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Neuroscience Letters 434 (2008) 218–223
Neuroscience Letters
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Sensory gating in young children with autism: Relation to age, IQ, and EEG gamma oscillations

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Received 8 September 2007; received in revised form 23 January 2008; accepted 29 January 2008

Abstract

Unusual reactions to auditory stimuli are often observed in autism and may relate to ineffective inhibitory modulation of sensory input (sensory gating). A previous study of P50 sensory gating did not reveal abnormalities in high-functioning school age children [C. Kemner, B. Oranje, M.N. Verbaten, H. van Engeland, Normal P50 gating in children with autism, J. Clin. Psychiatry 63 (2002) 214–217]. Sensory gating deficit may, however, characterize younger children with autism or be a feature of retarded children with autism, reflecting imbalance of neuronal excitation/inhibition in these cohorts. We applied a paired clicks paradigm to study P50 sensory gating, and its relation to IQ and EEG gamma spectral power (as a putative marker of cortical excitability), in young (3–8 years) children with autism ($N=21$) and age-matched typically developing children ($N=21$). P50 suppression in response to the second click was normal in high-functioning children with autism, but significantly ($p<0.03$) reduced in those with mental retardation. P50 gating improved with age in both typically developing children and those with autism. Higher ongoing EEG gamma power corresponded to lower P50 suppression in autism ($p<0.02$), but not in control group. The data suggest that ineffective inhibitory control of sensory processing is characteristic for retarded children with autism and may reflect excitation/inhibition imbalance in this clinical group.

Keywords: Autism; Children; ERP; P50 sensory gating; Gamma oscillations

Abnormal reactivity to sensory stimuli is commonly observed in young children with autism (CWA), pervasively presents in adult age [2,20], and is especially noticeable in the auditory modality. CWA may demonstrate both unresponsiveness to sound and acoustic hypersensitivity. It has been suggested that altered inhibitory control of sensory intake may cause sensory overload and disruption of higher order processing in autism, leading to active avoidance of external stimulation [12].

Suppression of processing of irrelevant repetitive sensory input is often studied using a 'sensory gating' paradigm. Pairs of clicks separated by short within-pair interstimulius intervals (ISIs) are presented with much longer inter-pair ISIs. The so-called 'preattentive' middle-latency P50 component of the auditory event-related potential markedly decreases in amplitude with repetition of stimuli with short ISIs, reflecting inhibitory gating of repetitive auditory input. Sensory gating is usually defined as the ratio of P50 amplitude after the second click (S2) to the P50 amplitude after the first click (S1). The pronounced P50 suppression to the second click corresponds to a robust inhibitory function of the brain, i.e. a normal sensory gating [1,7,19].

The sensory gating paradigm has been widely used to study neurophysiologic mechanisms in schizophrenia. The reduced sensory gating that was found in schizophrenic patients may contribute to sensory overload experienced by these patients [19]. This gating deficit has been related to decreases in inhibitory interneurons found in schizophrenia [13]. Similarly to schizophrenic patients, individuals with autism often demonstrate increased sensitivity to sensory stimuli. Moreover, pathology of inhibitory interneurons [14] and imbalance of excitation and inhibition processes [25] has been implicated in

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doi:10.1016/j.neulet.2008.01.066

autism as well. Therefore, similarly to schizophrenic patients individuals with autism may have sensory gating deficit. The only existing study of sensory gating in autism, by Kemner et al. [10], did not reveal P50 suppression abnormalities in a sample of 12 high-functioning children aged 7–13 years. Sensory gating, however, may be impaired in younger children with autism, but normalize during development [26].

We have recently described in boys with autism relationship between developmental delay and another putative index of inhibitory deficiency—excess of ongoing high-frequency oscillations in EEG [23]. It appears, therefore, that an altered balance of excitation–inhibition [25] may be especially characteristic for mentally retarded individuals with autism. Against this background, we suspected that the P50 suppression ratio may also correlate with mental delay, reflecting greater inhibitory deficit in severely cognitively disturbed CWA.

