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Social-emotional processing in nonverbal individuals with Angelman syndrome: Evidence from brain responses to known and novel names.

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Abstract

Background.—The combination of intellectual, communicative, and motor deficits limit the use of standardised behavioural assessments in individuals with Angelman syndrome (AS). The current study aimed to objectively evaluate the extent of social-emotional processing in AS using auditory event-related potentials (ERP) during passive exposure to spoken stimuli.

Method.—Auditory ERP responses were recorded in 13 nonverbal individuals with the deletion subtype of AS, age 4–45 years, during the name recognition paradigm, in which their own names and names of close others (relative, friend) were presented among novel names. No behavioural responses were required.

Results.—Contrary to findings in typical children and adults, there was no significant evidence of differential neural response to known vs. novel names in participants with AS. Nevertheless, greater amplitude differences between own and unknown names demonstrated the predicted association with better interpersonal relationships and receptive communication abilities.

Conclusions.—These findings indicate good tolerability of ERP procedures (85% success rate). The lack of own name differentiation is consistent with increased incidence of the autism-related symptoms in AS. Strong associations between the caregiver reports of adaptive functioning and neural indices of known name recognition support the utility of brain-based measures for objectively evaluating cognitive and affective processes in nonverbal persons with neurodevelopmental disorders.

Keywords

Angelman syndrome; auditory; event-related potential; name; nonverbal; social

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Conflict of Interest

There are no conflicts to declare.

Angelman syndrome (AS) is a rare neurodevelopmental disorder occurring in 1:10,000–20,000 births (Buckley et al., 1998; Petersen et al., 1995; Williams, 2010; Clayton-Smith & Pembrey, 1992; Steffenburg et al., 1996). It is caused by loss of function of the ubiquitin–protein ligase E3A (*UBE3A*) gene, typically expressed on the maternal chromosome 15 (Kishino et al., 1997; Buiting, 2010, 2016). The most common genetic mechanism of AS is deletion of the 15q11–13 region, occurring in up to 75% of the cases (Nicholls, 1994), while paternal uniparental disomy, imprinting defects, and *UBE3A* mutations are more rare (Williams et al., 2006).

When evaluated using standardised measures of cognitive and adaptive functioning, individuals with AS typically score in the range of severe functional impairment (Andersen et al., 2001; Peters et al., 2004a, 2012; Thompson & Bolton, 2003). Behavioural characteristics of AS include generally happy demeanor, frequent laughter, hyperactivity, and motor stereotypies (Williams et al., 2006; Williams, 2010). Most persons with AS exhibit communication difficulties due to lack of speech (Jolleff & Ryan 1993), social deficits (Penner et al., 1993), and many meet the diagnostic criteria for autism (Trillingsgaard & Ostergaard, 2004; Peters et al., 2004b; Hogart et al., 2010).

Detailed categorisation of the cognitive and social AS phenotype has been challenging due to the combination of intellectual, communication, and motor deficits that reduce feasibility of standardised behavioural assessments (Bird, 2014). To address the need for more sensitive measures, novel approaches are beginning to emerge, such as the quantification of communicative behaviours from recorded play sessions (Grieco et al., 2016) or social eye tracking and pupillometry metrics (Hong et al., 2017). Measures of electrical brain activity may offer another way to assess social information processing in AS. To date, electroencephalography (EEG) studies in AS noted distinct patterns of delta-band activity (Vendrame et al., 2012) that were also observed in animal models of AS (Sidorov et al., 2017). However, the connection between these EEG characteristics and behavioural or cognitive features of AS is currently unknown. Event-related potentials (ERPs), or stimulus-locked EEG, can be used to evaluate multiple stages of information processing, and therefore may yield more detailed information about social-emotional processes in AS.

Based on the existing evidence that visual attention span in AS may be limited (e.g., Hong et al., 2017), we focused on the auditory modality. Efficient auditory processing of spoken stimuli is important for adaptive communication and social functioning. Additionally, auditory stimuli place minimal attentional demands on the participants (a sound presented above the perceptual threshold will be heard even if a person is not actively attending), and passive listening paradigms avoid many confounds associated with comprehension of and cooperation with the task instructions.

