RESPONSE

Autonomic and Electrophysiological Evidence for Reduced Auditory Habituation in Autism

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Abstract
It is estimated that nearly 90% of children on the autism spectrum exhibit sensory atypicalities. What aspects of sensory processing are affected in autism? Although sensory processing can be studied along multiple dimensions, two of the most basic ones involve examining instantaneous sensory responses and how the responses change over time. These correspond to the dimensions of 'sensitivity' and 'habituation'. Results thus far have indicated that autistic individuals do not differ systematically from controls in sensory acuity/sensitivity. However, data from studies of habituation have been equivocal. We have studied habituation in autism using two measures: galvanic skin response (GSR) and magneto-encephalography (MEG). We report data from two independent studies. The first study, was conducted with 13 autistic and 13 age-matched neurotypical young adults and used GSR to assess response to an extended metronomic sequence. The second study involved 24 participants (12 with an ASD diagnosis), different from those in study 1, spanning the pre-adolescent to young adult age range, and used MEG. Both studies reveal consistent patterns of reduced habituation in autistic participants. These results suggest that autism, through mechanisms that are yet to be elucidated, compromises a fundamental aspect of sensory processing, at least in the auditory domain. We discuss the implications for understanding sensory hypersensitivities, a hallmark phenotypic feature of autism, recently proposed theoretical accounts, and potential relevance for early detection of risk for autism.

Keywords Habituation · Autism · Hypersensitivities · MEG · GSR

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Introduction

Clinical and scientific evidence converge on the notion that sensory processing differences are a core diagnostic feature of autism spectrum disorders (ASD) (American Psychiatric Association [APA] 2013; Le Couteur et al. 2003; Leekam et al. 2007; Robertson and Cohen 2017; Sinclair et al. 2017). Disparities in the sensory experience of ASD as compared to neurotypical (NT) individuals have been reported across multiple modalities (Bennetto et al. 2007; Ben-Sasson et al. 2009; Blakemore et al. 2006; Tomchek and Dunn 2007) and are potentially disruptive to socialization (Kleinhans et al. 2010), language learning, and everyday functioning (Hudac et al. 2017; Lane et al. 2010). Notwithstanding their high incidence and significance, little is known about the nature and origins of the sensory differences in ASD.

Two basic characterizations of sensory processing are 'sensitivity' and 'habituation' (Kuiper et al. 2019; Ben-Sasson and Podoly 2020). These correspond, respectively, to responses elicited instantaneously and over extended

periods of time. The notion of basic sensory sensitivity being affected in autism is intuitively appealing as the most direct explanation of the observed hypo- and, more often, hyper-sensitivities in autism (Rogers and Ozonoff 2005). Elevations or reductions in these thresholds would render normal intensity stimuli to appear hypo- or hyper-intense. However, studies of autonomic arousal, such as those using Galvanic Skin Response (GSR), have not yielded strong evidence for group level autonomic differences to sensory stimuli between autistic and control groups (e.g., van Engeland 1984; for a review, see Rogers and Ozonoff 2005), nor any relationship between magnitude of GSR and parent-reported sensory symptomology (McCormick et al. 2014). Likewise, investigations of sensory sensitivity have shown that basic thresholds are largely unchanged by ASD. A few studies have reported super-normal visual acuity and hyperacusis in autistic individuals (Ashwin et al. 2009; Khalfa et al. 2004) and others report differences in pitch perception (Bonnel et al. 2003; Ferri et al. 2003; Gomot et al 2002; Heaton et al. 1998). However, the acuity studies were criticized for methodological reasons and the pitch perception studies require participant judgments, such as comparisons from memory, as opposed to pure perception. Several other studies have found no significant differences in sensory acuity between ASD and NT groups (Bölte et al. 2012; DePape et al. 2012; Marco et al. 2011). For instance, Koh et al. (2010) and Haigh et al. (2015) have reported that the two groups are statistically indistinguishable in their visual contrast and auditory discrimination thresholds. In the somatosensory domain, Cascio et al. (2008) observed no differences in basic pressure and temperature thresholds, echoing results from O'Riordan and Passetti (2006) who found comparable tactile texture discrimination thresholds across the ASD and NT groups.