Apart from the sensory gating deficit, amplitude, and latency parameters of the P50 component may also reflect atypical pre-attentive sensory processing in autism. The study by Kemner et al. did not reveal differences in P50 amplitude between CWA and typically developing children (TDC). To our knowledge, no data on latency of P50 component in CWA have been reported.

In the present study, we used a paired clicks sensory gating paradigm to investigate ERP correlates of pre-attentive modulation of auditory processing in autism. *First*, we intended to analyze P50 sensory gating in young (3–8 years old) CWA. For this purpose, we analyzed between-group differences in P50 suppression scores. The P50 amplitudes and latencies were also analyzed. In addition, we checked whether P50 gating capacity improves with age in CWA, like it does in TDC [3,15]. The *second* aim of the study was to reveal a putative relationship between a P50 gating deficit and the degree of developmental disturbance assessed via IQ level in CWA. *Third*, we analyzed correlation between the two putative measures of altered excitation/inhibition (P50 gating and amount of gamma oscillations in ongoing EEG), testing the hypothesis that in autism lower P50 gating capacity would be associated with greater gamma power in ongoing EEG.

Written informed consent was obtained from parents of all participants. The clinical group included 21 children (4 girls) with autism aged 42–105 months (mean = 71, S.D. = 18.9), recruited from the Queen Silvia Children's Hospital, Gothenburg, Sweden. The diagnosis was based on DSM-IV-TR and ICD-10 criteria and confirmed by the DISCO-10 (Diagnostic Interview for Social and Communication disorders). None of the CWA had epilepsy and no other neurological comorbidity was found. All but one of the children were medication-free. In 13 children, IQ was accessed by WPPSI-R; in 3 oldest children WISC III was applied; in 5 youngest or most retarded children, DQ was measured using the Griffiths' test. Ten children ('normal/close-to-normal IQ group') had IQ $\geq$ 79 (mean IQ = 93.2, S.D. = 13.5). The other 11 children ('low IQ group') had IQ $\leq$ 72 (mean IQ/DQ = 63.1, S.D. = 10.1). Fifteen of the CWA, as well as 15 age-matched control subjects have participated in our previous study of high frequency EEG [23].

The controls were 21 TDC (3 girls) attending regular schools or day care centers. Children with behavioral problems or language delay (according to parental report) were not included. The TDC were pair-wise matched to the CWA by age (range: 48–107 months, mean = 71, S.D. = 18).

During the paired clicks paradigm, children watched silent cartoons on a computer monitor. Auditory stimuli were binaurally presented through wireless earphones (Sony MDR-IF140). One hundred pairs of clicks, composed of white noise (90 dB SPL, 4 ms in duration), were presented with a constant intra-pair ISI of 500 ms while the inter-pair ISIs ranged randomly from 7.5 to 9.5 s. Stimuli were organized into two roughly equal sessions with a 40 s interval corresponding to the end of the first and start of the second cartoon. Auditory stimuli were presented using Presentation® software (Neurobehavioral Systems Inc.).

For analysis of spontaneous gamma oscillation, EEG was recorded during sustained visual attention attracted by: (1) soap bubbles presented by an experimenter and (2) computer presentation of moving fishes. Each type of stimuli was presented for about 2 min. These experimental conditions have been earlier used to analyze rhythms of ongoing EEG in young CWA, because they allow EEG recording under fairly standard settings in this category of subjects [23,27]. The EEG data of one control subject were excluded from the analysis due to excessive artefacts.

Videorecords of the experimental session were stored synchronously with electrophysiological measures and analyzed off-line. Periods when children vocalized, displayed overt emotional reactions, performed gross body movements, hand movements or any stereotype movements were excluded from analysis of ongoing EEG of 'sustained attention'. In the paired clicks paradigm, only those trials when the child silently attended to cartoons were analyzed.

EEG was recorded at 19 standard electrode positions using Quik-cap with Ag/AgCl electrodes. The electrooculogram (EOG) electrodes were placed above and below the left eye and at the outer canthi of the both eyes. Linked earlobes served as reference. The electrophysiological signals were amplified using a Schwarzer EEG headbox with 0.4 s time constant and 70 Hz low-pass filter. EEG and EOG signals were visually inspected off-line for the presence of movement artefacts and the artefact-contaminated periods were excluded from analysis. The EOG signal was further recalculated in bipolar montage and used for correction of ocular artefacts with NeuroScan-4.3 software. In two poorly cooperative CWA application of the EOG electrodes was not possible and manual rejection of the data contaminated by eye movement artefacts was performed.

