
Article:
Al-Jawahiri, R. orcid.org/0000-0002-5689-3368, Jones, M. orcid.org/0000-0002-4580-7559 and Milne, E. orcid.org/0000-0003-0127-0718 (2019) Atypical neural variability in carriers of 16p11.2 copy number variants. Autism Research, 12 (9). pp. 1322-1333. ISSN 1939-3792

https://doi.org/10.1002/aur.2166

Atypical Neural Variability in Carriers of 16p11.2 Copy Number Variants

EEG activity in 16p11.2 copy number variants

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Acknowledgments

We are grateful to all of the families at the participating Simons Variation in Individuals Project (Simons VIP) sites, as well as the Simons VIP Consortium.

We appreciate obtaining access to phenotypic and imaging data on SFARI Base.

Approved researchers can obtain the Simons VIP population dataset described in this study (https://www.sfari.org/resource/simons-vip/) by applying at https://base.sfari.org/. We would like to thank Dr Jocelyn J. LeBlanc, Dr Charles A. Nelson, and research staff members at Boston Children's Hospital and Harvard Medical School for their contributions in generating this data. We also thank Dr Mike X. Cohen for his valuable advice.

Lay Summary

The study analyzed the consistency of patterns of brain waves and rhythms in those affected with a loss or gain of DNA material in the 16p11.2 region. Compared with typical individuals, 16p11.2 deletion carriers showed greater inconsistency in the way the brain responds to the same visual event. This high inconsistency in brain activity may play a role in some core symptoms in 16p11.2 copy number variation carriers.

Abstract

Copy number variations (CNVs) at the 16p11.2 chromosomal region are associated with myriad clinical features including intellectual disability and autism spectrum disorder. The aim of this study is to determine whether 16p11.2 deletion (DEL) and duplication (DUP) carriers demonstrate a distinct and reciprocal pattern of electroencephalography (EEG) activity as represented by neural variability measures. EEG data were previously collected as part of the Simons Variation in Individuals Project. Variability measures, as estimated by single-trial ERP and spectral power analyses in the alpha and beta frequency bands, in addition to signal-to-noise ratios (SNRs), were analyzed in DEL (n = 20), DUP (n = 8), and typical (n = 11) groups. We also analyzed mean visual evoked potentials and spectral power (alpha and beta power) to facilitate comparisons with other studies of associated disorders and CNVs. From measures of single-trial variability, we found higher intraparticipant variability in P1 amplitude and timecourse amplitude in DEL compared to controls. Compared to DUP, DEL showed higher variability in absolute alpha and absolute beta power but lower variability in P1 latency. SNRs did not differ between the groups. From measures of amplitude, latency, and spectral power, DUP showed lower relative alpha power compared to controls. Although it is yet unclear whether 16p11.2 CNV dosage impacts neural activity in an opposing manner, findings suggest that 16p11.2 DEL impacts the level of variability of neural responses. Higher neural variability may play a role in a range of cognitive processes in 16p11.2 CNV carriers.

Keywords: Alpha Rhythm, Genetic/Genomic Syndromes, Electroencephalography (EEG), Copy Number Variation/ Copy Number Variants (CNV), Cognitive Neuroscience, Event-Related Potentials (ERP), Gene-Dosage Effect.

Introduction

Copy number variations (CNVs) at the 16p11.2 chromosomal region (~600 kb breakpoints 4–5 [BP4–BP5]) are associated with myriad clinical features including intellectual disability, autism spectrum disorder (ASD), epilepsy, and language and motor delays [Weiss et al., **2008**; McCarthy et al., **2009**; Hanson et al., **2015**; D'angelo et al., **2016**; Snyder et al., **2016**; Steinman et al., **2016**]. This CNV is associated with a variable phenotype, in terms of the clinical profile and degree of symptom severity [Golzio & Katsanis, **2013**; D'angelo et al., **2016**; Snyder et al., **2016**; Steinman et al., **2016**]. The 16p11.2 chromosomal region spans approximately 29 genes, including *MAPK3* and *MVP*—both potentially influencing synaptic function and cortical plasticity [Park, Park, & Lee, **2017**]. The loss (DEL) or gain (DUP) of these ~29 genes in the 16p11.2 has a population prevalence of ~0.05% for DEL and ~0.04% for DUP [Kirov et al., **2014**]. Although rare, 16p11.2 CNVs are one of the most common risk factors for ASD (contributing up to ~1% of ASD cases) [Weiss et al., **2008**; Sanders et al., **2011**] and other disorders [e.g. Marshall et al., **2017**]. When inherited the pattern of inheritance is autosomal dominant, however, de novo 16p11.2 DEL and DUP cases are also frequently reported [Sanders et al., **2011**; Steinman et al., **2016**].

Regardless of inheritance status, many studies have consistently drawn the conclusion that the number of 16p11.2 copies may lead to observed opposing effects in certain phenotypes on deletions versus duplications, which is indicative of a gene-dosage effect [Shinawi et al., **2010**; Jacquemont et al., **2011**; Owen, **2014**; Qureshi et al., **2014**; Maillard et al., **2015**; Arbogast et al., **2016**; Chang et al., **2016**; Hippolyte et al., **2016**; Jenkins et al., **2016**; LeBlanc & Nelson, **2016**; Steinman et al., **2016**]. For example, 16p11.2 DEL is associated with atypically large brain volume, whereas DUP is associated with atypically small brain volume [Qureshi et al., **2014**]. Investigating whether particular 16p11.2 CNV phenotypes are gene-

dosage dependent or independent is important because it connects genotype to phenotype, enabling a deeper understanding of the pathological effects of 16p11.2 CNVs.

