Author(s): Guiraud, Jeanne A; Kushnerenko, Elena; Tomalski, Przemyslaw; Davies, Kim; Ribeiro, Helena; Johnson, Mark H.; The BASIS Team
Article Title: Differential habituation to repeated sounds in infants at high risk for autism
Year of publication: 2011
Citation: Guiraud, J. Kushnerenko, E., Tomalski, P., Davies, K., Ribeiro, H., Johnson, MH and the BASIS team (2011) 'Differential habituation to repeated sounds in infants at high risk for autism'. Neuroreport, 2011 Nov 16; 22(16):845-9.

Link to published version: http://dx.doi.org/10.1097/WNR.0b013e32834c0bec
DOI: 10.1097/WNR.0b013e32834c0bec

Differential habituation to repeated sounds in infants at high risk for autism

Abbreviated title: Poor auditory habituation in infants at-risk

Jeanne A. **Guiraud**, Elena **Kushnerenko**, Przemyslaw **Tomalski**, Kim **Davies**, Helena **Ribeiro**, Mark H. **Johnson**, and the BASIS team*

*Simon **Baron-Cohen**, Patrick **Bolton**, Susie **Chandler**, Tony **Charman**, Mayada **Elsabbagh**, Janice **Fernandes**, Teodora **Gliga**, Greg **Pasco**, & Leslie **Tucker**

Author responsible for correspondence concerning the submission, and to whom requests for reprints:

Jeanne A. Guiraud, Centre for Brain and Cognitive Development, Birkbeck, University of London, The Henry Wellcome Building, London, WC1E 7HX. jeanne_guiraud@hotmail.com

Sources of any support: BASIS is supported by a consortium of funders led by Autistica (see www.basisnetwork.org). This project is additionally supported by MRC grant G0701484 to M. H. Johnson.

Statement of conflicts: None declared.

Character count of main body text: 16,466.

Abstract

It has been suggested that poor habituation to stimuli might explain atypical sensory behaviours in autism, i.e. over-responsiveness to some stimuli and under-sensitivity to other. We investigated habituation to repeated sounds using an oddball paradigm in 9 month-old infants with an older sibling with autism and hence at high risk for developing autism. Auditory evoked responses to repeated sounds in control infants (at low risk of developing autism) decreased over time, demonstrating habituation, and their responses to deviant sounds were larger than responses to standard sounds, indicating discrimination. In contrast, neural responses in infants at high risk showed no habituation, and reduced sensitivity to changes in frequency. Reduced sensory habituation may be present at a younger age than the emergence of autistic behaviour in some individuals, and we propose that this could play a role in the sensory atypicalities observed in autism.

Keywords: Habituation, autism, infants, event-related potentials, auditory, MMN.

Introduction

Autism is a neurodevelopmental disorder typically diagnosed from around 3 years old, and which is characterized by impaired communication and social skills and repetitive or stereotypical behaviors [1]. It is highly associated with genetic risk: The prevalence of broader defined autism spectrum disorder (ASD) is around 1% in the general population, around 20% of those infants who have an older sibling diagnosed will go on to receive the diagnosis themselves [2]. Children and adults with autism often present with abnormal sensory behaviours, being easily distressed or preoccupied by innocuous sights, sounds, odours and textures, and under-responsive to other stimuli leading to atypicalities such as a high pain threshold [3]. Distortions in sensory input in early infancy could lead to a failure to develop more complex cognitive abilities, and sensory abnormalities at 14 months of age might be early indicators of later autism [4]. Infants later diagnosed with ASD and toddlers with autism between the ages of 6 to 35 months display unusual behaviours in response to changes in sensory stimuli [5]. This is particularly the case in the auditory modality, where unusual responses to sounds, both hypo- and hyper-reactivity, are reported [6]. While hypersensitivity is a trait that autistic children share with developmentally delayed children, and correlates with their mental age, hyposensitivity appears to be a characteristic specific to autism [7]. Further, a review by Rogers and Ozonoff (2005) [8] highlights the fact that there is more evidence that children with autism, as a group, are hypo- rather than hyper-responsive to sensory stimuli. It is possible that some behaviours observed in autism are an expression of compensatory responses to cope with hyposensitivity, and therefore play a role in the emergence of autistic characteristics. The reasons

why individuals with autism are hyposensitive, however, are as yet poorly understood.