EEG data were digitized on-line at 500 Hz and post hoc digitally filtered using 0.5 Hz high-pass filter and 46–54 Hz notch filter.

P50 gating was measured at the Cz location, to enable comparison with the previous studies [10,15]. The minimal number of artefact-free trials was 32. The number of averaged trials did not differ between CWA (mean = 50.3, S.D. = 9.6) and TDC (mean = 50.1, S.D. = 9.2). To facilitate extraction of the P50 waveform, the averaged vertex ERP was digitally pre-filtered with a 10 Hz high-pass filter [3]. P50 was established as an abso-

Table 1
Group means and standard deviations of amplitudes and latencies of P50 component elicited by the first (S1) and the second (S2) clicks

	Amplitudes (μV)		Latencies (ms)	
	S1	S2	S1	S2
Control	2.36, S.D. = 1.50	1.51, S.D. = 0.99	58.8, S.D. = 11.22	64.4, S.D. = 9.86
Autism	2.26, S.D. = 1.06	1.82, S.D. = 0.91	57.8, S.D. = 11.39	55.5, S.D. = 9.27

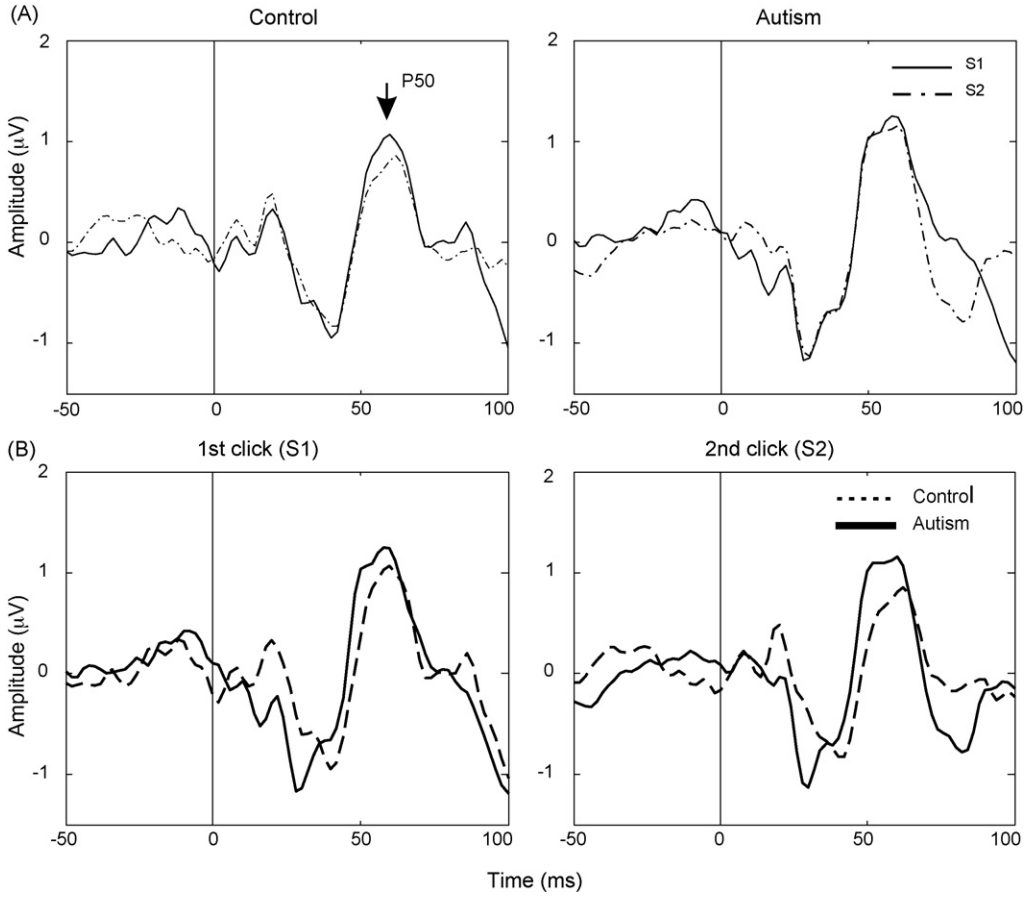

Fig. 1. Grand average P50 waveforms to the first (S1) and the second (S2) clicks in children with autism (CWA) and typically developing children (TDC): between-stimuli (A) and between-groups (B) comparisons. Vertical lines denote stimulus onset.

lute maximum in a 40–80 ms window after stimulus onset.[1] The P50 peak amplitudes were defined relative to a 200 ms prestimulus baseline. A P50 suppression percentage score was calculated as $(1 - (\text{P50 amplitude to S2})/(\text{P50 amplitude to S1})) \times 100$, where a higher score designates greater suppression of P50 upon repetitive stimulation.

For analysis of gamma spectral power, artefact-free EEG data obtained under conditions 1 and 2 were pooled. The relative amount of EEG epochs from condition 1 versus condition 2 did not differ between the experimental groups. EEG data were fast Fourier transformed using a 1 s window smoothed by Hanning weighting function and 50% overlap. For each participant, at least 68 1 s artefact-free epochs were analyzed. The number of averaged epochs did not differ between the groups (controls: mean = 135, S.D. = 46; autism: mean = 122, S.D. = 36, ns). For each subject, average log10-transformed gamma (25–44 Hz) spectral power was calculated at