Normal P50 Gating in Children With Autism

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Background: An important characteristic of children with autism is their unusual reaction to stimuli, which may be related to problems in the filtering of sensory input. For this reason, sensory filtering was measured in children with autism using the P50 gating paradigm.

Method: Twelve non–mentally retarded children with autism (i.e., having a DSM-IV diagnosis of either autistic disorder or pervasive developmental disorder not otherwise specified) and 11 healthy control children were tested for their ability to suppress P50, measured at the Cz electrode.

Results: No differences were found between the children with autism and the control children with regard to absolute P50 amplitudes and P50 suppression.

Conclusion: The excitability of the neuronal substrate that causes P50 is normal in children with autism, as are the early, inhibitory processes related to P50 gating. These results distinguish between subjects with autism and subjects with schizophrenia, in whom sensory gating is abnormal.

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Pervasive developmental disorder (PDD) is the umbrella term for several serious childhood psychiatric disorders in the autistic spectrum, all of which are thought to be biologically determined. Autism is the most severe PDD. The core symptoms of autism include problems in social interaction and communication. A third domain of abnormalities includes unusual reactions to the environment, such as hypersensitivity or hyposensitivity to sound. It has been suggested that people with autism have a problem in the filtering of sensory input.[1] Indeed, it is thought that some of the symptoms of autism, such as the withdrawal from social contact, serve to minimize sensory input and to prevent overloading of central processing systems.

There are 2 paradigms that are thought to measure aspects of stimulus filtering related to inhibitory mechanisms, namely, the prepulse inhibition (PPI) of the acoustic startle response and the gating of the auditory evoked (P50) potential. Although both paradigms involve the inhibitory effect of an initial stimulus on the response to a second stimulus, there are differences in the variables and probably differences in the basic circuitry between the 2 paradigms.[2] For instance, no correlation[2] or only a partial correlation[3] between P50 gating and PPI of the startle response has been found, leading to the conclusion that P50 gating and PPI of the startle response mainly reflect separate sensory processes.[3]

One study of several aspects of startle, including PPI of the startle response,[4] was performed with patients with autism, mostly children and adolescents. No differences in PPI were found between subjects with autism and healthy controls. Despite this negative result, in view of the weak correlation between the PPI of the startle response and the gating of the P50 potential, abnormalities in P50 gating could still be present in autism, but research in this area is lacking.

A second reason for interest in P50 gating in autism is the fact that abnormalities in this respect are consistently found in schizophrenic patients.[5,6] Although schizophrenia and autism are usually considered to be distinct syndromes, there is some resemblance between them. For example, autism "shares several deficit symptoms—negative thought disorders and affective blunting—with schizophrenia."[7(p777)] It would be interesting to see whether

individuals with autism or schizophrenia can be distinguished on the basis of a basic biological phenomenon, such as gating of the P50 potential.

In this study, gating of the P50 potential was analyzed in a group of non–mentally retarded children with autism and a healthy control group. Although most studies on P50 gating have been done in adults, the phenomenon can indeed be reliably measured in children, and healthy developing children between 10 and 14 years of age show the same ratio of P50 gating as adults.[8] Furthermore, there are no significant age effects on the amplitude of the conditioning stimulus.

METHOD

Subjects

Initially, 32 children were included in the study; 5 healthy control children were excluded because of technical problems, 1 child with autism was excluded because of excessive movements, and 3 children with autism were excluded because the P50 potential could not be measured reliably. In total, data from 12 children with autism and 11 healthy children were included in the analysis. The children with autism had a mean ± SD age of 10.4 ± 1.9 years (range, 7.3–13.6 years) and a mean total IQ of 96.2 ± 9.7 (based on 11 children); the control children had a mean age of 10.3 ± 1.5 years (range, 7.3–12.1 years) and a mean total IQ of 98.5 ± 9.3. All children except 2 of the children with autism were male.

All diagnoses were based on DSM-IV criteria and were made by a child psychiatrist (H.v.E.) after extensive diagnostic evaluation including review of prior records (developmental history, psychiatric and psychological observations and tests, and neurologic investigations), parent interview, and psychiatric observation. The children were diagnosed as having autistic disorder (299.00) according to DSM-IV, except for 1 child, who received a diagnosis of pervasive developmental disorder not otherwise specified (299.80). Ten children participating were also examined using the Autism Diagnostic Interview-Revised (ADI-R).[9] According to the rating algorithm, 6 children met criteria for autism, 3 children fell 1 point short on the domain of stereotypy, and 1 child did not have a stereotypy score. Enrollment in this protocol was voluntary. The Medical Ethics Committee of the University Medical Center Utrecht, Utrecht, the Netherlands, approved the study. Parents of all subjects provided informed consent prior to entry in the study. None of the children was taking psychotropic agents.