Reduced habituation to sensory stimulation could explain both hyposensitivity and hypersensitivity in autism. Neural habituation is a process by which the neural response decreases over time during repeated stimulation [9]. Reduced habituation could lead to an inability to discriminate novel from repeated sounds and therefore to a form of hyposensitivity to changes in the auditory environment. At the same time, failure to habituate could foster an experience of sensory overload, which in turn could lead to hypersensitivity. Several studies have suggested that habituation is reduced in individuals with autism. An event-related potential (ERP) study showed that children with autism may have reduced habituation [10]. In this study, the amplitude of the P50 component did not decrease in response to a click following another click in twelve 7-13 year-old high-functioning children with autism. This was in contrast to typically developing children, whose diminished electrophysiological response to repeated stimuli reflected habituation. Other studies have shown that severity of autistic symptoms in adults correlates with poor behavioural habituation to faces (e.g., [11]), as well as a reduced fMRI-adaptation effect in the amygdala due to repeated exposure to faces [12]. The fact that habituation is reduced in children with autism and that symptom severity correlates with poor habituation in adults suggest that poor habituation may play a role in the emergence of autistic symptoms, including atypical sensory responses.

Little is known about the underlying causes of autism or the process through which symptoms emerge (for a review, [13]). Researchers, until recently, have relied on limited retrospective data on infants younger than two years of age prior to diagnosis. Infants at high risk, by virtue of being genetic relatives of children with autism, might share some characteristics with affected individuals, even if they do not themselves go on to receive a diagnosis. In adults, the Broader Autism Phenotype (BAP) refers to clinical, behavioural and brain characteristics associated with autism found not only in affected individuals, but also in their relatives [14]. It is not known whether reduced habituation is a feature of the BAP, and/or is involved in the emergence of the sensory characteristics of autism.

In the present study, we used an oddball paradigm to investigate habituation and its role in auditory discrimination in 9 month-old infants at high risk of developing autism (younger siblings of a child with autism) to determine whether poor habituation is present before the onset of autism in some individuals. In oddball paradigms, neuronal adaptation [15] to repetitive standard sounds is necessary in order for infrequent deviant sounds to generate a mismatch neural response, MMN (for a recent review see [16]). We recorded the P150, an evoked potential component thought to reflect auditory sensory processes [17], in response to standard and deviant auditory tones. In low-risk infants with an older sibling without autism, we expected to find a decrease in P150 amplitude with repetitions of the standard tone, demonstrating habituation, as well as an enhanced electrophysiological response to pitch deviants compared to standards, reflecting discrimination [18]. In the group of infants at high risk, we predicted a reduced

decrease in neural responses to repeated standards, and no enhanced responses to deviants indicating poor habituation that might underlie their atypical behavioural responses to changes in sounds.

Materials and methods

Participants

We tested 35 infants (14 females) from the British Autism Study of Infant Siblings (BASIS; www.basisnetwork.org), all of whom had an older full sibling (of which 4 females) with a community clinical diagnosis of ASD. We also recruited 21 low-risk infants (11 females) with no reported family history (1st degree relative) of autism from a volunteer database at the Birkbeck Centre for Brain and Cognitive Development. Inclusion criteria included full-term birth, normal birth weight, and lack of any ASD within first-degree family members (as confirmed through parent interview regarding family medical history). All low-risk infants had at least one older full sibling. Infants were tested at around 9 months and 9 days of age (± 27 days in the high risk group, ± 23 days in the control group).

Stimuli

Sounds were presented in an oddball paradigm adapted from Kushnerenko et al. (2007): two different types of infrequent sounds (11.5% probability each) occurred at random positions within a sequence of 500 Hz pure tones (standards), with the restriction that these sounds were always followed by at least two standards. One infrequent sound was a pure tone of 650 Hz (the deviant), and the

other infrequent sound was white noise. In order to rule out that poor habituation and encoding of deviant pitch was due to the auditory processing difficulties often reported in children with autism [19], the white-noise deviants were used to assess the integrity of central auditory processing in high risk infants as reflected by ERP responses to a spectrally rich stimulus known to elicit the most reliable and invariant across individual infants response compared to all other types of deviants [17]. The duration of the sounds was 100 ms, including 5-ms rise and 5-ms fall times, with an inter-stimulus (offset-to-onset) interval of 700 ms. The intensity of the sounds was 70 dB SPL. We presented the stimuli until the infants became restless, i.e. on average 472 events were presented to low-risk infants and 507 events to high-risk infants.