Fz, Cz, and Pz electrode positions, because these positions are least contaminated by myogenic artefacts and reveal the most reliable differences in gamma power between CWA and TDC [23]. ANOVA with factor Group and Stimulus (S1, S2) was applied to test for between-group differences in P50 amplitudes, latencies and suppression scores. Univariate tests for planned comparisons were used for post hoc tests. Regression analysis was used to evaluate dependency of the P50 suppression scores on age, IQ/DQ level, and gamma spectral power. One-sided Wilcoxon matched pairs were used to test the prediction of a P50 sup-

[1] We also applied a second, more 'strict', criterion for P50s identification where amplitude maxima were identified as reliable S1 and S2 P50s only if their peak latencies were within 12 ms of each other. Using this 'strict' criterion, reliable P50s were detected in approx. half of the subjects. As the results were principally the same using both criteria, the data obtained from all subjects using the first criterion are reported.

pression deficit in low IQ CWA as compared with age-matched controls.

The mean amplitudes and latencies of P50 in CWA and TDC are presented in Table 1. Fig. 1 shows Grand average pre-filtered P50 waveforms the two groups.

The P50 suppression scores were positive in both autism (mean = 9.5, S.D. = 50) and control (mean = 28.4; S.D. = 34) subjects, being significantly different from zero in the control group only ($T_{(20)} = 3.8$, $p = 0.001$). The between-group difference in P50 suppression scores was non-significant ($p > 0.16$), suggesting unimpaired P50 suppression in autism at the group level. Convergently, ANOVA results for P50 amplitudes showed significant main effect for stimulus ($F_{(1, 40)} = 11.54$, $p = 0.0016$) due to P50 suppression to the second click, but no Group or Group × Stimulus effects (both p's > 0.29).

For P50 latency there was significant main effect for Group ($F_{(1, 40)} = 5.48$, $p = 0.024$). The latencies were shorter in CWA than in TDC. Neither effect of Stimulus nor Group × Stimulus interaction were significant (both $p > 0.11$). The P50 latencies depended neither on age nor on IQ/DQ (all $p > 0.15$).