Further evidence to indications of 16p11.2 CNV gene-dosage effects have been found in the form of M/EEG signals (or neurophysiological EEG and MEG activity) [Jenkins et al., **2016**; LeBlanc & Nelson, **2016**]. Specifically, Jenkins et al. [**2016**] found a significant delay in the M100 response (i.e., a typical waveform elicited at ~100 ms poststimulus onset in response to auditory events) in DEL compared to controls, whereas DUP showed an earlier (nonsignificant) M100 response compared to controls. Examining the amplitude of the P1 component (i.e., the equivalent of the M100 response, but to visual events), LeBlanc and Nelson [**2016**] similarly found opposing neural activity in DEL and DUP. In this case, a trend (albeit nonsignificant) of higher P1 amplitude in DEL compared to controls and lower P1 amplitude in DUP compared to controls. Notably, when DEL and DUP were compared to each other directly, a significant difference in P1 amplitude was found: DEL showed higher P1 amplitude than DUP. Certainly, as captured by M/EEG, these studies showed that 16p11.2 CNV carriers have atypical neural activity, which seems to be influenced by gene-dosage. Hudac et al. [**2015**] also contributed toward phenotyping the EEG behavior of 16p11.2 carriers. The authors studied power changes in the mu frequency band (8–12 Hz), to social and nonsocial motion. Typically, a greater attenuation in the mu band is expected in response to social stimuli, however, the CNV groups showed greater mu attenuation to nonsocial than social stimuli. Crucially, this study also conducted trial-to-trial analysis to examine whether the level of mu attenuation was altered differently over time between groups. They found that unique to DUP, an initial typical mu response was exhibited, which then decreased over time more rapidly compared to controls. Overall, even though no opposing EEG activity was found in 16p11.2 CNV group by Hudac et al. [**2015**], trial-to-trial analysis revealed that DUP's initial typical response distinguished it from DEL. Indeed, further research using other

measures of neural activity, especially trial-to-trial variability measures, is warranted to verify distinct and potentially reciprocal EEG responses in 16p11.2 CNV carriers.

In the ASD literature [Haigh, Heeger, Dinstein, Minshew, & Behrmann, **2015**; Dinstein et al., **2012**; Milne, **2011**], variability measures for both M/EEG and functional magnetic resonance imaging (fMRI) responses have been computed to study intraparticipant trial-to-trial neural variability via visual, somatosensory, and auditory paradigms. Despite finding no differences in the mean measures of stimulus–response amplitude, these studies identified neural responses that were variable across single trials in the ASD group relative to the typical group. Conducting trial-to-trial variability analyses, therefore, is useful in identifying these subtle yet significant differences in neural responses between clinical and typical populations, which would have been unnoticed in measures of averaged-trial responses. Neural variability in clinical populations has been increasingly studied and recognized as a useful sign of a typical brain function and development [Pernet, Sajda, & Rousselet, **2011**; Garrett et al., **2013**; Dinstein et al., 2015; David et al., **2016**]. Overall, intraindividual variability measures and analyses (e.g., multiple M/EEG and fMRI variability metrics) could present a possibly unifying multimodal approach to studying 16p11.2 CNV and, more generally, subtle differences in heterogeneous disorders that vary in their symptomology and severity from one person to another.

The purpose of the current study is to further determine the nature of the putative atypical and reciprocal EEG activity in 16p11.2 DEL and DUP carriers. To our knowledge, no existing study has investigated neural variability in this population. As such the current study conducts novel analyses of the dataset previously published by LeBlanc and Nelson [**2016**]. Neural variability was measured via the following metrics: intraparticipant response variability of visual evoked components (i.e., across-trial variability in the amplitude and

latency of C1, P1, N1), timecourse variability, spectral power variability (i.e., across-trial variability in absolute alpha power, relative alpha power, absolute beta power, and relative beta power), and mean signal-to-noise ratio (SNR). Further to these measures, we analyzed mean visual evoked potentials and spectral power (both absolute and relative alpha and beta frequencies) to facilitate comparisons with other studies relating to associated disorders and similar CNVs (e.g. ASD, 15q, 1q).

Materials and Methods

Participants

The findings in this article represent the analyses of a previously collected dataset (Simons Variation in Individuals Project [SVIP]) [The Simons VIP Consortium, **2012**], which was obtained via the Simons Foundation Autism Research Initiative (SFARI) data request process (**https://sfari.org/resources/sfari-base/request-data-and-biospecimens**). The data of individuals with 16p11.2 CNVs (~600 kb 16p11.12 BP4-BP5 DEL or DUP) and typically developing individuals were obtained from the SFARI database [The Simons VIP Consortium, **2012**]. Participant identification, recruitment, and inclusion/exclusion criteria of the SVIP have been described previously [see The Simons VIP Consortium, **2012**; Jenkins et al., **2016**; LeBlanc & Nelson, **2016**].

The control participants analyzed in this study did not undergo the Simon's VIP battery of assessments. LeBlanc and Nelson [**2016**] recruited the control group independently through the Boston Children's Hospital participant registry. The group consisted of neurotypical individuals without any neurological or developmental disorders.

Data from a total of 46 participants were obtained from the SVIP consortium for the current study. Seven participants were then excluded. Reasons for exclusions were: visual inspection indicated that EEG data were contaminated by artifacts (n = 2) and/or EEG datasets contained

fewer than 24 clean trials. The final dataset analyzed contained 39 participants: 8 DUP, 20 DEL, and 11 typically developing individuals.

Phenotypic data including intelligence quotient (IQ) scores, diagnoses, current medications, and vision problems were accessed from the Simons VIP Phase 1 16p11.2 dataset at SFARI Base (**http://www.sfari.org/resources/sfari-base**). Participant information relating to age, gender, CNV inheritance, ASD diagnosis, Autism Diagnostic Observation Schedule - Calibrated Severity Score (ADOS-CSS), and IQ scores are reported in Table **1**. Note that the reported IQ scores were not adjusted for prematurity. Other diagnoses and comorbidities are reported in Supporting Information Table S1. Information regarding current medication was extracted from the SFARI medication questionnaire (med_child.csv); two DEL carriers were reported to have been currently taking antiepileptic medication (i.e., Keppra and Topamax). Additionally, vision problems were reported for eight DEL and four DUP carriers in the SFARI development and medical history form (mhi_ped.csv).

Kruskal–Wallis tests revealed that there were no significant age or sex differences among the three groups (χ^2 (2) = 1.46, P = 0.481; χ^2 (2) = 0.65, P = 0.724). Also, there were no significant differences in IQ scores (full-scale IQ: χ^2 (1) = 2.97, P = 0.085; verbal IQ: χ^2 (1) = 2.34, P = 0.126; nonverbal IQ: χ^2 (1) = 1.71, P = 0.191) between DEL and DUP groups. Comparisons with the control group were not possible as, other than age and gender, participant details and phenotypic data were not available for the typical control group.

