.00; 0.20	0.10	−0.00; 0.20
WSR (composite)	Verbal memory			0.06	−0.05; 0.14	0.06	−0.05; 0.15
Processing speed (composite)	Processing speed			−0.01	−0.12; 0.10	−0.02	−0.13; 0.10
Letter-number sequencing	Verbal working memory			0.13*	0.02; 0.22	0.13*	0.02; 0.22
RVP A′	Attention			−0.02	−0.11; 0.08	−0.02	−0.11; 0.08
Home environment							
Active stimulation	Stimulating home environment					0.05	−0.06; 0.15
PSP	Parental personal and social functioning					0.03	−0.05; 0.10
Model squared R		0.064		0.168		0.172	
F change		8.870		4.290		0.781	
P-value		<0.001		<0.001		0.459	

Model 1: High-risk Status, sex, age; Model 2: High-risk Status, sex, CBCL Internalizing subscale, CBCL Externalizing subscale, ADHD-RS Inattention subscale, ADHD-RS Hyperactive-impulsive subscale, SRS, RIST, MFS (composite), WSR (composite), Processing Speed (composite), Letter-Number Sequencing, RVP A′; Model 3: High-risk Status, sex, CBCL Internalizing subscale, CBCL Externalizing subscale, ADHD-RS Inattention subscale, ADHD-RS Hyperactive-impulsive subscale, SRS, RIST, MFS (composite), WSR (composite), Processing Speed (composite), Letter-Number Sequencing, RVP A′, Active Stimulation, PSP. Abbreviations: A′, A prima; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale; CBCL, Child Behavior Checklist; CI, Confidence Interval; FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; MFS, Memory for Stories; PSP, Personal and Social Performance; PBC, Population-Based Controls; RIST, Reynold's Intellectual Screening Test; RVP, Rapid Visual Information Processing; SRS, Social Responsiveness Scale; WSR, Word Selective Reminding.
* Indicates significance ($p < .05$).

between our results and that of others may be attributed to the older mean age in these studies (mean ages: 35 to 43 years) (Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008), as normal maturation of olfaction is rapid during adolescence (Doty et al., 1984), olfactory maturational impairments may evolve in the later developmental phase. According to the developmental lag hypothesis, neurocognitive functions may worsen with increasing age due to slower than normal maturational growth (Reichenberg et al., 2010). Longitudinal research of odor identification could potentially specify the time point when olfactory deficits would arise.

Our explorative regression model with significant effects of sex, severity of autistic traits, and verbal working memory explained 17% of the variance of odor identification. The observed association between verbal working memory and odor identification is consistent with a finding in adult, unaffected FDR of patients with SZ.[9] Together this suggests that verbal working memory may be involved and thus impact odor identification in childhood and adulthood. Also, our results suggest that odor identification at this young age appears independent of intelligence, verbal memory, processing speed, sustained attention, and severity of ADHD-symptoms. This is in line with the lack of association between odor identification and intelligence in 11-year-old children with ASD (Muratori et al., 2017). Similarly, odor identification was associated with social impairments but not ADHD, depression, nor anxiety symptoms nor with executive functioning in adult patients with Tourette's Syndrome (Kronenbuerger et al., 2018). While our findings indicate that more autistic traits predict microsmia in boys at FHR-SZ, supporting the idea that social and olfactory dysfunction share common pathophysiology (Brewer et al., 1996; Goudsmit et al., 2003), this finding is not supported when using the, more relevant, Danish-based threshold for microsmia.

Strengths of this study include 1) the large sample size of children examined at the same age, 2) the inclusion of both children at FHR-SZ and FHR-BP, 3) valid olfactory data through exclusion of children with medical conditions involving the respiratory tracts, and 4) the blind status of assessors. However, several limitations to this study need to be addressed. First, the cross-sectional nature limits the possibility to study the maturation of olfaction, which could characterize the maturational development of olfactory functioning. Second, the cross-cultural validity of the BSIT may be questionable, as the recommended microsmic threshold may not be applicable to young Danish boys.

Table 5
Multiple Logistic Regression Analysis of psychopathological and cognitive measures on odor identification of boys at familial high-risk for schizophrenia (FHR-SZ).

