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Induced gamma oscillations differentiate familiar and novel voices in children with *MECP2* Duplication and Rett syndromes

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Abstract

Normal levels of the methyl CpG binding protein 2 (MeCP2) are critical to neurological functioning, and slight alterations result in intellectual disability and autistic features. It was hypothesized that children with *MECP2* duplication (overexpression of MeCP2) and Rett syndrome (underexpression of MeCP2) would exhibit distinct electroencephalographic indices of auditory stimulus discrimination. In this study, gamma-band oscillatory responses to familiar and novel voices were examined and related to social functioning in 17 children (3-11 years old) with *MECP2* duplication (n=12) and Rett syndrome (n=5). Relative to the stranger's voice, gamma activity in response to the mother's voice was increased in *MECP2* duplication but decreased in Rett syndrome. In *MECP2* duplication, greater mother vs. stranger differences in gamma activity were associated with higher social functioning. For the first time, brain responses in a passive voice discrimination paradigm show that overexpression and underexpression of MeCP2 have differential effects on cortical information processing.

Keywords

MECP2; gamma; electroencephalography; Rett

Introduction

Duplications of Xq28 underlie *MECP2* Duplication syndrome, a severe, X-linked neurodevelopmental disorder characterized by intellectual disability, seizures, absent speech, autistic features, and increased susceptibility to infections^{1, 2}. *MECP2* duplication syndrome

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Author Contributions: SUP developed the study idea, was responsible for patient enrollment and assessed all patients clinically, conducted data analyses, and wrote the draft of the article. The voice discrimination task was designed by RLG and APK. RLG implemented the task, carried out analysis and interpretation of EEG data, and edited the manuscript. APK contributed to data collection and interpretation of EEG results, and edited the manuscript.

Ethical approval: This study was approved by the Institutional Review Board of Vanderbilt University and all parents gave consent for their children to participate.

primarily affects males³, although some female cases are now being reported⁴. Mutations in the methyl CpG-binding protein 2 gene (*MECP2*) were first identified as a primary cause of Rett syndrome in females, and in spite of some overlapping phenotypic features, our initial studies reveal that *MECP2* duplication syndrome is distinct from Rett in terms of developmental course and symptom presentation². While Rett is associated with underexpression of the protein product (MeCP2), duplications of *MECP2* result in its overexpression^{5, 6}. Several studies in animal models and humans have shown that the MeCP2 protein is critical for normal neurological functioning⁷⁻⁹, and that even the slightest alterations (50% in either direction) can result in a broad range of phenotypes that include motor defects, stereotypies, seizures, anxiety, recurrent illnesses, and/or regression¹⁰.

MeCP2 overexpression results in increased dendritic spine density, and synaptic dysfunction with increase in glutamateric synapses, while underexpression has opposite effects (reduced spine density)^{11, 12}. Recent work also suggests that the overexpression of MeCP2 suppresses the expression of synaptic genes, resulting in an excitatory/inhibitory imbalance such that spontaneous excitatory transmission is augmented but the probability of evoked release is decreased⁶. Excitation/inhibition processes are associated with arousal as well as memory and other cognitive functions^{13, 14}. Yet, the functional correlates of an excitatory/inhibitory imbalance have been understudied in *MECP2* duplication as well as in Rett syndrome. Given the motor and language deficits associated with *MECP2* duplication syndrome and Rett, it can be challenging to use more traditional behavioral assessments to capture processing of sensory stimuli. The use of non-invasive methodologies such as electroencephalography (EEG) offers an opportunity to evaluate various stages of stimulus processing without an overt behavioral response by the participant. Examination of the resulting neurophysiological markers, such as altered patterns of gamma oscillations, may therefore provide important insights into pathophysiology and disease progression and serve as important markers of treatment response and/or outcome measures.

