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ORIGINAL PAPER

Abnormal Selective Attention Normalizes P3 Amplitudes in PDD

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Abstract This paper studied whether abnormal P3 amplitudes in PDD are a corollary of abnormalities in ERP components related to selective attention in visual and auditory tasks. Furthermore, this study sought to clarify possible age differences in such abnormalities. Children with PDD showed smaller P3 amplitudes than controls, but no abnormalities in selective attention. Adolescents with PDD showed abnormal selective attention, as reflected by larger auditory Processing Negativity (PN) and visual N2b, but no P3 abnormalities. Dipole localizations revealed that the locations of PN generators in subjects with PDD differed from controls. It was concluded that the abnormalities in selective attention in adolescents with PDD have a normalizing effect on P3, and possibly act as a compensatory process.

Keywords Event-related potentials · Pervasive developmental disorder · Source localization · P3 · Selective attention · Age

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Introduction

According to the DSM-IV (American Psychiatric Association, 1994), autism or Autistic Disorder (AD) falls within the broader category of Pervasive Developmental Disorders (PDD). This category includes a group of psychiatric disorders, which share impairments in social skills, language development and behavioural repertoire. The category of Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS) is reserved for patients who show such impairments, but who do not meet all criteria for autistic disorder or any other pervasive developmental disorder. There is still considerable debate over the exact boundaries between autistic disorder and PDD-NOS (Lord & Risi, 1996). PDD-NOS inevitably shares considerable clinical similarity with autistic disorder. The most common differences between the two disorders are age of onset and severity of symptoms (Ciaranello & Ciaranello, 1995). It could be argued that autistic disorder lies on the severe end of a continuum of autistic features, and PDD-NOS represents a milder, or sub-threshold form. The opposite and least severe end of the continuum may be represented by mild communicative and social deficits or stereotyped behaviours. Such milder deficits, often called the ''broader autism phenotype'', are more frequently observed in families of autistic individuals than in the general population (Piven, 1997; Rutter, 2000). It may well be that the disorders on this continuum share underlying neurobiological deficits (Ciaranello & Ciaranello, 1995).

One exponent of such a common neurobiological deficit may be attentional abnormalities. Such abnormalities have been a rather common finding in autism and may contribute to the clinical features of the disorder (Allen & Courchesne, 2001). For example, the clinical observation of heightened reactivity to seemingly meaningless stimuli

may be a sign of increased distractibility, while the narrowed interests and repetitive behaviours may be a representation of a deficit in attentional shifting. Such observations add to the perception that attention seems to be an important area of research in the autistic spectrum disorders. There are several steps in information processing that can be influenced by attention, or that may be ''under attentional control''. Attention may already operate very early, at the level of perception, but also on working memory or response selection (Luck, Woodman, & Vogel, 2000). In autism, narrowed attention on the preceptual level may lead to a tendency to process incoming information in a piecemeal fashion, disregarding the context in which information is presented (Frith, 1997; Happe, 1999; Jolliffe & Baron-Cohen, 1999; Plaisted, Swettenham, & Rees, 1999). On the level of response selection, autistic individuals may show errors of perseveration in go-nogo tasks (Ozonoff, Strayer, McMahon, & Filloux, 1994) and in incompatibility tasks, where a subject has to inhibit a cued response (Noterdaeme, Amorosa, Mildenberger, Sitter, & Minow, 2001). It may well be that autism lies on the severe end of a continuum of autistic features and PDD represents a milder form, however it is likely that both disorders share underlying neurobiological deficits (Ciaranello & Ciaranello, 1995).

Event related potentials (ERPs) are very well suited for the study of attention because of their high time resolution. A common ERP paradigm to study attention is the oddball manipulation, where a train of similar stimuli is presented with occasional deviants at irregular intervals. In such tasks, a large positivity (P3) can be observed around 300 ms after presentation of a deviant, which is thought to reflect attentional and memory related operations associated with target detection (Polich, 1998). In the first ERP study in autism (Novick, Kurtzberg, & Vaughn, 1979) the authors found that when autistic subjects were presented with a train of auditory (2 kHz tone) or visual (flash) stimuli in which at irregular intervals a stimulus was omitted, subjects were able to detect stimulus omissions, but they did not exhibit the same visual and auditory brain potentials between 300 and 500 ms as controls did following a deleted stimulus. Although this study had some methodological problems, like a very small sample size ($n = 3$), it was the incentive for further ERP studies in autism. In similar auditory tasks smaller P3 amplitudes have been found on electrode Pz (Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Lincoln, Courchesne, Harms, & Allen, 1993) and Cz (Courchesne, Lincoln, Kilman, & Galambos, 1985; Dawson, Finley, Phillips, Galpert, & Lewy, 1988). Adding highly unexpected or novel stimuli to the design revealed that autistic subjects process novel auditory information differently from controls, as indicated by abnormally small A/Pcz/300 amplitudes (Courchesne, Kilman, Galambos, & Lincoln, 1984; Courchesne et al., 1985; Kemner, Verbaten, Cuperus, Camfferman, & Van Engeland, 1995).

For the visual modality, similar to what was reported in the auditory modality, Courchesne and colleagues found smaller P3 amplitude on Pz in an autistic group (Courchesne et al., 1989). Furthermore, large P3 amplitude reductions in autism have been observed in oddball studies over central occipital electrodes in children (Kemner, Verbaten, Cuperus, Camfferman, & Van Engeland, 1994; Verbaten, Roelofs, Van Engeland, Kenemans, & Slangen, 1991).