Selecting the optimal auditory stimuli that would elicit the desired cognitive processes and associated neural activity can be challenging, especially when participants have intellectual disabilities. Names are among the developmentally earliest recognisable and most frequently occurring spoken stimuli (Holeckova et al., 2006, 2008) that are used to initiate, maintain, or terminate social interactions. Furthermore, own names are known for their attention-grabbing characteristics, have comparable significance across all participants (Holeckova et

al., 2008; Tamura et al., 2015), and therefore offer an effective means to assess social-emotional functioning (e.g., Baranek, 1999; Yurmiya et al., 2006; Zwaigenbaum et al., 2005).

Response to one's own name develops early in life. Infants as young as 4 months prefer to listen to their own rather than other names (Mandel et al., 1995). By adulthood, own names elicit a highly preferential neural response even without explicit instructions to attend (e.g., Eichenlaub et al., 2012), including in subjects with altered states of consciousness (e.g., asleep: Perrin et al., 1999; brain damage: Perrin et al., 2006; Laureys et al., 2007; Wang et al., 2015). Conversely, a lack of consistent response to own name has been reported in individuals with developmental disabilities and social difficulties (e.g., autism: Nadig et al., 2007, Cygan et al., 2014; severe intellectual disability: Tamura et al., 2015). Thus, spoken names are an optimal stimulus for examining social-emotional processing across the lifespan and range of functioning in AS.

Prior ERP studies examining response to spoken names in typical adults revealed that own name detection is most consistently reflected in the increased parietal amplitudes starting at 350 ms after stimulus onset (Tadikowski et al., 2013; Eichenlaub et al., 2012). This response overlaps in time and topography with several ERP components, including the P300, known to be sensitive to the attentional and memory demands (Polich, 2007), the late positive potential (LPP), reflecting affective processing (Hajcak et al., 2010; Sabatinelli et al., 2013), and posterior old/new effect (Rugg & Curran, 2007), associated with stimulus recognition and recall.

Recently, we demonstrated that the established adult pattern of increased parietal responses to personally relevant compared to novel names is also present in typically developing children between the ages of 4–12 years (Key et al., 2016). In that study, auditory ERPs recorded during passive listening successfully differentiated own and close other's names (e.g., best friend, sibling) from unknown names within 450–750ms after stimulus onset. Furthermore, using the same paradigm in nonverbal children with *MECP2* duplication and Rett syndrome (Peters et al., 2017), we established that auditory ERP responses to own vs. novel names can be used to evaluate social-emotional information processing in persons with atypical development. The *MECP2* duplication group demonstrated the increased parietal responses to own name previously observed in typically developing participants. Conversely, participants with Rett syndrome discriminated names of close others, but not own names, from novel distractors. Increased ERP amplitudes in response to own vs. novel names were associated with caregiver reports (e.g., Aberrant Behavior Checklist scores) of lower irritability and hyperactivity in children with *MECP2* duplication, while increased irritability was noted in girls with Rett syndrome. Importantly, in the typically developing population (Key et al., 2016) and in those with developmental disabilities (Peters et al., 2017), the social-emotional processing assessed by the ERPs was unrelated to cognitive abilities. This pattern of correlations between the ERP markers of name differentiation and the behavioural characteristics in typical and atypical populations further supports the idea that ERPs can be a valid direct measure of social-emotional processes previously assessed primarily using indirect, informant-based tools.

The goal of the current study was to examine response to own and novel names in nonverbal persons with AS using auditory ERPs. Specifically, we predicted that ERPs will be feasible in unsedated persons with AS, because modern EEG acquisition systems allow for fast and noninvasive electrode application, and these data are more tolerant of movement compared to other neuroimaging techniques. Contrasting a common auditory stimulus (own name) that participants are exposed to on a daily basis with a set of novel names allowed us to assess spontaneous auditory attention to and processing of complex, socially relevant information. In the current study, we targeted recognition of personally significant information (own name and that of a close other) among irrelevant distractors. Based on our prior work in typical and atypical populations (Key et al., 2016; Peters et al., 2017), we hypothesised that participants with AS whose caregivers report higher levels of social and communicative functioning will demonstrate greater parietal amplitudes in response to known than unknown names within 450–750ms.