Since instantaneous sensory sensitivity appears to be largely unaffected in autism, it is worth examining whether ASD and NT individuals differ in terms of their responses to repetitive stimuli over temporally extended periods. In one study of continuous EDA measurements, during non-sensory naturalistic tasks, it has been demonstrated that variability in EDA measurements is related to autism symptomology (Fenning et al. 2017). There is a hint that the dimension of time is perceived differently in ASD, with evidence coming from auditory temporal order judgments (Kwakye et al. 2011) and temporal reproduction paradigms (Maister and Plaisted-Grant 2011; Szelag et al. 2004) as well as gap detection (Foss-Feig et al. 2018). However, data on the broad question of how sensory sequences with extended temporal extents are processed are limited and do not yet provide a consistent picture. This is due to a number of factors inherent in the research on ASD. For example, the diagnostic criteria for ASD have evolved over time and the diagnosis itself encompasses a wide range of features and levels of functioning (APA 2013). As such, diagnostic classifications have changed from earlier studies, making it difficult to compare older findings with more contemporary ones. An example of such a discrepancy is found in Bernal and Miller (1970) in which there were no differences between the resting skin-conductance levels or habituation responses of "autistic schizophrenic" and control children. Whereas White (1974), on the other hand, found differences in responses to repeated tones across four groups of children: "nonorganic schizophrenic," "organic schizophrenic," "minimal brain dysfunction," and "normal". Even with a more nuanced subject classification, but predating modern diagnostic criteria, Van Engeland (1984) and Stevens and Gruzelier (1984), found no differences in habituation rates across autistic and non-autistic participants. A similar lack of group differences was reported in Kuiper et al. 2019. Underscoring the variability of outcomes, James and Barry (1984) reported flatter cardiovascular and electro-dermal responses in autistic children relative to controls. Some recent studies of sensory processing over time in ASD have employed adaptation paradigms (e.g. Lawson et al. 2015), showing that subjective perception of loudness does not attenuate in ASD, whereas in NT, perceived loudness decreases over time.

Motivated by the need to move beyond characterizations of instantaneous sensory sensitivity in autism, and by the mixed set of empirical results thus far, the goal of the work we describe in this paper is to examine sensory habituation over time in individuals with ASD. We focus, in particular, on audition.

In order to objectively and quantitatively study habituation, we used two assessment modalities: galvanic skin response (GSR) and magneto-encephalography (MEG), which reflect sympathetic autonomic activity and cerebral cortical activity, respectively. GSR is the well-established gold-standard for arousal measurements in autonomic studies, and is often used as a physiological response to assess habituation (e.g. James and Barry 1984). Importantly, there is evidence that GSR is a reliable measure of sensory processing in autism (Schupak et al. 2016). On the other hand, MEG uses an array of sensors surrounding the head to measure magnetic signals emanating from active neurons (Cohen 1968; Hämäläinen et al. 1993). It represents a direct measure of neuronal activation with millisecond resolution, the time scale at which neurons communicate. MEG can thus capture the dynamics of neurophysiological responses to habituation, in the form of sensory evoked response fields (ERFs) modulated by stimulus repetition (Rosburg et al. 2002, 2006). Both assessment modalities offer ease of use, which is critical for experimental studies with individuals with ASD, and have the potential to reveal complementary dimensions of habituation, reflecting a complex interaction of thalamo-hypothalamo-cortical networks (Lim et al. 1996). It is worth noting that having two distinct measurement modalities also allows us to assess the robustness of

our results to different experimental assays. They can help ensure that any results we find are not artifactual in nature, evident only in a specific measurement technique with a constrained set of experimental parameters. The two studies we report here are independent (i.e. the subject pools are non-overlapping). Thus, although they cannot be used to assert that autonomic and electrophysiological measures of habituation within the same set of subjects are correlated, they can be used to investigate whether the phenomenology of habituation is discernible across different measurement modalities.

To summarize, our objective here is to determine whether the habituation profiles of autistic participants differ systematically from those of neurotypical individuals. Specifically, we shall investigate whether ASD is associated with a reduction in sensory habituation. We shall examine temporally-extended physiological (GSR) and neurophysiological (MEG) responses to search for evidence of any such reduction.

Methods

Participants

26 volunteers participated in the GSR study. There were 13 autistic participants (27.1 ± 5.9 years; age range 18.9–36 years; 5 females) and 13 age-matched NT participants (28.9 ± 5.1 years; age range 18.3–35.9 years; 5 females). All participants in the ASD group had received a prior community diagnosis of autism, autism spectrum disorder, Asperger's or Pervasive Developmental Disorder—Not Otherwise Specified. Autism diagnosis was confirmed by a research reliable administrator using the ADOS-2 (Lord et al. 2012). Only participants with scores in the ASD range were included in the study. No IQ measures were obtained from the ASD or control groups.