The P50 suppression scores depended on age in both TDC and CWA groups (TDC: $R^2 = 0.21$, $F_{(1, 19)} = 5.02$, $p = 0.04$; CWA: $R^2 = 0.37$, $F_{(1, 19)} = 11.0$, $p = 0.004$) due to developmental enhancement of the P50 suppression (Fig. 2A). There was no significant autism-control difference in the age regression slopes ($F_{(1, 38)} = 1.4$, $p = 0.24$). To assess whether the observed age effect on the P50 scores was explained by changes in response to the first or second click, we considered the regression to age of the S1 P50 and the S2 P50 amplitudes separately. The S1 P50 amplitude changed with age in neither autism nor control group (both $p > 0.36$), while the S2 P50 amplitude decreased with age in CWA ($R^2 = 0.30$, $F_{(1, 19)} = 8.2$, $p = 0.01$), but not in TDC ($R^2 = 0.04$, $F_{(1, 19)} = 0.85$, $p = 0.37$). There was, however, no difference in regression slope between the two groups ($F_{(1, 38)} = 0.96$, $p = 0.33$) and the effect of age on the S2 P50 amplitude remained significant when the groups were pooled ($R^2 = 0.14$; $F_{(1, 40)} = 6.3$, $p = 0.016$). This result suggested that, at least in CWA, the age-related enhancement of P50 suppression mainly resulted from a decrease of P50 amplitude to the second click.

To test whether the P50 suppression scores in CWA depended on IQ, both age and IQ/DQ scores were introduced as independent predictors of P50 suppression. P50 suppression scores positively correlated with IQ/DQ level ($R^2 = 0.52$, $F_{(2, 18)} = 9.8$, $p = 0.001$; age: $T_{(18)} = 3.39$, $p = 0.0033$, IQ/DQ: $T_{(18)} = 2.42$, $p = 0.026$). Thus, more developmentally disturbed CWA were

