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Increased subcortical neural responses to repeating auditory stimulation in children with autism spectrum disorder

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ABSTRACT

Recent research has highlighted atypical reactivity to sensory stimulation as a core symptom in children with autism spectrum disorder (ASD). However, little is known about the dysfunctional neurological mechanisms underlying these aberrant sensitivities. Here we tested the hypothesis that the ability to filter out auditory repeated information is deficient in children with ASD already from subcortical levels, yielding to auditory sensitivities. We recorded the frequency-following response (FFR), a non-invasive measure of the neural tracking of the periodic characteristics of a sound in the subcortical auditory system, to compare repetition-related effects in children with ASD and typically developing children. Results revealed an increase of the FFR with stimulus repetition in children with ASD compared to their peers. Moreover, such defective early sensory encoding of stimulus redundancy was associated with sensory overload. These results highlight that auditory sensitivities in ASD emerge already at the level of the subcortical auditory system.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication, restricted and stereotyped patterns of behavior, narrow interests and reliance on routine (American Psychiatric Association, 2013; World Health Organization, 1993). Among the non-social symptoms of ASD, aberrant responses to sensory stimulation are a key characteristic (see Robertson & Baron-Cohen, 2017, for a review), particularly in the auditory domain (Dahlgren & Gillberg, 1989). Atypical sensory processing has been recently included in the diagnostic criteria of the new DSM-5, and despite being thought to precede (Estes et al., 2015), predict (Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013), and aggravate (Gomot & Wicker, 2012; Jasmin et al., 2009; Schaaf, Toth-Cohen, Johnson, Outten, & Benevides, 2011) both social and non-social manifestations of the disorder, evidence is still lacking concerning the dysfunctional mechanisms leading to these sensory processing deficits.

It has been suggested that a failure to filter out repeated information in ASD may account for the atypical interpretation of sensory inflow (Karaminis et al., 2015), often leading to sensory overload and over reactivity (Kleinhans et al., 2009; O'Riordan & Passetti, 2006). It is well known that the repetition of a given stimulus results in a reduction of neural responses (i.e., "repetition suppression"), which is in turn considered as an indicator of stimulus processing efficiency (Grill-Spector, Henson, & Martin, 2006) and, in terms of predictive coding accounts of brain function, as prediction error suppression (Friston, 2005; Garrido, Kilner, Stephan, & Friston, 2009). Importantly, while in neurotypical population adaptation to sound repetition has been reported in the auditory domain at multiple temporal and spatial scales (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Cacciaglia, Costa-Faidella, Zarnowiec, Grimm, & Escera, 2019; Cooper, Atkinson, Clark, & Michie, 2013; Costa-Faidella, Baldeweg, Grimm, & Escera, 2011; Costa-Faidella, Grimm, Slabu, Díaz-Santaella, & Escera, 2011; Gorina-Careta, Zarnowiec, Costa-Faidella, & Escera, 2016; Haenschel, Vernon,

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Dwivedi, Gruzelier, & Baldeweg, 2005; Recasens, Leung, Grimm, Nowak, & Escera, 2015), previous studies in individuals suffering from ASD –or at high risk– have shown reduced neural adaptation to repeated sounds (Guiraud et al., 2011; Martineau, Roux, Garreau, Adrien, & Lelord, 1992; Millin et al., 2018). To our knowledge, these repetition-related effects have solely been described at higher, cortical, levels of the auditory system. Yet, given the potential cascading influence of the brainstem in the pathophysiology of this disorder (see Dadalko, Travers, Martin, & Travers, 2018), it is of great interest to establish whether these repetition-related effects are present at subcortical levels of the auditory hierarchy in ASD (Nordt, Hoehl, & Weigelt, 2016).

Theories on perception in ASD, such as the enhanced perceptual functioning (EPF) (Mottron et al., 2006) or the intense world theory (Markram & Markram, 2010), postulate the excessive functioning of local neural circuits in primary sensory areas, mainly by excitatory neurons, as the cause of enhanced low-level sensory processing. Furthermore, animal models and human research have suggested that anomalous brainstem neurotransmission is a key contributor to ASD symptomatology, including abnormal auditory function, which could be cascading at other subcortical levels (Dadalko et al., 2018). The present study sought, thus, to examine whether abnormal processing of repeated stimulation is present at subcortical stages of the auditory hierarchy, which would indicate a deeper origin of the sensory processing atypicalities.

