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Diminished Infant P50 Sensory Gating Predicts Increased 40-Month-Old Attention and Anxiety/Depression Symptoms

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Abstract

Background—Attentional difficulties often first present in preschool years, but it is unknown whether they result from concurrent brain developmental problems or whether normal developmental processes uncover alterations in brain development from an earlier age. This study addresses this issue, examining the relationship between an infant's sensory gating of auditory evoked potentials and parent-reported behavior at 40 months of age.

Methods—P50 sensory gating, an auditory evoked potential measure reflective of inhibitory processes in the brain, was measured in 50 infants around 70 days of age. Parents, using the Child Behavior Checklist, reported on the child's behavior at 40 months of age.

Results—Controlling for gender, infants with diminished sensory gating had higher externalizing scores ($F=4.17$, $ndf=1$, $ddf=46$, $p=.047$), as well as higher scores in the specific domains of attention ($F=5.23$, $ndf=1$, $ddf=46$, $p=.027$) and anxious/depressed ($F=5.36$, $ndf=1$, $ddf=46$, $p=.025$).

Conclusions—Diminished infant P50 sensory gating predicts attention related symptoms 3 years later, at 40 months of age. These results support the hypothesis that preschool attentional

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dysfunction is related, at least in part, to alterations in brain development that begin years prior to symptom onset.

Keywords

attention; evoked potentials; infant; preschool; sensory gating

Background

As children reach preschool age, problems with attention-driven behavior may emerge and interfere with the child's ability to function. This initial preschool presentation of attention-driven behavior impairments often presages other behavior problems such as oppositional behavior and aggression (Duchesne, Larose, Vitaro, & Tremblay, 2010; Wahlstedt, Thorell, & Bohlin, 2008; Farmer & Bierman, 2002; Caspi, Henry, McGee, Moffitt, & Silva, 1995), and mood and anxiety disturbance (Duchesne et al., 2010; Wahlstedt et al., 2008). While preschool years are often the youngest age at which attention-driven behavioral deficits can be clinically identified, it is unknown whether the brain dysfunction associated with these behavioral deficits also develops in the preschool years. The initial clinical presentation of many neuropsychiatric impairments may be not due solely to concurrent brain changes, but instead may represent the uncovering of a brain developmental aberration which preceded symptom onset by years (Ross, Kisley, & Tregellas, 2005; Murray & Lewis, 1987; Censits, Ragland, Gur, & Gur, 1997; Rapoport, Addington, Frangou, & Psych, 2005; Galera et al., 2011; Poelmans, Pauls, Buitelaar, & Franke, 2011). Thus, it is possible that preschool emergence of attention-driven behavioral deficits may be related to aberrant brain development at a younger age. This report explores this issue by utilizing a biomarker of infant brain development, P50 sensory gating, to assess whether preschool attention-driven behavioral impairments are predicted by infant brain dysfunction.

P50 sensory gating utilizes an auditory evoked potential paradigm to measure inhibitory processes in the brain. In the P50 sensory gating paradigm, auditory evoked potentials to two successive auditory stimuli, in this case 2 "clicks" are compared. Most healthy adults show an attenuated response to the second stimulus reflecting the ability of the brain to unconsciously block reception of irrelevant repetitive stimuli (Adler, Pachtman, Franks, & Freedman, 1982; Siegel, Waldo, Milner, Adler, & Freedman, 1984; Suzuki & Azuma, 1977). Sensory gating is often considered an automatic and involuntary first step in the attentional process (Potter, Summerfelt, Gold, & Buchanan, 2006; Jerger, Biggins, & Fein, 1992; Lijffijt et al., 2009; Braff & Light, 2004; Boutros, Belger, Campbell, DFCÖSouza, & Krystal, 1999), and, in adults, sensory gating deficits are associated with neurocognitive and behavioral problems in attention (Adler et al., 1982; Potter et al., 2006; Paus, 1989; Chen & Faraone, 2000; Freedman et al., 1987; Wan, Friedman, Boutros, & Crawford, 2008). Further emphasizing the association between P50 sensory gating deficits and attentional dysfunction, P50 sensory gating is impaired in a number of psychiatric disorders characterized by attentional dysfunction, including schizophrenia (Adler et al., 1982), bipolar disorder (Martin et al., 2007), attention deficit-hyperactivity disorder (Olinicy, Ross, Harris, & Freedman, 1999), lower IQ autism (Orekhova et al., 2008), post-traumatic stress disorder (Stewart & White, 2008; Ghisolfi et al., 2004; Neylan et al., 1999), panic disorder

(Ghisolfi et al., 2006) and Parkinson's Disease (Abel, Friedman, Jesberger, Malki, & Meltzer, 1991).