Ethical approval

The local institutional ethical review board reviewed and approved the secondary analyses presented here. Our request to obtain access to phenotypic and imaging data on SFARI Base was approved after submitting the required information and signing the joinder to the researcher distribution agreement (**https://www.sfari.org/resource/sfari-base/**). SFARI

obtained initial ethical approval for the SVIP (IRB of record: Columbia University Medical Center) [The Simons VIP Consortium, **2012**]. As part of the SVIP, approval was obtained for data collection on individuals with 16p11.2 deletions or duplications and for their deidentified data to be shared with approved researchers.

Stimuli and procedure

The stimuli and procedure were as described in previous studies [LeBlanc & Nelson, **2016**; LeBlanc et al., 2015; Varcin et al., **2016**].

EEG pre-processing conducted in the current study

EEG recording and preprocessing steps conducted prior to the current study are described in Supporting Information. Additional preprocessing steps were conducted by the current authors after obtaining the dataset, which consisted of rejecting obvious bad trials (three trials in total) based on manual visual inspection. In addition, the number of trials selected for analysis was adjusted per group in order to control the average number of trials analyzed per group and avoid bias in analysis outcomes [original trial number range after participant exclusions: 24–147; original mean trial number for control = 67, original mean for DEL = 49, original mean for DUP = 71; new trial number range: 24–97; new mean = 49 trials per group]. This was done via an algorithm that applied a different number of trial limits per participant depending on the group the respective participant belonged to, which in turn was designed to result in the same trial number averages for all groups.

EEG channel selection

In accordance with previous studies [e.g., Foxe & Simpson, **2002**; Milne, **2011**; Gonen-Yaacovi et al., **2016**; Arazi, Censor, & Dinstein, **2017**], for each participant, the channel

within the occipital and parietal regions with the highest amplitude within the time window 60–140 ms poststimulus onset was selected for timecourse variability analyses and C1, P1, and N1 analyses (both mean and variability analyses; Supporting Information Table S2). We also analyzed data based on an alternative criterion of selecting the channel with the lowest C1 amplitude, highest P1 amplitude, and lowest N1 amplitude for the respective C1, P1, and N1 analyses (both mean and variability analyses; Supporting Information Table S3); this analysis produced identical variability results, in addition to certain minor differences in the mean ERP results (see the **Results** section). For power analyses and SNR analyses, the average of a set of channels positioned above the occipital cortex was computed (Supporting Information Fig. S1).

Extracting C1, P1, and N1 amplitude and latency

C1, P1, and N1 were identified for each trial and participant. Using a peak-picking algorithm, which identified either the maximum or minimum amplitude within a given time window, negative and positive deflection points were identified in overlapping period ranges consistent with those previously reported by LeBlanc and Nelson [**2016**]. C1 was identified as the minimum amplitude occurring in the poststimulus period range of 0–70 ms; P1 was the highest amplitude in the period range of 56–132 ms; N1 was the lowest amplitude in the 108–266 ms range. The amplitude and latency of C1, P1, and N1 were first extracted from every trial. Respectively, the C1, P1, and N1 average single-trial amplitudes were then given by computing the median of all the single-trial C1, P1, and N1 amplitude deflection points. Similarly, C1, P1, and N1 average single-trial latency were given by the median of all the single-trial time points at which the C1, P1, and N1 amplitude peaks (therefore, following the same approach as Milne [**2011**]).

Measures of neural variability

Because there are many variables that have been suggested to indicate neural variability [e.g., Milne, **2011**; Weinger, Zemon, Soorya, & Gordon, **2014**; Haigh et al., **2016**; Arazi et al., **2017**; Butler, Molholm, Andrade, & Foxe, **2017**], it is good practice to apply more than one measure and examine whether there is concordance between the metrics. Measures of neural variability examined in the current study were C1, P1, and N1 variability; intertrial variability in ERP amplitude across the timecourse (timecourse variability); alpha and beta power variability; and EEG SNR. Although it could be argued that SNR is not a true reflection of intertrial variability, it is often used as a proxy measure of variability, with lower SNRs interpreted as higher neural variability [Dinstein et al., **2012**; Butler et al., **2017**]. Thus, SNR is provided in the current study for comparison with previous research.

C1, P1, N1, and timecourse variability

For each participant, C1, P1, and N1 variability were given by computing the median absolute deviation (MAD) of the single trial amplitude and latency values. Timecourse variability was given by computing the MAD of all 2 ms interval amplitudes across trials for the full length of the signal in order to investigate the precise timing of any differences in variability between the three groups. In other words, we computed the MAD of single-trial amplitudes of each individual datapoint in the signal (encompassing all the prestimulus and poststimulus periods; range: −100 ms, 300 ms).

Alpha and beta power variability

Power variability was given by computing the MAD of single-trial absolute and relative alpha (8–14 Hz) and beta power (14–30 Hz) for each participant (see Supporting Information for detailed methodology). Mean absolute and relative alpha and beta power were also

measured to facilitate comparisons with other studies. These analyses were conducted using in-house code (code available upon request) derived from codes shared by Dr. Mike X. Cohen [Cohen, **2014**] with functions from the EEGlab toolbox [Delorme & Makeig, **2004**].

Signal-to-noise ratio

SNR is the ratio of poststimulus signal (i.e., 0 to 100 ms in the current study) strength to the prestimulus signal (i.e., −100 to 0 ms relative to stimulus time) strength (the latter traditionally termed as noise) and is usually expressed in decibels. The current study followed the same SNR formula used in Butler et al. [**2017**] to compute SNRs (see Supporting Information for detailed methodology).

