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ARTICLE

Auditory sensory gating in young adolescents with early-onset psychosis: a comparison with attention deficit/hyperactivity disorder

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Numerous studies have demonstrated impaired sensory gating in schizophrenia and this impairment has been proposed as a candidate biomarker for the disorder. The typical age of onset for schizophrenia is early adulthood, however a sizable group of patients present with psychotic symptoms before the age of 18, commonly referred to as early-onset psychosis (EOP). How an earlier onset influences sensory gating is currently unknown. Impaired sensory gating may not be specific to psychosis, but rather a shared disturbance of neurodevelopmental disorders, such as attention deficit/hyperactivity disorder (ADHD). Therefore, the current study investigated P50 suppression in young adolescents (12–17 years old) with either EOP ($N = 55$) or ADHD ($N = 28$) and age and gender matched healthy controls (HC) ($N = 71$). In addition to P50 suppression, N100 and P200 suppression data were also analyzed. No significant group differences in either raw mean P50 amplitude or mean P50 gating ratios were observed between EOP, ADHD, and HC. Additionally, we observed no P50 suppression deficit in those EOP patients diagnosed with schizophrenia ($N = 39$). Similarly, we observed no differences in N100 or P200 between the three groups. Healthy levels of P50 suppression were found in both patient groups. The results are in line with some previous studies showing healthy levels of P50 suppression in the early phases of schizophrenia. Our findings do not support P50 sensory gating as a valid biomarker for EOP or ADHD.

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INTRODUCTION

Psychotic disorders usually manifest in early adulthood. However, 11–18% of patients experience their first psychotic episode during childhood or adolescence [1, 2], commonly referred to as early-onset psychosis (EOP) [3]. Patients with EOP have an increased risk of developing schizophrenia later in life compared to the general population [4, 5]. In most studies, EOP is associated with a more insidious onset, longer durations of untreated psychosis (DUP), a more severe course of illness and ultimately a poorer prognosis compared to adult-onset psychosis [5–7], albeit some studies find a better prognosis for EOP than hitherto concluded [1, 8].

Sensory gating refers to the brain's ability to filter sensory information by reducing responses to repeated exposure to the same sensory stimulus [9]. It is a pre-attentional phenomenon thought to serve as protection against information overload or sensory "flooding" [9]. A widely used method assumed to assess sensory gating is the so-called P50 suppression paradigm. In a typical P50 suppression paradigm, two identical auditory stimuli are presented in close temporal proximity. Healthy subjects show a decreased P50 amplitude in their electroencephalogram (EEG) response to the second stimulus, whereas schizophrenia patients on average show a significantly smaller decrease [10, 11]. In addition, impaired P50 suppression has been demonstrated in antipsychotic-naive, first-episode patients [12, 13], unaffected first-degree relatives, and individuals at high-risk for psychosis [13, 14]. P50 suppression has, therefore, been proposed as a candidate biomarker for schizophrenia [15]. However, there are also studies reporting healthy levels of P50 suppression in patients with schizophrenia, primarily in the early phases of the disease [16–19]. To the best of our knowledge, only one study previously investigated P50 suppression in children with psychosis [20]. The study included patients with childhood-onset schizophrenia (onset prior to age 13). They reported decreased P50 suppression in all patients (age 7–15 years, mean age 10.3 years), indicating that sensory gating is already disturbed during childhood in patients with schizophrenia. However, this study did not include a healthy control group, but instead used previously published P50 ratios from 29 typically developing children (aged 10–15 years), thus not fully covering the age range of the patients. There is evidence suggesting that sensory gating is highly variable in childhood [21–23], and it is, therefore, crucial to include an age-matched healthy control group. Moreover, the study only included a small number of patients ($N = 10$), thus limiting the conclusions that can be drawn.