Twenty-four volunteers, different from those in the GSR study, participated in the MEG study. Twelve participants had a clinical diagnosis of autism (15.12 ± 5.6 years; age range 8–27 years; all male) and met criteria on the ADOS-2 (Lord et al. 2012). The remaining twelve participants were NT individuals age matched with the ASD group (14.75 ± 5.9 years; age range 7–27 years; 2 females).

The experimental protocols described herein were reviewed and approved by the Committee on the Use of Humans as Experimental Subjects (COUHES) at MIT. Informed consent was obtained for all adult participants. For participating minors, informed consent was obtained from the guardian of the child; in addition to parental consent, all participating minors who were capable signed an accompanying assent form. Participants and/or their guardians were

free to discontinue the experiment at any time if they experienced any discomfort.

As a precursor to the study described here, we had conducted a two-site study examining GSR responses to metronomic auditory sequences. The two sites were Boston and New Delhi. We have included a description of the pilot study in the supplementary material.

Experimental Procedure

Our experimental design sought to maximize ease of compliance for subjects on the autism spectrum. While sitting comfortably in a quiet room, participants listened to a periodic sequence of short tone bursts (250 Hz, 73 dB, onset 116 ms, inter-stimulus interval of one second). The sequence consisted of a 2-min-long period of silence, followed by 240 to 300 tone bursts presented at a rate of 1 Hz (for all subjects, data were analyzed for the first 240 tones). GSR and MEG recording sessions were conducted separately, with non-overlapping groups of participants.

GSR Signal Acquisition and Analysis

For GSR acquisition, electrodermal responses were recorded continuously using a Flexcomp Infinity™ encoder (Thought Technology Ltd., Canada) with a sampling rate of 2048 Hz. Ag–AgCl electrodes were affixed to the thenar and hypothenar eminences of the subject's left hand.

These signals were analyzed using MATLAB. The DC offset (including low frequency motion artifacts) was removed by subtracting the mean of each trace from the original raw signal. The signal was band passed between 0.05–10 Hz and then base line corrected by subtracting the mean of 50 ms pre stimulus data). The recorded signals were down sampled from 2048 to 400 Hz in order to bring all signals into the same range (as described above, our data were collected in two different acquisition devices with two different frequencies). Data were normalized to zero mean and unit variance using a 100 s pre-stimulus period, and then averaged across the subjects as shown in the first row of Fig. 1.