Statistical Analysis

As sample sizes were small and the data were skewed, permutation tests were conducted to investigate whether there were group differences in neural activity between the three groups [see Rodgers, 1999]. The advantage of this technique is it makes no a priori assumptions about the distribution of the data and uses the actual data to conduct the test. For each group comparison (i.e., DEL/control, DUP/control, and DEL/DUP), the whole group data were randomly permuted, this new permuted data were assigned to two groups with identical sample sizes to the respective original dataset. The mean difference between these two new groups was calculated; this procedure was then repeated 10,000 times. The actual absolute mean difference was compared to the randomized distribution of absolute mean differences. The *P* value is the number of (absolute) mean differences' values above the actual (absolute) mean difference obtained and divided by the number of iterations (10,000). This was conducted for each EEG averaged and variability metric described in earlier sections. To account for multiple companions, the false discovery rate (FDR) was controlled using the

Benjamini–Hochberg procedure, with $q < 0.05$. We also applied the permutation approach to correlation analyses to examine whether age, IQ, and autistic traits impact neural responses in 16p11.2 CNV carriers. For each group, the null hypothesis ($P = 0$) is tested by holding the *X*-variable (e.g., age) constant and permuting the Y-variable (e.g., P1 amplitude variability) against it. In other words, the *r*-coefficient for the respective actual X-variable and the random permutated Y-variable pair is computed, with the expectation of $r = 0$. This process is repeated 10,000 times, where only the *Y*-variable is permuted. The actual absolute *r*-coefficient of the respective variables were then compared to the randomized distribution of absolute *r*-coefficients, which were produced by the 10,000 correlation permutations. The *P*-value is the number of (absolute) *r*-coefficients' values above the actual (absolute) *r*-coefficients obtained and divided by the number of iterations (10,000). All the outcomes were corrected for FDR using the Benjamini–Hochberg procedure, with $q < 0.05$.

Results

C1, P1, N1, and timecourse variability

DEL, DUP, and control group averages and differences in the variability of C1, P1, and N1 amplitude and latency are presented in Tables 2 and 3. Significant differences were found in P1 amplitude variability (Fig. 1A) between DEL and controls. Specifically, DEL showed significantly higher variability in P1 amplitude compared to controls. Also, DEL showed significantly lower variability in P1 latency compared to DUP (Fig. 1B). No other significant differences were found between the three groups in C1, P1, and N1 intraparticipant variability.

Timecourse variability, that is, trial-to-trial variability in the amplitude of each individual datapoint (2 ms) in the signal [range: −100 ms, 300 ms], was also compared between the three groups compared to controls, DEL showed higher 2 ms-interval trial-to-trial variability

almost consecutively for the whole period between −100 and 172 ms (length of gaps <31 ms) and at 286 ms (see Fig. 2 for a precise illustration of the timepoints during the epoch where timecourse variability was significantly greater in DEL than controls). No other differences were found in timecourse variability between the three groups.

Mean amplitude and latency of C1, P1, and N1 were compared between the three groups (Tables 2 and 3). DEL showed higher C1 (i.e., lower negative peak) amplitude compared to controls. Note that when the channel selected for analysis was based on the alternative criterion of selecting the electrode showing the lowest C1 and N1 amplitude for the respective C1 and N1 analyses, this group difference was no longer significant and a new result of increased C1 latency in DUP compared to controls was found. In line with LeBlanc and Nelson [**2016**], DEL showed higher P1 amplitude compared to DUP. No other significant differences were found.

Alpha and beta power variability

Trial-to-trial variability in absolute and relative power within the alpha and beta frequency bands were compared between the three groups (Tables 2 and 3). Variability in absolute alpha and beta power was significantly higher for DEL compared to DUP (Fig. 3A and B). No other significant group differences were found in alpha or beta power variability.

Mean absolute and relative power in the alpha and beta frequency bands were also compared between the three groups (Tables 2 and 3). Relative alpha power was lower for DUP compared to controls. Additionally, absolute alpha and absolute beta power were higher for DEL compared to DUP. No significant group differences were found in mean alpha or beta power.

Signal-to-noise ratio

The analysis revealed no significant differences in SNR between the three comparisons (Tables **2** and **3**).

Correlations between IQ, ADOS-CSS, and EEG measures in 16p CNV

For each of the DEL and DUP groups, correlation permutation tests [Rodgers, 1999] were performed between IQ and ADOS-CSS against EEG measures of interest (C1, P1, and N1 variability; alpha and beta power variability; SNR; C1, P1, and N1 mean; alpha and beta power mean), respectively. No significant correlations were found (Supporting Information Table S4).

The impact of age on neural activity

For each of the three groups, correlation permutation tests were performed between age and the EEG measures of interest (C1, P1, and N1 variability; alpha and beta power variability; SNR; C1, P1, and N1 mean; alpha and beta power mean), respectively. No significant correlations were found (Supporting Information Table S5).

The number of trials available for analysis differed for each subject which could potentially influence estimates of variability. Thus, to investigate whether the number of trials per subject was associated with variability, SNR, and/or averaged EEG measures, permutation correlation tests [Rodgers, **1999**] were conducted, and the outcomes were corrected using the Benjamini–Hochberg procedure, with $q < 0.05$. The results showed that there were no significant relationships between the EEG measures and trial number (Supporting Information Table S6). In the current study, the number of retained trials in the three groups were the same on average (mean = 49 trials per group, Kruskal–Wallis [χ^2 (2) = 0.58, P =

0.748] indicates no difference in median). Therefore, the variable trial number per participant is unlikely to explain any observed group differences in any of the EEG measures of interest.

Discussion

The aim of the study was to determine whether 16p11.2 CNVs show opposing atypical EEG signals, which could broadly indicate gene-dosage effects playing a differential role in cognitive processes and neural plasticity. Multiple measures of neural variability were estimated from EEG data, most of which were single-trial intraparticipant analyses. Overall, our results suggest that 16p11.2 DEL carriers showed highly variable neural responses to visual stimuli, compared to controls. Variability of timecourse amplitude (i.e., variability in amplitude at time-points throughout the epoch; Fig. **2**) and variability of P1 peak amplitude were higher in DEL compared to controls. Compared to DUP, DEL showed higher variability in absolute alpha and beta power but lower variability in P1 latency variability. Overall, it is unclear from our findings whether 16p11.2 dosage has an opposing effect on neural activity. Despite finding significant differences in neural variability between DEL and DUP, we did not find any differences between DUP and controls (although note that we did find DUP-control group differences in mean relative alpha power). Differences in neural activity between DEL and DUP are not sufficient evidence of an opposing effect. For a true opposing effect to be seen, we would need to show that both groups differ in opposing directions from the control group.