Method

Participants

Thirteen individuals with the deletion subtype of AS participated in the study, but data for two individuals were excluded due to insufficient number of artifact-free trials (fewer than 5 trials per condition). Thus, the final sample included 11 participants (four females; M age = 15.11 years, SD = 11.82 years, range 4–45 years). Due to the level of intellectual and motor disability, IQ or handedness could not be directly and reliably assessed using standardised behavioural measures. Parents/guardians of all participants provided written informed consent and remained present throughout the test session to help identify any dissenting behaviours. The study was conducted with approval from the Institutional Review Board of Vanderbilt University Medical Center.

Behavioural and electrophysiological assessments

Measures of adaptive functioning—Caregivers completed the Parent/Caregiver Rating Form of the Vineland Adaptive Behavior Scales-3 (VABS-3; Sparrow et al., 2016). The domains of Communication and Socialization were selected a priori because they measure the strongest areas of functioning in AS and are also most likely to be related to social-emotional processing skills. These domains yield standardised scores with a mean of 100 and a standard deviation of 15. The scores can also be interpreted in the terms of age equivalence.

Names task—The task used the same stimuli and procedures as Key et al. (2016) and Peters et al. (2017). The preferred version of the participant's first name (e.g., "Billy" for "William"), his/her close other (e.g., sibling, friend), and unknown stranger names served as the stimuli. All names were one to four syllables long. There were no significant length differences among the conditions: participants' own names ($M=2.06$, $SD=.72$), close other ($M=2.10$, $SD=.70$), strangers ($M=2.09$, $SD=.63$). Each participant's caregiver reviewed the list of possible stranger names prior to the test session and identified all potentially known names (e.g., neighbors, classmates). These names were excluded from the test run.

The stimuli were recorded by an adult female native English speaker unfamiliar to the participants and spoken with a friendly intonation, digitized at 44,100 Hz, and equalised in loudness. Although several prior studies suggested that own names spoken by a familiar voice may elicit more pronounced brain responses (e.g., Holekova et al., 2006; del Giudice et al., 2014), the use of the same unknown adult speaker across all participants reduced the possibility of confounds due to differences in personal experience with the speaker.

Participant's own name and the name of the close other were presented 32 times each. To control for potential within-session learning effects due to repeated exposures, one stranger name (selected by the caregiver from the unknown set) was also presented 32 times. The three repeated names were interspersed among 96 unique names of strangers (randomly selected from a list of 160+ possible options). Thus, the repeated- and single-presentation names were delivered equally often within a test session. The entire task included 192 trials and lasted approximately 12 minutes. The interstimulus interval varied randomly between 1800–2800 ms to prevent habituation to stimulus onset.

ERP Data Acquisition

All testing was completed during a single visit. A high-density array of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net; EGI, Inc., Eugene, OR) was used to record the ERPs. Electrode impedance levels were at or below 50 kOhm. During testing, data were sampled at 250Hz with the filters set to .1–100 Hz. All electrodes were referred to vertex and then re-referenced offline to an average reference, the recommended reference for high-density arrays (Picton et al., 2000).

Stimulus presentation was controlled by E-prime (v.2.0, PST, Inc., Pittsburgh, PA). The auditory stimuli were delivered at 75 dB SPL from a speaker positioned behind the participant. In accordance with the passive listening design, the participants were informed that they would “hear the computer say some words,” but no explicit attention or behavioural responses were required. A parent/guardian and a researcher were present in the testing room to monitor participants' behaviour. Participants were tested while seated independently or in the parent's lap and were allowed continuous access to their preferred comfort or entertainment items (e.g., sippy cups, snacks, toys, etc.). A TV show presented without sound served as the visual distractor. If participants became excessively restless, stimulus presentation was suspended until the source of motor artifacts was addressed.

Data Analyses

Following the established procedures (Key et al., 2016; Peters et al., 2017), continuous EEG signals were filtered offline using a 30Hz low-pass filter, segmented on stimulus onset to include a 100ms prestimulus baseline and a 900ms post-stimulus interval, and screened for ocular and movement artifacts using an automated algorithm in NetStation 5.3 (EGI, Inc., Eugene, OR) followed by a manual review. Any channel with voltage exceeding 200 μ V was marked as bad. Data for electrodes with poor signal quality within a trial were reconstructed using spherical spline interpolation procedures. Trials with motor artifacts or containing more than 15 electrodes with poor signal quality were excluded from analysis.