MEG Signal Acquisition and Analysis

MEG signals were recorded from 306 channels (Elektra Neuromag TRIUX with 102 magnetometers and 204 gradiometers), at a sampling rate of 1000 Hz, band-pass filtered between 0.03 and 330 Hz, and subjected to Elekta's proprietary artifact rejection pre-processing filter (Maxfilter software) to remove noise and compensate for head movement during the scan. Raw data was pre-processed with the Maxfilter software (Elekta, Stockholm) to perform noise reduction with spatiotemporal filters (Taulu et al. 2004;
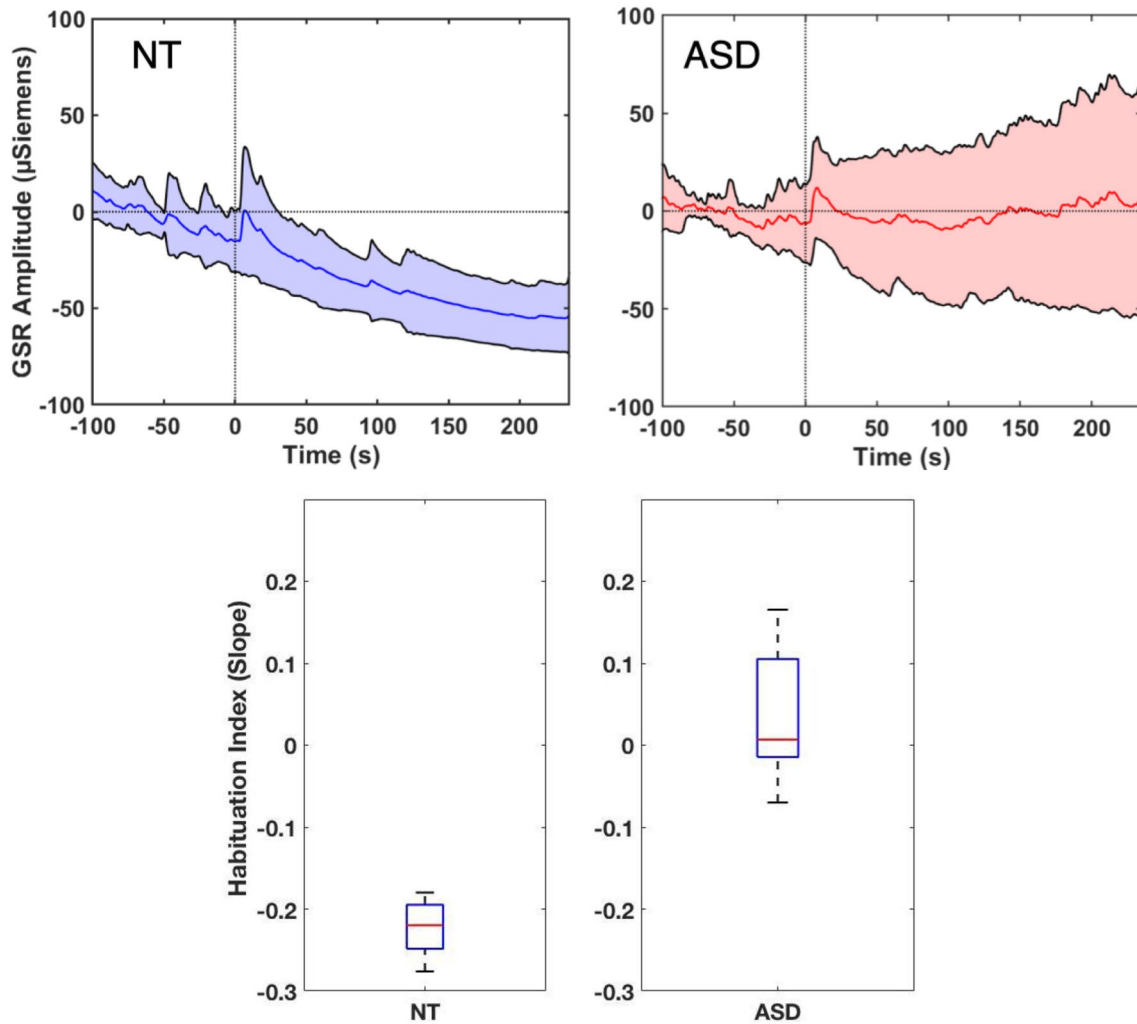
Fig. 1 GSR habituation profiles for NT and autistic participants. (Upper panels) Average GSR traces (and standard deviations) for 13 NT participants and 13 autistic participants as they listened to a metronomic auditory sequence lasting 6 min (First 2 min data acquired without any sensory stimuli, represented from 0 to − 120 s and the rest 4 min data acquired during metronomic auditory sequence from 0 to 240 s. The two panels show data from − 100 to 260 s from the experimental sessions. (Lower panels) Slope as a Habituation index of GSR traces for autistic and NT participants. NT participants exhibit pronounced habituation (as indicated by negative value), in contrast to autistic participants. (Individual GSR traces for the NT and autistic participants are shown in supplementary figure S2.)

Taulu and Simola 2006). We used default parameters (harmonic expansion origin in head frame [0 0 40] mm; expansion limit for internal multipole base 8; expansion limit for external multipole base 3; bad channels automatically excluded from harmonic expansions 7 s.d. above average; temporal correlation limit 0.98; buffer length 10 s). The pre-processed MEG signals were analyzed using Brainstorm (Tadel et al. 2011). Individual trials were extracted with 100 ms baseline and 900 ms post-stimulus with respect to the onset of the tone bursts. The baseline mean of each channel was removed, and signals were low-pass filtered with a cut-off frequency at 40 Hz. Evoked responses were computed by averaging separately the first 50 trials (early response), the last 50 trials (late response), and the entire 300 trials (average response). Since we did not have subject-specific structural MR scans to localize sources of auditory signals on the cortex, analysis proceeded in the channel domain. Using the average evoked response, we selected magnetometer sensors with the strongest auditory signals between 200 and 260 ms post-stimulus. We were guided by prior work showing that evoked responses related to central auditory processing and auditory memory (both of which are relevant for our study) occur around 200 ms post stimulus onset (e.g. Naatanen and Winkler 1999). We considered potential age-related changes in latency and past work (Kotecha et al. 2009) suggested that the youngest ages included in our sample are likely to have ERF latencies longer than those of the older participants by approximately 10 ms.