From a potential biomarker point of view, it is also important to investigate whether impaired P50 suppression is specific to

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psychosis or rather a common deficit among neurodevelopmental disorders, such as attention deficit/hyperactivity disorder (ADHD). Although the clinical symptoms of ADHD differ from schizophrenia, there are common characteristics. Both disorders have been shown to be heritable [24, 25] and there is some overlap in early life risk factors [26, 27]. Moreover, dopamine is thought to be the primary neurotransmitter involved in the pathophysiology of both disorders, although schizophrenia is hypothesized to be associated with a combination of hypo- (frontal areas) and hyperactivity (striatal area) in the dopaminergic system, while ADHD is hypothesized to only involve dopaminergic hypoactivity (frontal areas) [25, 28]. Compared to the overwhelming literature on adult schizophrenia patients, relatively few studies have investigated P50 suppression in ADHD and the results are inconsistent. Deficient P50 suppression has been demonstrated in adults with ADHD, although to a lesser extent than in schizophrenia [29, 30], yet normal levels of P50 suppression have also been reported [31]. Only one study investigated P50 in children with ADHD and they reported significantly impaired P50 suppression compared to healthy controls [32].

The aim of the present study was to investigate P50 suppression in young adolescents with EOP or ADHD. Based on the literature, we expected the EOP patients to show impaired P50 suppression [10, 11, 20], with more pronounced deficits in the subgroup of EOP patients who fulfilled the criteria for early-onset schizophrenia (EOS) given that these might represent more severe cases. Additionally, we expected the ADHD patients to show impaired sensory gating, although to a lesser extent than the EOP patients [30, 32].

MATERIALS AND METHODS

The study was approved by the Ethical Committee of the Capital Region of Denmark (H-C-2008-076 & H-6-2014-068). Informed consent was obtained from parents as well as participants.

Participants

Patients were recruited from in- and outpatient units at the Child and Adolescent Mental Health Center in the Capital Region of Denmark. Healthy participants were recruited from the local community using internet advertisement and via the Danish Civil Registration System. All participants were between 12 and 17 years old at inclusion. For the present paper, two projects were combined resulting in a sample size of 28 patients with ADHD, 55 patients with EOP and 71 healthy controls (HC). The first project recruited patients with psychosis or ADHD and healthy controls from 2011 to 2014. The subsequent project (2015–2017) was designed as a modified extension study, with no changes in the psychophysiological battery or psychopathological ratings applied but recruiting patients with psychosis and healthy controls only.

In study 1, inclusion criteria for patients with psychosis included a diagnosis of schizophrenia, other non-affective psychosis, or affective psychosis according to DSM-IV-TR criteria [33]. Given that no patients with affective psychosis were actually included for Study 1, Study 2 only included patients with a diagnosis of schizophrenia and other non-affective psychoses. Further inclusion criteria for the EOP group were a score of ≥4 on a minimum of one (or ≥3 on a minimum of two) of the following items of the Positive and Negative Syndrome Scale (PANSS): P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution) and G9 (unusual thought content) [34], and a maximum of 12 months cumulative psychopharmacological treatment. Inclusion criteria for the ADHD group were: A diagnosis of ADHD according to DSM-IV-TR [33] and no psychostimulant treatment for the last three months. HC were included if they had no psychiatric illnesses according to DSM-IV-TR criteria, no history of psychosis or ADHD in first-degree family members and no ongoing pharmacological treatment (longer than 10–14 days) except for the use of contraceptives.

Exclusion criteria for all groups included: Hearing impairments; A history of neurological illness or significant head injury (loss of consciousness >5 min); and a diagnosis of alcohol or drug dependence according to DSM-IV-TR.

Evaluations of psychopathology

Somatic examinations were performed to rule out somatic illnesses potentially causing psychiatric symptoms. Diagnoses were assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) [35]. The same interview was used to screen HCs for psychopathology. Psychotic symptoms were rated with the PANSS interview in all three groups. The level of functioning was rated using the Children's Global Assessment Scale (CGAS) [36] and the Social and Occupational Functioning Assessment Scale (SOFAS) [37]. The assessments were based on consensus ratings between two experienced clinicians, a child and adolescent psychiatrist (J.R.) and a child neuropsychologist (J.R.M.J). The Danish version of the ADHD Rating Scale (ADHD-RS) was completed by the parents [38].

Design

P50 suppression was assessed as part of the Copenhagen Psychophysiological Test Battery (CPTB), additionally consisting of prepulse inhibition of the startle reflex (PPI), mismatch negativity (MMN) and selective attention paradigms [39, 40], results from which have been (partly) published already [41, 42]. To avoid the acute effects of nicotine and caffeine, all participants were asked to refrain from smoking one hour before testing and from drinking caffeinated beverages two hours before testing. A urine sample was obtained to screen for drug use. Participants were seated in a dimly lit sound-isolated cabin that reduced outside noise with a magnitude of 40 dB and instructed to sit still with their eyes fixed on a spot on the wall directly in front of them.