Recently, P50 sensory gating has been described in early infancy (Suzuki & Azuma, 1977; Kisley, Polk, Ross, Levisohn, & Freedman, 2003) with stable performance from infancy to 4 years of age (Gillow, Hunter, & Ross, 2010). Having a parent with psychosis as a presumed increased genetic vulnerability or a mother with anxiety, and/or prenatal exposure to nicotine or other illicit substances as possible environmental risk factors are well-established larger effect size risk factors for later attention-driven behavioral impairment. Each of these risk factors is associated with impaired infant P50 sensory gating, with effects identifiable in even relatively small samples (Hunter, Kisley, McCarthy, Freedman, & Ross, 2011; Hunter et al., 2012).

Thus, at least some of the same prenatal factors are associated with both impaired infant P50 sensory gating and later attentional dysfunction. This manuscript reports on an attempt to bridge the gap, addressing whether impaired infant P50 sensory gating predicts later behavioral symptoms. Such a relationship would suggest that preschool emergence of attention-driven behavioral deficits, like many other neuropsychiatric symptoms, are neurodevelopmental in nature, where onset of clinical symptoms represents, at least in part, an uncovering of aberrant brain growth from an earlier stage of development.

Method

Participants

Infants and their families were initially recruited from the Denver metropolitan area through a state birth registry as part of a study focusing on the impact of maternal factors on infant psychophysiology (Hunter et al., 2011). Exclusionary criteria included known birth defect, chromosomal abnormality, infant major neurological disorder, infant visual or auditory sensory disorder, or maternal non-nicotine substance use disorder active during pregnancy. Ninety-three (93) infants, born between January 2007 and February 2009 completed an auditory evoked potential recording with an age adjusted for gestational age at birth of 70.6 days (s.d 30.9 days). Fifty infants (54%) had a parent complete the Child Behavior Checklist (mean $\pm$ s.d child age at time of CBCL report: 40.9 $\pm$ 0.7 months). The infants who later had parental report of behavior at 40 months did not differ from those lacking later parental report on gender, gestational age at birth, mother's age at birth, mothers years of education, race/ethnicity, maternal education level, or frequency at living with both biological parents (all p values >.11).

Demographic information for the 50 infants is summarized in Table 1. Infants with robust sensory gating were more likely than infants with diminished sensory gating to be female (65% versus 33%; $\chi^2=5.13$ (d.f. = 1), $p=.024$), but did not differ in gestational age at birth, age at P50 recording, race and ethnicity, or whether they lived with both biological parents. Gender was included in all subsequent group comparisons.

Procedures

Informed parental consent was obtained and monitored by a local institutional review board.

P50 sensory gating—The methods used for the infant P50 sensory gating have been previously described (Suzuki & Azuma, 1977). Briefly, 50 ms auditory stimuli (clicks) were presented in pairs with an interstimulus interval of 500 ms and an interpair interval of 10 seconds. This interstimulus interval has been established among other intervals to be the amount of time in which sensory gating is the most active (Nagamoto, Adler, Waldo, Griffith, & Freedman, 1991; Dolu, Süer, & Çigdem, 2001). Auditory evoked potentials from the vertex were recorded during active sleep which is the infant equivalent of REM sleep. Active sleep was identified by combined electroencephalogram, electrooculography, submental electromyography, behavioral criteria (e.g. eyes closed) and respiratory pattern (Anders, Emde, & Parmelee, 1971). From the identified active sleep periods, the first 15-min period (approximately 85 stimulus pairs) was retained and used for further analyses. Single-trial-evoked potentials were extracted from 100 ms before each click to 200 ms following each click. Trials, in which the signal on the recording of any of these identified periods exceeded 75mV, were excluded from further analysis. The average waveforms computed from these single trials were bandpass filtered between 10 and 50 Hz, to accentuate middle latency components.