In humans, a direct approach to examine non-invasively the high-fidelity transcription of auditory stimuli into a subcortical neural code, preserving its spectrotemporal characteristics, is provided by recording with EEG the frequency-following response (FFR), a sustained auditory evoked potential that accurately tracks the harmonic characteristics of the eliciting sounds (Skoe & Kraus, 2010). The FFR is context-sensitive, modulated by short-term stimulus history (probability) (Chandrasekaran, Hornickel, Skoe, Nicol, & Kraus, 2009; Parbery-Clark, Strait, & Kraus, 2011; Skoe & Kraus, 2010; Skoe, Krizman, Spitzer, & Kraus, 2013; Slabu, Grimm, & Escera, 2012), which suggests the involvement of regularity-detection processes that operate to increase the fidelity by which complex stimuli are encoded (Skoe, Chandrasekaran, Spitzer, Wong, & Kraus, 2014), as well as to separate auditory objects from background noise (Chandrasekaran et al., 2009). In ASD, the FFR is described as unstable across trials (Otto-Meyer, Krizman, White-Schwoch, & Kraus, 2018) and exhibits inconsistent pitch tracking and deficient transcription of speech in quiet and in noise (Russo et al., 2008; Russo, Nicol, Trommer, Zecker, & Kraus, 2009).

The present study aimed at determining whether short-term sound repetition would yield enhanced responses at lower hierarchical levels of the auditory system in ASD compared to TD children, and to establish whether these effects would relate with auditory and motor anomalies that reflect sensory overload. To that end, we retrieved the FFR from EEG recordings in a group of 17 children with ASD and 18 matched controls while they were passively listening to amplitude-modulated (AM) pure tones presented in a roving-frequency paradigm (Costa-Faidella, Grimm et al., 2011; Haenschel et al., 2005). We hypothesized that the signal-to-noise ratio (SNR) of the FFR at the AM rate would be overall larger in ASD children than in their typically developing (TD) peers, and that this effect could be mainly explained by an increase in the SNR with stimulus repetition, and furthermore that it should be related with auditory processing abnormalities as retrieved from Sensory Profile scores (Dunn, 1999).

2. Materials and methods

2.1. Participants

A total of 17 children diagnosed with ASD (mean age = 9.1, SD = 1.7; mean IQ = 103.8, SD = 20.3; one girl) and 18 typically developing children (TD; mean age = 8.8, SD = 1.9; mean IQ = 111.4, SD = 13.9; two girls) participated in the study. Mean age and IQ did not differ between groups ($t(28.12) = 1.282$, $p = .210$; $t(33) = -0.482$, $p = .633$, respectively; age range ASD and TD: 6–12 years old; IQ range, ASD: 72–131, TD: 84–127). IQ measures were obtained using the Wechsler Intelligence Scale for Children (WISC-IV) (Weschler, 2003) and, thus, we also compared four primary index scores. There were no differences between groups on Verbal Comprehension (ASD: mean = 106.1, SD = 18.6; TD: mean = 112.9, SD = 11.1; $t(25.86) = 1.301$, $p = .205$) and Fluid Reasoning (ASD: mean = 104.3, SD = 18.1; TD: mean = 108.3, SD = 12.1; $t(27.76) = .772$, $p = 0.447$). However, we did find significant differences on Working Memory (ASD: mean = 89.2, SD = 19.1; TD: mean = 102.6, SD = 13.2; $t(33) = 2.418$, $p = .021$) and Processing Speed (ASD: mean = 93.4, SD = 12.6; TD: mean = 105.8, SD = 13.7; $t(33) = 2.777$, $p = .009$). All participants did not present any other confounding neurological disorder and had normal peripheral hearing tested with a pure tone audiometry. Some children, particularly from the ASD group, could not complete the testing due to fatigue or inability to follow the long testing procedure. In those cases, we received parental verbal confirmation that the child underwent a previous audiometry and had normal peripheral audition.

The control participants were children from University of Barcelona's colleagues or classmates of the ASD children that were aware of the study. Children diagnosed with ASD were recruited from Sant Joan de Déu Hospital in Barcelona (Spain), where we obtained their background information. Participants were required to have a formal diagnosis of ASD made by a psychiatrist according to the DSM-IV-TR criteria. This included diagnoses of Asperger's disorder and pervasive developmental disorder not otherwise specified, that per the DSM-V (American Psychiatric Association, 2013) now correspond to the umbrella diagnosis of ASD. In addition, they were evaluated at the Sant Joan de Déu Hospital with ADI-R and ADOS algorithms for ASD (Lord, Rutter, & Le Couteur, 1994). Parents were informed about the study prior to the recording sessions and were asked to give signed informed consent. The study was also explained to the children, who gave verbal approval to participate. Families received a monetary compensation to cover time and transportation costs. The experiment was approved by the Ethical Committee of the University of Barcelona and was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Behavioral measures. Sensory profile