Recent publications on both humans with Rett syndrome and relevant animal models have demonstrated brainstem auditory evoked potential abnormalities¹⁵, and EEG studies in Rett mouse models reveal delayed latency of the P2 component and reduced reactivity of induced gamma-band oscillations in response to repeated auditory stimulus presentations¹⁵⁻¹⁷. Our previous studies reveal that individuals with *MECP2* duplication syndrome also do not respond in a typical manner to sensory stimuli¹, but very little is known about their cortical/sensory processing. In the current study, we focused on gamma-band oscillatory activity, since abnormalities in gamma activity are thought to reflect deficits in excitatory-inhibitory balance, and are associated with coordination of neural activity^{15, 18} and support of higher-order cognitive processes such as attention and memory, including acoustic/auditory object representation^{19, 20}.

To investigate the effects of altered MeCP2 protein expression on auditory stimulus discrimination and processing, we conducted a proof-of-concept electroencephalography study of gamma-band activity using a passive, non-invasive paradigm to examine discrimination of familiar and unfamiliar voices independently of IQ. Previous studies using similar methodology have shown that even shortly after birth (as early as the first day of life outside the womb), typical infants process their mother's voice versus stranger's voice

differently²¹. Familiar versus novel voice discrimination ability is important for the development of social interactions²¹⁻²³. Atypical responses to auditory stimuli in infancy are predictive of a later diagnosis of an autism spectrum disorder²⁴, and atypical response to human voices has been found in populations of individuals with autism^{25, 26}. Although individuals with Rett and *MECP2* duplication syndromes have phenotypic similarities, those with *MECP2* duplication syndrome have more features of autism¹. Animal models of *MECP2* duplication syndrome further substantiate this aspect of the phenotype²⁷. Recently, several studies have reported irregular gamma modulation in response to auditory stimuli for both children and adults with autism¹⁶, but these responses have yet to be examined in humans with *MECP2* duplication or Rett syndrome. As such, we hypothesized that individuals with Rett and *MECP2* duplication syndrome would show different patterns of brain responses to familiar and novel auditory stimuli, and that the extent of stimulus discrimination may be correlated with clinical measures related to socialization.

Methods

Participants

This proof-of-concept study population was comprised of 12 boys between the ages of 3-11 years with a diagnosis of *MECP2* duplication syndrome and 5 girls with Rett syndrome between the ages of 3-11 years (Table 1). The participants with *MECP2* duplication syndrome were all male, and had a confirmed genetic diagnosis. All participants were ascertained and tested during their attendance at the inaugural worldwide conference on *MECP2* duplication syndrome. The participants with Rett syndrome were all female, were all beyond the phase of regression, had a confirmed mutation in *MECP2*, and were tested during their visit to the university lab. Three additional boys with *MECP2* duplication syndrome and one additional girl with Rett syndrome were enrolled but did not provide usable electroencephalographic data. The study was approved by the Institutional Review Board of Vanderbilt University, and all parents gave informed consent for their child's participation.

Stimuli

Auditory stimuli included digitized recordings of the word “hi” spoken by the child's mother (all of whom were the primary caregivers) and two female strangers (one stranger voice was constant, the other varied across the participants so that the mother of one child served as the stranger for another). The mother's voice was recorded prior to the start of the experiment using a USB microphone (MXL studio 1) and Praat software²⁸. All stimuli were equated in intensity, but because they were natural speech, they varied in length (Mother's voice/ Stranger varied: M=432 ms, SD=179 ms; Stranger constant: 364 ms).

Procedure

Participants were tested individually while seated alone (either in a chair, wheelchair, or stroller) or in a parent's lap in a quiet testing room. Auditory stimuli were presented using E-prime software (v. 2.0, PST, Inc., Pittsburgh, PA) using an equiprobable design, with a variable inter-stimulus interval of 650-1250ms. Sixty trials of each condition were presented in a random order at intensity levels of 75 dB SPL(A) through a speaker positioned above

(Rett) or in front (*MECP2* duplication) of the child. A silent children's movie was shown during electrode placement and throughout the experiment. This was a passive task, with no overt response required from participants. No additional stimuli were presented during the inter-stimulus period.

Electroencephalogram was recorded using a high-density array of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net, EGI, Inc., Eugene, OR, USA) connected to a high-impedance amplifier. Data were collected at 500 Hz with a 0.1-200 Hz filter and all electrodes referenced to vertex. Prior to the recording, impedance was adjusted to below 40 kOhm and then re-checked after the test session.