For each participant, the amplitude and latency of the largest positive peak between 50 and 150 ms after a click, preceded by a negative trough, was determined (Figure 1). The auditory evoked response in infants occurs about 70 ms after the stimulus rather than the 50 ms after the stimulus generally seen in adult populations. However, to keep terminology consistent with adult literature, the wave is termed P50 even in the infant subject. P50 sensory gating was measured by dividing the average amplitude of P50 evoked by the second click by the average amplitude evoked by the first click. A P50 ratio closer to 0 is indicative of robust suppression (gating), where as a ratio closer to 1 is indicative of diminished sensory gating.

Parent Report of Child Behavior—The Child Behavior Checklist (CBCL 1.5-5) is one broadly validated parental report tool to help parse out problematic behaviors (Achenbach & Rescorla, 2000). The CBCL consists of 99 items for the parent to report on child behavior. Each question is scored on a scale from 0–2 with scores summed across items. The CBCL produces 7 subscales; two domain scores—externalizing behavior which is the sum of 2 subscales and internalizing behavior consisting of the sum of 4 subscales—and an overall Total Problems Score. These classical subscales are based on factor analysis and have internal reliability ranging from acceptable to excellent (Cronbach's α 's of .66-.95), although somatic complaints may be less reliable in some populations (Tan, Dedrick, & Marfo, 2007). In addition, items can be regrouped into DSMIV-oriented scales, including affective problems, anxiety problems, pervasive developmental problems, attention deficit-hyperactivity problems, and oppositional defiant problems. For 49 of the 50 children (98%), the CBCL was completed by the mother.

Results

Infant P50 sensory gating

Ratios have more variance than the underlying amplitude measurements. Dichotomization of P50 values into robust and diminished sensory gating decreases this variance and has been

used to detect genetic and treatment effects. Children were split into two groups: P50 sensory gating ratios ≤ 0.4 considered robust sensory gating and scores > 0.4 indicating diminished sensory gating. This division into robust and diminished P50 sensory gating is similar to values often used in adults, where a sensory gating ratios of < 0.4 is considered normal.¹²

For the group as a whole, mean P50 amplitude in response to the second stimulus ($1.00 \pm 0.80 \mu\text{V}$) was significantly lower (paired $t=9.88$, d.f. =49, $p<.001$) than response to the first stimulus ($2.29 \pm 1.12 \mu\text{V}$) demonstrating the presence of sensory gating. Mean $\pm$ standard deviation for P50 sensory gating ratios was 0.44 ± 0.31 , consistent with reported infant values (Hunter et al., 2011; Hunter et al., 2012). Those infants with robust sensory gating were older than infants with diminished sensory gating although the difference did not reach significance and no relationship between age and P50 sensory gating values has previously been identified (Suzuki & Azuma, 1977). Those infants with robust sensory gating did not significantly differ from those with diminished sensory gating in latency of responses to the first or second sound or in the amplitude of response to the first sound (Table 1). The difference in ratios was due to infants with robust sensory gating having lower amplitude of P50 response to the second sound relative to infants with diminished sensory gating (Students $t=11.75$, d.f. = 48, $p<.001$).

40-month-old Child Behavior—Results from the Child Behavior Checklist (CBCL) are summarized in Table 2. As expected from a normally developing population, the modal score for the majority of subscales was the lowest possible score ‘0,’ reflecting a strong floor effect with the instrument. For each scale, zero to four percent of children had scores in the clinically affected range, consistent with what has been found with other populations recruited from non-clinical sources (Tan et al., 2007).

Relationship Between Infant P50 Sensory Gating and 40-month-old Behavior Scores—Due the non-normal distribution of CBCL scores, a non-parametric (distribution-free) analysis of covariance was applied to the 40-month-old behavior scores after a rank transformation (Conover & Iman, 1982) to estimate the association with infant P50 sensory gating after adjusting for gender (Table 2). It has been shown that such a parametric analysis of covariance of the ranks is extremely well approximated by normal theory software after transforming the dependent variable to ranks (Zeng, Pan, MaWhinney, Barron, & Zerbe, 2011).