To accommodate this latency difference we chose a sufficiently large temporal window (200–260 ms) to ensure that we would not miss the ERFs in the younger participants. Selection was constrained to temporal sensors in proximity to auditory cortices, included sensors measuring both incoming and outgoing magnetic fields with respect to the head, and sensors had to show auditory ERFs in the specified temporal window. These spatial and temporal constraints led to largely overlapping electrodes across subjects. This approach of using clusters of sensors from similar regions across participants, rather than identical individual sensors, is conventionally adopted in electrophysiological studies with a high density of sensors, since a given sensor may be situated over slightly different regions of different participants' brains (e.g. Ince et al. 2016). Once the sensors with strongest auditory signals were identified, we computed the total signal power in these sensors separately for the early and late responses. Finally, for each individual participant, the power measurements were normalized with the baseline standard deviation to produce z-scores of power for the early and late responses. This produced z-score power time series for each participant of the ASD and NT groups. We performed t-tests among all control subjects, for each ms, and corrected for multiple comparisons using False Discovery Rate (FDR).

Results

GSR Results

Figure 1 shows data from 26 participants (13 ASD and 13 age-matched NTs) ranging in age from 18 to 36 years. NT subjects showed a predicted steady decline in the GSR signal consistent with habituation. On the other hand, autistic participants did not show such a decline and many exhibited a steady increase in the GSR over the course of the session. In order to demonstrate the effect of habituation with respect to sensory stimuli presentation, we have adopted the double regression approach (Avery et al. 2016; Plichta et al. 2014) used in past studies. The technique is based on the regression equation $Y = bX + a$. The coefficient of regression 'b' is an estimate of habituation. However, the value of 'b' has been shown to be dependent on the intercept of the regression line 'a' (Montagu 1963; Plichta et al. 2014; Tam et al. 2017). Therefore, the absolute habituation index 'b' is a measure independent of the initial amplitude of the response. It has been determined according to Plichta et al. (2014) and Tam et al. (2017) using the formula $b' = b - c(a - \bar{a})$, where 'c' is the slope of 'b' on 'a', and '$\bar{a}$' is the mean of 'a'. A negative value of 'b' indicates habituation. From the regression analysis, we found the NT had negative habituation index (slope), while autistic participants showed positive ones (t(24) = 5.5376, p < 0.001; ASD (mean = 0.034, SD = 0.165); NT (mean = − 0.221, SD = 0.053), Student t-test was conducted between slope of two groups).

As a follow up, we compared the amplitudes of GSR signals (First two minutes and last two minutes of beep presentation) acquired from both NT and ASD subjects. The NTs show statistically significant decrease in response amplitude (t(12) = 7.3321, p < 0.001), whereas the ASDs show statistically significant increase in the same (t(12) = − 1.127, p = 0.05). The combined results show that individuals with ASD display impaired habituation of auditory signals evoked by repetitive sound signals, whereas NTs habituate significantly to the continuous presentation of repetitive signals.

We conducted Mixed model ANOVA to observe between group effect and interactions in their amplitude values (first two-minute data and last two-minute data following beep presentation). The main effect of impairment is significant at F1,24 = 66.128, p < 0.001. The interaction between category and change in amplitude was also significant at F1,24 = 69.072, p < 0.001.