Covariates	Assessed function	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
SRS	Social responsiveness	1.61*	1.06–2.45	1.62*	1.07–2.46	1.59*	1.07–2.38
MFS (composite)	Verbal memory	1.27	0.84–1.91	1.29	0.87–1.91		
Letter-Number Sequencing	Verbal working memory	1.08	0.65–1.80				

Model 1: SRS, MFS (composite), Letter-Number Sequencing; Model 2: SRS, MFS (composite); Model 3: SRS. Abbreviations: CI, Confidence interval, MFS, Memory for Stories; OR, Odds Ratio; SRS, Social responsiveness Scale.
* Indicates significance ($p < .05$).

Please cite this article as: A.H. Ver Loren van Themaat, M.J. Uddin, C.J. Christiani, et al., Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorde..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.12.028

Third, the restricted number of items of the BSIT (12 items) may have limited the sensitivity to detect subtle differences between the groups, especially because the majority of these children did not have any psychiatric diagnoses, and the test was originally designed for patient samples. Future studies should include tests that examine more aspects of olfaction to broaden its characterization, such as odor sensitivity and discrimination. Additionally, subthreshold symptoms of psychosis should be included in the analyses (Keshavan et al., 2009), as well as analyses of subgroups of parental clinical diagnoses.

In summary, no significant difference in odor identification was observed between children at FHR-SZ, children at FHR-BP and control children at age 7. Regarding previous studies reporting odor identification deficits in youth at CHR for psychosis, our finding indicates that olfactory dysfunction might be part of the prodromal phase or appear in a later developmental phase in older subjects at FHR-SZ and possibly FHR-BP, but olfactory dysfunction may not be part of the earlier developmental phase. Shared risk factors for SZ and BP may not be involved in odor identification at this young age. Further, our dimensional findings emphasize the link between olfaction and sex, social skills and verbal working memory in children at age 7, independent of risk groups.

Contributors

AAET, JRMJ, OM, MN, and KJP developed the study design, provided methodological advice, and supervised the conduct of the study. BKB, DE, KSS, CJC, NH, DG, AG collected the data. AHVT, JMD, and JRMJ made the statistical plans and performed the analyses. AHVT conducted the literature search and created the tables and figures. AHVT and JRMJ wrote the first draft. All authors interpreted data, commented on and edited the manuscript, and agreed on the final version.

Funding body agreements and policies

This study was supported by The Mental Health Services - in the Capital Region of Denmark, the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen (Grant No. J.NR 11531), Aarhus University, Central Denmark Region, and The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) (Grant Nos. R102-A9118 and R155-2014-1724).

Declaration of competing interest

There are no conflicts of interest for any of the authors.

Acknowledgments

We wish to thank all children and families participating in the Danish High Risk and resilience Study-VIA 7. Also we want to thank Carsten Bøcker Pedersen and Marianne Giørtz Pedersen for assistance with the Danish Registers; Jessica Ohland for her assistance with data management; Thomas Werge, Preben Bo Mortensen, David Hougaard, and Anders Børglum for the collaboration in iPSYCH; Anne Ranning, Heidi Jensen, Marianne Melau, Mette Skjærbæk, Cecilie Gregersen, Kate Kold Zahle, Henriette Stadsgaard, and Maria Toft Henriksen for assistance with data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.12.028.

References

Achembach, T.M., Rescorla, L.A., 2001. Manual for the ASEBA School-age Forms & Profiles. University of Vermont, Burlington, VT.

Bradley, R.H., Caldwell, B.M., Rock, S.L., Hamrick, H.M., Harris, P., 1988. Home observation for measurement of the environment: development of a home inventory for use with families having children 6 to 10 years old. Contemp. Educ. Psychol. 13 (1), 58–71.