Male children had higher ranking on attentional symptoms, with a trend towards an increased ranking on total problems. No effects of gender were identified on any other scale (all p values $>.13$). The impact of sensory gating was more wide-spread. Infants with diminished sensory gating were, 3 years later, ranked significantly higher (Figure 2) on attention ($F=5.23$, $ndf=1$, $ddf=46$, $p=.027$), anxious/depressed ($F=5.36$, $ndf=1$, $ddf=46$, $p=.025$), and externalizing symptoms ($F=4.17$, $ndf=1$, $ddf=46$, $p=.047$); and ranked significantly higher on the DSM-Oriented scales of Anxiety Disorders ($F=5.64$, $ndf=1$, $ddf=46$, $p=.022$) and Attention Deficit-Hyperactivity Disorders ($F=5.40$, $ndf=1$, $ddf=46$, $p=.025$), with a strong trend toward higher ranking on Oppositional Defiant Disorders ($F=3.94$, $ndf=1$, $ddf=46$, $p=.053$). There was also a non-significant trend for infants with diminished sensory

gating to be later ranked higher on Aggression Symptoms ($F=2.93$, $ndf=1$, $ddf=46$, $p=.09$) and Total Problems ($F=3.31$, $ndf=1$, $ddf=46$, $p=.08$).

Discussion

Infants with diminished sensory gating deficit ranked higher, at 40 months of age, on parent-reported problems in attention and anxiety/depression, in the overall externalizing symptoms domain, and in DSMIV-oriented scales of anxiety disorders and attention deficit-hyperactivity disorders. Infants with diminished sensory gating were later higher rated for oppositional defiant symptoms although the difference did not reach statistical significance. Externalizing problems in early childhood have been linked to continuing problems with attention and behavior as children develop (Hill, Degnan, Calkins, & Keane, 2006; Bellanti & Bierman, 2000; Campbell, Pierce, March, Ewing, & Szumowski, 1994; Olson, Schilling, & Bates, 1999; Mesman & Koot, 2001; Fischer, Rolf, Hasazi, & Cummings, 1984; Lavigne et al., 1998), including higher risk for oppositional defiant disorder, conduct disorder and attention deficit-hyperactivity disorder (Swaab-Barneveld et al., 2000). Preschool externalizing symptoms also predict later internalizing symptoms, perhaps because children with early externalizing symptoms may have a hard time forming relationships with peers and this rejection may later lead to internalizing symptoms like anxiety and depression (Mesman, Bongers, & Koot, 2001). Internalizing and externalizing symptoms detected in early preschool account for most of the variance in predicting preadolescent psychopathology with the only other main contributor being physical health problems (Mesman & Koot, 2001). Similarly, adolescents and adults with major psychiatric diagnoses often report that they exhibited symptoms like problems with attention or aggression when young (Biederman et al., 1995; Busch et al., 2002; Banaschewski et al., 2005; Hollis, 1995; Doerfler, Connor, & Toscano, 2011; Harty, Miller, Newcorn, & Halperin, 2009). Thus, diminished infant sensory gating may not only suggest increased behavior problems in preschool years, but may also be predictive of increased risk for later childhood, adolescent, and even adult psychopathology.

P50 sensory gating is reflective of the ability to subconsciously filter out irrelevant auditory information and is fully developed by early infancy (Kisley et al., 2003), stable over time (Hunter, Corral, Ponicsan, & Ross, 2008; Gillow et al., 2010), and, in adults, correlated with attentional function (Cullum et al., 1993; Kisley, Noecker, & Guinther, 2004). The finding reported here that diminished infant P50 sensory gating is associated, 3 years later, with an elevation of attention-driven dysfunctional behavior support the hypothesis that symptoms of inattention, are, at least in part, due to abnormalities in brain development detectable in infancy.