Procedure

Infants were seated on their caregiver's lap within a sound attenuated room, while sounds were presented through two speakers one metre apart and located one metre in front of the infant. An experimenter blew bubbles during the presentation of the sounds to direct the infant's attention away from the sounds, as is usual practice in MMN studies [11]. Parents gave their consent for their infant to participate in the study. The study was approved by London NHS Research Ethical Committee (reference number: 06/MRE02/73) and conducted in accordance with the Declaration of Helsinki (1964).

Data acquisition and analysis

Brain electrical activity was measured using an EGI 128-channel Hydrocel Sensor Net. We could not record electroencephalographic data from one high risk infant and 3 low risk infants who did not like having the net on their head. The reference electrode at recording was the vertex (Cz in the conventional 10/20 system). The electrical potential was filtered with 0.1–200 Hz bandpass, digitized at 500 Hz sampling rate. Continuous data were filtered offline with a 15 Hz low-pass filter. Epochs of 800 ms duration, including 100-ms pre-stimulus interval, were extracted for each stimulus. Further, the first three epochs and those exceeding 150 μV at any signal channel were excluded from averaging. The average amount of trials per condition was 284 standards (±76), 44 tone deviants (±12), and 41 noises (±11) in the 35 high risk infants remaining in the study, and 243 standards (±56), 34 tone deviants (±9), and 38 noises (±11) in the 18 remaining controls. Epochs were separately averaged for the different conditions (standards, deviants, noise) and re-referenced to average reference. Responses to standards were further processed by averaging separately the responses to the first, second, and third standards following a deviant or noise to look at habituation. We looked at ERPs generated over the right hemisphere, consistent with the previous literature on tone processing in infants (e.g., [20]). Amplitude measurements were extracted from 7 electrodes around the C4 area, where mismatch responses are commonly studied (e.g., [17]), and baseline-corrected using a 100-ms long pre-stimulus baseline. For each analysis, we selected time windows for amplitude measurement spanning 50% of the peak amplitude of the grand averaged waveforms across groups in both directions, i.e. from 110 ms to 250 ms for P150 in response to the first three standards following a deviant/noise for the habituation analysis within

and across groups, from 90 ms to 170 ms for P150 in response to all the standards and deviants for the sensitivity to deviant analysis across groups, and from 120 ms to 320 ms for the comparison of P150 amplitudes in response to noise across groups. Amplitudes were calculated as the average voltage within each latency window.

Results

Poor habituation in high risk infants

As shown in Figure 1, low risk infants habituated to standards, with the amplitude in response to third standards following a tone deviant/noise decreasing significantly when compared with first standards (repeated-measures ANOVA: $F(1, 87) = 4.804$, $p = 0.043$), while, as a group, high risk infants did not (repeated ANOVA: $F(1, 147) = 1.029$, $p = 0.318$). Further evidence that low risk infants habituated more than high risk infants was provided by the fact that while the amplitude in response to first standards following a deviant/noise did not differ across groups (two-tailed independent sample t-test: $t(51) = 0.406$, $p = 0.687$), the amplitude in response to third standards was significantly smaller in controls compared to high risk infants (two-tailed independent sample t-test: $t(51) = 2.005$, $p = 0.050$).

Figure 1.

Hyposensitivity to deviants in high risk infants

There was a significant increase in the amplitude of responses to deviants compared with standards in low risk infants (two-tailed paired t-test: $t(17) = 2.102$, $p = 0.051$), but not in high risk infants (two-tailed paired t-test: $t(34) = 0.427$, $p = 0.672$). Lack of differential response to deviants compared to standards could not be due to impaired auditory processing in the infants at high risk, as there was no significant difference in amplitude of the responses to noise in high risk infants compared to low risk infants (two-tailed independent t-test: $t(51) = 0.406$, $p = 0.686$). Figure 2 shows the ERPs in response to the various stimuli in both groups.