MEG Results: Auditory evoked responses were computed by averaging separately the first 50 trials (early response), and the last 50 trials (late response). Changes in the amplitudes of the early versus late ERFs were used to assess habituation, consistent with standard practice in electrophysiology (e.g. Lim et al. 1996; Rosburg et al. 2006). Neurotypical (NT) participants exhibited marked habituation over the course of the auditory sequence; ERFs elicited by the impulses in the initial section of the auditory train were stronger than those evoked by the latter ones (paired t-test; t(10): − 2.619; p = 0.009; see Fig. 2a and c). By contrast, the amplitude of auditory evoked responses in autistic participants did not show reduction as a function of time, staying unchanged (paired t-test; t(11): 0.0169; p = 0.11; see Fig. 2b and d) or, in some cases, increasing (supplementary Fig. 3B) to produce a stronger magnetic deflection during the final 50 trials relative to the first 50 trials. The ratio of ERF amplitude for the last 50 trials and the first 50 trials was significantly different between the ASD and NT groups (t(21): − 4.17; p < 0.001). Since our MEG participants spanned a broad age range, we had an opportunity to examine whether habituation rates were correlated with age. Figure 2e shows ERF amplitude ratios (amplitude of ERF for last 50 trials/amplitude of ERF for first 50 trials) for individual NT and autistic participants. As is apparent from the scatterplot, such a correlation is not evident for either of the two groups. However, this observed lack of a correlation should be considered tentative at present given the modest group sizes.
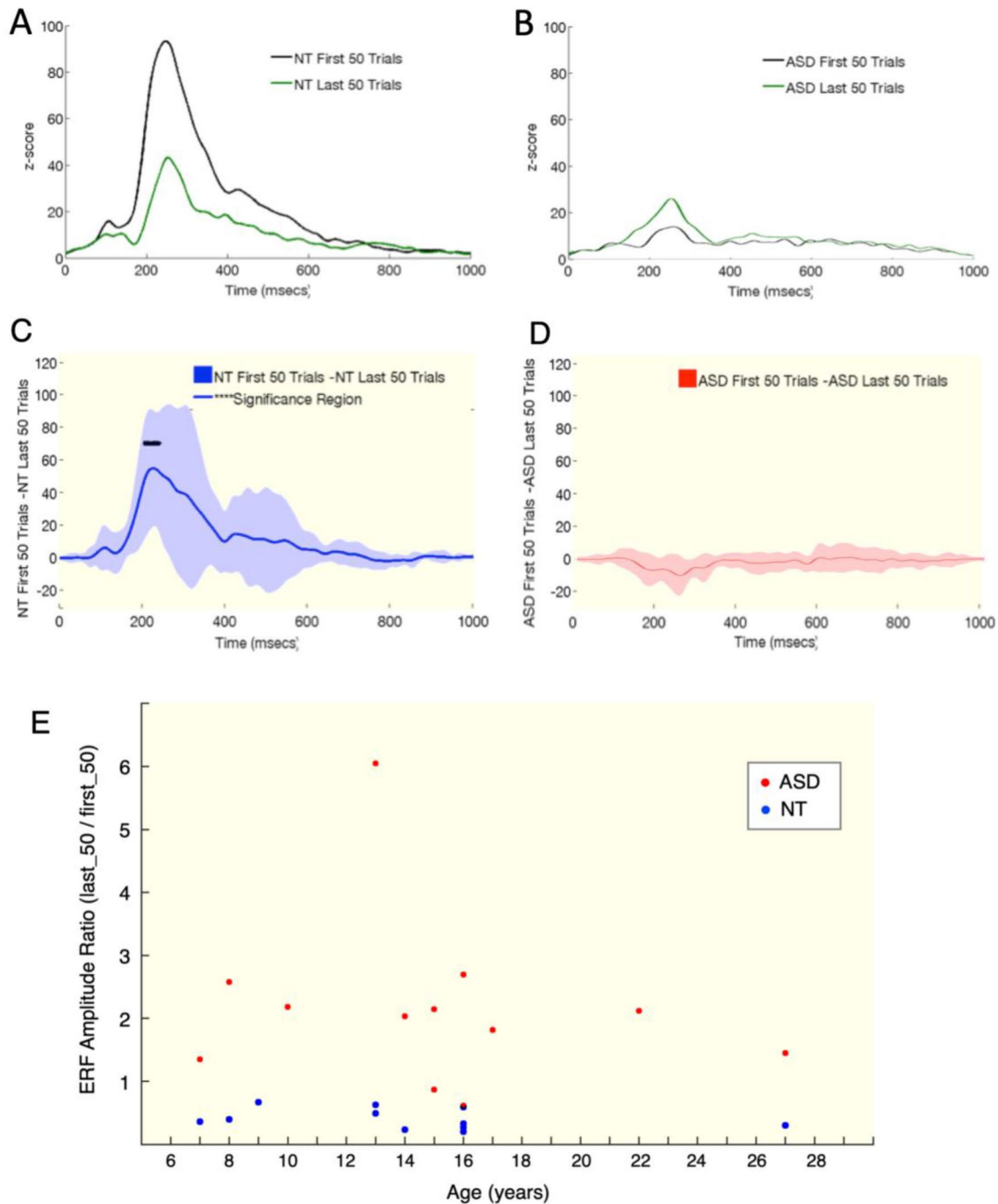
Fig. 2 **a** and **b** Group average auditory evoked responses from neurotypical and autistic individuals. Neurotypical individuals habituate and produce weaker auditory responses towards the end of the metronomic auditory sequence in contrast to autistic participants, consistent with the hypothesis of reduced habituation in autism. **c** and **d** Difference curves for NT and autistic participants obtained by subtracting the ERFs for the last 50 trials from those corresponding to the first 50 trials. **e** Ratio of ERF amplitudes corresponding to the last 50 and first 50 trials of the full sequence for autistic participants (red discs) and NTs (blue discs). Our data do not show a statistically significant correlation between age and change in magnitude of evoked response