Brainstorm, C., Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G.J., Gormley, P., Malik, R., Patsopoulos, N.A., Ripke, S., Wei, Z., Yu, D., Lee, P.H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., Berr, C., Letenneur, L., Hannequin, D., Amouyel, P., Boland, A., Deleuze, J.F., Duron, E., Vardarajan, B.N., Reitz, C., Goate, A.M., Huentelman, M.J., Kamboh, M.I., Larson, E.B., Rogaeva, E., St George-Hyslop, P., Hakonarson, H., Kukull, W.A., Farrer, L.A., Barnes, L.L., Beach, T.G., Demirci, F.Y., Head, E., Hulette, C.M., Jicha, G.A., Kauwe, J.S.K., Kaye, J.A., Leverenz, J.B., Levey, A.I., Lieberman, A.P., Pankratz, V.S., Poon, W.W., Quinn, J.F., Saykin, A.J., Schneider, L.S., Smith, A.G., Sonnen, J.A., Stern, R.A., Van Deerlin, V.M., Van Eldik, L.J., Harold, D., Russo, G., Rubinsztein, D.C., Bayer, A., Tsolaki, M., Proitsi, P., Fox, N.C., Hampel, H., Owen, M.J., Mead, S., Passmore, P., Morgan, K., Nothen, M.M., Rossor, M., Lupton, M.K., Hoffmann, P., Kornhuber, J., Lawlor, B., McQuillin, A., Al-Chalabi, A., Bis, J.C., Ruiz, A., Boada, M., Seshadri, S., Beiser, A., Rice, K., van der Lee, S.J., De Jager, P.L., Geschwind, D.H., Riemenschneider, M., Riedel-Heller, S., Rotter, J.I., Ransmayr, G., Hyman, B.T., Cruchaga, C., Alegret, M., Winsvold, B., Palta, P., Farh, K.H., Cuenca-Leon, E., Furlotte, N., Kurth, T., Ligthart, L., Terwindt, G.M., Freilinger, T., Ran, C., Gordon, S.D., Borck, G., Adams, H.H.H., Lehtimaki, T., Wedenoja, J., Buring, J.E., Schurks, M., Hrafnsdottir, M., Hottenga, J.J., Penninx, B., Artto, V., Kaunisto, M., Vepsalainen, S., Martin, N.G., Montgomery, G.W., Kurki, M.I., Hamalainen, E., Huang, H., Huang, J., Sandor, C., Webber, C., Muller-Myhsok, B., Schreiber, S., Salomaa, V., Loehrer, E., Gobel, H., Macaya, A., Pozo-Rosich, P., Hansen, T., Werge, T., Kaprio, J., Metspalu, A., Kubisch, C., Ferrari, M.D., Belin, A.C., van den Maagdenberg, A., Zwart, J.A., Boomsma, D., Eriksson, N., Olesen, J., Chasman, D.I., Nyholt, D.R., Avbersek, A., Baum, L., Berkovic, S., Bradfield, J., Buono, R., Catarino, C.B., Cossette, P., De Jonghe, P., Depondt, C., Dlugos, D., Ferraro, T.N., French, J., Hjalgrim, H., Jamnadas-Khoda, J., Kalviainen, R., Kunz, W.S., Lerche, H., Leu, C., Lindhout, D., Lo, W., Lowenstein, D., McCormack, M., Moller, R.S., Molloy, A., Ng, P.W., Oliver, K., Privitera, M., Radtke, R., Ruppert, A.K., Sander, T., Schachter, S., Schankin, C., Scheffer, I., Schoch, S., Sisodiya, S.M., Smith, P., Sperling, M., Striano, P., Surges, R., Thomas, G.N., Visscher, F., Whelan, C.D., Zara, F., Heinzen, E.L., Marson, A., Becker, F., Stroink, H., Zimprich, F., Gasser, T., Gibbs, R., Heutink, P., Martinez, M., Morris, H.R., Sharma, M., Ryten, M., Mok, K.Y., Pulit, S., Bevan, S., Holliday, E., Attia, J., Battey, T., Boncoraglio, G., Thijs, V., Chen, W.M., Mitchell, B., Rothwell, P., Sharma, P., Sudlow, C., Vicente, A., Markus, H., Kourkoulis, C., Pera, J., Raffeld, M., Silliman, S., Boraska