The ERP studies in autism reviewed above have for the most part found abnormally small P3 amplitudes over the parietal and occipital scalp and these smaller P3 amplitudes have been interpreted as a reflection of abnormal neuronal organization of posterior brain areas (Ciesielski, Courchesne, & Elmasian, 1990; Courchesne, 1987; Kemner et al., 1994, 1995)

Abnormalities in P3 amplitudes are consistently reported in both adult and paediatric autistic groups. Most of these studies have used an oddball paradigm, in which the subject is only required to detect stimulus deviance in a single stream of information. Although oddball studies have resulted in fairly consistent P3 abnormalities, none have found abnormalities in attentional components preceding the P3. It may well be that oddball manipulations are not sensitive enough to detect abnormalities in selective attention.

Tasks that are better suited to measure the effects of selective attention typically present the subject with two streams or ''channels'' of standard and deviant stimuli presented simultaneously (e.g., in both ears), where one channel is to be attended and the other is to be ignored. The basic comparison to identify the effects of selective is then to compare the ERP waveform elicited by an attended stimulus to the waveform evoked by the same stimulus when it is ignored. In many cases these waveforms are subtracted, such that a difference wave remains. Whenever this wave significantly deviates from zero, this can be interpreted as an effect of attention. Such comparisons allow inferences on inter-channel selection (between attended and unattended streams of information) and on intra-channel selection (between standards and deviants within the attended channel). This early attentional processing occurs in modality specific areas of the brain (Luck et al., 2000; Woods, Knight, & Scabini, 1993), and the timing is dependent on the nature of the task involved.

Indeed, a study by Ciesielski et al. (1990), which to date is the only study to use some form of a selective attention paradigm, proved that there may be attention related abnormalities preceding the P3. Participants were simultaneously presented with auditory standard and deviant tones (1 and 2 kHz) and visual standards and deviants (red

and green flashes). Subjects were instructed to attend only to one kind of deviant stimuli (e.g., high pitched tones), while ignoring all others. By repeating the experiment with the instruction to attend to deviants in the other modality, the comparison could be made between stimuli when they were attended and the same stimuli when they were not attended to. When subjects were required to pay attention only to auditory stimuli, autistic subjects not only showed smaller P3 amplitudes on Pz, but also an absence of attention related negativity Nd (Ciesielski et al., 1990). Similar abnormalities were also found in visual selective attention components (a smaller N270) and parietal P3. However, none of these effects proved to be present in a later study by these authors, using the same task (Ciesielski, Knight, Prince, Harris, & Handmaker, 1995).

The present paper describes a systematic study of selective attention in autism, in order to examine whether the abnormal P3 amplitudes in autism are a corollary of earlier deficits in attention, as reflected in the Processing Negativity (PN) in an auditory task and N2b, occipital selection negativity (OSN) and frontal selection positivity (FSP) in a visual task. Auditory PN is a representation of inter-channel selection, as it is best observed by subtracting ERPs to unattended stimuli from those to attended stimuli (Alho, Teder, Lavikainen, & Naatanen, 1994). In visual tasks, FSP may be the representation of a fast filtering mechanism, coding the primary stimulus characteristics to be selected. When the difference between stimulus characteristics is too small, slower mechanisms take over, as manifested in OSN. Finally, N2b represents the integration of different stimulus characteristics that together discriminate the target (Kenemans, Lijffijt, Camfferman, & Verbaten, 2002).

In order to establish whether only attention-related endogenous components are affected in PDD or that the stream of information processing is already at fault at the level of exogenous components, auditory N1 and P2 and visual P1 are also tested. Since abnormal P3s have been found in different modalities and different age groups, the present study used auditory and visual tasks in both children and adolescents. Based on the consistency in the current literature regarding P3 in autism, one would not expect to find differences between these age groups. On the other hand, recent structural MRI studies by Courchesne and colleagues (Courchesne et al., 2001; Courchesne, Carper, & Akshoomoff, 2003) indicated that brain growth in autism may be excessive at early age, but that this is later followed by an attenuation of growth, such that autistic brain volumes are normalized by early adolescence. If such age differences do exist, they could ultimately lead to age-related differences in brain potentials measured on the scalp. However, to date no ERP studies that directly compare two age groups of PDD patients in one and the same design have been published.

Based on the current standing in the literature, we expect to find smaller P3 amplitudes in both PDD groups for the auditory and the visual modality. Furthermore, we expect to find abnormal (smaller) amplitudes for the Processing Negativity (PN) in the PDD groups in the auditory modality, comparable to the effect on the Nd in the study by Ciesielski et al. (1990). Comparable to the abnormal N270 in the Ciesielski study, we expect to find abnormal N2b amplitudes in the visual modality in the PDD groups. Studies of auditory evoked (brainstem) potentials suggest that abnormalities in auditory processing may be present at a very early stage in autism, within several milliseconds after stimulus presentation (Bruneau, Roux, Adrien, & Barthelemy, 1999; Buchwald et al., 1992; Thivierge, Bedard, Cote, & Maziade, 1990). However, no abnormalities were found at a somewhat longer latency in a recent study of P50 gating (Kemner, Oranje, Verbaten, & Van Engeland, 2002). Therefore, we do not expect to find differences in exogenous components in the auditory modality. We also do not expect such differences in the visual modality.

Identification of abnormalities on single electrodes or subsets of electrodes with statistical analyses does not directly identify the locations of abnormal brain activity. To improve the characterization of the brain areas that produce the measured potentials, an extensive electrode montage was used in the present study and source analysis was applied to exogenous and attention related components to take the information of all scalp electrodes into account.