Following artifact screening, individual ERPs for each stimulus category were averaged, re-referenced to an average reference, and baseline-corrected by subtracting the average microvolt value across the 100ms prestimulus interval from the post-stimulus segment. Data from the electrodes corresponding to midline frontal, central, and parietal regions (Figure 1) were used in the remaining statistical analyses. Averaging data over several spatially contiguous locations improved signal-to-noise ratio.

Mean ERP amplitudes were derived for the 450–750ms window. The specific time interval was selected a priori based on temporal windows identified in previously published ERP studies of own name processing (e.g., Key et al, 2016; Peters et al., 2017; Tacikowski et al., 2014), and confirmed by visual inspection of the grand-averaged waveforms. To account for potential variability in scalp topography previously observed in some individuals with developmental disabilities (Peters et al., 2017), frontal and central scalp locations were considered for analysis in addition to the hypothesised differences at the parietal sites. The resulting values were entered into a repeated-measures ANOVA with Name (4: own, close other, stranger repeated, unknown) $\times$ Electrode Cluster (3: frontal, central, parietal) as within-subject factors with Huynh-Feldt correction, and Age as a covariate. Planned comparisons and post-hoc pairwise two-tailed t-tests with Bonferroni correction were used to examine name differentiation at parietal scalp locations. Brain-behaviour interactions were examined using correlations between the caregiver reports of communication and socialization abilities and ERP indices of name discrimination (own or close other vs. repeated stranger and unknown names).

Results

Caregiver reports of adaptive functioning

Families of two participants did not return the VABS-3 questionnaires. The remaining 9 participants achieved higher standard scores for the socialization than communication domain, 36.33 vs. 22.44, $t(8)=3.441$, $p=.009$, $d=1.15$, although on average, their scores fell in the severely affected range (see Table 1 for detailed sample categorisation).

ERP responses to names

Eleven of 13 subjects (85%) provided usable ERP data. The trial retention rates were comparable to those observed in prior studies using the same paradigm (Key et al., 2016; Peters et al., 2017) and not significantly different across the three repeated names (own name: $M=12.91$, $SD=6.22$; close other: $M=12.55$, $SD=6.04$; repeated stranger: $M=12.00$, $SD=5.08$; $p's=.41-.67$). The novel names condition had slightly fewer trials than the sum of all repeated trials ($M=31.09$, $SD=13.34$, and $M=37.45$, $SD=16.62$, respectively; two-tailed paired $t(10)=3.369$, $p=.007$).

The ANOVA resulted in no significant main effects or interactions indicative of name discrimination in the 450–750 ms window (Figure 2), even though the main effect of Name type was associated with a medium effect size ($\eta_p^2=.118$; $F(3,27)=1.208$, $p=.326$). Planned comparisons at the parietal scalp region also failed to reach significance, with effect sizes not exceeding .2. However, better discrimination of the repeated stranger name from the

unknown names (quantified as a more positive difference wave) at the parietal cluster was associated with higher adaptive functioning in communication and socialization domains, $r(8)=.866$, $p=.003$ and $r(8)=.848$, $p=.004$, respectively. Correlations with the age equivalence scores for interpersonal relationships or receptive communication subdomains were not significant.

Exploratory analyses at the frontal and central sites suggested that ERP indices of own name recognition (more positive amplitudes compared to the repeated stranger name) at central scalp locations were associated with higher age equivalence scores for interpersonal relationships, $r(8)=.831$, $p=.006$, and receptive communication, $r(8)=.818$, $p=.007$. Correlations with the standard scores for socialization and communication domains failed to reach significance after correction for multiple testing. The amplitudes of brain responses to names also did not correlate with age.

Discussion

The purpose of this project was to evaluate social-emotional functioning in nonverbal individuals with AS using auditory ERPs in response to known and unknown names. Our results revealed that the evidence for spontaneous recognition of familiar names among repeated and novel distracters was less clear than expected, although the predicted patterns of brain-behaviour correlations were observed.