Is atypical neural variability unique to 16p11.2 CNVs?

Atypical neural variability has been shown in several diagnoses including ASD [Milne, **2011**; Dinstein et al., **2012**; Weinger et al., **2014**; Edgar et al., **2015**; Haigh et al., **2015**, **2016**; but see Coskun et al., **2009**; and Butler et al., **2017**], attention deficit hyperactivity disorder

(ADHD) [Woltering, Jung, Liu, & Tannock, **2012**; McLoughlin, Palmer, Rijsdijk, & Makeig, **2014**; Gonen-Yaacovi et al., **2016**; Sørensen, Eichele, van Wageningen, Plessen, & Stevens, **2016**], and schizophrenia [Shin et al., **2015**; Haigh et al., **2016**]. Interestingly, all of these conditions are associated with 16p11.2 CNVs [Williams et al., **2010**; Sanders et al., **2011**; Snyder et al., **2016**; Marshall et al., **2017**]. For example, similar to the current study's finding with respect to P1 variability found in DEL, atypically high visual evoked P1 amplitude variability was also reported for ASD [Milne, **2011**] and ADHD groups [Gonen-Yaacovi et al., **2016**]. However, Milne [**2011**] also found atypical P1 latency variability in ASD, whereas here, neither the DEL or DUP group showed latency variability that differed from the control group, although, P1 latency variability was decreased in DEL compared to DUP. Further group differences between DEL and DUP in neural variability were found in EEG spectral power; here, DEL showed higher absolute power variability, in beta and alpha bands, compared to DUP (again, neither CNV groups differed in power variability when compared to controls). Woltering et al. [**2012**] similarly reported lower (absolute) alpha and beta power variability in ADHD compared to controls [Woltering et al., **2012**].

Previous studies also found higher timecourse variability in ADHD (time window: 0–500 ms [Gonen-Yaacovi et al., **2016**] and time window: 0–600 ms [Myatchin, Lemiere, Danckaerts, & Lagae, **2012**]), similar to our finding in relation to timecourse variability in DEL. Gonen-Yaacovi et al. [**2016**] also computed baseline variability (previsual stimulus onset; time window: −200-0 ms) and reported higher variability in ADHD—again consistent with our DEL findings. There is an extensive literature on the putative interactions between evoked and ongoing activity raising the possibility that the increased variability prior to stimulus onset contributed to that observed poststimulus [Busch, Dubois, & VanRullen, **2009**]. Standard approaches to correct baseline simply subtract the average of the prestimulus period from each trial and do not take into account variability both in the prestimulus timeseries of

single trials or variability across trials. As such, it is important to examine both ERP amplitude and variability before and after stimulus onset.

Evidently, it would not be plausible to regard atypical neural variability, whether in the form of P1 variability, timecourse variability, or other, as distinct to 16p11.2 CNVs in light of the several heterogeneous disorders that show general similar variability dynamics. Rather, this study highlights that 16p11.2 CNVs—specifically deletions—should be added to the list of clinical conditions which show increased neural variability. The overall picture alludes to certain similarities in the behavior of neural responses, which would be informative and useful for further investigations.

Interpreting neural variability

Although, neural variability has become a topic of interest in many research areas including clinical populations [Pernet et al., **2011**; Garrett et al., **2013**; Dinstein et al., **2015**; Butler et al., **2017**; David et al., **2016**], the interpretation of neural variability remains a challenge. Nevertheless, it has been widely recognized that optimal neural variability is a characteristic of typical and healthy brain function, facilitating learning, adaptation to a changing environment, and other cognitive processes [Basalyga & Salinas, **2006**; Faisal, Selen, & Wolpert, **2008**; McDonnell & Abbott, **2009**; Heisz, Shedden, & McIntosh, **2012**]. Deviations from the typical levels of neural variability in the 16p11.2 DEL group, therefore, could be regarded as a signature of neuropathology and cognitive dysfunction, as was similarly indicated in the aforementioned studies of related disorders. IQ and autism symptom severity did not relate to any of the neural variability and averaged measures in the current study's 16p11.2 CNV sample (Supporting Information Table S4). Although consistent with previous studies [LeBlanc & Nelson, **2016**; Jenkins et al., **2016**] this lack of relationship could simply be due to sample size and needs to be further validated in future studies with larger samples.

Furthermore, neural variability could be related to other 16p11.2 CNV symptoms and traits, which could not be revealed *via* the phenotypic assessments used in the current and previous studies.

Of note, a recent study suggested that neural variability (on a macrolevel as measured by intertrial variation of the BOLD signal) is negatively related to dopamine concentration levels, quantified using PET [Guitart-Masip et al., **2016**]. In a mouse model of 16p11.2 CNV [Portmann et al., **2014**], dopamine-related deficits were found in the basal ganglia, therefore indicating the potential role of certain genes within the 16p11.2 region in establishing typical dopaminergic synaptic activity. Accordingly, a potential factor driving atypical neural variability in the CNV groups could be the dysregulation of dopamine levels; this, in turn, would lead to deficits in processes mediated by dopamine such as motivation and learning processes, movement, and social behavior [Wise, **2004**; Portmann et al., **2014**], all of which are seen in 16p11.2 CNV carriers and related disorders.

The observed atypical EEG activity in 16p11.2 CNV carriers could also reflect cellular electrophysiological and synaptic abnormalities. To examine cellular characteristics of 16p11.2 CNV carriers, a recent study used fibroblasts obtained from 16p11.2 CNV carriers and generated induced pluripotent stem cells, which were then differentiated into (forebrain cortical) neurons [Deshpande et al., **2017**]. Compared to neurons derived from typical controls, the authors found an increase in the amplitude of miniature excitatory postsynaptic currents in both DEL and DUP (excitatory) neurons. As the authors suggest, the increase in amplitude may be compensating for the reduced density of synapses in the CNV neurons. These altered cellular properties could affect overall neural plasticity and connectivity, which ultimately leads to the behavioral symptoms related to 16p11.2 CNV carriers and possibly to the activity recorded by EEG. Indeed, our EEG findings of atypical neural variability in

16p11.2 CNV carriers could signify synaptic impairment of excitatory neurons as that observed in vitro [Deshpande et al., **2017**] and also possibly of dopaminergic neurons.