Discussion

Two distinct measurements, GSR and MEG, of responses to a metronomic sequence of tones showed remarkably different patterns of habituation in NT individuals on the one hand, and autistic individuals on the other. Whereas the former group exhibited steady habituation as the stimulus sequence progressed, the latter group did not. Consistency

of the findings across measurement modalities and participant pools (the main study and the supplemental one) attest to their robustness. Several, though not all, autistic participants exhibited impaired habituation in contrast to results from NT individuals. With GSR, the reduced habituation in the ASD group manifested as a reduction in the slopes of the lines of best fit to the skin-conductance signal (meaning a less negative slope value and a correspondingly lower diminishment of skin-conductance as a function of time) recorded over the course of a session. With MEG, when comparing results between NT and autistic participants, we observed for the latter a diminished reduction in the evoked response amplitude later in the presented sequence relative to earlier in the sequence. Secondarily, we found that the computed z-scores for the evoked responses in the ASD group were lower than those for the NT group. We do not yet have a definitive explanation for these group level differences. A candidate account to consider is that the baseline signal in autistic participants may be noisier than in NTs. Given that this baseline signal is used to calculate z-scores, an increase in baseline standard deviation would have the effect of reducing the z-scores of the subsequent sections of the evoked responses. The possibility of noisier signals in ASD is consistent with previous reports indicating greater neural variability in autism (Dinstein et al. 2015).

How can we reconcile these results with previous studies such as those from van Engeland (1984) and Stevens and Gruzelier (1984), who reported no differences in habituation between autistic and control participants? As mentioned above, the diagnostic criteria for ASD have evolved over time and the diagnosis itself encompasses a wide range of features and levels of functioning (APA 2013). As such, diagnostic classifications have changed from earlier studies, making comparisons between older findings and more recent ones difficult. Additionally, the stimuli used in earlier studies might not have been effective at highlighting habituation differences between groups. The metronomic sequences we used induce rapid habituation in NT individuals; this serves as a strong reference against which to compare impairments in habituation. By contrast, van Engeland (1984) and Stevens and Gruzelier (1984) used widely temporally separated, randomly presented stimuli that, because of their irregular structure, are not ideal inducers of habituation (Sokolov 1960). Another stimulus-dependent factor that may underlie some of the inter-study differences in the nature of the auditory stimulus itself. It remains to be seen whether habituation can be modulated by the acoustic properties of the items in the sequence train. These properties include low-level aspects such as tone frequency, but also higher-order ones such as whether the sound has an animate or inanimate origin. Recent work has elucidated listening preferences of autistic children to different kinds of sounds (Kuhl et al. 2005). It will be interesting to examine whether these listening preferences correlate with the extent of habituation obtained with the sounds are repeated.

The findings here may inform clinical and educational practices. If habituation is found to be affected across a range of stimuli, then measures of habituation responses might inform clinicians and educators in tailoring their best practices for improved outcomes for those with ASD and sensory differences. An example of such a practice could include monitoring changes in physiological arousal, building on studies by Goodwin et al. (2019), to alert clinicians and educators to the onset of sensory over-arousal, and prevent the type of full dysregulation that can be disruptive to learning and safety, particularly in autistic individuals with limited spoken language. Furthermore, reducing demands and teaching adaptive strategies to request breaks during periods of hyper-arousal, paired with interventions to improve sensory adaptation may better empower autistic individuals to heed physiological discomfort until they are able to better habituate to stimuli that causes over-arousal. It is very important to partner with autistic colleagues to increase societal acceptance and understanding of sensitivity-related behaviors. The neurodiversity movement that began in the 1990s, stresses the importance of understanding and accepting differences associated with autism, as well as the importance of including those with 'lived experience' when designing interventions and informing research agendas (Baron-Cohen 2017). The motto 'nothing about us without us' (Autistic Self-Advocacy Network, ASAN) indicates that autistic individuals must be involved in developing environments and therapeutic interventions that will enhance the quality of life for them (Owrens and Stenhammer 2013). Some of the above examples stand in contrast with common behavioral intervention strategies that aim to prevent or reduce escape and avoidance behaviors, however, such behaviors might also be considered essential to the independence and autonomy of autistic individuals with whom "compliance" is often stressed over comfort and choice.