Materials and Methods

Subjects

School Age Children

The total initial samples consisted of 19 controls and 25 children with PDD. After exclusion of subjects with poor task performance (>50% omissions) or poor EEG quality (e.g., excessive alpha, slow drift or movement artefacts), the final clinical and control groups consisted of 16 and 11 subjects for the auditory task and 18 and 14 subjects for the visual task. The controls were all boys; one girl was included in the clinical group. There was no significant age difference between groups; mean ages were 10.6 (range 8.0–13.6; *SD* 1.66) and 10.5 (range 9.2–12.2; *SD* 1.11) for the clinical and control groups, respectively. The clinical subjects were recruited from the Department of Child and Adolescent Psychiatry at the Academic Hospital Utrecht. Controls were recruited from elementary schools in and around Utrecht.

All subjects were administered the Wechsler Intelligence Scale for Children, revised Dutch edition (WISC-RN).

There were no differences in IQ scores between the final groups (for IQ scores, see Table 1). For PDD subjects, all diagnoses were based upon DSM-IV criteria and were made by a child psychiatrist (HvE) after extensive diagnostic evaluation, including a review of prior records (developmental history, child psychiatric and psychological observations and tests and neurological investigations). Furthermore, all included PDD subjects were administered the Autism Diagnostic Interview Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) by a trained rater. Five subjects did not meet the ADI-R criteria for autism (all were one point short on stereotypical behaviours) but they did however meet the criteria for PDD-NOS as indicated by the psychiatrist. All subjects were medication free and had no significant neurological history.

The medical ethical committee of the Academic Hospital approved the study and all parents or caretakers gave written informed consent prior to participation. Furthermore, the child's assent was obtained and it was pointed out that participants or their caretakers could stop the experiment at any time and for any reason.

Adolescents

Clinical subjects were recruited from a residential institution for autistic adolescents (the Dr. Leo Kanner huis). Control subjects were recruited from a secondary school in Utrecht. The total initial sample consisted of 13 subjects in both clinical and control groups. After exclusion of subjects with poor task performance and poor EEG quality, the final sample consisted of 9 PDD subjects and 13 controls for the auditory task and 10 and 13 subjects for the visual task. There were no significant differences in age between the initial groups (mean ages 19.1 (range 15.2–24.6; *SD* 3.43) and 18.2 (range 17.2–19.6; *SD* 0.74) for clinical subjects and controls. All controls were administered the Wechsler Adult Intelligence Scale (WAIS), Dutch edition. For one subject with PDD, the Wechsler Intelligence Scale revised Dutch edition (WISC-RN) was used. There were no significant differences in IQ measures between groups (Table 1). All PDD subjects were extensively diagnosed by psychiatrists at the Dr. Leo Kanner house. The ADI-R was administered to all subjects in the clinical group by a skilled rater. All subjects met the ADI-R criteria for autism.

All subjects were extensively informed about the experimental procedures prior to participation. All subjects gave written informed consent. For subjects who were not of legal age, parents or caretakers were also asked to give written consent.

IQ × Age effects showed that the in the visual task, the young groups had significantly lower total ($F(1,47) = 5.24$, $P = 0.027$) and performance ($F = 4.45$, $P = 0.04$) IQ scores. Since no significant IQ differences between diagnostic groups exist, any diagnosis related effects in the electrophysiological measures or in task performance in this task could not be contributed to IQ. In the auditory task, the PDD groups had significantly lower total and performance IQ than controls (TIQ; $F(1,53) = 4.28$, $P = 0.043$: PIQ; $F(1,53) = 4.54$, $P = 0.038$). The means suggest that these differences are especially large in the adolescent groups (see Table 1). Post-hoc analyses of IQ scores for each age group separately confirmed that the IQ differences were significant in the adolescent groups (TIQ; $F(1,21) = 10.1$, $P = 0.005$: PIQ; $F(1,21) = 9.79$, $P = 0.005$), but not in the young groups. Although IQ scores showed significant differences between groups, we chose not to take further steps in controlling for these differences since this would likely introduce a selection bias (Yeung-Courchesne & Courchesne, 1997).

Tasks

Auditory

The auditory selective attention task consisted of 300 stimuli, 150 presented in the left and 150 in the right ear.

Table 1 Mean IQ scores for autistic and control groups

	Total	Performance	Verbal
Visual			
Young groups			
Control	98.2 (9.68); *81–116*	103.2 (13.15); *73–120*	93.3 (9.04); *81–114*
PDD	97.2 (14.03); *62–119*	100.6 (19.88); *59–133*	95.5 (14.26); *68–118*
Adolescent groups			
Control	109.5 (8.19); *96–120*	115.7 (9.76); *94–126*	103.6 (7.99); *89–114*
PDD	96.9 (10.91); *80–112*	100.7 (13.25); *78–118*	95.1 (11.13); *77–107*
Auditory			
Young groups			
Control	101.0 (8.7); *84–116*	106.1 (10.0); *85–120*	96.6 (8.7); *85–114*
PDD	96.9 (13.7); *62–119*	98.8 (19.9); *59–133*	96.3 (15.3); *68–116*
Adolescent groups			
Control	109.5 (8.2); *96–120*	115.7 (9.8); *94–126*	103.6 (8.0); *89–114*
PDD	103.7 (10.7); *91–125*	108.6 (12.3); *94–132*	100.1 (11.3); *77–116*

Standard deviations in parentheses, range in italics

Within each ear (or channel), 20% were deviant and 80% were standard stimuli. The stimuli were sine waves of 1,000 and 1,100 Hz with a duration of 50 ms each, with an inter-stimulus interval (ISI) randomised between 1,750 and 2,150 ms. Stimuli were presented through stereo in-ear headphones at 95 dB sound pressure level. Total task duration was about 10 min. The stimulus attribute to define relevant and irrelevant channels was the ear in which stimuli were presented (i.e., left or right). Standards or deviant stimuli were defined by the frequency (1,000 vs. 1,100Hz) of the tones. Which frequency was deviant or standard was balanced across subjects, as was the relevant ear. The instruction was to press a hand held button as fast as possible to tones with a deviant frequency in the attended ear.