To obtain a measure of auditory sensitivities and motor activity, parents were asked to complete two of the grouping subcategories of the Sensory Profile test (Dunn, 1999): *Auditory Processing* and *Modulation of Movement Affecting Activity Level*. The Sensory Profile is a parent-reporting questionnaire based on a 5-point Likert scale (range from 1, Always, to 5, Never) that measures the child's responses to sensory events in everyday life. Parents are asked to indicate how often their child behaves the way described by the item. The complete questionnaire has 14 grouping subcategories divided into three main categories. The *Auditory Processing* subscale of the Sensory Profile, which corresponds to the sensory processing category, consists of 8 items (e.g., *"Holds hands over ears to protect ears from sound"*, *"Doesn't respond when name is called but you know the child's hearing is OK"*), with raw scores ranging between 8 and 40. The *Modulation of Movement Affecting Activity Level* subscale, which corresponds to the modulation category, consists of 7 items (e.g., *"Prefers sedentary activities"*, *"Becomes overly excitable during movement activity"*), with raw scores ranging between 7 and 35. High scores reflect normal sensory and motor behaviors, whereas low scores may indicate the presence of problems with auditory processing (i.e., hyper and hypo-sensitivities and sensory seeking) and with modulation of motor activity (i.e., retracted and agitated behaviors), respectively.

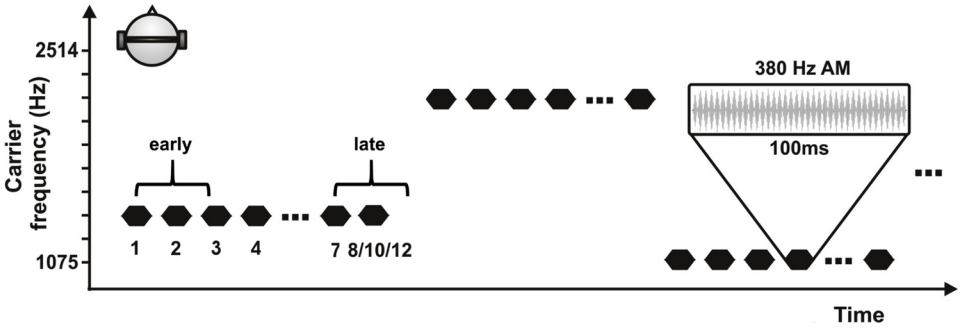

Fig. 1. Experimental design. Amplitude modulated (AM) tones of 100 ms with ten possible different carrier frequencies (range: 1075–2514 Hz) and a constant AM of 380 Hz were presented binaurally in a continuous roving-standard paradigm, consisting of stimulus trains of either 8, 10 or 12 identical tones. Train length and carrier frequencies were pseudo-randomized so that the parameters were not repeated in two consecutive trains. All trains presented a stimulus-onset-asynchrony (SOA) and an inter-train interval (ITI) of 333 ms.

2.3. Stimuli and procedure

Stimuli consisted of 100 ms amplitude modulated (AM) pure tones with 5 ms rise/fall times. Stimuli were presented binaurally with alternating carrier frequency polarities (i.e., one polarity every other stimulus) via Beyerdynamic DT48A headphones (Beyerdynamic, Germany) at an intensity level of 75 dB SPL. The experimental paradigm consisted of a modified version of the passive listening roving-standard paradigm (Baldeweg et al., 2004), designed to explore short-term repetition effects in the FFR while greatly reducing experimental time (Fig. 1).

We presented trains of either 8, 10 and 12 identical tones, continuously delivered with a fixed stimulus onset asynchrony (SOA) and inter-train interval of 333 ms. A total of ten different tones were used with carrier frequencies ranging from 1075 until 2514 Hz, with a frequency ratio between adjacent frequencies of 0.05 according to the formula: $\Delta f = (f2 - f1) / (f2 \times f1) \frac{1}{2}$ (Costa-Faidella, Grimm et al., 2011; Ulanovsky, Las, & Nelken, 2003), so that the frequencies used were: 1075, 1188, 1313, 1451, 1603, 1772, 1958, 2059, 2275, and 2514 Hz. All tones were modulated with a constant AM rate of 380 Hz with a symmetric triangle function and 100% modulation depth. This manipulation allowed us to analyze the subcortical neural tracking of the AM rate as a function of stimulus repetition independently of the carrier frequency being used, hence avoiding the presentation of a great number of identical stimuli, typical of classic FFR recording protocols (Bidelman, 2015; Skoe et al., 2014). This manipulation also ensured that we obtained the neural tracking measure of the AM rate generated by tonotopically arranged subcortical neural populations (Joris, Schreiner, & Rees, 2004) most likely arising from the inferior colliculus (IC) (Bidelman, 2018; Chandrasekaran & Kraus, 2010; Zhang & Gong, 2019). It should be noted that the orthogonal arrangement of tonotopy and periodotopy in the IC ensured that we stimulated different neural populations (Baumann et al., 2011) albeit keeping a constant AM across trains of frequencies.

Auditory sequences were presented in a total of 9 blocks, each lasting about 5 min. In each block, 30 trains of either 8, 10 or 12 repetitions were presented pseudorandomly with the constraint that no carrier frequency was repeated in two consecutive trains. During the recording, participants sat in an electrically shielded, sound-attenuated room and were asked to play a silent videogame of their choice. We invited the participants to bring their preferred videogame from home, but they typically chose to play an unfamiliar one from our set, which further ensured a high engagement with the experimental protocol. Participants were constantly monitored to make sure that they were playing the videogame and not paying attention to the sounds. After each block, a short break was introduced to allow children to move.