It is important to note that the passive auditory ERP paradigms in combination with a soft electrode array placed minimal demands on participants' cooperation, and therefore we observed low attrition due to poor data quality: 85% (11/13) of subjects provided usable data for the 12-minute name recognition task. For comparison, only 47% (8/17) yielded sufficient data in a 60-second social eye tracking and pupillometry paradigm (Hong et al., 2017). The difference in success rate is most likely due to the stimulus modality: visual tasks require higher levels of behavioural cooperation (e.g., looking at the screen) compared to the auditory paradigms, in which audible stimuli will be processed in the brain even if attention is not explicitly directed toward them. Also, the number of artifact-free ERP trials in participants with AS was comparable to that previously observed using the same paradigm in children with typical and atypical development between 4–12 years of age (Key et al., 2016; Peters et al., 2017), suggesting that social information processing rather than data quality likely explain the observed findings.

Contrary to the expectations, we observed no significant evidence of differentiating own and close other names from stranger names, potentially due to high inter-individual variability among participants with AS. Qualitative review of the data suggested that recognition of own names may increase with age, but our small sample size was not sufficient to detect such an interaction. Of note, similar lack of name discrimination was recently reported in Rett syndrome (Peters et al., 2017), which shares many phenotypic features with AS (Jedele, 2007). Relevant to this study, both syndromes exhibit autism-related symptoms, including deficits in social communication (Penner et al., 1993; Peters et al., 2004; Bonati et al., 2007), and individuals with autism as well as infants at risk for developmental delays are known to

show diminished spontaneous orienting to own name (Dawson et al, 1998; Nadig et al., 2007).

Alternatively, it is possible that our paradigm, which included 64 distinct novel names as well as two known and one unknown repeated names, was too complex for participants with AS. This design allowed to control for the long-term social relevance (known vs. novel names) and within-session familiarisation effects (repeated stranger vs. known names). Previously, it successfully elicited adult-like ERP indices of own name recognition in typically developing children and in nonverbal participants with *MECP2* duplication from four years of age (Key et al., 2016; Peters et al., 2017). However, cognitive and adaptive functioning of individuals with AS, regardless of their actual chronological age, may be closer to that of two-year-olds or even younger, as reported by previous studies using a variety of standardised assessments (e.g., Andersen et al., 2001; Duker et al., 2002; Peters et al., 2004a) and further reflected by the VABS-3 age equivalence scores in our study. In typically developing young infants, the use of multiple unknown names instead of the single stranger comparison resulted in the loss of the significant ERP amplitude differences in response to subject's own name (Parise et al., 2010). In our study, greater differentiation of own name from the repeated stranger's (i.e., own vs. a single novel name contrast) was observed in participants with AS characterised by more adaptive interpersonal relationships and receptive communication abilities (i.e., higher age equivalence scores). These findings support the explanation that the more typical ERP responses to own name expected based on the chronological age were not detected in the participants with AS because of their younger developmental level.

While the differences between name types did not reach significance, the observed brain-behaviour associations were in the predicted direction and indicated that better own name recognition (more positive amplitudes to own than novel names) was related to more adaptive social and communicative functioning. Previous research in typical development indicated that recognition of own name is important for language learning (e.g., Bortfeld et al., 2005), communicative development (Csibra, 2010), and can facilitate engagement with the environment by guiding attention to relevant events (Parise et al., 2010). Consequently, future interventions aimed at improving communication abilities in persons with AS may want to consider responses to own name as one of the early treatment targets.

The evidence of higher standard scores in VABS-3 communication and socialization domains for participants with AS who demonstrated greater discrimination of the repeated stranger name from the unknown names replicated and extended our previous findings from the auditory incidental memory paradigm reflecting successful within-session familiarisation with novel stimuli (Key et al., in press). Together, these results suggest the possibility of increased spontaneous attention to novel (vs. well-known and socially relevant) auditory stimuli in AS, which will need to be explored in greater detail in future studies. Earlier, we reported a similar pattern of increased attention to voices of strangers vs. mothers in girls with Rett syndrome (Peters et al., 2015).