Data preprocessing—During preprocessing, data were bandpass-filtered at 0.5 to 55 Hz, and re-referenced to an average reference. Electroencephalogram was epoched separately for the three conditions: mother's voice, stranger's voice (constant), stranger's voice (varied), from 500 ms before stimulus onset to 1200 ms post. The long epochs were required for wavelet analyses (see Time-Frequency Analysis below). Trials with ocular artifacts or other movement were excluded from analysis using an automated NetStation screening algorithm and verified using manual review. To further reduce error variance, data from the 17 perimeter channels of the sensor net were excluded due to their high susceptibility to movement artifacts. The remaining 111 scalp electrodes were used in the time-frequency analysis. Trial retention rates were comparable across conditions (mother's voice: $M=24.5$, $SD=4.6$; stranger voice (varied): $M=26.2$, $SD=4.8$; stranger voice (constant): $M=26.3$, $SD=5.3$).

Time-Frequency Analyses: Wavelet-based time-frequency decomposition was conducted from 26 to 50 Hz for gamma power, using the open-source Fieldtrip Toolbox (<http://www.ru.nl/neuroimaging/fieldtrip>)²⁹. We selected this particular frequency range because stimulus-induced responses to auditory/sensory stimuli tend to have the greatest power close to the 40 Hz range²⁰. This is also the range where altered auditory responses were previously found in children with autism and their first degree relatives¹⁶. Induced (phase-invariant) time-frequency representations were computed by convolving single trial data with a Morlet wavelet with a width of five cycles, resulting in a frequency resolution with a standard deviation (SD) of $f/5$ and a temporal resolution with SD of $1/(f/5)$. Wavelet analysis offers an ideal trade-off between frequency resolution and temporal resolution, and is considered a biologically plausible method of conducting time-frequency transformations of EEG data (see³⁰ for an overview). The convolution was completed with a frequency step of 1 Hz and a time step of 2 ms, between -100 and 800 ms from stimulus onset. The resulting representations were then averaged across trials for each condition and participant. To control for differences in absolute power between individuals, time-frequency representations were normalized for each participant (similarly to^{31, 32}). This normalization was performed by first calculating average baseline values at each frequency for each participant, which was the mean power of all three conditions, averaged across all time points; the percent change in power spectra at each time point and frequency for each condition was then calculated for each condition relative to baseline. Thus, normalized time-

frequency representations represent how much the activity in each condition differs from the average activity across conditions.

Condition difference testing: Between-conditions differences in normalized gamma power were tested for the entire 0-800ms post-stimulus period using cluster randomization procedures with planned comparisons³³. Clustering identifies groups of channels, at each time point within a frequency band, that show a similar pattern of condition differences and then tests the significance of the cluster in a given condition (e.g., stranger's voice) versus another condition (e.g., mother's voice), compared with clusters computed from 3000 random permutations of values drawn from both conditions via the Monte Carlo method. The number of permutations was selected based on our previous studies³¹. As described in Maris & Oostenveld (³¹), this cluster randomization method is a data-driven way to identify contiguous time periods in which significant condition differences occur. The Monte Carlo significance probability (cluster p-value) was determined by calculating the proportion of clusters from random partitions of the data that resulted in a larger “test statistic” (the sum of the t-statistics from comparing two conditions within each cluster) than the clusters computed from the observed test statistic. Because only pair-wise comparisons are possible in this analysis method, gamma band responses for Mother's voice vs. Stranger voice (constant) and Mother's Voice vs. Stranger Voice (Varied) were tested separately. Due to the small numbers of subjects in each group, and the very conservative nature of the Monte Carlo test, cluster p-values <.10 were considered significant.

Data for the *MECP2* duplication and Rett groups were analyzed separately. This was done in part because different patterns of brain responses were anticipated for these two groups based on work in animal models, and the small sample size of the Rett group prohibited formal statistical between-group comparisons.