2.4. EEG acquisition

Electroencephalographic (EEG) signals were continuously recorded with Neuroscan 4.4 acquisition software in a vertical montage mounted on an elastic nylon cap (Quik-Cap, Compumedics NeuroScan) according to the 10–20 system. Responses were retrieved from the electrodes Cz (active), right earlobe (reference) and AFz (ground). During the EEG acquisition, all electrode impedances were kept below 10 kΩ. EEG signals were amplified using a SynAmps RT amplifier (Compumedics NeuroScan), with an online band-pass filter from 0.05 to 3000 Hz and a sampling rate of 20,000 Hz.

2.5. Data processing

Data were offline high-pass filtered at 80 Hz with a FIR filter (Kaiser window; TBW = 1 Hz). Epochs of 150 ms, including a −20 ms baseline relative to stimulus onset were extracted for each of the tone presentations of each frequency train. Epochs with relative amplitudes larger than 35 μV were excluded from further analysis.

To analyze the effects of repetition we computed the signal-to-noise ratio of the FFR elicited to the AM rate for two segments along the stimulus train: early and late, as shown in Fig. 1. The average to the first 3 presentations of a stimulus in a train, across all trains, corresponded to the early FFR, and the late FFR included the average of the signals to repetitions 7–12. Averaging stimuli with different carrier frequencies and opposite polarities ensured the cancellation of the cochlear microphonic and other stimulus artifacts and highlighted the neural tracking of the sound envelope –the AM rate here (Skoe & Kraus, 2010).

A frequency decomposition of each participant's averaged single trials (all trials after rejection and for each of the two segments, separately) was performed using a Fast-Fourier Transform (FFT) with a Hanning taper as implemented in Fieldtrip (www.ru.nl/fcdonders/fieldtrip). The frequency band of interest ranged between 180 and 580 Hz, and the FFT was conducted within the 20–100 ms time-period from stimulus onset to avoid the transient response. The spectral SNR was computed by dividing the mean of the obtained spectral power in a 10 Hz window centered at each frequency by the mean spectral power at flanking frequencies in windows of 100 Hz (one per flank), separated by 20 Hz from the center frequency of the 10 Hz window (e.g. SNR at 380 Hz = (mean power from 375 to 380 Hz) / (mean power from 260 to 360 Hz and 400 to 500 Hz).

2.6. Statistical analysis

Signal to noise ratio at 380 Hz across all trials were compared between groups by conducting a two-tailed independent sample t-test. Repetition effects were measured by conducting a 2 × 2 mixed-design analysis of variance (ANOVA) with group as between-subject factor (TD, ASD) and segment as within-subject factor (early, late). If appropriate, pairwise Bonferroni-corrected t tests were conducted to control for multiple comparison. Bivariate linear correlations were performed between the strength of the FFR repetition effects, computed as the difference between the SNR to the early minus the late segments, and the raw scores of the two Sensory Profile subscales. Pearson's r and significance values are reported. A result was considered significant when $p < .05$ using a two tailed analysis.