P50 paradigm

The P50 paradigm has been described in detail before [39]. In short, the paradigm consisted of three identical blocks of 40 click-pairs. Each click was 1.5 ms and had an intensity of 80 dB (white noise). The interstimulus interval was 500 ms and all click-pairs were separated by 10 s. Clicks were presented binaurally via stereo insert earphones (Eartone ABR, C and H Distributors Inc., Milwaukee, WI, USA). To avoid drowsiness, participants were instructed to count the number of click-pairs.

Signal processing

Signal recording and analysis procedures have been described before [39]. BESA software (version 6.0, MEGIS Software GmbH, Gräfelfing, Germany) was used for processing of the EEG data: First, the data was down-sampled from a rate of 2048 to 250 Hz after which it was corrected for eye-movement by applying the surrogate model of BESA [43]. Then, data were epoched between 100 ms prestimulus and 400 ms poststimulus. Thereafter, correction of movement and other non-paradigm related artifacts was performed by removing those epochs from the database that exceeded amplitude differences of 100 µV between maximum and minimum in the relevant (between 0 and 120 ms) part of the epoch. After averaging, the epochs were band-pass filtered between 1.6 and 70 Hz. P50 amplitudes were obtained from electrode Cz (with average reference), where maximum P50 amplitude was generally reached in our dataset. P50 amplitude was defined as the largest (preceding) trough to peak amplitude within an interval of 40–90 ms following the first (conditioning or "C") stimulus in each paired click. The P50 amplitude following the second (testing or "T") stimulus was identified as the largest (preceding) trough to peak amplitude within an interval of 10 ms of the latency of the maximum P50 amplitude to the C-stimulus.

P50 suppression was expressed as the ratio "T/C", where T is the amplitude to the averaged T-stimuli and C is the amplitude to the averaged C-stimuli. For the interested reader, we also scored the N100 (65–130 ms) and P200 (110–320 ms) waveforms (Supplementary Materials and Methods).

Statistical analysis

All statistical analyses were performed with SPSS (version 22.0, SPSS Inc.). Group differences in gender, age, psychopathology, smoking, and medication status were analyzed with the Chi-Squared test or one-way analyses of variance (ANOVA), as appropriate. The PANSS and the ADHD-RS was not normally distributed according to the Kolmogorov–Smirnov test, and was thus analyzed using non-parametric tests. Moreover, neither the P50 raw amplitude data or ratios were normally distributed, however, given the lack of a non-parametric equivalent, the raw P50 amplitude data were analyzed with repeated measures ANOVA, with group as between-factor (ADHD, EOP or HC), and stimulus type as within-factor (C or T stimulus). The P50 ratio was analyzed using univariate ANOVA to enable inclusion of covariates. We additionally split our EOP group into those patients with and without a schizophrenia diagnosis after which the analyses were repeated. Associations between P50 data and psychopathology rating scales were explored by means of Spearman correlation tests. Similar to the P50 data, the N100 and P200 amplitudes and ratios were not normally distributed, and group differences were analyzed in the same way as the P50 data.

RESULTS

General

There were no significant differences in age between the three groups, but there were significant differences in gender and smoking status. The EOP patients scored significantly higher on the PANSS positive, negative, general, and total scale compared to both ADHD patients and HC. The ADHD patients scored significantly higher on the ADHD-RS compared to both EOP and HC (Table 1).

Of the 28 patients with ADHD, 23 were diagnosed with the combined type and five with the inattentive type. Of the 55 EOP patients, 39 fulfilled the diagnostic criteria for schizophrenia, six for schizoaffective disorder and 10 were diagnosed with a psychotic disorder not otherwise specified; no patients had an affective psychosis. Thirty-six of the EOP patients were being treated with second-generation antipsychotics at the time of testing. 15 were antipsychotic-naive and four had previously used antipsychotics (one patient had been antipsychotic free for a month, two patients for 3 weeks and the last one up until 2 weeks prior to testing). At the time of testing, none of the ADHD patients were being treated with psychostimulants. Three had previously been treated, yet not within 3 months prior to inclusion.