Behavioral assessments

We selected instruments assessing social-communicative functioning as they were expected to reflect behaviors most closely related to the brain processes measured by the voice discrimination paradigm. The Vineland Adaptive Behavior Scales – II³⁴ was completed as a semi-structured interview with parents to assess overall adaptive behavior. While more detailed results from this assessment have been reported in other papers^{1, 35}, here we focus only on the scores from the socialization domain. Standard scores with a mean of 100, and a standard deviation of 15 points are reported on this scale.

To assess Social Affect (inclusive of communication and reciprocal social interaction), the Autism Diagnostic Observation Schedule (ADOS)³⁶, Module 1 was completed on all participants with appropriate mobility (pulling to stand and cruising around furniture) and hand use. Eight of the twelve participants with *MECP2* duplication syndrome completed this measure. In the Rett group, four of the five participants were not mobile. One participant with Rett did complete this measure, but her scores are not reported here. The purpose of utilizing the ADOS in this study was not for diagnosis, but rather as an objective assessment or “index” of social interaction skills. The details of scores and diagnostic profiles have been described elsewhere¹. Scores are reported according to the research algorithm (No Words)

for the domain of Social Affect³⁷, and high scores reflect greater impairment in Social Affect. The Communication and Reciprocal Social Interaction domains are combined as part of the Social Affect domain using this research algorithm³⁸, which results in improved predictive validity³⁷. All psychologists who administered the ADOS attained research reliability.

Parents also completed the Aberrant Behavior Checklist³⁹. This is a questionnaire that evaluates the presence of specific maladaptive behaviors in 5 categories (irritability, lethargy/withdrawal, inappropriate speech, hyperactivity, and stereotypic behavior). This questionnaire has been previously utilized in individuals with a variety of genetic syndromes^{1, 40}. For this study, we selected only the lethargy/withdrawal and hyperactivity subscales. Higher scores on these measures reflect greater impairment.

Visual reception/nonverbal cognitive abilities, and expressive/receptive language abilities were assessed using the Mullen Scales of Early Learning. This instrument has been utilized extensively within these populations and in large scale autism research studies beyond the normative age ranges⁴¹. In fact, a recent study demonstrated support for the practice of using Mullen age-equivalents beyond the typical age range of the test⁴¹. We utilized these measures to ascertain the degree to which performance on our brain-based measures were dependent upon either cognition and/or language skills.

Brain-Behavior correlations

To relate electroencephalographic results to behavioral measures, we created a single summary gamma power value for each participant by summing power values over significant clusters per condition (see Lense et al., 2013 for further procedural details³¹). A gamma voice discrimination index was then computed as the difference between the summary values for the response to mother's and stranger's voices. This index score was then used in correlations with behavioral data for participants in the *MECP2* duplication group. The small number of participants with Rett syndrome (n=5) did not provide sufficient statistical power for correlational analyses in that group.

Results

EEG results

In both groups, time-frequency analysis revealed differences in the induced gamma-band activity associated with familiar (mother) and unfamiliar (stranger) voices. In the *MECP2* group, a cluster of mostly central electrodes showed increased gamma power to the mother's voice relative to decreased gamma power to the stranger (constant) voice (*cluster p*=0.072) from 600 to 800 ms after stimulus onset (Figure 1). No significant difference was found between the mother's voice and the stranger (varied) voice for boys with *MECP2* duplication syndrome.

Participants with Rett syndrome also showed late gamma differences between familiar and unfamiliar voices, but in the opposite direction, with increased power to stranger's (constant) voice and decreased power to the mother's voice (*cluster p* = 0.030) from 660 to 758 ms

(Figure 2). No significant difference was found between the mother's voice and the stranger's (varied) voice for girls with Rett syndrome.

Thus, while boys with *MECP2* duplication syndrome demonstrated higher gamma power in response to the mother's voice, girls with Rett showed higher gamma power to stranger's voice. The timing of these condition differences was similar for both of the diagnostic groups.