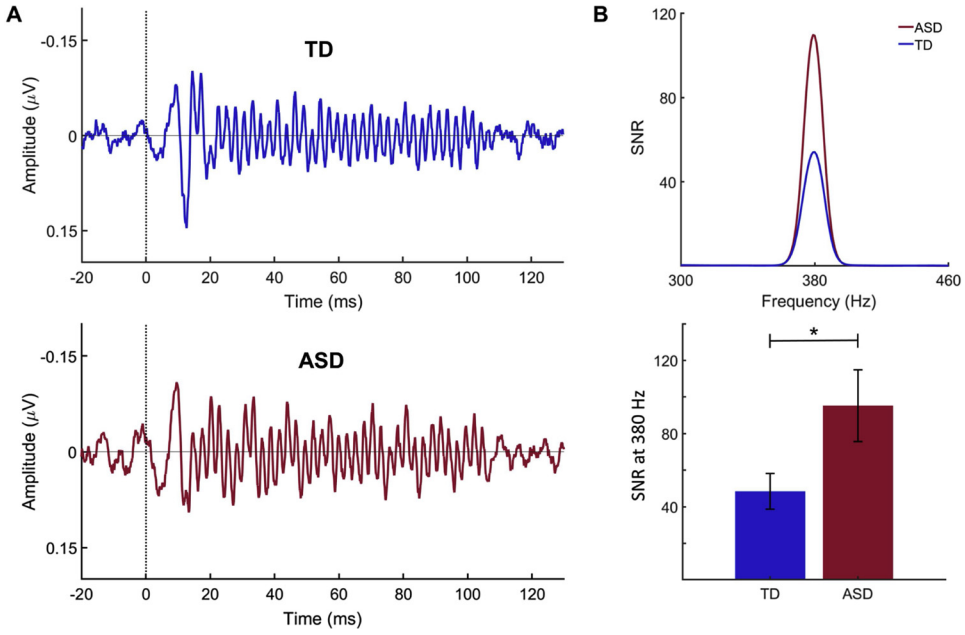

Fig. 2. Neural encoding of the AM rate. A) Grand average FFR responses across all stimuli measured at Cz electrode. B) Top, spectral analysis of the FFR averaged across all stimuli, expressed as SNR. Bottom, bar graph showing the SNR at the 380 Hz AM rate (error bars depict the standard error of the mean). All plots are depicted in blue for the TD group (Typically developing children) and in red for the ASD group (children with Autism Spectrum Disorder). Asterisks represent significance levels: *p < .05.

3. Results

We recorded the FFRs in 17 children with ASD and 18 controls elicited to amplitude modulated tones at 380 Hz rate. We used a roving-standard carrier frequency paradigm to study the effects of repetition on neural encoding as reflected by the SNR of the FFR at the AM rate. Additionally, we related the strength of the repetition effects with parent-reported measures of auditory and motor anomalies assessed with two Sensory Profile subscales.

3.1. Encoding of the AM rate

To examine the strength with which the AM rate was being encoded, we computed the FFR as the average signal to all stimuli within the sequence and compared group differences (ASD, TD) of the SNR values at 380 Hz. ASD children showed a significantly higher SNR (M = 109.46, SEM = 23.23) as compared to TD children (M = 54.13, SEM = 11.22; t(23.1) = -2.145, p = .043, 95% CI [-108.7, -1.9], g = .739), indicating a stronger encoding of the AM rate, as illustrated in Fig. 2B.

3.2. Repetition effects in the FFR

A mixed-design ANOVA revealed a main effect of Segment (F(1,33) = 18.896, p < .001, η_p^2 = .364), Group (F(1,33) = 4.272, p = .047, η_p^2 = .115) and a Group X Segment interaction F(1,33) = 9.129 p = .005, η_p^2 = .217). When comparing the effects of Segment between the two groups, there were no differences in the early segment (ASD: M = 23.73, SEM = 5.48; TD: M = 17.33, SEM = 4.6; t(33) = -0.898, p = .376, 95% CI [-20.9, 8.2], g = .304); however, significant differences between ASD and TD were found at the late segment (ASD: M = 52.86, SEM = 11.2; TD: M = 22.57, SEM = 4.6; t(21.41) = -2.526, p = .019, 95% CI [-54.2, -6.4], g = .872) with larger SNRs elicited in the ASD group, as shown in Fig. 3 (A and B). These results show that differences in the encoding of the AM rate in ASD children are not present in the early presentations of auditory stimuli but rather become evident after repetition.

3.3. Sensory profile scores and correlations with FFR modulations

Finally, we examined the relationship between the repetition effects on the FFR and two measures extracted from the Sensory Profile test: auditory scores (*Auditory Processing* subcategory) and motor scores (*Modulation of Movement Affecting Activity Level* subcategory). Low scores in these two subcategories are indicative of auditory sensory problems (auditory hyper- and hypo-sensitivities and sensory seeking) and more sedentary or agitated behaviors, respectively. The ASD group presented significantly lower auditory scores (ASD: mean = 21.3, SD = 6.4; TD: mean = 31.5, SD = 4.5; t(33) = 5.504, p < .001) and motor scores (ASD: mean = 16.6, SD = 4.2; TD: mean = 23.1, SD = 3.7; t(33) = 4.869, p < .001) than the TD. First, to assess the overall relationship between behavioral measures and the FFR, we performed bivariate linear correlations between the raw behavioral scores obtained from the Sensory Profile test and the SNR at 380 Hz extracted from the average of all trials. Then, we correlated the behavioral measures with the strength of the repetition effects of the FFR at the AM rate (Fig. 3, C and D). The strength of the FFR repetition effects was calculated by computing the difference between the SNRs to the late and the early segments for each participant. Whereas the SNR at 380 Hz extracted from the average of all trials revealed only a tendency of correlation with auditory scores (r = -301, p = .079), an enhancement of the SNR with repetition, reflected by positive strength values, was correlated with low acoustic responsiveness scores (r = -0.346; p = .042), indicating higher auditory sensitivities. This latter significant correlation did not survive, however, after applying the Bonferroni correction for multiple comparisons. Motor activation scores showed no correlation with the SNR at 380 Hz (r = -0.152; p = .383) and a tendency of correlation with the strength of the repetition effects (r = -0.291; p = .090). These findings highlight that higher auditory (and eventually motor) anomalies are associated with a stronger encoding of repetitive auditory stimulation