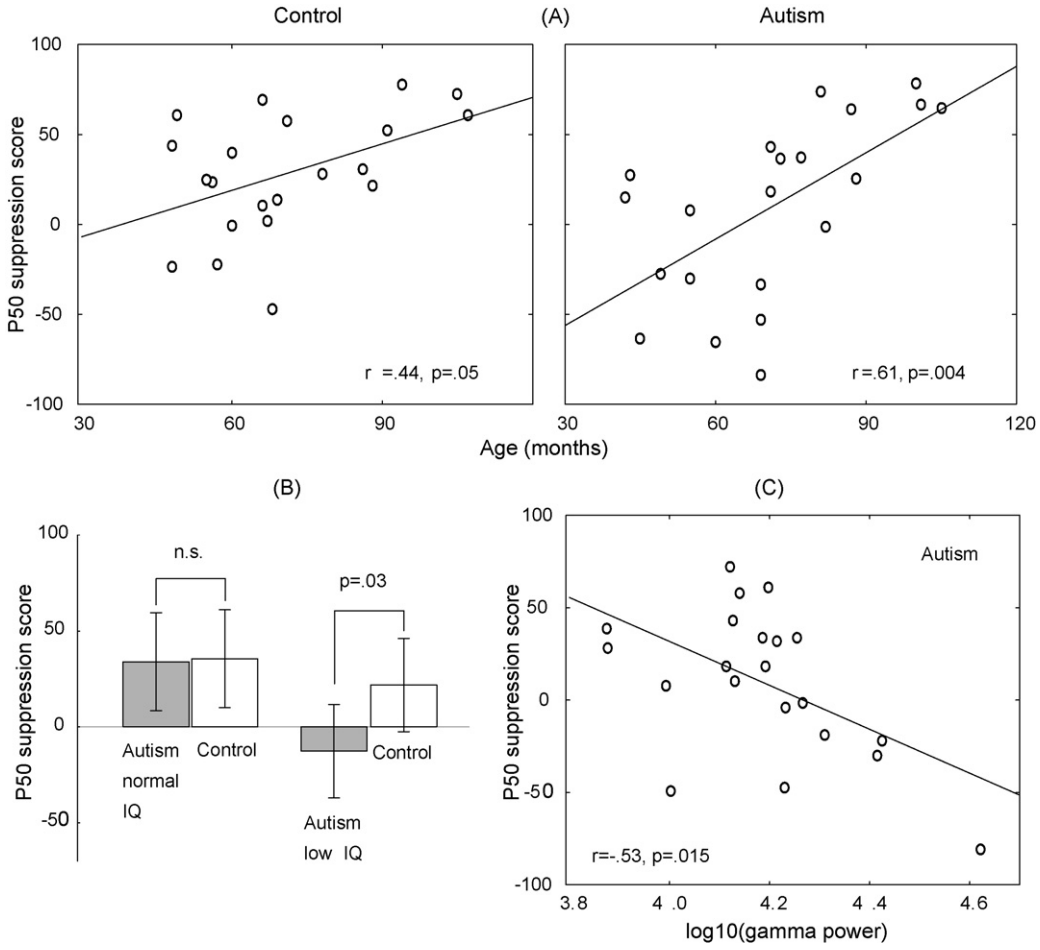

Fig. 2. P50 suppression scores. Higher scores indicate more efficient P50 suppression to the second click. (A) Correlation with age in CWA and TDC. (B) Comparison of low-IQ/normal-IQ CWA with age-matched TDC. p-Values represent one-tailed probabilities (Wilcoxon matched pairs test). Vertical bars denote 0.95% confidence intervals. (C) Correlation with Fz gamma spectral power in CWA. The P50 suppression scores presented on the subplot 'C' are corrected for age.

characterized by reduced or absent P50 gating. We further analyzed differences in P50 gating capacities between CWA and age-matched TDC separately in 'low IQ' and 'normal IQ' groups using one-tailed Wilcoxon matched pairs test (Fig. 2B). Noteworthy, there were no differences in the number of averaged trials between the low-IQ and normal-IQ CWA or their age-matched controls. The P50 suppression scores were on average 34% (S.D. = 24.5) in normal-IQ CWA and 35.6% (S.D. = 36.0) in their age-matched controls. In both cases, the suppression scores significantly differed from zero (autism: $p < 0.002$; control: $p < 0.02$). In the low-IQ group, the average P50 suppression score was −12.7% (S.D. = 57) and did not significantly differ from zero ($p = 0.48$). The age-matched TDC, again, demonstrated significant P50 suppression (mean = 21.8%, S.D. = 32.2, $p < 0.05$). The difference in P50 suppression between low-IQ/DQ children and their age-matched controls was significant ($p = 0.031$). Thus, S1–S2 gating of P50 amplitude was reduced or even inverted (Fig. 2B) in the severely cognitively disturbed part of the autistic spectrum, being unimpaired in high-functioning CWA.

As the subjects participating in this study were not exactly the same as in our previous study, in which excess of the EEG gamma power in autism was found, we analyzed whether this finding would be replicated. For gamma power at midline sites, ANOVA was performed with factor Group and repeated measures factor electrode (Fz, Cz, Pz). Age was introduced as a covariate. The only significant effect was that of Group ($F_{(1, 38)} = 5.5636$, $p = 0.024$). As expected, children with autism had greater power of gamma activity.

To check our prediction on the link between P50 gating deficit and abundance of spontaneous EEG gamma oscillations in CWA, the regression of P50 suppression scores to gamma spectral power was computed. Given the observed dependency of P50 suppression scores on age, both gamma spectral powers (at Fz, Cz, and Pz) and chronological age were stepwise entered into forward regression (F-to-enter = 3) as the predictors of P50 suppression score. Age and Fz gamma spectral power reliably explained inter-individual variability in the P50 suppression scores ($R^2 = 0.54$, $F_{(2, 18)} = 10.7$, $p = 0.0009$), with significant independent contribution of age ($T_{(18)} = 3.45$, $p = 0.003$) and Fz gamma ($T_{(18)} = -2.64$, $p = 0.02$). Introduction of Cz and Pz gamma spectral power did not significantly improve the prediction. As expected, higher gamma power in CWA correlated with poorer P50 sensory gating capacities (Fig. 2C). In TDC, the same analyses revealed significant independent contribution of age ($T_{(17)} = 2.77$, $p = 0.013$) and Pz gamma power ($T_{(17)} = 2.14$, $p = 0.05$). In contrast to CWA, higher gamma spectral power was associated with *better* P50 sensory gating in TDC.