Limitations

Although we addressed the issue of small sample size with randomization techniques, larger datasets would have been desirable to enable examination of confounding variables such as epilepsy than was possible here. A further limitation is the lack of IQ data for the control group. As participant IQ data were not available for the typical control participants, it was not possible to adequately account for cognitive ability in this study. Although in our current sample there were no IQ differences between DEL and DUP, other larger scale phenotypic studies have reported differing IQ profiles, with the DUP group tending to show higher IQ [Hippolyte et al., **2016**] and a wider range of IQ scores [D'angelo et al., **2016**]. A further limitation concerns the wide age ranges of the participants in the three groups. Consistent with LeBlanc and Nelson [**2016**], we found no effect of age on any of the EEG measures of interest (Supporting Information Table S5). Furthermore, our sample showed no significant group differences in age. This, however, does not preclude the possibility of some minor effect of maturational changes on neural variability, which might be better expressed in a different 16p11.2 CNV sample.

Concluding remarks.

The overall results, drawn from multiple measures of neural variability, strongly suggest that 16p11.2 DEL carriers, in particular, show visual-evoked neural responses that are highly variable compared to controls. Levels of neural variability were atypical and, thus, were postulated to have deviated from the optimal variability levels necessary for healthy brain function and cognitive processing. Future work should corroborate current findings using a larger sample and conduct further group cross-comparisons among 16p11.2 CNV groups,

CNV inheritance (de novo vs. inherited CNV), associated disorders (e.g., ASD), and similarly rare deleterious CNVs.

Tables

Table 1. Participant information

Group	N	Age mean in months (SD)	Age range in months	Gender	CNV inheritance			ASD diagnosis[c]			ADOS-CSS mean (SD)[a c d]	FSIQ mean (SD)[b c d]	VIQ mean (SD)[b c d]	NVIQ mean (SD)[b c d]
					De novo	Inherited	unknown	Yes	No	unknown				
DEL	20	69.05 (36.93)	12 - 163	M 12	7	2	3	2	8	2	4.29 (2.87)	78.32 (14.23)	72.84 (16.22)	83.58 (14.93)
				F 8	6	1	1	2	6	0				
DUP	8	110 (86.22)	40 - 256	M 4	0	4	0	1	3	0	2.71 (1.50)	82.25 (13.29)	83.63 (17.61)	84.88 (10.23)
				F 4	1	3	0	0	4	0				
Typical	11	68.36 (23.31)	39 - 109	M 5	-	-	-	-	-	-	-	-	-	-
				F 6	-	-	-	-	-	-	-	-	-	-

ADOS-CSS Autism Diagnostic Observation Schedule - Calibrated Severity Score; *FSIQ* full-scale IQ, *VIQ* verbal IQ, *NVIQ* nonverbal IQ.
[a]Missing data from DEL carriers (n = 6), DUP carriers (n =1), typical group (n = 11).
[b]Missing data from DEL carriers (n = 1), typical group (n = 11).
[c]IQ and diagnosis data were extracted from diagnosis_summary.csv
[d]The reported IQ scores were not adjusted for prematurity.

Table 2. Variability and averaged measures of neural activity of 16p CNV.

		DEL	Control	DUP
C1, P1, N1 variability	C1 amplitude (μV)	15.2 [6 17.75]	12.18 [3.91 14.39]	12.11 [4.5 17.8]
	C1 latency (ms)	21.5 [10 31]	16 [2 26]	16 [6 24]
	P1 amplitude (μV)	17.67 [10.17 26.27]	11.01 [5.48 19.4]	13.62 [3.11 25.25]
	P1 latency (ms)	8 [4 16]	10 [4 24]	13 [8 26]
	N1 amplitude (μV)	19.4 [9.52 25.88]	14.54 [6 26]	17.56 [4.02 30.51]
	N1 latency (ms)	34.5 [12 56]	32 [23 40]	42 [22 52]
Power variability	Absolute alpha (μV^2)	13.39 [7.36 44.27]	9.01 [2.78 34.85]	8.10 [1.49 14.28]
	Relative alpha (%)	0.09 [0.05 0.17]	0.11 [0.07 0.14]	0.08 [0.04 0.09]
	Absolute beta (μV^2)	5.36 [1.93 19.74]	3.15 [0.54 10.55]	2.28 [1.25 5.35]
	Relative beta (%)	0.04 [0.02 0.09]	0.05 [0.03 0.06]	0.04 [0.01 0.07]
SNR	(dB)	4.73 [3.22 6.29]	4.89 [3.93 7.87]	4.83 [4.40 6.35]
C1, P1, N1 mean	C1 amplitude (μV)	0.03 [-10.23 6.48]	-6.49 [-20.1 0.52]	-4.54 [-7.91 -1.41]
	C1 latency (ms)	40 [2 72]	64 [20 70]	52 [2 72]
	P1 amplitude (μV)	23.13 [8.08 43.06]	14.42 [1.47 28.73]	10.41 [3.21 16.76]
	P1 latency (ms)	98 [78 126]	98 [68 134]	92 [88 134]
	N1 amplitude (μV)	-10.05 [-24.53 5.83]	-7.8 [-13.08 -1.34]	-7.3 [-11.79 -0.53]
	N1 latency (ms)	213 [144 268]	210 [136 250]	199 [162 268]
Power mean	Absolute alpha (μV^2)	31.62 [18.01 98.28]	24.52 [5.95 51.55]	18.18 [3.60 35.93]
	Relative alpha (%)	0.20 [0.14 0.35]	0.23 [0.18 0.33]	0.16 [0.12 0.23]
	Absolute beta (μV^2)	15.48 [6.09 66.96]	10.08 [1.81 22.92]	6.78 [3.40 13.38]
	Relative beta (%)	0.10 [0.04 0.24]	0.11 [0.08 0.16]	0.09 [0.05 0.20]

The data are reported as median [range].