Visual

The visual task consisted of 300 stimuli, 150 red and 150 yellow rectangles. The rectangles subtended a length of 4.5 and a width of 3.7° of arc. They were each presented for 50 ms, with an inter-stimulus interval (ISI) randomised between 1,750 and 2,150 ms. Total task duration was about 10 min. The stimulus attribute to define relevant and irrelevant channels was colour (i.e., yellow or red). Standards or deviant stimuli were defined by the orientation (to upper left \\ or upper right //, respectively) of thin, black diagonal bars in the rectangles. Within each colour, 20% were deviant and 80% were standard stimuli. Which orientation was deviant or standard was balanced across subjects, as was the relevant colour. Stimuli were presented in the centre of the visual field on a computer monitor positioned approximately 70 cm from the subject's eyes. The instruction was to press a button, which was held in the preferred hand, as fast as possible to rectangles of one colour in which the orientation of the bars was deviant.

Procedure

A parent or caretaker always accompanied children who participated in the study. The adolescent patients were in most cases accompanied by a supervisor. On arrival, they were familiarised with the procedure. After an electrocap and EOG electrodes were attached, a teeth mould was made which was used in the measurement of electrode positions after EEG recording (see below). The subject was then seated in a dentist's chair in an acoustically shielded room. The chair was adjusted so that the subject's head was approximately parallel to a computer monitor, positioned slightly above and in front of the subject. Instructions for the task were given orally, and the experimenter checked whether the subject was able to hear the subtle difference in frequency by letting them listen to a random set of stimuli which had to be classified (with an oral response) as ''high'' or ''low'' by the subject. After that, a short practice series was presented during which the experimenter gave feedback. When the experimenter was convinced that task requirements were met, the subject was instructed to move as little as possible during the task and to keep his eyes fixed on a fixation cross on the computer screen. The experimenter then left the room, closed the door and dimmed the lights. During the task, EEG was monitored on a computer screen. With children, in most cases the accompanying person was seated behind the child during recordings.

After the recording session was completed, the teeth mould was used in the digitisation of electrode positions by means of a Polhemus IsoTrak digitiser. Subjects were then transferred to the MRI department where whole-head MRI scans were made for use in future high-resolution electrical source imaging of the present data and volumetric analyses, which will be reported elsewhere. When all experimental procedures were completed, children were rewarded with a toy, while adolescents were paid for their participation.

EEG and EOG Recordings

The electroencephalogram (EEG) was recorded from 62 tin electrodes by means of an electrocap. Electrodes were placed on the scalp according to the 10% system of the American Electroencephalographic Society. From this array, four midline electrodes (Fz, Cz, Pz, Oz) were used in the statistical analysis. An electrode attached to the left mastoid was used as reference. Horizontal EOG was recorded from tin electrodes, which were attached to the outer cantus of each eye by means of adhesive rings. Vertical EOG was measured from electrodes placed at the superior and inferior orbit of the left eye. A ground electrode was placed at the middle of the forehead. All electrodes were filled with electrolyte paste (ECI Inc.). Impedances of the ground and reference electrodes were kept below 5 kΩ. All signals were amplified with a time constant of 10 s by a Sensorium EPA-5 amplifier (Sensorium Inc., Charlotte, VT). All signals were digitised on-line by a computer at a rate of 256 Hz and stored as a continuous signal. After sampling, signals were epoched off-line starting 100 ms before stimulus onset, and lasting for 1 s. After epoching, all signals were filtered with a 30 Hz, 24 dB/octave digital low pass filter.

Signal Analysis

EEG and EOG data were analysed off-line using the SCAN software package (Neuroscan Inc., El Paso, TX). All signals were baseline corrected on the basis of the 100 ms

pre-stimulus interval. All epochs containing artefacts like saturation of the A/D converter, flat lines or amplitudes larger than ±125 μV were removed. After that, the EEG was corrected for vertical EOG artefacts by subtracting vertical and horizontal EOG from EEG epochs by a regression method in the time domain (Kenemans, Molenaar, Verbaten, & Slangen, 1991).

ERPs were computed by averaging all remaining trials with correct performance (hits and correct rejections) for each subject per lead and for each stimulus category (performance measures are given in Table 2). The time windows for the identification of auditory ERP peaks were chosen according to Jonkman et al. (1997). Statistical analyses of ERPs were limited to four electrodes because the studied components are typically maximal at these electrodes and to improve the comparability of results with previous studies. In order to examine the complete scalp distribution of effects and possible laterality differences, source localizations were performed which are described below. For the analysis of P3, ERPs to all stimulus types were pooled in a 300–750 ms window for the four midline electrodes (Fz, Cz, Pz and Oz.). This pooling was done since we only wanted to confirm the presence of (overall) smaller P3 amplitudes; attention effects are evaluated in components preceding P3. Auditory N1 was measured on electrodes Fz and Cz from 50 to 175 ms, P2 from 110 to 250 ms and PN from 150 to 350 ms. In the school age group visual P1 was scored on Oz from 50 to 150 ms, FSP on Fz from 175 to 275 ms, N2b on Cz from 250 to 450 ms and OSN on Oz from 150 to 200 ms. Based on visual inspection of the data, these windows were adjusted in adolescents to 150–250 ms for FSP, 200–350 ms for N2b and 150–300 ms for OSN.

Analyses of exogenous components were done on unattended standards only because these stimuli were not attended to or reacted upon and therefore largely free of endogenous effects. For attention-related components, difference waves were constructed by subtracting unattended from attended standards as is the common comparison for these components.