P50 data

The average P50 measures are presented in Table 2. A repeated measures ANOVA on the raw amplitude data revealed a main effect of stimulus type, indicating that the P50 amplitude to C-stimuli was significantly higher than the amplitude in response to T-stimuli [$F(1,151) = 136.92$, $p < 0.001$, $\eta^2 = 0.47$] in all three groups. No significant main effect of group, [$F(2,151) = 0.45$, $p = 0.63$, $\eta^2 = 0.01$], nor a significant interaction between stimulus and group were found, [$F(2,151) = 0.83$, $p = 0.44$, $\eta^2 = 0.01$] (see Fig. 1). The analysis was repeated with the EOP group split into schizophrenia and non-schizophrenia cases resulting in four groups, which did not change the results significantly.

Analysis of the P50 suppression data (T/C ratio) showed no main effect of group, neither between the three original groups, [$F(2,151) = 1.37$, $p = 0.26$, $\eta^2 = 0.018$] nor when split into the four above mentioned groups, [$F(3,150) = 1.35$, $p = 0.26$, $\eta^2 = 0.03$]. Adding age, gender and smoking status as covariates in the analyses did not change any of the results significantly, nor did removing participants with a positive urine screening.

Given that more than half of the EOP sample was being treated with antipsychotic medication at the time of testing, we (post-hoc) investigated whether antipsychotic medication had an influence on P50 suppression. We observed no significant differences in P50 ratios between antipsychotic-naive and medicated EOP patients, ($U = 232.00$, $p = 0.194$, $r = -0.18$).

Correlations between P50 and psychopathology

In the EOP group, we did not find any significant correlations between either DUP or DUI and P50 suppression. Furthermore, we observed no significant correlations between the P50 measures and the PANSS scale scores in the EOP patients. However, we did find a positive correlation between the T-amplitude and items 10–18 (hyperactivity/impulsivity items) of the ADHD-RS rating scale in this EOP group ($r_s(50) = 0.364$, $p = 0.008$). Similarly, we found a positive correlation between the P50 ratio and items 10–18 on the ADHD-RS (hyperactivity/impulsivity items) ($r_s(50) = 0.367$, $p = 0.007$). When splitting the EOP group into schizophrenia and non-schizophrenia cases, the observed correlations were no longer significant. In the ADHD group, both the T-amplitude and the P50 ratio correlated with the PANSS positive score, $r_s(26) = 0.412$, $p = 0.029$ and $r_s(26) = 0.424$, $p = 0.024$, respectively. There were no significant correlations between the P50 data and ratings of psychopathology in the HC group.

N100 & P200 data

No significant group differences were found in either raw amplitude or ratio data on N100 and P200 responses (Supplementary Materials and Methods).

DISCUSSION

To the best of our knowledge, the current study of P50 suppression included the largest sample of EOP patients to date. Furthermore, this is the first study to directly compare sensory gating between EOP and ADHD.

We found healthy levels of P50 suppression in the EOP patients, which is in contrast with the majority of previous findings from adult patients with schizophrenia [10, 11]. Given the comparatively large sample size, in combination with the rather weak effect-sizes, the negative findings cannot merely be ascribed to power issues. Our EOP findings are in contrast with the single previous study investigating sensory gating in children with schizophrenia, reporting abnormal P50 suppression in all patients [20]. This study by Ross and colleagues [20] only included 10 patients, whereas we included a comparably large group of 55 EOP patients. Furthermore, they only included children with schizophrenia, whereas we included patients with more broadly defined first-episode psychosis. One may speculate that schizophrenia patients exhibit more pronounced P50 suppression deficits compared to other psychotic disorders. Nevertheless, even those patients in our EOP cohort with a diagnosis of schizophrenia ($N = 39$) did not show P50 suppression deficits. Moreover, the study of Ross and colleagues [20] included patients as young as seven years old. Evidence suggests that P50 suppression matures around the age of 8–10 [22, 23], and it is, therefore possible, that the abnormal P50 suppression observed in their study may, in fact, be an expression of underdeveloped sensory gating. Given our age range (12–17 years old), sensory gating was expected to be fully developed in our participants. Finally, the study of Ross and colleagues [20] defined abnormal P50 suppression as ratios above 0.50, which may not be an appropriate cut-off, and underscores the importance of including age-matched healthy controls. In a meta-analysis of P50 sensory gating, the mean P50 ratio for healthy controls was found to be 0.39, ranging from 0.09 to 0.73