Our results also highlighted the attention span and endurance limitations that should be taken into account when designing assessments for AS. Even though EEG/ERP measures

are relatively tolerant of movement, motor artifacts were a frequent concern in our study sample. The majority of the participants with AS, particularly the adolescents and young adults, found the need to sit relatively still to be the most challenging part of the testing experience. Thus, future studies will need to carefully plan the length of the testing session and explore more effective management of motor artifacts through the use of seating options that offer both comfort and upper body support.

While reporting novel findings, this study has several limitations. First, our sample included only individuals with the deletion subtype of AS, the most common as well as the most severely affected. Future studies will need to examine whether similar or different results would be observed in persons with the uniparental disomy, imprinting deficits, or *UBE3A* mutations. We predict that the described procedures will be feasible regardless of the specific genetic subtype. Second, while average for a study of higher-order processes in a rare genetic disorder (e.g., 8 subjects in Hong et al., 2017; 9 in Grieco et al., 2016), the number of participants was small, which limited statistical power to detect medium or small effect sizes. However, the attrition rates due to poor data quality were relatively low and comparable to those reported in other typical and atypical populations of similar chronological age. It is also possible that our criterion for data inclusion was too lenient. Of note, our ERP response of interest overlapped in time, topography, and functional interpretation with the late positive potential, a robust response that achieves high reliability with as few as eight trials (Moran et al., 2013). Excluding four subjects who contributed less than 10 artifact-free trials per condition did not yield new evidence of known name differentiation, and there were no significant correlations between the number of retained trials and ERP amplitudes (see also Moran et al., 2013 for evidence that late positive potential amplitudes within 400–700ms are not statistically different when averaged across two to 16 trials). Related to the sample size concern, the magnitude of the observed correlations should be interpreted with caution until further replication, because extreme values are more likely to be observed in smaller samples. Nevertheless, the presence of any significant correlations in the current study highlights the strength of these results. Finally, our participants represented a wide age range, from young children to adults. Previously published studies suggest that passive measures of name recognition yield comparable data in children (Key et al., 2016) and adults (Tacikowski et al., 2014), and we observed no significant correlations with age. However, little is known about the trajectory of social-emotional development over the lifespan in AS, and future studies in this population will need to examine possible age-related differences in greater detail.

In conclusion, our results demonstrate that measuring cortical brain responses associated with higher-order information processing, such as known name recognition, in nonverbal children and adults with AS is possible and can provide objective information complementary to the caregiver reports of adaptive social and communicative functioning. Additionally, unlike the standardised behavioural assessments, many of which were not designed for use in persons with intellectual and developmental disabilities, ERPs recorded during passive stimulus exposure paradigms offer a direct way to capture individual differences in persons with AS and other neurodevelopmental disorders. Without the requirement of motor or verbal responses, the use of salient and ecologically valid auditory stimuli during brief test sessions made the procedures suitable for a wide range of ages and

ability levels, positioning ERP responses to serve as a potentially more sensitive marker of outcomes in future treatment studies targeting social-emotional and communicative skills.

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Figure 1.
Electrode layout of the 128-channel geodesic net (EGI, Inc.) and the frontal, central, and parietal midline clusters used in data analysis.

Figure 2. Averaged ERP waveforms and mean amplitudes (450–750ms) in response to four name types at Fz, Cz, and Pz scalp locations. Rectangular marquees identify time windows used in the analysis.

Table 1.

Caregiver categorisation of communicative and social skills in participants with Angelman syndrome (n=9) according to Vineland Adaptive Behavior Scales-3.

Domain/Subdomain	Score	M	SD	Range
Communication	Standard	22.44	4.88	20–32
Receptive	Raw	35.56	17.05	13–60
	Age Equivalence (mo)	18.11	8.34	9–33
Expressive	Raw	15.78	8.06	6–30
	Age Equivalence (mo)	10.11	5.90	2–19
Written	Raw	6.56	5.66	0–16
	Age Equivalence (mo)	27.67	18.65	0–52
Socialization	Standard	36.33	16.00	20–71
Interpersonal Relationships	Raw	30.67	9.08	17–45
	Age Equivalence (mo)	14.78	7.53	4–27
Play and Leisure	Raw	18.22	9.02	4–30
	Age Equivalence (mo)	16.33	8.37	2–27
Coping skills	Raw	17.56	7.40	8–28
	Age Equivalence (mo)	17.22	7.93	12–30