Dipole Analyses

Dipole analyses were performed with the BESA package (version 2.2; MEGIS GmbH, Gräfelfing, Germany), using a four-shell spherical head model. For the purpose of source localization, all signals were average referenced. First, a mirror symmetrical dipole pair was fitted on the grand-average waveform for each group. The mirror constraint was applied to both location and orientation parameters. An additional energy criterion was used with a weight of 20% in the cost-function of the fitting algorithm, counteracting solutions with large dipole moments. Visual P1 and auditory N1 and P2 were fitted on the unattended standard stimuli. Attention components were fitted on difference waves of attended minus unattended standard stimuli. If the residual variance (RV) was greater than 10%, an additional symmetrical dipole pair was added. The grand average models for each component were then optimised on individual waveforms of each subject with individual electrode locations. The fit latency for individual models was determined as the point where the grand average model produced the lowest peak in the residual variance curve of the individual data (Kenemans et al., 2002). Individual solutions with a RV > 30% were excluded from further analysis, as were solutions that were anatomically or physiologically implausible. Because of the symmetry constraints, three location parameters and three orientation parameters as well as two dipole moments were computed for each subject.

Table 2 Mean error proportions and reaction times (in ms) in control and autistic groups for visual and auditory tasks (*SD* in parentheses)

	RT	Omissions	FA as	FA ud	FA us
Visual					
Young groups					
PDD	752 (128)	0.10 (0.07)	0.07 (0.10)	0.004 (0.01)	0.004 (0.008)
Control	705 (148)	0.06 (0.07)	0.03 (0.05)	0.005 (0.01)	0.0006 (0.002)
Adolescent groups					
PDD	571 (165)	0.02 (0.03)	0.02 (0.02)	(–)	(–)
Control	530 (77)	0.02 (0.03)	0.005 (0.007)	– (–)	– (–)
Auditory					
Young groups					
PDD	710 (98)	0.15 (0.12)	0.04 (0.05)	0.03 (0.05)	0.0005 (0.002)
Control	675 (104)	0.28 (0.24)	0.05 (0.06)	0.02 (0.03)	0.004 (0.01)
Adolescent groups					
PDD	530 (144)	0.05 (0.06)	0.02 (0.03)	– (–)	0.001 (0.003)
Control	514 (92)	0.08 (0.1)	0.03 (0.06)	0.008 (0.01)	– (–)

FA, false alarms; as, attended standard; ud, unattended deviant; us, unattended standard

Statistical Analysis

Analyses of variance were performed for ERPs and task performance (proportions of omissions and false alarms and reaction times) separately. The significance level for all tests was set at $P < 5\%$, two-tailed. All analyses included a factor Diagnosis (PDD vs. controls) and Age (school-age vs. adolescent) as between-subjects factors.

Five dipole parameters (three location parameters and two dipole moments) of each individual model were entered in analyses of variance with age and diagnosis as between factors. Comparisons were only made between groups where the localization procedure produced an equal number of dipoles. For visual FSP, N2b and OSN, data was only available from for the adolescent control group and the two younger groups. Therefore, a different strategy was adopted here: Dipole parameters were entered in an analysis of variance with group as between factor. Significant overall effects were then tested further with post-hoc Bonferroni tests, testing each pair-wise combination of group means. By using post-hoc Bonferroni tests, alpha levels were adjusted for the total number of tests, thus protecting against the increased possibility of type I errors. The significance level of $P < 0.05$ was adopted for all tests.

Results

Auditory Task

Behavioral Measures

Five variables were defined as measures of response accuracy: omissions (not pressing a button to a target), three types of false alarms (to unattended deviants and to attended and unattended standards) and reaction times to hits. No differences involving Diagnosis were present in the data. However, the young groups showed longer reaction times than adolescents ($F(1,48) = 31.16$, $P = 0.000$). Also, the young groups produced more omissions ($F(1,30) = 10.37$, P=0.002) and false alarms to unattended deviants ($F(1,30) = 4.55$, $P = 0.038$).

ERPs

Attention effects P3 amplitude on Pz was significantly diminished in the young PDD group ($F(1,25) = 8.181$, $P = 0.008$) (Fig. 1). All groups showed a significant PN ($F(1,33) = 25.521$, $P = 0.000$), confirming our successful manipulation of attention. Furthermore, there was a significant Age×Diagnosis interaction for PN on electrode Fz ($F(1,45) = 4.540$, $P = 0.039$). When this interaction was analysed further, it appeared that the adolescent PDD groups showed a larger PN than the young PDD subjects on electrode Fz ($F(1,23) = 6.899$, $P = 0.015$) (Fig. 2). Since Fig. 2 seems to suggest that this effect could be due to latency jitter, the analysis was repeated with an adjusted scoring window for PN ranging from 250 to 450 ms in the young PDD group. This adjustment even enhanced the initial difference ($F(1,23) = 14.272$, $P = 0.001$).

Exogenous Effects There were no significant differences in N1 and P2 amplitude.