Table 3. Group differences in variability and averaged measures of neural activity of 16p CNV.

	DEL/Control			DUP/Control		DEL/DUP	
		Actual difference	P-value	Actual difference	P-value	Actual difference	P-value
C1, P1, N1 variability	C1 amplitude (μV)	2.92	0.048	1.45	0.437	1.48	0.330
	C1 latency (ms)	7.25	0.010	1.45	0.702	5.80	0.020
	P1 amplitude (μV)	6.16	**0.001**	2.79	0.282	3.37	0.100
	P1 latency (ms)	0.80	0.650	5.05	0.108	5.85	**0.003**
	N1 amplitude (μV)	4.01	0.080	3.15	0.368	0.86	0.724
	N1 latency (ms)	5.61	0.154	9.66	0.021	4.05	0.372
Power variability	Absolute alpha (μV^2)	4.67	0.226	4.80	0.231	9.47	**0.004**
	Relative alpha (%)	0.01	0.510	0.03	0.016	0.02	0.064
	Absolute beta (μV^2)	2.28	0.085	1.17	0.325	3.45	**0.002**
	Relative beta (%)	< 0.01	0.599	<0.01	0.950	<0.01	0.687
SNR	(dB)	0.23	0.556	0.04	0.931	0.27	0.400
C1, P1, N1 mean	C1 amplitude (μV)	6.50	**0.006**	2.75	0.349	3.75	0.025
	C1 latency (ms)	18.07	0.022	9.52	0.277	8.55	0.323
	P1 amplitude (μV)	8.65	0.010	3.06	0.359	11.71	**0.0003**
	P1 latency (ms)	0.45	0.926	1.45	0.862	1.00	0.836
	N1 amplitude (μV)	0.98	0.702	0.63	0.728	1.61	0.565
	N1 latency (ms)	20.41	0.191	20.91	0.284	0.50	0.975
Power mean	Absolute alpha (μV^2)	13.87	0.067	8.22	0.225	22.09	**0.003**
	Relative alpha (%)	0.02	0.208	0.07	**0.003**	0.04	0.019
	Absolute beta (μV^2)	7.51	0.053	2.78	0.289	10.29	**0.003**
	Relative beta (%)	0.01	0.731	<0.01	0.892	0.01	0.681

Significant results of permutation tests after correcting for FDR (significance threshold at $p < 0.006$) are in bold.

Figures

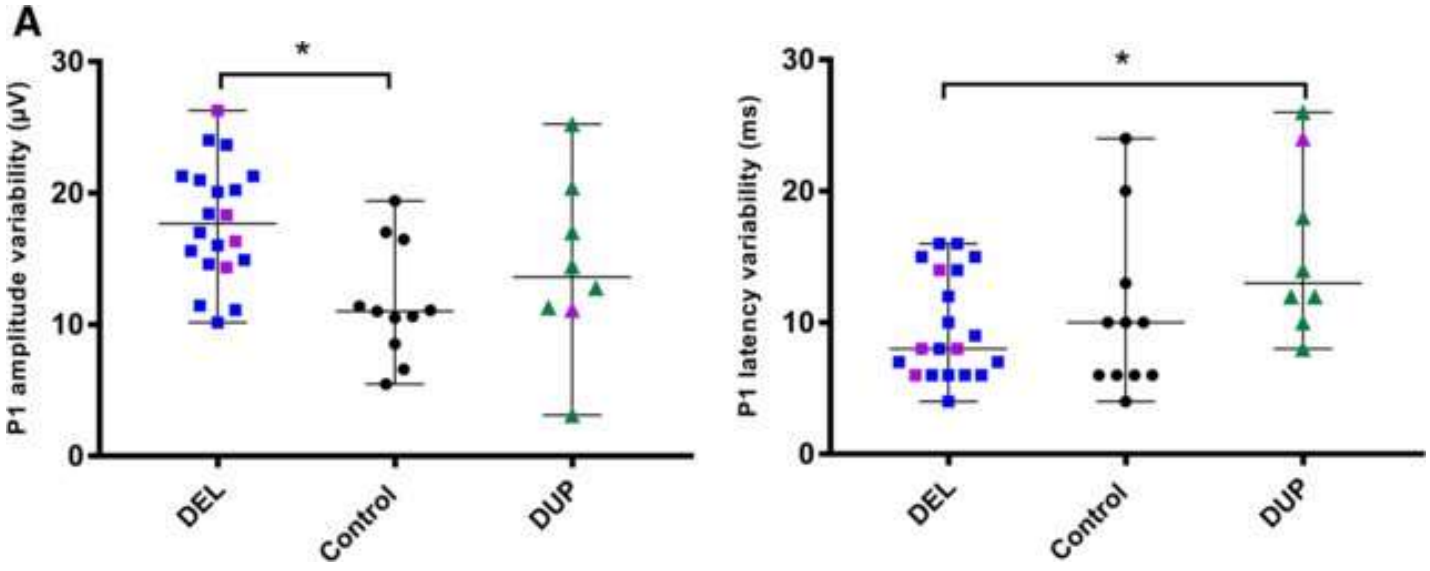

Figure. 1

P1 variability in 16p11.2 CNV. All three groups are presented similarly in both subfigures with the DEL group shown in blue, the DUP group shown in green, and the typical control groups shown in black. In addition, participants within the CNV groups with a diagnosis of autism spectrum disorder are indicated in purple. (A) The left graph shows scatter plots representing the distributions (median and range) of intraparticipant amplitude variability (MAD) of the peak P1 component, averaged across groups. (B) The right graph shows group distributions of latency variability of peak P1.