Table 1. Demographics

	HC ($N = 71$)	ADHD ($N = 28$)	EOP (N = 55)	Statistical test
Age in years	15.65 (0.17)	15.39 (0.28)	16.07 (0.18)	$F(2,153) = 2.67$, $p = 0.07$
Gender				
Males (%)	23 (32.4%)	15 (53.6%)	12 (21.8%)	$\chi^2(2) = 8.53$, $p = 0.014$*
Females (%)	48 (67.6%)	13 (46.4%)	43 (78.2%)	
Smoking				
Yes (%)	2 (2.8%)	11 (39.3%)	25 (45.5%)	$\chi^2(2) = 34.2$, $p < 0.001$**
No (%)	69 (97.2%)	17 (60.7%)	30 (54.5%)	
PANSS				
Positive scale	7.11 (0.04)	12.39 (0.64)	19.18 (0.44)	$\chi^2(2) = 130.29$, $p < 0.001$**
Negative scale	8.75 (0.16)	13.71 (0.73)	22.87 (0.87)	$\chi^2(2) = 114.01$, $p < 0.001$**
General scale	17.46 (0.18)	26.14 (0.99)	38.95 (1.06)	$\chi^2(2) = 119.93$, $p < 0.001$**
Total	33.32 (0.25)	52.25 (1.75)	81.00 (1.80)	$\chi^2(2) = 126.82$, $p < 0.001$**
ADHD-RS				
Item 1–9	2.06 (0.22)	17.05 (1.06)	12.58 (0.91)[a]	$\chi^2(2) = 99.47$, $p < 0.001$**
Item 10–18	1.13 (0.20)	13.50 (1.24)	4.85 (0.65)[a]	$\chi^2(2) = 78.47$, $p < 0.001$**
Item 1–18	3.18 (0.35)	31.00 (1.95)	17.42 (1.34)[a]	$\chi^2(2) = 104.42$, $p < 0.001$**
CGAS	89.41 (0.37)	53.64 (1.38)	41.02 (0.90)	$\chi^2(2) = 124.74$, $p < 0.001$**
SOFAS	91.16 (0.35)[b]	55.89 (1.38)	43.60 (1.04)	$\chi^2(2) = 121.37$, $p < 0.001$**
Positive urine screening test[c]	2	2	11	$\chi^2(2) = 11.41$, $p = 0.003$*
Benzodiazepine	0	0	6	
Cannabis	1	2	3	
Tricyclic antidepressant	0	0	2	
Morphine	1	0	0	
DUP (days)	–	–	623.73 (76.53)	–
DOI (days)	–	–	720.09 (72.67)	–
Antipsychotic at time of testing	–	–	36 (out of 55)	–
Aripiprazole			18	
Quetiapine			12	
Ziprasidone			1	
Risperdal			1	
Olanzapine			1	
Quetiapine + Aripiprazole			1	
Ziprasidone + Clozapine			1	
Aripiprazole + Risperdal			1	
Chlorpromazine equivalent (mg pr. day)	–	–	209.27 (28.00)	–

Gender & smoking status are given in numbers (percentages). The urine screening test and use of antipsychotics are given as number of participants. All other values are mean (SEM)
PANSS The Positive and Negative Syndrome Scale, *ADHD-RS* The attention deficit/hyperactivity disorder rating scale, *CGAS* The Children's Global Assessment Scale, *SOFAS* The Social and Occupational Functioning Assessment Scale, *DUP* duration of untreated psychosis, *DOI* Duration of illness
*Significant at the 0.05 level
**Significant at the 0.001 level
[a]Missing data from 3 EOP patients
[b]Missing data from 3 HC
[c]Missing data from four participants (none of which reported frequent use of cannabis or met the criteria for substance dependency)

[11]. The mean P50 gating ratio of our HC group (0.49) is well within this range, thus making abnormal gating in the healthy controls an unlikely argument for the lack of group differences in our study.