Dipoles Analysis of dipole locations of N1 indicated a significant Age × Diagnosis interaction ($F(3,25) = 3.753$, $P = 0.024$), but further analysis of this effect did not reveal any significant differences between groups. A

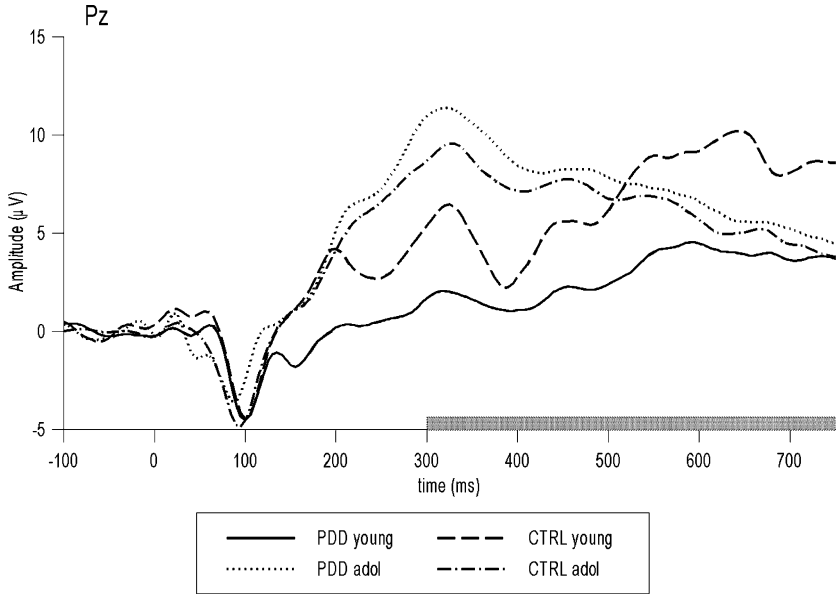

Fig. 1 Young PDD subjects show significantly smaller P3 amplitudes to auditory stimuli on electrode Pz when compared to controls. The grey bar indicates the timeframe in which P3 was measured

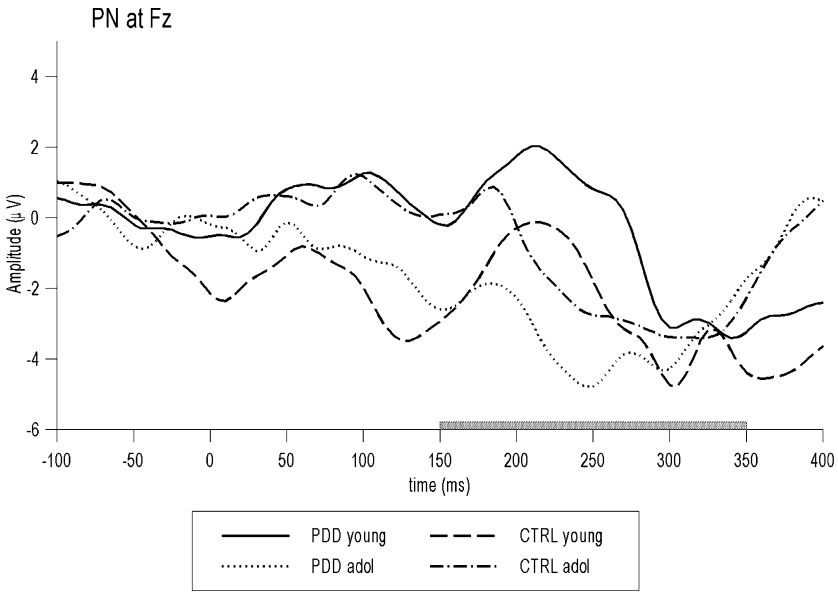

Fig. 2 Difference wave of attended minus unattended auditory standard stimuli on electrode Fz. Adolescent PDD patients show larger PN amplitudes on electrode Fz than young PDD patients. The timeframe for PN is indicated by the grey bar

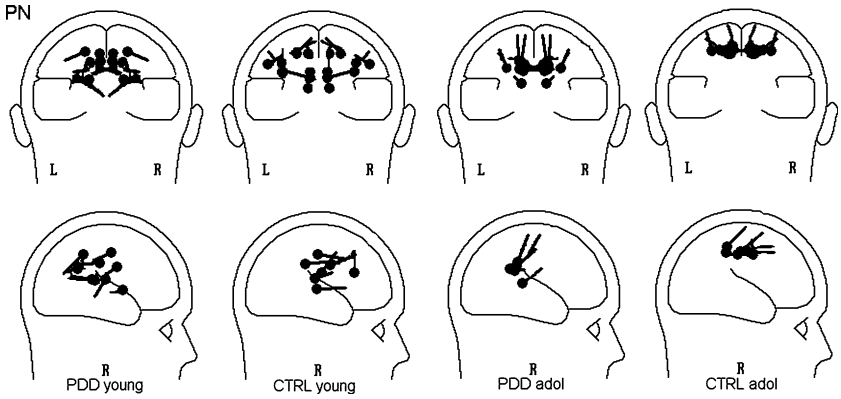

Fig. 3 Individual dipole plots of all groups for PN. In PDD patients, sources are located more medial, posterior and ventral than in controls

significant main effect of Diagnosis ($F(3,31) = 4.662$, $P = 0.008$) indicated that the PDD groups showed less lateral, anterior and dorsal locations for PN than controls (Fig. 3). This effect remained significant also when N1 or P2 locations were entered as covariates. No location differences were found for P2. Finally, the young PDD groups showed larger dipole moments than controls for all localized auditory dipoles (smallest $F(1,17) = 5.920$, $P = 0.026$).

Visual Task

Behavioral Measures

The young groups showed significantly longer reaction times ($F(1,53) = 26.1$, $P = 0.000$), more omissions ($F(1,53) = 16.35$; $P = 0.000$) and false alarms to the attended standard ($F(1,53) = 5.96$, $P = 0.018$) than the adolescent groups. No effects of Diagnosis were found.