Figure 2.

Discussion

In the present study, we show that low risk infants typically have a bigger P150 in response to deviants compared to standards, reflecting better discrimination of the deviants, while the electrophysiological activity of infants at high risk of developing autism is similar in response to deviants and standards. This finding is in line with previous studies, which have failed to show a typical mismatch response to tones deviant in frequency in children with autism (e.g., [21]). A recent theory proposes that the mismatch response to deviants in an oddball paradigm arises from neuronal adaptation in auditory cortex [15]. It is suggested that repetition of auditory standards leads to frequency specific inhibition of the tonotopic representation of the standard, and in parallel, release from inhibition of all other (nonadapted) frequency representations. Absence of a mismatch

response in infants at high risk could thus be a result of the reduced habituation effect that we observe here.

Stimulus-specific adaptation can be shown by a gradual decrease in auditory ERP amplitude in response to repetitive tones during passive listening [22]. Unlike low risk infants, our group of high risk infants do not show a decrement in P150 amplitude to standards, confirming our prediction that they have reduced habituation to repeated sounds. The effect of reduced habituation on performance has been studied in adults with autism in a tactile task, where, in contrast with controls, prior history of tactile stimulation failed to alter tactile spatial localization [23]. Hence, reduced neural habituation in infants at high risk may prevent their mismatch responses to deviant sounds.

According to the "over-arousal theory", poor habituation to stimuli in the environment in children with autism contributes to general levels of over-arousal followed by heightened arousal in response to specific stimulation (for a review, [8]). However, there is also accumulating evidence that supports the opposite hypothesis of under-arousal, which states that impairment of a child with autism's ability to connect previous experiences with current ones prevents learning and generalization, and contributes to non-typical reactions and/or underreactivity to stimuli [8]. Our results show how habituation, a neuronal mechanism thought to reflect plasticity and learning [24], has the capacity to explain both theories. Reduced habituation leads to hyposensitivity to a stimulus change and at the same time an over-reactivity to repeated stimulation. Reduced habituation could also

result in other characteristics of autism, such as restrictive and repetitive behaviours [25].

Conclusion

This study shows that reduced neural habituation is present in infants at high risk for autism, and results in reduced neural responses to tone frequency changes. We speculate that reduced habituation may generate hyposensitivity to subtle changes in auditory environment, at the same time resulting in over-reactivity to repeated, irrelevant information and play a role in the emergence of other autistic characteristics in some children. In future work we will follow up the infants who participated in this study over time to further investigate how decreased habituation may affect later emerging behaviour, particularly in those who go on to receive a diagnosis of autism at 3 years old.

Acknowledgements

We are very grateful for the generous contribution BASIS families have made towards this study.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders—Text revision (DSM-IV-TR; 4th ed.). Washington, DC: Author; 2000.

[2] Ozonoff S, Young G, Carter AS, Messinger D, Yirmiya N, Zwaigenbaum L, et al. Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium Study. Pediatrics; In press.

[3] Dunn W, Smith-Myles BS, Orr S. Sensory processing issues associated with Asperger syndrome: A preliminary investigation. Am J Occup Ther. 2002;56:97–102.

[4] Willemsen-Swinkels S, Dietz C, van Daalen E. Screening for autism spectrum disorders in children 14–15 months. I: The development of the Early Screening of Autistic Traits Questionnaire (ESAT). J Autism Dev Disord. 2006;36:723–732.

[5] Malvy C, Barthelemy D, Damie P, Lenoir C, Bodier C, Roux S. Behaviour profiles in a population of infants later diagnosed as having autistic disorder. Eur. Child Adolesc. Psychiatry. 2004;13(2):115–122.

[6] Wing L. The Autistic Spectrum: A Guide for Parents and Professionals (2nd ed.). London: Constable and Robinson; 2003.

[7] Baranek GT, David FJ, Poe MD, Stone WL, Watson LR. Sensory experience questionnaire: Discriminating sensory features in young children with autism, developmental delays, and typical development. J Child Psychol Psychiatry. 2006;47:591–601.