Perica, V., Thornton, L.M., Huckins, L.M., William Rayner, N., Lewis, C.M., Gratacos, M., Rybakowski, F., Keski-Rahkonen, A., Raevuori, A., Hudson, J.I., Reichborn-Kjennerud, T., Monteleone, P., Karwautz, A., Mannik, K., Baker, J.H., O'Toole, J.K., Trace, S.E., Davis, O.S.P., Helder, S.G., Ehrlich, S., Herpertz-Dahlmann, B., Danner, U.N., van Elburg, A.A., Clementi, M., Forzan, M., Docampo, E., Lissowska, J., Hauser, J., Tortorella, A., Maj, M., Gonidakis, F., Tziouvas, K., Papezova, H., Yilmaz, Z., Wagner, G., Cohen-Woods, S., Herms, S., Julia, A., Rabionet, R., Dick, D.M., Ripatti, S., Andreassen, O.A., Espeseth, T., Lundervold, A.J., Steen, V.M., Pinto, D., Scherer, S.W., Aschauer, H., Schosser, A., Alfredsson, L., Padyukov, L., Halmi, K.A., Mitchell, J., Strober, M., Bergen, A.W., Kaye, W., Szatkiewicz, J.P., Cormand, B., Ramos-Quiroga, J.A., Sanchez-Mora, C., Ribases, M., Casas, M., Hervas, A., Arranz, M.J., Haavik, J., Zayats, T., Johansson, S., Williams, N., Dempfle, A., Rothenberger, A., Kuntsi, J., Oades, R.D., Banaschewski, T., Franke, B., Buitelaar, J.K., Arias Vasquez, A., Doyle, A.E., Reif, A., Lesch, K.P., Freitag, C., Rivero, O., Palmason, H., Romanos, M., Langley, K., Rietschel, M., Witt, S.H., Dalsgaard, S., Borglum, A.D., Waldman, I., Wilmot, B., Molly, N., Bau, C.H.D., Crosbie, J., Schachar, R., Loo, S.K., McGough, J.J., Grevet, E.H., Medland, S.E., Robinson, E., Weiss, L.A., Bacchelli, E., Bailey, A., Bal, V., Battaglia, A., Betancur, C., Bolton, P., Cantor, R., Celestino-Soper, P., Dawson, G., De Rubeis, S., Duque, F., Green, A., Klauck, S.M., Leboyer, M., Levitt, P., Maestrini, E., Mane, S., De-Luca, D.M., Parr, J., Regan, R., Reichenberg, A., Sandin, S., Vorstman, J., Wassink, T., Wijsman, E., Cook, E., Santangelo, S., Delorme, R., Roge, B., Magalhaes, T., Arking, D., Schulze, T.G., Thompson, R.C., Strohmaier, J., Matthews, K., Melle, I., Morris, D., Blackwood, D., McIntosh, A., Bergen, S.E., Schalling, M., Jamain, S., Maaser, A., Fischer, S.B., Reinbold, C.S., Fullerton, J.M., Guzman-Parra, J., Mayoral, F., Schofield, P.R., Cichon, S., Muhleisen, T.W., Degenhardt, F., Schumacher, J., Bauer, M., Mitchell, P.B., Gershon, E.S., Rice, J., Potash, J.B., Zandi, P.P., Craddock, N., Ferrier, I.N., Alda, M., Rouleau, G.A., Turecki, G., Ophoff, R., Pato, C., Anjorin, A., Stahl, E., Leber, M., Czerski, P.M., Cruceanu, C., Jones, I.R., Posthuma, D., Andlauer, T.F.M., Forstner, A.J., Streit, F., Baune, B.T., Air, T., Sinnamon, G., Wray, N.R., MacIntyre, D.J., Porteous, D., Homuth, G., Rivera, M., Grove, J., Middeldorp, C.M., Hickie, I., Pergadia, M., Mehta, D., Smit, J.H., Jansen, R., de