Attention Effects

P3 amplitude was significantly smaller in the young PDD group on electrodes Pz and Oz (smallest $F(1,30) = 11.721) = 0.002$) (Fig. 4). All groups showed a significant FSP ($F(1,51) = 13.39$, $P = 0.001$) and N2b ($F(1,51) = 28.35$, $P = 0.000$), thus demonstrating the successful manipulation of selective attention. There was a significant Age × Diagnosis interaction for N2b ($F(1,51) = 4.970$, $P = 0.030$). The adolescent PDD group showed more negative N2b amplitudes than young PDD patients ($F(1,26) = 4.343, P = 0.047$) (Fig. 5). No differences were found in FSP amplitude.

Exogenous Effects

For visual P1, the Age × Diagnosis interaction just missed significance ($F(1,51) = 3.944$, $P = 0.052$) when tested only on unattended standards. Because of the strong trend, the

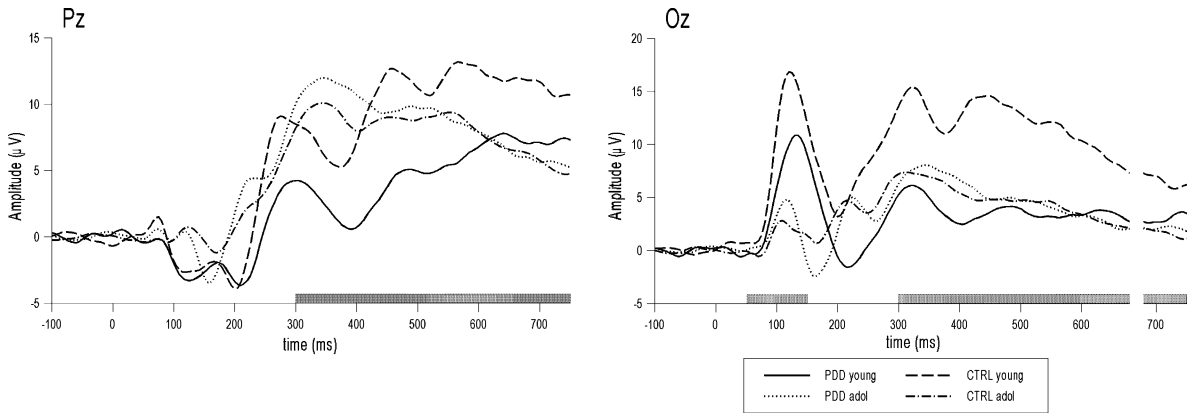

Fig. 4 ERPs pooled over all visual stimuli on posterior electrodes Pz and Oz. Young PDD patients show smaller P3 amplitudes on these electrodes than controls. The timeframe for P3 is indicated by the large grey bar. The markedly reduced overall P1 amplitude on Oz can also be observed. The small grey bar in the Oz graph indicates the time window for P1

analysis was repeated with amplitudes pooled over all stimulus types. This resulted in a significant Age × Diagnosis interaction ($F(1,51) = 5.076$, $P = 0.029$). The young PDD groups showed smaller overall P1 amplitudes than their controls ($F(1,30) = 5.941$, $P = 0.021$) (Fig. 4).

Dipoles

No group differences were found in the dipole locations or moments for P1.

The frontal selection positivity (FSP) and occipital selection negativity (OSN) could not be reliably localized in the adolescent PDD group. Therefore, analyses of FSP and OSN were limited to the young groups and the adolescent control group. Comparisons were first made between the young groups only. No differences in location or dipole moment were encountered between these groups. When the adolescent control group was entered in the analysis, still no significant differences emerged.

Discussion

The investigations in the present paper were motivated by the often-reported abnormalities in P3 amplitude in pervasive developmental disorders. Especially in autism, abnormally small P3 amplitudes have been reported quite consistently. Not only have such abnormalities been demonstrated in different modalities, but also in different age groups. To address the subject of possible age-related differences directly, the studies described in this paper have included PDD children and adolescents and their control groups. Aiming at an in-depth analysis of the abnormal P3

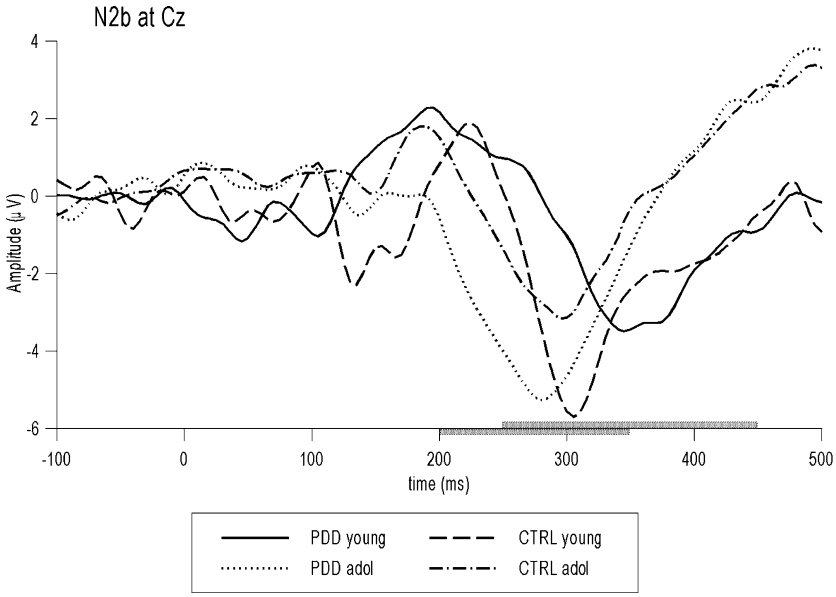

Fig. 5 Difference wave of attended minus unattended visual standards on electrode Cz. Adolescent PDD patients show larger N2b than young subjects with PDD. Time windows for N2b are indicated with grey bars: top bar for young groups, lower bar for adolescents

responses in autism, an attempt was made to answer the following questions:

Is the Abnormal P3 Preceded by, or Related to, Deficiencies in Selective Attention?