Despite the overwhelming evidence demonstrating P50 suppression deficits in schizophrenia patients, there are also studies reporting no such deficits [17, 18]. We experienced such contrasting findings ourselves in two distinct cohorts of antipsychotic-naive, first-episode adult schizophrenia patients using the same paradigm [12, 16], which either raises concerns about the reliability of these findings or suggest heterogeneity in the two datasets. Given that at least two studies have reported high reliability of P50 measures in healthy controls [44, 45], the inconsistent findings more likely point towards the latter; i.e. heterogeneity in schizophrenia, reflected in variability in P50 suppression, at least in the early phases of the disease. Interestingly, this appears not to be the case for other aspects of sensory gating, such as those reflected by prepulse inhibition of the startle reflex (PPI) [16]. Although P50 suppression and PPI are both thought to reflect aspects of sensory gating, results from these paradigms do not correlate [46–48]. In support of this, we previously demonstrated impaired PPI in the first half of our

Table 2. P50 measures

	HC ($N = 71$)	ADHD ($N = 28$)	EOP		
			Combined ($N = 55$)	Schizophrenia ($N = 39$)	Non-Schizophrenia ($N = 16$)
C-amplitude	2.12 (0.14)	1.83 (0.23)	2.21 (0.21)	2.22 (0.25)	2.19 (0.38)
T-amplitude	0.68 (0.08)	0.68 (0.13)	0.65 (0.09)	0.57 (0.11)	0.83 (0.16)
P50 ratio	0.49 (0.10)	0.43 (0.09)	0.31 (0.04)	0.25 (0.05)	0.46 (0.09)
C-latency	58.37 (0.76)	57.64 (1.31)	62.51 (1.14)	61.69 (1.26)	64.50 (2.45)
T-latency	54.04 (2.39)	55.20 (2.01)	61.95 (1.61)	60.00 (1.93)	65.57 (2.71)

Values are given as mean (SEM)
C conditioning, *T* testing. No significant group differences were found in P50 suppression. Please note: Lower P50 ratios are generally believed to indicate better sensory gating abilities

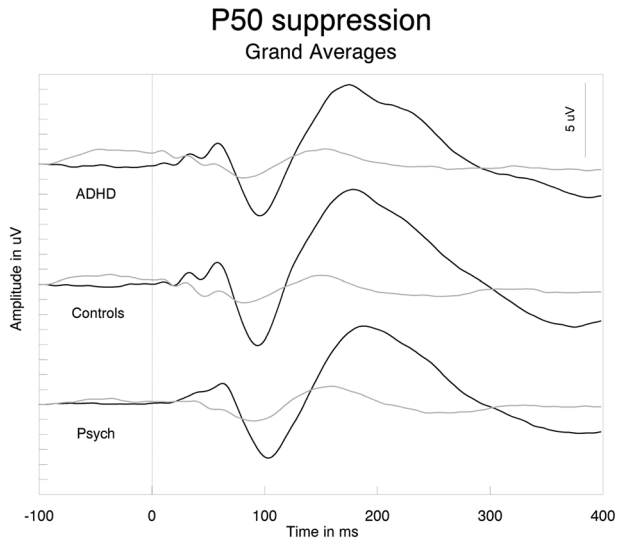

Fig. 1 Grand average data of the P50 waveforms, specified for controls, EOP patients and ADHD patients, showing no significant group differences

current EOP cohort (Study 1) in those EOP patients already diagnosed with schizophrenia [42]. Moreover, we observed impaired MMN in the entire EOP group [41]. These findings suggest that these are not highly atypical patients, given similar findings in previous studies showing deficient MMN and PPI in schizophrenia [49–53].

The primary measure of sensory gating investigated in this study was P50. The suppression of mid-latency auditory evoked responses is thought to include a multistage process. Therefore, we also included analyses of the N100 and P200 waveforms. Here, it is important to realize that previous studies have indicated that N100 suppression is based on refractory mechanisms, rather than pure sensory gating processes, therewith indicating that suppression of the N100 and P50 amplitudes reflect two different phenomena [54, 55]. Nevertheless, reduced N100 and P200 suppression have been reported in adult patients with schizophrenia [13, 56]. In line with our P50 data, we failed to find significant group differences in either N100 and P200 amplitudes or ratios between the EOP, ADHD and HC groups.