4. Discussion

Sensory overload has been implicated as a hallmark of ASD. How sensory information and, in particular, redundant information is processed and encoded in ASD is highly important to characterize the pathophysiology of the disorder. Previous studies have demonstrated a major role of sensory cortices in the failure to suppress irrelevant, repetitive stimulation in ASD (Ewbank et al., 2017; Guiraud et al., 2011; Martineau et al., 1992; Millin et al., 2018; Puts, Wodka, Tommerdahl, Mostofsky, & Edden, 2014). Yet, the involvement of the subcortical

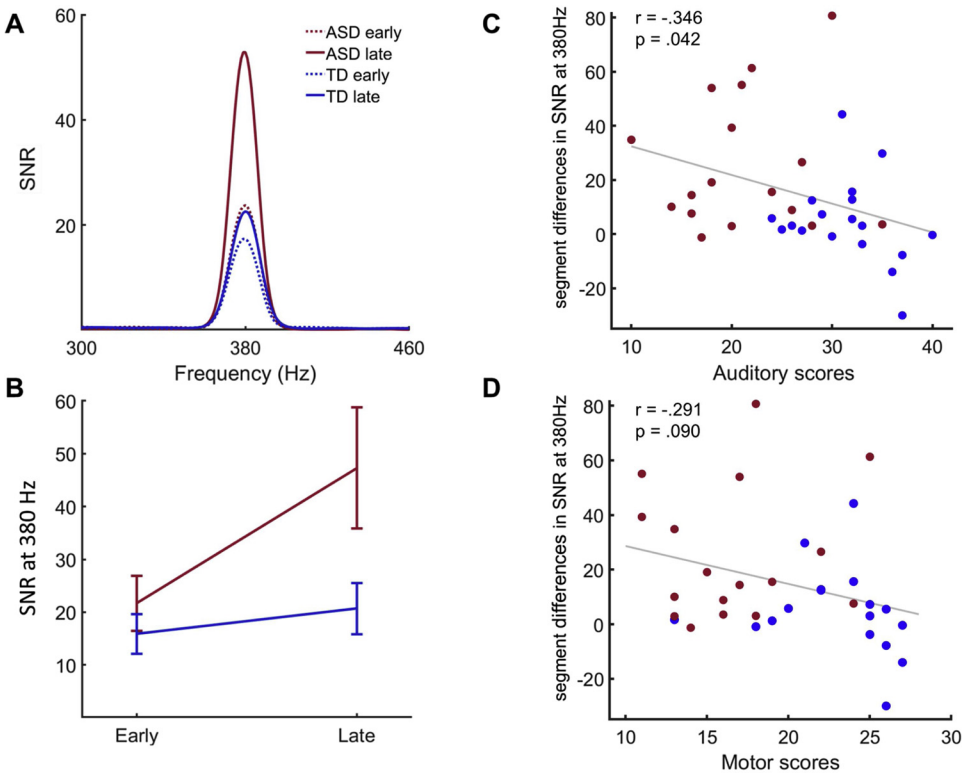

Fig. 3. Repetition effects within each train of sounds and correlations between response variability and auditory and motor scores in the sensory profile test. A) Spectral analysis of the FFR elicited to the two stimulus repetition conditions and groups expressed as SNR. Early SNRs are depicted as dashed lines and late SNRs as solid lines. B) SNR at the 380 Hz AM rate elicited with respect to the segment of the stimulation train. The first segment (stimuli 1–3) corresponds to the early SNR and the last segment (stimuli 7–12) to the late SNR for the TD (blue) and ASD (red) groups. C and D) Correlation between the variation of SNR at 380 Hz with repetition and the auditory responsiveness and motor activity scores obtained from the Sensory Profile, respectively. A positive value in the y-axis reflects an increase of the neural response with repetition, whilst a negative value reflects a decrease. Low values in the x-axis indicate higher auditory (C) or motor (D) anomalies.

auditory system in the pathophysiology of sensory overflow deficits in ASD has not been described so far. Here, we took advantage of the FFR's capability to reflect subcortical auditory encoding (Bidelman, 2018; Chandrasekaran & Kraus, 2010; Skoe & Kraus, 2010) to examine the neurophysiological correlates of subcortical acoustic repetition-related effects in ASD and in TD children. We observed that the neural tracking of the periodic characteristics of auditory stimulation increased with repetition in ASD but not in TD children, whose neural tracking was stable with short-term repetition. Moreover, the SNR increase by repetition correlated with the severity of auditory anomalies and tended towards correlation with lower motor activation. These findings point to atypical neural responses to repetition as one factor underlying aberrant auditory processing in ASD, that are evident even at early stages of the auditory hierarchy.