Geus, E., Dunn, E., Li, Q.S., Nauck, M., Schoevers, R.A., Beekman, A.T., Knowles, J.A., Viktorin, A., Arnold, P., Barr, C.L., Bedoya-Berrio, G., Bienvenu, O.J., Brentani, H., Burton, C., Camarena, B., Cappi, C., Cath, D., Cavallini, M., Cusi, D., Darrow, S., Denys, D., Derks, E.M., Dietrich, A., Fernandez, T., Figee, M., Freimer, N., Gerber, G., Grados, M., Greenberg, E., Hanna, G.L., Hartmann, A., Hirschtritt, M.E., Hoekstra, P.J., Huang, A., Huyser, C., Illmann, C., Jenike, M., Kuperman, S., Leventhal, B., Lochner, C., Lyon, G.J., Macciardi, F., Madruga-Garrido, M., Malaty, I.A., Maras, A., McGrath, L., Miguel, E.C., Mir, P., Nestadt, G., Nicolini, H., Okun, M.S., Pakstis, A., Paschou, P., Piacentini, J., Pittenger, C., Plessen, K., Ramensky, V., Ramos, E.M., Reus, V., Richter, M.A., Riddle, M.A., Robertson, M.M., Roessner, V., Rosario, M., Samuels, J.F., Sandor, P., Stein, D.J., Tsetsos, F., Van Nieuwerburgh, F., Weatherall, S., Wendland, J.R., Wolanczyk, T., Worbe, Y., Zai, G., Goes, F.S., McLaughlin, N., Nestadt, P.S., Grabe, H.J., Depienne, C., Konkashbaev, A., Lanzagorta, N., Valencia-Duarte, A., Bramon, E., Buccola, N., Cahn, W., Cairns, M., Chong, S.A., Cohen, D., Crespo-Facorro, B., Crowley, J., Davidson, M., DeLisi, L., Dinan, T., Donohoe, G., Drapeau, E., Duan, J., Haan, L., Hougaard, D., Karachanak-Yankova, S., Khrunin, A., Klovins, J., Kucinskas, V., Lee Chee Keong, J., Limborska, S., Loughland, C., Lonnqvist, J., Maher, B., Mattheisen, M., McDonald, C., Murphy, K.C., Nenadic, I., van Os, J., Pantelis, C., Pato, M., Petryshen, T., Quested, D., Roussos, P., Sanders, A.R., Schall, U., Schwab, S.G., Sim, K., So, H.C., Stogmann, E., Subramaniam, M., Toncheva, D., Waddington, J., Walters, J., Weiser, M., Cheng, W., Cloninger, R., Curtis, D., Gejman, P.V., Henskens, F., Mattingsdal, M., Oh, S.Y., Scott, R., Webb, B., Breen, G., Churchhouse, C., Bulik, C.M., Daly, M., Dichgans, M., Faraone, S.V., Guerreiro, R., Holmans, P., Kendler, K.S., Koeleman, B., Mathews, C.A., Price, A., Scharf, J., Sklar, P., Williams, J., Wood, N.W., Cotsapas, C., Palotie, A., Smoller, J.W., Sullivan, P., Rosand, J., Corvin, A., Neale, B.M., Schott, J.M., Anney, R., Elia, J., Grigoroiu-Serbanescu, M., Edenberg, H.J., Murray, R., 2018. Analysis of shared heritability in common disorders of the brain. Science 360(6395).