Signal Recording

A tin electrode was placed at the Cz electrode for measuring the P50 potential. Horizontal electro-ocular activity (EOG) was recorded by attaching an electrode to the outer canthus of each eye. Similarly, vertical EOG was recorded from infra-orbital and supra-orbital electrodes placed in line with the pupil of the left eye. A ground electrode was attached to the middle of the forehead, and a reference electrode was placed at the right mastoid. For both electroencephalogram (EEG) and EOG, electrode paste was used. Impedance was kept below 5 kΩ. All EEG and EOG signals were recorded with high/low pass filter settings at 0.1/200 Hz for the EEG and 0.3/40 Hz for the EOG, respectively. Sampling started as soon as an experimental block started and lasted until the end of it (continuous recording). All signals were digitized at a sampling rate of 900 Hz.

Procedure

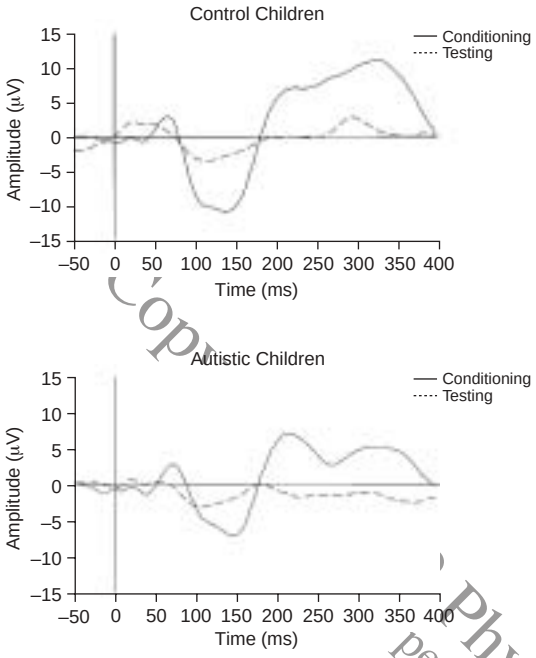
All auditory stimuli were delivered almost instantaneously (rise/fall time < 0.1 ms) and were presented binaurally using ABR EAR-earphones (Veenhuis, Gouda, the Netherlands). The software settings were calibrated by means of an artificial ear (Brüel and Kjær, type 4152, Fa. Brüel and Kjær, Veenendaal, the Netherlands) to make sure that the stimulus had the intended intensity at the subject's ear. The artificial ear is constructed to imitate the performance of the ear as closely as possible. The sound intensity measured this way (dBa) closely resembles the intensity the human ear would register.

Each child was seated upright in a dentist's chair in a dimly lit cabin. At the child's request, a parent or caretaker was seated next to him or her in the cabin. To prevent unnecessary movements of the head or neck muscles, a vacuum cushion was attached to the top of the chair to fix the subject's head. Subjects were instructed to close their eyes during the experiment. The experimenter and the equipment were in an adjacent control room.

The actual experimental blocks were preceded by 3 pairs of clicks to ascertain that a click did not elicit a startle response in the subject (which it did not). After this, the experiment started: 3 identical blocks of 20 pairs of clicks (each click of 75-dB intensity; duration, 2 ms) were presented. The interval between the 2 stimuli of the pair (interstimulus interval) was 500 ms, and the interval between the pairs (intertrial interval) was 10 s. The subjects were instructed to count the pairs of clicks. After each block, the subject was asked how many pairs of clicks he or she had counted.

After recording, the EEG and EOG signals were processed using the software package Neuroscan (Tefa-Portanje, Woerden, the Netherlands). First, the signals were epoched at an interval between 100 ms prestimulus and 400 ms poststimulus and corrected for the baseline. Then, the EEG was corrected for vertical eye movements, by subtracting the vertical EOG from EEG epochs by means of regression in the time domain. After this, all epochs containing artifacts were removed from the database. Finally, the 3 experimental blocks were put together, and averaged P50 peaks elicited by the first (conditioning)

Figure 1. Auditory Evoked Potentials in Response to the Conditioning and Testing Stimuli for the Control and Autistic Children



stimulus were identified as the greatest positivity in a window from 40 to 90 ms after stimulus presentation.[10] If more than 1 peak was identified, the last was selected. Amplitude was assessed as the difference between this peak and the preceding trough, and the latency was assessed as the time from the onset of the conditioning stimulus to the maximum amplitude of this peak. The P50 peaks elicited by the second (testing) stimulus were assessed in the same way, but with the peak latency being constrained to a window formed by the latency of the conditioning stimulus ± 10 ms. Two raters identified the P50 wave; the interrater reliability was greater than 0.95. The P50 ratio was calculated as the amplitude of the P50 potential elicited by the testing stimulus divided by the amplitude elicited by the conditioning stimulus (T/C). The SPSS 9.0 for Windows software package (SPSS, Inc., Chicago, Ill.) was used for the statistical analysis.