[8] Rogers SJ, Ozonoff S. Annotation: What do we know about sensory dysfunction in autism? A critical review of the empirical evidence. J Child Psychol Psychiatry. 2005;46:1255–1268.

[9] Thompson RF, Spencer WA. Habituation: A model phenomenon for the study of neuronal substrates of behavior. Psychol. Rev. 1966;73:16–43.

[10] Kemner C, Orange B, Verbaten MN, Van Engeland H. Normal P50 gating in children with autism. J Clin Psychiatry. 2002;63:214 –217.

[11] Webb SJ, Jones EJH, Merkle K, Namkung J, Toth K, Greenson J, Murias M, Dawson G. Toddlers with elevated autism symptoms show slowed habituation to faces. Child Neuropsychol. 2010;16(3):255–278.

[12] Kleinhans NM, Johnson LC, Richards T, Mahurin R, Greenson J, Dawson G, et al. Reduced Neural Habituation in the Amygdala and Social Impairments in Autism Spectrum Disorders. Am J Psychiatry. 2009;166:467–475.

[13] Elsabbagh M, Johnson MH. Getting answers from babies about autism. Trends Cogn Sci. 2010;14(2):81-87.

[14] Pickles A, Starr E, Kazak S, Bolton P, Papanikolaou K, Bailey A, Goodman R, Rutter M. Variable expression of the autism broader phenotype: findings from extended pedigrees. J. Child Psychol. Psychiatry. 2000;41:491–502.

[15] Jääskeläinen IP, Ahveninen J, Bonmassar G, Dale AM, Ilmoniemi RJ, Levänen S, et al. Human posterior auditory cortex gates novel sounds to consciousness. Proc Natl Acad Sci U S A. 2004;101(17):6809-6814.

[16] Näätänen R. Mismatch negativity (MMN) as an index of central auditory system plasticity. Int J Audiol. 2008;47(Suppl 2):16-20.

[17] Kushnerenko E, Winkler I, Horváth J, Näätänen R, Pavlov I, Fellman V, Huotilainen M. Processing acoustic change and novelty in newborn infants. Eur J Neurosci. 2007;26:265-274.

[18] Morr ML, Shafer VL, Kreuzer JA, Kurtzberg D. Maturation of mismatch negativity in typically developing infants and preschool children. Ear and Hearing. 2002;23:118–136.

[19] Nieto Del Rincòn PL. Autism: Alterations in auditory perception. Rev Neurosci. 2008;19:61–78.

[20] Homae F, Watanabe H, Nakano T, Taga G. Functional development in the infant brain for auditory pitch processing. Hum Brain Mapp. 2011; In press.

[21] Tecchio F, Benassi F, Zappasodi F, Gialloreti LE, Palermo M, Seri S, et al. Auditory Sensory Processing in Autism: A Magnetoencephalographic Study. Biol Psychiatry. 2003;54:647–654.

[22] Haenschel C, Vernon DJ, Dwivedi P, Gruzelier JH, Baldeweg T. Event-Related Brain Potential Correlates of Human Auditory Sensory Memory-Trace Formation. J Neurosci. 2005;25(45):10494–10501.

[23] Tommerdahl M, Tannan V, Cascio CJ, Baranek GT, Whitsel BL. Vibrotactile adaptation fails to enhance spatial localization in adults with autism. Brain Res. 2007;1154:116–123.

[24] Prescott SA. Interactions between depression and facilitation within neural networks: Updating the dual-process theory of plasticity. Learn. & Mem. 1998;5:446–466.

[25] Perry W, Minassian A, Lopez A, Maron L, Lincoln A. Sensorimotor Gating Deficits in Adults with Autism. Biol Psychiatry. 2007;61(4):482-486.

Figure 1. Amplitude of P150 on right central electrodes (see bottom right corner for the region selected) in response to the first, second, and third standards following a deviant/noise (ST1, ST2, and ST3 respectively). Bars are standard errors of the mean. * $p < 0.05$

Figure 2. ERPs in response to standards (black line), tone deviants (dark-grey line), and noise (light-grey line) in low risk infants (left) and high risk infants (right) on C4.