Brewer, W.J., Edwards, J., Anderson, V., Robinson, T., Pantelis, C., 1996. Neuropsychological, olfactory and hygiene deficits in men with negative symptom schizophrenia. Biol. Psychiatry 40, 1021–1031.

Brewer, W.J., Wood, S.J., McGorry, P.D., Francey, S.M., Phillips, L.J., Yung, A.R., Anderson, V., 2003. Impairment of olfactory identification ability in UHR for psychosis who later develop schizophrenia. Am. J. Psychiatry 160, 1790–1794.

Burton, B.K., Vangkilde, S., Petersen, A., Skovgaard, L.T., Jepsen, J.R., Hemager, N., Christiani, C.J., Spang, K.S., Ellersgaard, D., Greve, A., Gantriis, D., Eichele, H., Mors, O., Nordentoft, M., Thorup, A.A.E., Plessen, K.J., 2018. Sustained attention and interference control among 7-year-old children with a familial high risk of schizophrenia or

bipolar disorder–a nationwide observational cohort study. Biol. Psychiatry 3 (8), 704–712.
Christiani, C.J., Jepsen, J.R.M., Thorup, A., Hemager, N., Ellersgaard, D., Spang, K.S., Burton, B.K., Gregersen, M., Sondergaard, A., Greve, A.N., Gantriis, D.L., Poulsen, G., Uddin, M.J., Seidman, L.J., Mors, O., Plessen, K.J., Nordentoft, M., 2019. Social cognition, language, and social behavior in 7-year-old children at familial high-risk of developing schizophrenia or bipolar disorder: the Danish High Risk And Resilience Study VIA 7–a population-based cohort study. Schizophrenia Bull. 45 (6), 1218–1230. https://doi.org/10.1093/schbul/sbz001.
Compton, M.T., McKenzie Mack, L., Esterberg, M.L., Bercu, Z., Kryda, A.D., Quintero, L., Weiss, P.S., Walker, E.F., 2006. Associations between olfactory identification and verbal memory in patients with schizophrenia, first-degree relatives, and non-psychiatric controls. Schizophr. Res. 86 (1–3), 154–166.
Constantino, J.N., Gruber, C.P., 2005. Social responsive scale (SRS) manual. Western Psychological Services, Los Angeles, CA.
Corcoran, C., Whitaker, A., Coleman, E., Fried, J., Feldman, J., Goudsmit, N., Malaspina, D., 2005. Olfactory deficits, cognition and negative symptoms in early onset psychosis. Schizophr. Res. 80 (2–3), 283–293.
Cumming, A.G., Matthews, N.L., Park, S., 2011. Olfactory identification and preference in bipolar disorder and schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 261 (4), 251–259.
Doty, R.L., 2001. The Brief Smell Identification Test Administration Manual. Sensonics.
Doty, R.L., Shaman, P., Dann, M., 1984. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol. Behav. 32 (3), 489–502.
Ellersgaard, D.V., Plessen, K.J., Jepsen, J.R., Spang, K.S., Hemager, N., Burton, B.K., Christiani, C.J., Gregersen, M., Søndergaard, A., Uddin, M.J., Poulsen, G., Greve, A.N., Gantriis, D., Mors, O., Nordentoft, M., Thorup, A., 2018. Psychopathology in 7-year-old children with familial high risk of developing schizophrenia spectrum psychosis or bipolar disorder - the Danish High Risk and Resilience Study - VIA 7, a population-based cohort study. World Psychiatry 17, 210–219.
Good, K., Whitehorn, D., Rui, Q., Milliken, H., Kopala, L., 2006. Olfactory identification deficits in first-episode psychosis may predict patients at risk for persistent negative and disorganized of cognitive symptoms. Am. J. Psychiatry 163, 932–933.
Goudsmit, N., Coleman, E., Seckinger, R.A., Wolitzky, R., Stanford, A.D., Corcoran, C., Goetz, R.R., Malaspina, D., 2003. A brief smell identification test discriminates between deficit and non-deficit schizophrenia. Psychiatry Res. 120 (2), 155–164.
Hemager, N., Plessen, K.J., Thorup, A., Christiani, C., Ellersgaard, D., Spang, K.S., ... Gantriis, D.L., 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), 844–852.
Insel, T.R., 2010. Rethinking schizophrenia. Nature 468 (7321), 187–193.
Kamath, V., Turetsky, B.I., Calkins, M.E., Kohler, C.G., Conroy, C.G., Borgmann-Winter, K., Gatto, D.E., Gur, R.E., Moberg, P.J., 2014. Olfactory processing in schizophrenia, non-ill first-degree family members, and young people at-risk for psychosis. World J Biol Psychiatry 15 (3), 209–218.
Kamath, V., Lasutschinkow, P., Ishizuka, K., Sawa, A., 2018. Olfactory functioning in first-episode psychosis. Schizophrenia Bull 44 (3), 672–680.
Keshavan, M.S., Vora, A., Montrose, D., Diwadkar, V.A., Sweeney, J., 2009. Olfactory identification in young relatives at risk for schizophrenia. Acta Neuropsychiatry 21 (3), 121–124.
Kopala, L., Good, K., Martzke, J., Hurwits, T., 1995. Olfactory deficits in schizophrenia are not a function of task complexity. Schizophr. Res. 17, 195–199.
Kopala, L., Good, K.P., Morrison, K., Bassett, A.S., Alda, M., Honer, W.G., 2001. Impaired olfactory identification in relatives of schizophrenic patients. Am. J. Psychiatry 158, 1286–1290.