Generally, our data agree with the previous results on normal sensory gating in high-functioning CWA [10]. The P50 suppression scores, however, significantly correlated with IQ/DQ level: mentally retarded CWA did not suppress or even augmented P50 wave in response to the second click (Fig. 2B).

The deficit in the P50 suppression has been suggested to reflect an impairment of central inhibitory circuits that modulate cortical responses to sensory inputs [1]. On the other hand, people with autism may have abnormally high excitation/inhibition ratio in key neural systems [25]. The P50 gating deficit in retarded CWA may, therefore, reflect such excitation/inhibition imbalance. Recently, we have described an excess of high frequency rhythms in ongoing EEG of young boys with autism [23]. The current study revealed that P50 suppression deficit and EEG gamma excess were directly interrelated, suggesting their common underlying mechanism in autism. Interestingly, the relation between gamma power and P50 suppression was the opposite in CWA and TDC, pointing to difference of underlying neuronal mechanisms.

One possible explanation of negative correlation between P50 suppression score and gamma excess in autism could be a dysfunction of inhibitory interneurons which are implicated in the generation of both EEG gamma activity [28] and the P50 component of auditory ERP [7]. As both P50 suppression ratio and ongoing gamma power in CWA significantly correlated with mental retardation, the excitation/inhibition imbalance may be more characteristic of retarded CWA. The important limitation of the present study is, however, the usage of TDC as a control group. It is not clear whether this trait is a non-specific characteristic of mentally retarded individuals. Therefore, the additional control groups of retarded children without autism are required to clarify whether P50 gating deficit retarded children with autism is related to severity of the autistic disorder, or mental retardation per se.

Capacity to filter auditory input depends on mechanisms within the temporal auditory cortex, intra-thalamic and fronto-thalamic pathways regulating sensory transmission through thalamic relay nuclei, and cholinergic input to the nucleus reticularis thalami from basal forebrain nuclei [8]. A failure at any of these levels may hypothetically cause the auditory gating deficiency. Hence, it is hardly surprising that a P50 suppression deficit, originally demonstrated in schizophrenia, has been found also in Alzheimer's disease [5], prefrontal damage [11], benign idiopathic epilepsy [6] and bipolar disorder [21]. All the above-mentioned 'gating-deficient' disorders, are characterized by abnormalities in prefrontal functioning [9,18]. As prefrontal cortex modulates cortical responses to repetitive sensory stimuli [11], the association between P50 gating deficit and frontal dysfunction in a number of neurological and psychiatric disorders including autism is a plausible suggestion. The putative roles of cortical hyperexcitation and frontal deficit in reducing sensory gating in CWA are not mutually exclusive. In particular, impaired inhibitory function of the frontal cortex has been implicated in enhanced cortical excitation and gamma excess in patients with generalized epilepsy [17,29].

It is noteworthy, that the reliable impairment of he other measure of inhibition—prepulse inhibition of the startle reflex (PPI) was reported in autism [16,24]. Although both P50 gating and PPI depend on functional integrity of the prefrontal cortex, the two measures do not correlate with each other [4,22] and may reflect fundamentally different aspects of inhibitory deficit in autism.

In agreement with previous developmental studies [3,15], the P50 suppression scores in our study significantly improved with age. The age-related increase of P50 suppression mainly depended on a decrease of P50 amplitude to the second click. This age trend may reflect maturation of inhibitory mechanisms

and age-related improvement of a capacity for pre-attentive suppression of irrelevant repetitive auditory input.

In our study, CWA had significantly shorter P50 latencies than healthy controls. This finding may point to an autism-control difference in early stages of cortical auditory processing.

To summarize, our data suggest that ineffective inhibitory control of sensory processing and excitation/inhibition imbalance are more characteristic of retarded CWA. The normal P50 suppression in high-functioning children implies that the altered inhibitory modulation of sensory input is not an obligatory feature of young children with autism.

Acknowledgements

We thank Ulla Sandblom Tomas Karlsson, Johan Kling and Lennart Magnusson for their valuable technical support. This study was supported by the Swedish Research Council (proj. 12170, proj. 2003-4581), the Gothenburg medical faculty, and the Russian Foundation for Humanities (proj. 070600208).

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