Behavioral assessments

Mean scores on all behavioral measures for the *MECP2* duplication and Rett groups are shown in Table 1. Formal statistical comparisons were not made between the groups on any behavioral outcomes, given the small sample sizes. In general, both groups scored within the mild deficits range for the Socialization subscale of the Vineland Adaptive Behavior Scales. Corroborating our previous work¹, the *MECP2* duplication group exhibited impairments in Social Affect on the Autism Diagnostic Observation Schedule that are consistent with individuals who have idiopathic autism. Five of the eight boys met cutoff criteria for an autism spectrum disorder. On the Lethargy/Social Withdrawal subscale of the Aberrant Behavior Checklist, boys with *MECP2* Duplication syndrome (as a group) had clinically elevated scores (indicative of social withdrawal) while girls with Rett scored near the floor of the instrument (indicating that they are not socially withdrawn). Neither group scored within a clinically elevated range for the Hyperactivity subscale. Finally, both groups exhibited significant delays on the Mullen Scales of Early Learning. The cognitive/visual reception scores of girls with Rett are even lower, in part, because of their difficulties with hand use and not being able to pick up manipulatives.

Brain-behavior correlations—Importantly, brain-based indices in the *MECP2* duplication group were virtually unrelated to cognition ($r=-.04$; $p=.91$) or to expressive language ($r=.13$; $p=.69$). Correlations between the ability to discriminate voices and receptive language were also non-significant ($r=.22$; $p=.49$). Thus, a child's ability to discriminate between the mother's voice and the stranger's voice was unrelated to cognitive or to language abilities. Correlations were also non-significant with the Aberrant Behavior Checklist Hyperactivity subscale ($r=-.23$; $p=.47$) and the Lethargy subscale ($r=-.18$; $p=.58$).

While correlations between brain-based measures and the variables that were linked to socialization skills did not reach statistical significance, the effect sizes for these correlations were medium to large (Table 2). More specifically, those individuals with *MECP2* duplication who exhibited greater discrimination between the mother's voice vs. the stranger's voice were the least impaired on the measure of Social Affect ($r=-.51$; $p=.19$; large effect size), and the Vineland Socialization scale ($r=-.35$; $p=.27$; medium effect size).

Discussion

In this proof-of-concept study, we demonstrated that boys with *MECP2* duplication syndrome (overexpression of MeCP2 protein) exhibited distinct electroencephalographic indices of auditory stimulus discrimination that contrasted with indices observed in girls with Rett syndrome (underexpression of MeCP2 protein). Specifically, boys with *MECP2*

duplication syndrome showed a marginally significant voice discrimination effect in the form of a late peak in induced gamma band power for mother (familiar) vs. stranger (unfamiliar) voices. Conversely, girls with Rett also showed gamma band differences, but with the opposite pattern than boys with *MECP2* duplication syndrome; girls with Rett showed increased gamma band power to the novelty of the stranger's voice. The results suggest that similar to findings in Rett mouse models (post-regression)⁴², girls with Rett attend more to novel stimuli (stranger's voice), while boys with *MECP2* duplication syndrome focus on a familiar rather than a novel stimulus. The results further suggest that there are distinct neurophysiological patterns in both of these populations that warrant further investigation.

It is important to note that there was no difference for the varied stranger voice in either the Rett or *MECP2* duplication boys. In the condition "stranger voice (varied)", the mother's voice from a prior participant served as the stranger voice for the next participant. The voice in the stranger voice (constant) condition was the same across participants. Since the time-frequency representations were normalized to the average activity across the three conditions, it is possible that acoustic variations may have contributed to the pattern of results where the discrimination was observed for mother vs. stranger voice (constant) but not stranger voice (varied). This difference in outcomes could potentially be attributed to the variability in prosody (i.e. the intonation and timbre, and durations) across parents' voices, which contributed to increased variability in EEG, therefore reducing power to detect significant differences for the contrast between mother's and stranger (varied) voice.

The small numbers of participants in this study prevented the examination of correlations between brain and behavioral measure for the Rett group. Nonetheless, for individuals with *MECP2* duplication syndrome, it is important to note that performance on this passive task appears to be unrelated to nonverbal cognition, language abilities, hyperactivity or social withdrawal measures. Conversely, medium-to-large effect sizes were observed for the association between greater condition differences in induced gamma and Vineland Socialization subscale and the Social Affect subscale of the Autism Diagnostic Observation Schedule. Although these correlations were statistically non-significant, likely due to the small sample size, they are consistent with the results from studies in individuals with autism spectrum disorders demonstrating that impaired discrimination between familiar vs. novel stimuli corresponds to greater social impairment⁴³. Therefore, future studies should investigate these potential relationships in *MECP2* duplication and Rett syndromes.