P50 sensory gating is a psychophysiological measure of primarily inhibition involving the hippocampus and cortex (Freedman et al., 1994). However, this inhibitory process is also part of the physiology of other cortical brain regions and is critical for multiple cognitive processes including working memory (prefrontal cortex), somatosensory specificity (somatosensory cortex), associative fear learning (auditory cortex), and recognition memory (hippocampus) (Lewis, Melchitzky, & Burgos, 2002; Pouille, Marin-Burgin, Adesnik, Atallah, & Scanziani, 2009; Staiger, Zschatter, Luhmann, & Schubert, 2009; Letzkus et

al., 2011; Wiebe & Stäubli, 2001). Factors which disturb normal development of cerebral inhibition in the hippocampus are likely to also increase risk for less-than-optimal development of cerebral inhibition, and related cognitive processes, in other brain regions. This “comorbidity” of abnormal brain development may contribute to the relationship found in this study between infant P50 sensory gating and anxiety at 40 months of age.

This study is limited by a lack of data related to environmental factors between infancy and 40-months-of age. It is possible that there may be some maternal factor which effects both infant early sensory gating performance and later behavior without there being a direct relationship between the two. In addition, the relatively small sample size limits power to include maternal variables, such as education level or socio-economic status, in the analysis. The limited number of 40-month-old children with clinically important symptoms also raises questions about generalizability of results into clinical populations. Future work with larger sample sizes and which includes post-infant maternal assessments may help clarify these issues.

In summary, impaired sensory gating is predictive of parent-reported problems with attention, anxiety and externalizing problems at preschool age. The identification of infant brain changes associated with later onset of symptoms suggests that attentional dysfunction may, at least in part, be due to alterations in brain development which occur years prior to clinical presentation. Identification of early brain changes may be useful in identifying infants who would benefit from primary prevention interventions.

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Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
CBCL	Child Behavior Checklist

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Key Points

- Preschool age is the earliest that attentional symptoms that may interfere with the child's ability to function can be clinically identified.
- Diminished infant P50 sensory gating predicts attention and related symptoms 3 years later, at 40 months of age.
- Diminished infant sensory gating suggest not only increased behavior problems in preschool years, but may also be predictive of increased risk for later childhood, adolescent, and even adult psychopathology.
- Preschool attentional dysfunction is related, at least in part, to alterations in brain development that begin years prior to symptom onset

Figure 1.

Representative individual examples of P50 sensory gating responses during active sleep. Clicks are presented 500 ms apart; the P50 response is noted by hashmarks. The positive P50 peak (hashmark above) was measured relative to the preceding negative trough (hashmark below). (A) An example of robust sensory gating in a male infant with an age, adjusted for gestational age at birth, of 51 days. Note that the response to the second stimulus (on the right) is suppressed in comparison to the response to the first stimulus (on the left) for a P50 sensory gating ratio of 0.22. (B) An example of diminished sensory gating in a male infant with an age, adjusted for gestational age at birth, of 58 days. This infant's P50 response to the second stimulus (on the right) is closer in amplitude to that for the response to the first stimulus (on the left), demonstrating diminished response suppression with a sensory gating ratio = 0.65.

Figure 2.

Distribution of parent-report symptoms for 40-month-old preschoolers who had robust and diminished P50 sensory gating based on assessment in infancy. Parent-report preschool scores are based on the Child Behavior Checklist. A significant main effect for gender is identified for attention symptoms ($F=6.27$, $ndf=1$, $ddf=46$, $p=.016$), so attention symptoms are separated by gender. There is a significant effect of robust versus diminished infant P50 sensory gating for A) the domain of externalizing symptoms ($F=4.17$, $ndf=1$, $ddf=46$, $p=.047$), the specific subscales B) anxiety/depressed subscales ($F=5.36$, $ndf=1$, $ddf=46$, $p=.025$).

and for (C and D) attention ($F=5.23$, $ndf=1$, $ddf=46$, $p=.027$). There was also a significant effect on robust versus diminished P50 sensory gating for Child Behavior Checklist DSM categories of E) anxiety ($F=5.64$, $ndf=1$, $ddf=46$, $p=.022$) and G) attention-deficit hyperactivity problems ($F=5.40$, $ndf=1$, $ddf=46$, $p=.025$), as well as a notable trend for F) oppositional defiant problems ($F=3.94$, $ndf=1$, $ddf=46$, $p=.053$). All statistical results are nonparametric, based on a rank transformation for Child Behavior Checklist results.