We stress that the findings presented here need significant further development before they can be translated to the clinical setting. First, their robustness needs to be established and second, their generality needs to be determined. Is this effect observed only in lab settings with a narrow set of stimuli, or is this result obtained across several kinds of sustained stimulus trains? Studies will also need to examine whether the atypicalities of habituation reported here are specific to audition or generalize to other sensory modalities like vision or touch. Additionally, it will be important to situate habituation assays in the context of the overall autism phenotype. Several tests have been developed for assessing autism severity across different phenotypic dimensions. These include the Sensory Profile (Dunn 1999), the ADI-R (Le Couteur et al. 2003), and anxiety measures. Correlating these data with the strength of habituation will help to

determine the extent to which habituation impairments are predictive of different aspects of the phenotype. Exploring whether atypicalities of habituation are evident early in childhood is a promising avenue from the perspective of early diagnosis. Past studies have indicated that infants at elevated risk of autism show atypical responses to auditory sequences (Kolesnik et al. 2019; Guiraud et al. 2011).

Additionally, a better understanding of individual habituation profiles might allow for adaptive sensory environments for autistic individuals. Improving the design of clinical and learning environments to reduce the need for sensory processing of novel stimuli not relevant to learning and that result in overstimulation, may improve educational outcomes for those with reduced habituation profiles. A child with reduced auditory habituation, for instance, might be more comfortable in a playroom with lower ambient sound levels. Also, habituation profiles may be one factor to take into consideration for determining class/playgroup compositions. More broadly, characterization of sensory habituation across modalities could provide useful information in the design of comfortable study/play areas for autistic children and adults. The results would also be important from the basic scientific perspective since they will help determine if the mechanisms underlying impaired habituation transcend specific sensory modalities, or if there is something special about audition.

On a more fundamental level, what might be the factors that account for impaired habituation in ASD? Addressing this issue may allow us to make headway on broader conceptualizations and mechanistic accounts of autism. One account may be provided by the possibility of inadequate sensory gating in autism, leading to the observed reduction in habituation (Orekhova et al. 2008). Alternatively, a recently proposed theoretical account (Sinha et al. 2014) suggests that ASD may be associated with impairments in prediction. To the extent that predictability is a key modulator of habituation, it seems possible that the impairments we have observed might be manifestations of an underlying difficulty in anticipating the progression of a stimulus sequence. More mechanistically, given that habituation is tied intimately to the changing balance between excitation and inhibition in neural circuits (Cohen-Kashi Malina et al. 2013; Coppola et al. 2013; Swartz et al. 2013), and that disruptions of this balance have been implicated in neurological disorders (Horvath and Meares 1973; Hornix et al. 2019; Sinclair et al. 2017; Yizhar et al. 2011), this work may help discern the connections between sensory processing differences and other, seemingly distinct, aspects of the autism phenotype.

In summary, we have reported here results from two different measurement modalities, galvanic skin response and magneto-encephalography, showing atypical habituation in autistic individuals. Whereas neurotypical participants showed clear habituation to a sequence of repeated auditory tones, the autistic participants exhibited little, if any, reduction in their physiological and neural responses as the sequence progressed. These results point to a potentially important endophenotype of autism – a diminishment of sensory habituation. However, at present the findings that we have reported can, at best, be considered tentative. There are several caveats that we need to note in interpreting the significance of, and confidence in, these results. Most evident among these is the small size of our participant pools. Although we derive encouragement from the consistency of results across the measurement modalities, and the statistical significance of the findings within each, the well-noted heterogeneity of autism requires that these results be replicated with larger subject groups to lend confidence that this is a strongly associated feature of autism. Also, since we did not measure our participants' IQ, we cannot be certain that there are not systematic differences between the groups on this dimension which could drive some of the observed differences in their habituation profiles. Past research has suggested that individuals with severe mental retardation (IQ 45–55) exhibit non-systematic habituation profiles (Yehuda et al. 1979). However, no habituation differences are observed between individuals with normal and above normal IQs. The broad age-ranges included in our participant pools may also inject some variability in our results, rendering them noisier than if there was greater homogeneity in participant ages. Another caveat derives from the gender imbalance in our participant pool. Specifically, all of the autistic participants in our MEG study were male and, hence, the NT group was chosen to be predominantly so too. This renders it difficult to extrapolate the reported results to female autistic individuals. Finally, to be able to evaluate the real-world implications of these results, we need to have measures of participants' sensory experiences when immersed in real settings, as well as scores from a range of clinical measures of ASD severity. This will enable an investigation of the covariance of these measures with metrics of habituation derived from the kinds of experiments described here.

It is clear that a substantial amount of work remains to be done to further test and interpret findings from the experiments reported here. Notwithstanding the open questions ahead, we hope that this work will serve a useful purpose by providing hints of a potentially interesting difference in sensory processing of autistic individuals relative to their neurotypical counterparts.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest for this study.

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