A limitation of this study is that all participants in the *MECP2* duplication group were male. It will be important to determine whether females with *MECP2* duplication syndrome (who are now being identified⁴) exhibit a similar pattern of performance. This could assist in determining the degree to which patterns of performance on this task are attributable to under- vs. over-expression of MeCP2 protein and features of autism as opposed to gender. Including both genders with the *MECP2* duplication could also help interpret the inter-group variability in the channel clusters sensitive to condition differences, whether they reflect genuine diagnostic group differences in the topographic patterns of observed brain activity or are due to varied gender composition and sample sizes.

This study also demonstrated the utility of the passive listening task in differentiating between these two groups of nonverbal participants. Notably, the participants were remarkably compliant with the task, and very little data were lost to attrition. Because this paradigm did not require any motor abilities or hand use, it may be more suitable as a measure of cognitive processing assessing recognition and discrimination as well as processing of socially relevant stimuli as compared to conventional behavioral/psychological measurements. As such, it has been suggested that outcomes such as induced gamma may eventually serve as possible biomarkers of clinical severity in clinical/translational studies in these populations.

In sum, this proof-of-concept study demonstrated that measures of brain activity can be used to examine the effects of *MECP2* gene over- and underexpression on cortical functioning. Girls with Rett and boys with *MECP2* duplication syndrome exhibit different patterns of cortical processing associated with the discrimination of familiar and novel stimuli. Within the *MECP2* duplication group, stimulus-related differences in gamma power correlated with the degree of social impairment independently of nonverbal cognitive and verbal skills. Further studies with larger sample sizes should determine the degree to which the different patterns of brain activity associated with information processing are attributable to different levels of MeCP2 protein expression, and imbalance in excitation/inhibition.

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Figure 1.

Differences in induced gamma (26-50 Hz) power in response to mother's voice (top) vs. stranger's voice -varied (bottom) in children with *MECP2* duplication syndrome. Electrodes belonging to the significant clusters at the time point indicated in each topographic plot (right) are represented with asterisks, and overlay activity for the data used in the contrast. The scale is the percent change from each participant's average activity across conditions. Time-frequency representations (left) were generated by averaging together all of the electrodes belonging to the significant cluster, the time and frequency of which is delineated in the black box; the same power scale applies to both topographic plots and time-frequency representations.

Figure 2.

Differences in induced gamma (26-50 Hz) power in response to mother's voice (top) vs. stranger's voice –varied (bottom) in children with Rett syndrome. See legend of Figure 1 for an explanation of plotting.

Figure 3.
Correlation between Social Affect and induced gamma cluster sum differences in MECP2 duplication syndrome.

Table 1

	Age, years	Vineland Socialization	Social Affect Score (Autism Diagnostic Observation Schedule)	Aberrant Behavior Checklist		Mullen Scales of Early Learning Age Equivalent		
				Lethargy	Hyperactivity	Visual reception/nonverbal cognition	Receptive Language	Expressive Language
MECP2 Duplication (n=12)	5.75 (2.95)	56.5 (7.15)	9.22 (4.79) *	12.08 (9.17)	9.33 (6.18)	13.83 (8.64)	12.92 (9.69)	8.75 (5.67)
Rett (n=5)	6.80 (2.95)	54.6 (8.68)	N/A	4.25 (6.5)	5.0 (8.04)	7.6 (3.58)	10.20 (3.70)	5.20 (5.81)

Autism cutoff=12, autism-spectrum cutoff=7; High scores reflect greater impairment
* High scores reflect greater impairment

Table 2

Brain-Behavior Correlations in MECP2 duplication syndrome

	Vineland Socialization	Cognition	Expressive Language	Receptive Language	Social Affect	Lethargy	Hyperactivity
Induced Gamma	-.35	-.04	.13	.22	-.51	-.18	-.23

No correlations reached statistical significance