In line with our results, previous studies have shown that autistic children display increased auditory evoked potential (AEP) amplitudes with repeated auditory stimulation at the cortical level (Martineau et al., 1992). Even infants at high risk of developing ASD showed less habituation to repetitive sounds compared to controls (Guiraud et al., 2011), which might explain the atypical auditory behaviors presented in ASD. This enhancement was also observed with fMRI as a sustained response of the auditory cortex and was suggested to appear only as a result of repeated auditory stimulation (Millin et al., 2018). Research in other sensory domains, such as in vision and touch, has revealed similar altered adaptation to repetition (Ewbank et al., 2017; Puts et al., 2014), favoring the hypothesis of a disturbance in neural responses to repeated auditory stimulation. As per the present results, this altered neural adaptation in ASD seems to be also present at subcortical levels of the auditory system. The findings of the present study and those discussed above are apparently at odds but not necessarily incompatible with the wealth of studies showing reduced auditory evoked potentials in ASD. Indeed, several studies have shown that the characteristic P1 and N1 auditory components are attenuated in children with ASD compared to their typically developing pairs (Bruneau, Roux, Adrien, & Barthelemy, 1999; Gandal et al., 2010; Madsen, Bilenberg, Jepsen, Glenthoj, & Cantio, 2015; Seri, Cerquiglini, Pisani, & Curatolo, 1999; Stroganova et al., 2013). These findings have been suggested to result from a reduced neural recruitment or a defective coordinated activity in the underlying thalamic and cortical generators (Modi & Sahin, 2017), an interpretation that may hold as well for the subcortical lack of suppression observed here. In fact, repetition suppression in subcortical auditory structures may depend on stimulus-specific adaptation, a phenomenon that involves the complex circuitry of the auditory midbrain and thalamus, and eventually the auditory cortex (Malmierca, Carbajal, & Escera, 2018; Parras et al., 2017).

Theories on perception in autism, such as the enhanced perceptual functioning (EPF) (Mottron et al., 2006) or the intense world theory (Markram & Markram, 2010), postulate that the existence of enhanced local neural circuits in primary sensory areas are the cause of enhanced sensitivity to sensory stimulation and sensory overload in autism. In particular, the EPF posits that sensory sensitivities in ASD result from an imbalance between excitatory and inhibitory connections in local neural circuits in sensory networks (Mottron et al., 2006). Based on these accounts, the increase with repetition observed in the present study may be the result of an imbalance between excitatory and inhibitory inputs operating in the inferior colliculus (IC) and other subcortical nuclei.

Interestingly, we observed that the increase of the subcortical FFR power with repetition was related to lower auditory responsiveness scores, reflecting a higher sensitivity to auditory stimulation. Previous studies reported correlations of atypical latency of the magnetic M50 AEP with auditory hypersensitivities in ASD measured using the auditory subcategory of the Sensory Profile (Matsuzaki et al., 2014). However, other studies failed to find such correlations when examining cortical AEPs (Brandwein et al., 2015). Given that individuals with ASD present equally hyper and hyposensitivity in response to sensory stimulation (Rogers & Ozonoff, 2005), a low auditory responsiveness score (Sensory Profile) could reflect either one of them. The reduced adaptation in ASD is speculated to explain both ends of these sensory anomalies. Hypersensitivity would come as a result of an enhanced neural response to repeated sensory information and hyposensitivity as a reduced response to deviants in the auditory environment (Guiraud

et al., 2011). Although our findings should be interpreted with caution, since the Sensory Profile is a parent report measure, we suggest that the study of the subcortical FFR might be used as a biomarker to examine auditory sensitivities in ASD.

In addition to auditory responsiveness, we tested whether the differences in adaptation were related to lower motor scores, which reflect higher motor anomalies related to movement activity that can both indicate more retracted and agitated behaviors. We speculated that the failure to reduce redundant information would be irritating for the autistic child, thus affecting his/her direct overt behavior, eventually inducing "freezing" behaviors that would be reflected in the motor scores. In the same vein, this overloaded information may result in irritative behaviors which would be reflected in the motor scores as well. A previous study linked sensory processing features (Dunn, 1999) to lower participation in social, physical and informal activities in children with ASD (Hochhauser & Engel-Yeger, 2010). It is, thus, plausible that the lack of appropriate filters to reduce repeated auditory information could have an influence on other behavioral and social symptoms related to ASD. In other words, early auditory deficits might propagate to higher levels of the auditory hierarchy, influencing the way stimuli are processed in higher stages (Jääskeläinen, Ahveninen, Belliveau, Raij, & Sams, 2007). Ultimately, these impairments may be affecting the ability to extract temporal regularities in the environment (Millin et al., 2018), build flexible predictions (Lawson, Rees, & Friston, 2014; Van de Cruys et al., 2014), as well as to adapt behavior to unexpected events (Gomot & Wicker, 2012). Future studies should aim to elucidate the relationship between lack of suppression at the subcortical level and motor scores. Nevertheless, as the results of the present study revealed only a tendency, they should be interpreted with caution.