RESULTS

Multivariate analysis of variance (MANOVA) with the within-subjects factor stimuli (conditioning vs. testing stimulus) and the between-subjects factor group (autistic vs. normal control) showed only a main effect of stimuli ($F = 22.7$, $df = 1,21$; $p < .0001$). Comparison of the response elicited by the conditioning stimulus with that elicited by the testing stimulus revealed a highly significant difference in P50 wave amplitude ($t = 4.9$, $df = 22$, $p < .001$), indicating P50 suppression (Figure 1).

Table 1. Amplitude (μV) of the P50 Potential Elicited by the Conditioning and the Testing Stimuli, and Ratio of the Testing and the Conditioning Stimuli (T/C), for Each Subject and Each Group[a]

Subjects	Conditioning	Testing	T/C	No. of trials
Healthy controls				
1	4.31	5.24	1.22	60
2	3.85	3.55	0.92	57
3	3.08	0.25	0.08	57
4	11.14	0	0	47
5	6.01	0	0	59
6	14.30	0	0	59
7	3.36	0	0	55
8	3.28	1.84	0.56	59
9	2.19	2.27	1.04	49
10	2.64	2.74	1.04	33
11	8.20	2.41	0.29	54
Total group, mean (SD)	5.7 (3.9)	1.7 (1.7)	0.47 (0.50)	…
Autistic subjects				
1	7.30	8.39	1.15	58
2	3.86	0	0	50
3	1.17	0.78	0.67	40
4	7.96	2.27	0.29	55
5	5.95	1.14	0.19	60
6	1.89	0	0	57
7	5.92	0	0	54
8	4.23	0	0	59
9	10.48	1.67	0.16	56
10	2.79	0	0	51
11	12.62	7.99	0.63	49
12	4.27	1.07	0.25	57
Total group, mean (SD)	5.7 (3.4)	1.9 (3.0)	0.28 (0.36)	…

[a]The last column indicates the number of trial pairs used for the analysis.

No group (interaction) effect was noted (Table 1). The T/C ratio was tested separately and found to differ significantly from zero ($t = 4.1$, $df = 22$, $p < .001$). There was no group difference with respect to the T/C ratio, using a t test.

DISCUSSION

In the present study, P50 gating was analyzed in children with autism and in healthy children. It is thought that in the P50 paradigm, 2 processes occur upon presentation of the first (conditioning) stimulus. The conditioning stimulus causes a neuronal response, the P50 potential, but at the same time activates inhibitory pathways. These inhibitory pathways are still active when the second stimulus is presented shortly thereafter (i.e., after about 500 ms) and suppress the P50 potential in response to the second stimulus. Results showed that both children with autism and healthy control children showed gating of the P50 wave. Moreover, the amplitude of the P50 potential elicited by the conditioning and testing stimuli was similar in both groups. Thus, children with autism show a normal excitability of the neuronal substrate that causes the P50 potential and a normal early, inhibitory process

related to P50 gating. However, the data should be interpreted with some caution, since they are based on a relatively small number of subjects. Also, since only children between 7 and 13 years of age were tested, it is possible that P50 abnormalities occur in younger children, but improve with age.

The normal P50 gating response clearly distinguishes children with autism from individuals with schizophrenia, in whom P50 gating is abnormal. Likewise, the often-observed smaller amplitude of the response to the conditioning response in schizophrenic patients was not seen in children with autism, thus confirming the notion that autism and schizophrenia have a different etiology.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Kootz JP, Marinelli B, Cohen DJ. Modulation of response to environmental stimulation in autistic children. J Autism Dev Dis 1982;12:185–193
2. Schwarzkopf SB, Lamberti JS, Smith DA. Concurrent assessment of acoustic startle and auditory 50 evoked potential measures of sensory inhibition. Biol Psychiatry 1993;33:815–828
3. Oranje B, van Berckel BN, Kemner C, et al. P50 suppression and prepulse inhibition of the startle reflex in humans: a correlational study. Biol Psychiatry 1999;45:883–890
4. Ornitz EM, Lane SJ, Sugiyama T, et al. Startle modulation studies in autism. J Autism Dev Dis 1993;23:619–637
5. Clementz BA, Geyer MA, Braff DL. Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. Am J Psychiatry 1998;155:1691–1694
6. Freedman R, Adler LE, Myles-Worsley M, et al. Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects: human recordings, computer simulation, and an animal model. Arch Gen Psychiatry 1996;53:1114–1121
7. Rumsey JM, Andreasen NC, Rapoport JL. Thought, language, communication and affective flattening in autistic adults. Arch Gen Psychiatry 1986;43:771–777
8. Myles-Worsley M, Coon H, Byerly W, et al. Developmental and genetic influences on the P50 sensory gating phenotype. Biol Psychiatry 1996;39:289–295
9. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 1994;24:659–685
10. Nagamoto HT, Adler LE, Waldo MC, et al. Sensory gating in schizophrenics and normal controls: effects of changing stimulation interval. Biol Psychiatry 1989;25:549–561

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