In order to answer this question, auditory and visual tasks were used that elicit typical ERP components that are related to selective attention. Posterior P3 amplitude in both modalities was indeed found to be abnormal in PDD, but only in the young group. P3 amplitudes in the adolescent PDD group appeared to be normal. However, the opposite was true for the, peaks related to selective attention, the frontal auditory PN and central visual N2b. Both peaks were more pronounced in adolescent patients than in the young PDD group. Except for a smaller amplitude on P1, no other differences were found, meaning that processes that are directly related to the processing of physical stimulus characteristics as reflected by N1, P2 are normal, as well as other visual attention components. The smaller P1 amplitude that was found for all stimulus categories could indicate that the generators of P1 have matured more rapidly in the young PDD group than in the young controls, as P1 amplitudes tend to diminish with age (Allison, Hume, Wood, & Goff, 1984; Onofrj, Thomas, Iacono, D'Andreamatteo, 2001). The absence of localization differences for P1 in PDD children suggests that the amplitude differences are not a consequence of a different anatomical organization of its generators.

The findings of this study contrast in part with earlier findings. First, abnormal P3 amplitudes have been found in the visual and auditory domain in autistic adults and adolescents (Ciesielski et al., 1990; Courchesne et al., 1984, 1985). Furthermore, in a selective attention study by Ciesielski and colleagues, it was found that visual and N270 and auditory Nd (comparable to N2b and PN in the present study) were not present in autistic adults. There are several possible explanations for this discrepancy in findings. First, the selective attention tasks used in the present study are very different from the oddball tasks used by Courchesne and colleagues. The selective attention task used by Ciesielski et al. also differs strongly. In this task, stimuli of both modalities were present in one stimulus block, and subjects were instructed to respond to one and ignore the other. Thus, discriminating between relevant and irrelevant stimuli probably was much easier than in the tasks used in the present study. Yet, in contrast to the present data, autistic subjects performed far worse than controls in these earlier studies.

Where the data by Ciesielski et al. were interpreted as an absence of the neurophysiological manifestation of inter-channel selection, our data seem to indicate the contrary. Adolescents with PDD show a larger frontal PN and central N2b than controls. It is known from clinical observations that persons with disorders in the autistic spectrum may react to stimuli in their surroundings in a hypo- or hypersensitive manner (O'Neill & Jones, 1997). The larger negativities observed in our data could be interpreted in terms of overselectivity, but the behavioural data do not support this. No performance gains are seen in adolescent PDD patients as compared to controls, but this could be due to the relative ease of the task. Still, it could be that these patients are overly selective in inter-channel discrimination in order to boost the less efficient within channel discrimination reflected by the P3 to normal levels. In the young PDD patients, where such tentative compensatory overselectivity is not observed, P3 amplitudes are indeed abnormal, in line with previous studies (Kemner et al., 1994; Verbaten et al., 1991).

Are there Abnormalities in the Neural Sources of Scalp-recorded Activity?

Up to now, only limited electrode configurations have been used in ERP studies in PDD. Therefore, source localization studies have never before been reported. In the present studies a large number of electrodes was used for the scalp recordings, but only a limited set was statistically analysed. The source localizations take the entire potential distribution on the scalp into account, thus providing additional information that may have been missed by the statistical analyses.

In the present study, differences in dipole locations were only found for PN: in PDD patients, PN dipoles were localized more posterior, medial and ventral than in controls. There was no significant difference in the dipole parameters of any of the other localized peaks. An important caveat is that we were unable to come to a stable solution for the sources for visual attention components in the adolescent PDD group, and for N2b altogether. Therefore, it is impossible to conclude whether these effects observed for PN also have a visual counterpart in N2b. However, the fact that none of the visual attention related peaks could be localized in the adolescent PDD group may be a finding of great importance, although it is not backed by statistical data. It may be that in this group the brain does not function in such an organized manner that its activity can be modelled by a limited number of sources. Indeed, in a recent fMRI study it was demonstrated that autistic patients show very scattered activations even when performing a simple motor task (Muller, Pierce, Ambrose, Allen, & Courchesne, 2001).

A recent study suggested that children with autistic spectrum disorder show smaller head sizes at birth and excessive increases in head size between 1 and 2 months and 6 to 14 months (Courchesne et al., 2003). A structural

imaging study of brain volume further indicated that this early overgrowth in brain size may be compensated by an abnormal attenuation in growth after 4 years, such that brain volumes were normalized at early adolescence (Courchesne et al., 2001). It could be that such different growth patterns result in altered neuronal organization in PDD patients, which is reflected in the abnormal source models and scalp potentials in this group. The early overgrowth followed by a developmental arrest that leads to near normal brain volumes may be an explanation for the age-related differences found in the present data. However, it remains to be established to what extent similar differences in brain development can be detected in our PDD groups.

Summarizing, the data from the present study suggest that not abnormalities in P3 amplitude, but normalizations of P3 amplitude in PDD are accompanied by abnormal selective attention. Indeed, young PDD subjects show markedly reduced P3 amplitudes in visual and auditory tasks. In contrast, adolescent PDD patients showed normal P3 amplitudes, but also showed abnormalities in attention related components preceding P3. Thus, in addition to the P3 reductions reported in earlier studies, the present tasks showed that abnormalities in selective attention could indeed be detected in PDD. Furthermore, these abnormalities in selective attention result in different source models in the auditory modality, and probably also in the visual domain. These abnormal neuronal generators of attention-related components can be observed in the absence of abnormalities in components related to the perception of the stimulus per se and with a concurrent normalization of P3 amplitudes.

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