Recently, there has been an interest in explaining autistic perception in terms of predictive coding (Friston, 2005), which posits that every level of the sensory hierarchy receives top-down predictions about incoming (bottom-up) sensory information. In short, statistical regularities extracted from the acoustic input are used as priors to generate predictions of, and be compared to, upcoming sounds, and the difference ("prediction error"), weighted by the precision of the prediction (i.e., how sure I was about what I predicted), is used iteratively to update a generative internal model of the sensorium. In ASD, it has been suggested that sensory overload would be the result of a failure to suppress and contextualize prediction errors, thereby resulting in an increased reliability on sensory input (Lawson et al., 2014). This interpretation is consistent with our findings: in the ASD group, we observed an increase of the neural response with repeated stimulus presentation, whereas in the TD group repeated stimulation led to no further response change. The lack of short-term repetition effects found in the TD group stands in line with the literature on FFR showing that this reduction becomes evident after 200–300 repetitions (Gorina-Careta et al., 2016). Therefore, it seems possible that with the few repetitions used in this study there is no significant change in the stimulus encoding. Compared to the absence of change in the TD group, it is interesting that we found an increased SNR in the ASD children. From a predictive coding perspective, the most plausible explanation for this failure to habituate is that a heightened precision is causing a high reliance on sensory input (Van de Cruys, Van der Hallen, & Wagemans, 2017). Based on this knowledge, the high sensory precision (Lawson et al., 2014; Van de Cruys et al., 2014) renders sensory prediction errors too precise and unaffected by context, which would be leading to a reliance on bottom-up sensory evidence (Friston, Lawson, & Frith, 2013).

Previous research has implicated subcortical structures in regularity encoding (Cacciaglia et al., 2015) and the FFR has been proven as an adequate brain potential to study these processes (Slabu et al., 2012). The FFR has also been used as an index of the tracking accuracy of stimulus' periodic features, which has shown to have functional implications during development in healthy children (Krizman, Marian, Shook, Skoe, & Kraus, 2012; Krizman, Skoe, Marian, & Kraus, 2014), as well as in children with neurodevelopmental disorders (Chandrasekaran et al., 2009). Aberrant subcortical encoding of variable pitch features has been observed in individuals with ASD when presenting speech syllables (Russo et al., 2008). The authors showed that 20% of children with ASD exhibited aberrant tracking of variable pitch contours in speech syllables as compared to controls. A subsequent study showed that children with ASD exhibited less efficient subcortical encoding of speech syllables in quiet and in noise as compared to controls (Russo et al., 2009). In the same line, a recent study found that the FFR elicited to multiple speech sounds of children with ASD was less stable across trials compared to their matched controls (Otto-Meyer et al., 2018). We observed that children with ASD showed a higher SNR as compared to TD children, thus reflecting a stronger encoding of the AM rate. This frequency, 380 Hz, is probably well above the limits of cortical tracking, which ensures that the response is of subcortical origin (Bidelman, 2018). Our findings are in line with the general view that there is an enhancement of low-level information processing in ASD (Bertone, Mottron, Jelenic, & Faubert, 2005), as opposed to a deficient processing of spectrally and temporally complex stimuli. Given that the FFR is unreliable across trials (Otto-Meyer et al., 2018), this enhancement could be explained by an over activation of the local neural circuits, in line with what the EFP (Mottron et al., 2006) and Intense World Theory (Markram & Markram, 2010) postulate. In summary, there are fundamental differences in the way simple versus complex stimuli are encoded in ASD, which are also affected by the context in which they are presented. Investigating repetition-related effects to complex auditory stimuli at low levels of the auditory hierarchy might shed further light into how complex stimuli are encoded and into the mechanisms involved in language acquisition in children with ASD.

Regarding the limitations of this study, we have previously mentioned that the present results should be interpreted with caution given the small sample size and significance power, especially regarding the correlations with the auditory and motor scores. Additionally, we must consider the limitations of using a parent report measure to quantify sensory overload and motor activity. The Sensory Profile was the most commonly used scale in research of sensory processing at the time this experiment started. Nevertheless, parents tend to over- or under estimate their children's disorder, sometimes in favor of the symptoms that they believe their child should present (Dahlgren & Gillberg, 1989). Therefore, future studies, with an increased sample size and a more reliable measure of auditory and motor impairments, would be needed to provide further evidence the present conclusions.

In conclusion, our findings indicate that the atypical mechanisms of repetition-related modulations that have been reported to occur at cortical stations of auditory processing are also present at a subcortical level. Anomalies in sensory processing have often been considered as one of the main sensory processing impairments in ASD (Ludlow et al., 2014), and have been described as an early sign of autism during the first months of life (Sacrey et al., 2015). By studying repetition effects to different types of auditory stimuli, one might be able to understand the mechanisms underlying the encoding of auditory regularities, needed to create a proper representation of the auditory environment. FFR might prove as a useful electrophysiological marker to test auditory sensory processing in ASD in the subcortical auditory system, and it may provide a putative candidate endophenotype to characterize sensory overload in these individuals.

Declaration of Competing Interest

The authors declare no competing financial interests

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