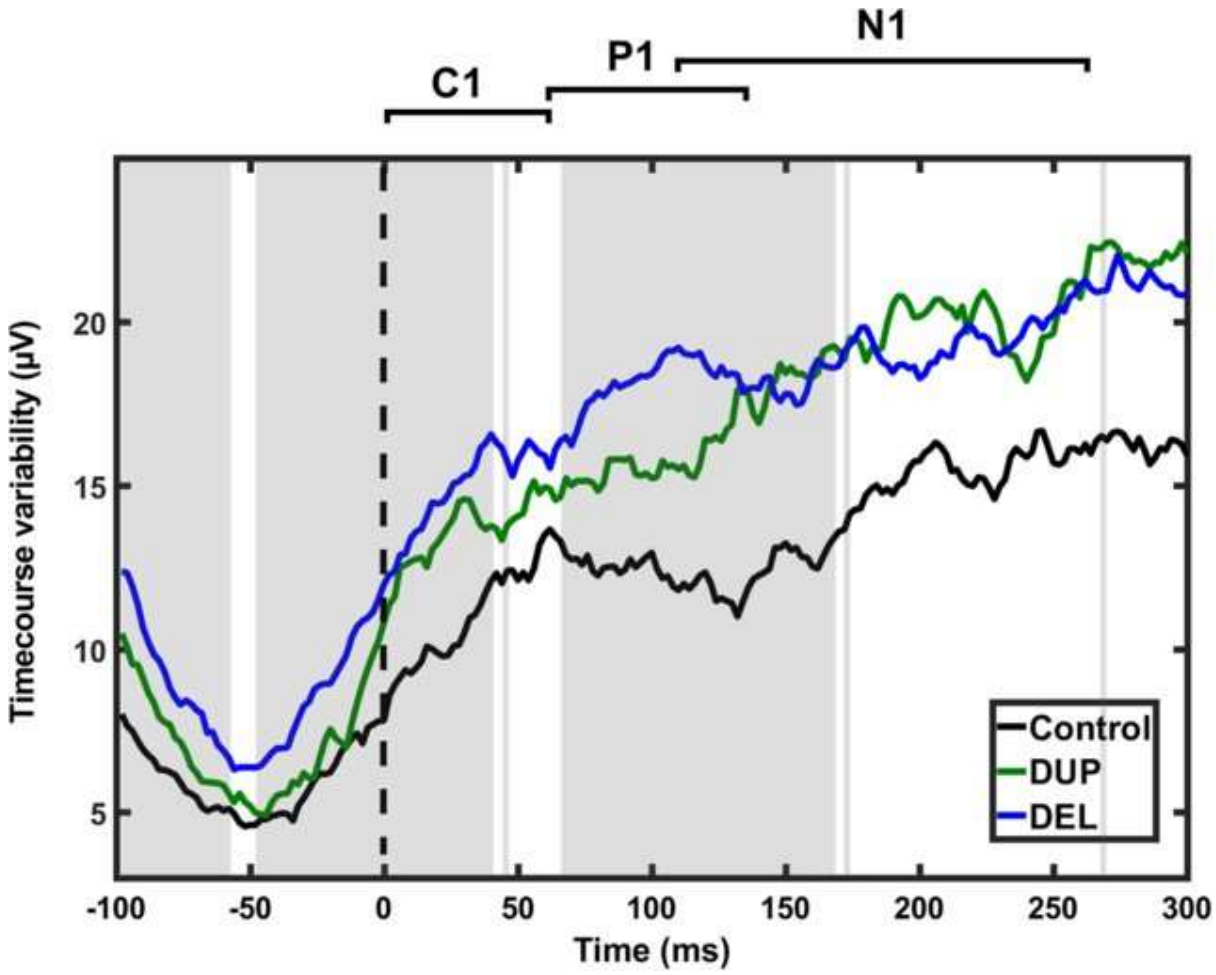

Figure. 2

Timecourse variability in 16p11.2 CNV. Timecourse variability in 16p11.2 CNV. The DEL group is indicated with blue, DUP group with green, and control group with black. The figure shows the timecourse variability (i.e., variability in amplitude at each time-point, 2 ms interval, throughout the signal) for all three groups. The gray shaded areas represent the durations by which DEL significantly differed from controls in amplitude (significance threshold at $P < 0.029$).

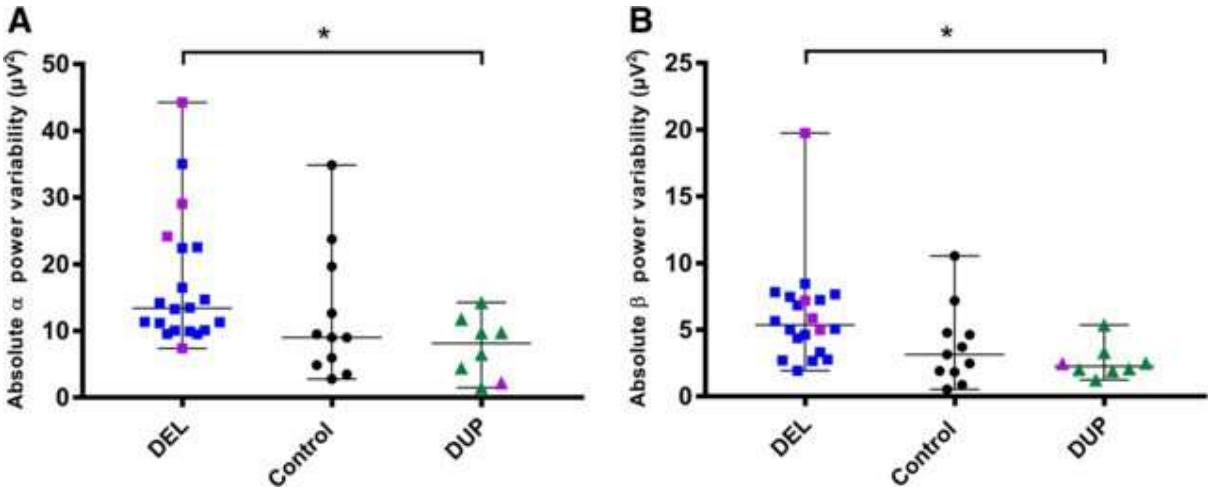

Figure. 3

Alpha and beta power variability in 16p11.2 CNV. All three groups are presented similarly in both subfigures with the DEL group shown in blue, the DUP group shown in green, and the typical control groups shown in black. In addition, participants within the CNV groups with a diagnosis of autism spectrum disorder are indicated in purple. (A) The left subfigure shows scatter plots representing the group distributions of intraparticipant variability of absolute alpha power (8–14 Hz). (B) The right subfigure shows group distributions of absolute beta variability (14–30 Hz).

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