We included patients with ADHD as a clinical control group to investigate the specificity of P50 suppression. Our finding of healthy levels of P50 suppression in the ADHD group is in line with a previous study of unmedicated adult patients with ADHD [31], but in contrast with those of the sole previous study in children with ADHD [32] as well as two other studies on adult patients with ADHD [29, 30]. The negative findings in our study cannot be explained by medication effects given that no psychostimulants were allowed at least three months prior to testing and approximately 90% of our ADHD sample had never been treated with psychostimulants before. Overall, the inconsistent reports on P50 suppression in ADHD patients suggest heterogeneity in this patient group as well.

In EOP patients, we failed to find a relationship between P50 suppression and psychopathology measured by the PANSS, consistent with a review on clinical correlates of P50 sensory gating [57]. We did find a significant correlation between P50 measures and items 10–18 from the ADHD-RS, indicating that poor P50 suppression is associated with a higher degree of hyperactivity/impulsivity symptoms in EOP. Speculatively, there is an interaction between the psychotic symptoms and symptoms of ADHD in the EOP patients, that causes decreased sensory gating. This may also explain the inconsistent results between studies; if a study is based on a population with high comorbid ADHD symptoms of hyperactivity and impulsivity then P50 suppression is likely decreased (increased P50 ratio) while a study with a population with low comorbid ADHD symptomatology is likely to find no P50 suppression deficits (normal P50 ratio). In the ADHD group, we found a significant correlation between the testing amplitude and the PANSS positive score, indicating that a larger response to the second stimuli, reflective of poor gating, is associated with more subclinical positive symptoms. There are several indicators of overlap between ADHD and schizophrenia that could explain the observed correlations. Higher rates of ADHD have been reported in offspring of schizophrenia patients [58] and attentional deficits in children of parents with schizophrenia has been associated with later development of psychosis [59]. Furthermore, high rates of comorbid ADHD in children and adolescents with schizophrenia has been reported [60, 61].

A major strength of the present study is the inclusion of a clinical control group in addition to healthy controls, thus enabling us to evaluate the diagnostic specificity of P50 suppression. Moreover, we included a relatively large cohort of EOP patients given that these patients are rare and often difficult to recruit. Our cohort contained a four times larger number of schizophrenia patients than that of the sole previous report on P50 suppression and EOS in the literature, making our findings far less susceptible to power issues. The fact that the majority of our ADHD patients were unmedicated might raise concerns about whether the included patients represent milder cases of the disorder. However, the ADHD group scored high on the ADHD-RS, very similar to scores observed in a nationwide multicenter study of children and adolescents with ADHD in Denmark [36], suggesting that these are valid cases. Another potential limitation is the inclusion of medicated EOP patients. Even though we did not detect any effects of antipsychotic

medication on P50 suppression in the current study it might still have added "noise" to our data that 65% of the EOP patients were treated with antipsychotics at the time of testing; this, especially given that previous reports indicated that some atypical antipsychotics can normalize P50 suppression deficits in schizophrenia [12, 62]. One may speculate that the lower average P50 ratio observed in schizophrenia patients (0.25) compared to both non-schizophrenia cases (0.46) and healthy controls (0.49) although not statistically significant, could be explained by schizophrenia patients receiving more antipsychotic medication. However, this do not seem to be the case given that more or less the same percentage of the non-schizophrenia patients as schizophrenia patients were treated with antipsychotics during the time of testing (63 and 67%, respectively), in spite of the fact that they show such dissimilar average P50 ratios. Moreover, there was no significant difference in the mean chlorpromazine equivalents between the two psychosis groups. More likely the differences are caused by the heterogeneity of our research population, given that the differences did not reach statistical significance. Furthermore we asked participants to count the numbers of clicks to avoid drowsiness. Some studies suggest that mental effort directed at the auditory stimuli may influence sensory gating mechanisms [63–65]. However, the negative findings in the present study are unlikely to be explained by any technical or methodological issues, given that we previously demonstrated P50 suppression deficits in (adult) schizophrenia patients using the same experimental paradigm and instructions [12, 66]. Finally, this study was cross-sectional, thus limiting the possibility of making causal inferences regarding the effects of maturation and progress of disease.

Summarized, we observed no P50, N100 or P200 amplitude or suppression differences between adolescents with either EOP or ADHD and healthy controls. Based on these results, our study does not supply evidence for sensory gating deficits being a potential biomarker for either EOP or ADHD. Longitudinal studies are needed to examine how sensory gating abilities develop during adolescence and interacts with the initial onset and later progress of psychosis.

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ADDITIONAL INFORMATION

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