Kronenbuerger, M., Belenghi, P., Ilgner, J., Freiherr, J., Hummel, T., Neuner, I., 2018. Olfactory functioning in adults with Tourette syndrome. PLoS One 13 (6), e0197598.
Larsson, M., Nilsson, L.G., Olofsson, J.K., Nordin, S., 2004. Demographic and cognitive predictors of cued odor identification: evidence from a population-based study. Chem. Senses 29 (6), 547–554.
Makransky, G., Bilenberg, N., 2014. Psychometric properties of the parent and teacher ADHD Rating Scale (ADHD-RS): measurement invariance across gender, age, and informant. Assessment 21 (6), 694–705.
Malaspina, D., Coleman, E., 2003. Olfaction and social drive in schizophrenia. Arch. Gen. Psychiatry 60, 578–584.
Malaspina, D., Goetz, R., Keller, A., Messinger, J.W., Bruder, G., Goetz, D., Opler, M., Harlap, S., Harkavy-Friedman, J., Antonius, D., 2012. Olfactory processing, sex effects and heterogeneity in schizophrenia. Schizophr. Res. 135 (1–3), 144–151.
Moberg, P.J., Kamath, V., Marchetto, D.M., Calkins, M.E., Doty, R.L., Hahn, C.G., Borgmann-Winter, K.E., Kohler, C.G., Gur, R.E., Turetsky, B.I., 2014. Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. Schizophrenia Bull 40 (1), 50–59.
Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatr. Scand. 101 (4), 323–329.
Mors, O., Perto, G.P., Mortensen, P.B., 2011. The Danish Psychiatric Central Research Register. Scand J Public Health 39 (7 Suppl), 54–57.
Muratori, F., Tonacci, A., Billeci, L., Catalucci, T., Igliozzi, R., Calderoni, S., Narzisi, A., 2017. Olfactory processing in male children with autism: atypical odor threshold and identification. J. Autism Dev. Disord. 47 (10), 3243–3251.
Pedersen, C.B., Gøtzsche, H., Møller, J., Mortensen, P.B., 2006. The Danish Civil Registration System: a cohort of eight million persons. Dan. Med. Bull. 53, 441–449.
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.
Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R.S., Murray, R.M., Poulton, R., Moffitt, T.E., 2010. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am. J. Psychiatry 167, 160–169.
Reynolds, C., Bigler, E.D., 1996. Factor Structure, Factor Indexes, and Other Useful Statistics for Interpretation of the Test of Memory and Learning (TOMAL). Arch. Clin. Neuropsychol. 11 (1), 29–43.
Reynolds, C., Voress, J.K., 2007. Test of Memory and Learning. Second edition. PRO-ED, Austin, TX.
Reynolds, C.R., Kamphaus, R.W., 2003. Reynolds Intellectual Assessment Scales: Professional manual. PAR, Lutz, FL.
Sahakian, B.J., Owen, A.M., 1992. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J Roy Soc Med 85 (7), 399.
Sanches, M., Keshavan, M.S., Brambilla, P., Soares, J.C., 2008. Neurodevelopmental basis of bipolar disorder: a critical appraisal. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 32 (7), 1617–1627.
Seidman, L.J., Goldstein, J.M., Goodman, J.M., Koren, D., Turner, W.M., Faraone, S.V., Tsuang, M.T., 1997. Sex differences in olfactory identification and Wisconsin card sorting performance in schizophrenia: relationship to attention and verbal ability. Biol. Psychiatry 42, 104–115.
Thorup, A.A., Jepsen, J.R., Ellersgaard, D.V., Burton, B.K., Christiani, C.J., Hemager, N., Skjaerbaek, M., Ranning, A., Spang, K.S., Gantriis, D.L., Greve, A.N., Zahle, K.K., Mors, O., Plessen, K.J., Nordentoft, M., 2015. The Danish High Risk and Resilience Study-VIA 7–a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. BMC Psychiatry 15, 233–248.
Turetsky, B.I., Moberg, P.J., Yousem, D.M., Doty, R.L., Arnold, S.E., Gur, R.E., 2000. Reduced olfactory bulb volume in patients with schizophrenia. Am. J. Psychiatry 157 (5), 828–830.
Turetsky, B.I., Moberg, P.J., Arnold, S.E., Doty, R.L., Gur, R.E., 2003. Low olfactory bulb volume in first-degree relatives of patients with schizophrenia. Am. J. Psychiatry 160 (4), 703–708.
Turetsky, B.I., Kohler, C.G., Gur, R.E., Moberg, P.J., 2008. Olfactory physiological impairment in first-degree relatives of schizophrenia patients. Schizophr. Res. 102 (1–3), 220–229.
Turetsky, B.I., Moberg, P.J., Quarmley, M., Dress, E., Calkins, M.E., Ruparel, K., Prabhakaran, K., Gur, R.E., Roalf, D.R., 2018. Structural anomalies of the peripheral olfactory system in psychosis high-risk subjects. Schizophr. Res. 195, 197–205.
Wechsler, D., 2003. Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV). The Psychological Corporation, San Antonio, TX.
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. Schizophrenia Research 146, 87–94. https://doi.org/10.1016/j.schres.2013.01.017.

Please cite this article as: A.H. Ver Loren van Themaat, M.J. Uddin, C.J. Christiani, et al., Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorde..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2019.12.028