Table 1

Demographic information for infants with robust and diminished sensory gating. All values are number of subjects (percentage) or mean $\pm$ s.d.

	Robust infant sensory gating N=26	Diminished infant sensory gating N=24	Statistic	p
Age at P50 (days $\pm$ s.d.)	81.8 $\pm$ 34.26	64.0 $\pm$ 29.5	t=1.96 (d.f. = 48)	.056
Gestational Age at birth (days $\pm$ s.d.)	272.9 $\pm$ 13.1	273.0 $\pm$ 11.9	t=.02 (d.f. = 48)	.98
Number female (%)	17 (65%)	8 (33%)	$\chi^2=5.13$ (d.f. = 1)	.024
Number of each race/ethnicity (%)				
Caucasian Non-Hispanic	16 (62%)	12 (50%)	$\chi^2=1.57$ (d.f. = 2)	.46
Caucasian Hispanic	7 (27%)	6 (25%)		
Other/Mixed	3 (12%)	6 (25%)		
Lives with both biological parents	23 (89%)	19 (79%)	$\chi^2=.80$ (d.f. = 1)	.37
Auditory evoked potentials				
Latency $\pm$ s.d. of P50 response to...				
First Stimulus (ms)	73.0 $\pm$ 17.9	70.0 $\pm$ 13.8	t=.64 (d.f. = 47)	.53
Second Stimulus (ms)	73.2 $\pm$ 16.5	71.0 $\pm$ 14.3	t=.52 (d.f. = 47)	.62
Amplitude $\pm$ s.d. of P50 response to...				
First Stimulus (μ V)	2.23 $\pm$ 1.07	2.36 $\pm$ 1.19	t=.48 (d.f. = 48)	.67
Second Stimulus (μ V)	0.50 $\pm$ 0.36	1.55 $\pm$ 0.81	t=11.75 (d.f. = 48)	<.001
P50 sensory gating ratio	.22 $\pm$.12	.69 $\pm$.25	*	*

* variable used to sort into groups, so statistical test not performed

Table 2

Measures of child behavior from parent-report utilizing the Child Behavior Checklist and the impact of gender and infant sensory gating ability.

Nonparametric analyses of covariance were applied to each 40-month-old behavior score after a rank transformation^{38, 39} to estimate the association with gender and infant P50 sensory gating. All analyses of covariance have the same degrees of freedom: $\text{ndf}=1$, $\text{ddf}=46$.

Raw Score for	Mode	Median	Mean	% subjects in clinical range	gender		Infant P50 sensory gating	
					F	p	F	p
Total problems	12	20.5	24.34	4	3.63	.06*	3.31	.08*
Externalizing	1	10	10.72	2	2.34	.13	4.17	.047**
Attention	0	2	2.08	0	6.27	.016**	5.23	.027**
Aggression	8	8	8.16	0	1.10	.30	2.93	.09*
Internalizing	2	4.5	5.98	2	0.91	.35	1.55	.22
Emotionality	0	1	1.70	2	0.17	.68	.21	.65
Anxious/depressed	0	1	1.72	2	0.00	.96	5.36	.025**
Somatic	0	1	1.70	2	0.15	.70	0.14	.72
Withdrawn	0	0	0.84	0	0.61	.48	.53	.47
Other								
Sleep	0	2	2.26	2	1.25	.27	.52	.48
DSM-Oriented Scales								
Affective	0	1	1.60	2	0.52	.48	1.48	.23
Anxiety	0	1	2.12	0	1.12	.30	5.64	.022**
Pervasive Developmental	2	2	2.24	4	0.20	.66	1.06	.31
Attention Deficit-Hyperactivity	1	3.5	3.94	2	3.28	.07*	5.40	.025**
Oppositional Defiant	3	3	2.94	4	0.65	.43	3.94	.053*

* $p<.10$

** $p<.05$