Research in Autism Spectrum Disorders 60 (2019) 25–35

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

journal homepage: www.elsevier.com/locate/rasd

Homozygosity for the 10-repeat dopamine transporter (*DAT1*) allele is associated with reduced EEG response in males with ASD

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ARTICLE INFO

Number of reviews completed is 2

Keywords:
ASD
Autism
Electroencephalogram
DAT1
Dopamine
Face processing

ABSTRACT

Background: Individuals with autism spectrum disorder (ASD) have reduced interest in human faces and atypical event-related brain potentials (ERPs) in response to face stimuli, suggesting that face processing may be a functional marker of ASD susceptibility.
Method: This report explored the visual processing of individuals with ASD (n = 50) compared with their first-degree relatives (n = 117) using electroencephalogram (EEG), and associated EEG response with specific polymorphisms in the COMT, OXTR, SLC6A4 and DAT1 genes.
Results: Polymorphisms in the COMT and OXTR genes were not associated with any specific EEG response; on the other hand, the 5-HTTLPR polymorphism located upstream of SLC6A4 was associated with increased latency of the P1 component of the EEG response, and DAT1 genotype correlated with reduced amplitude of the N170 component in male participants with ASD.
Conclusion: These results suggest an interaction between DAT1 genotype and male participants with ASD characterized by reduced cognitive performance when processing faces as measured by EEG. Identifying ASD functional markers and grouping individuals with shared genetic biomarkers or endophenotypes may facilitate greater understanding of the heterogeneity underlying ASD leading to improved diagnosis and treatment of ASD.

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by deficits in communication and social functioning, as well as repetitive, stereotyped behaviors (American Psychiatric Association, 2013). ASD is common, affecting about 1/68 individuals (Christensen et al., 2016), and heterogeneous, with genetic and environmental factors affecting both ASD presentation and etiology. Currently, ASD is classified and diagnosed largely based on symptom presentation rather than biology-based etiology; therefore, the etiology underlying ASD cannot be expected to have a single pathology and similarly, no single genetic variant could produce the wide array of behavioral manifestations (Damiano, Mazefsky, White, & Dichter, 2014; Licinio & Wong, 2013). It is likely that autism susceptibility genes increase the probability of developing one or more components of the syndrome,

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https://doi.org/10.1016/j.rasd.2018.12.003
Received 14 August 2018; Received in revised form 11 December 2018; Accepted 13 December 2018
Available online 22 January 2019
1750-9467/

and the accumulation of related genetic traits cross a threshold into a clinical diagnosis of autism (Dawson et al., 2005). To better understand the varying degrees of dysfunctions in mental illness, a recent NIMH initiative, the Research Domain Criteria (RDoC), quantifies molecular, genetic, neural, and behavioral features of mental disorders, and groups these features into higher-level domains of human behavior and functioning including cognition, social processes, arousal/regulatory systems, and negative- and positive-valence systems (Damiano et al., 2014; Licinio & Wong, 2013; Insel et al., 2010; Insel & Cuthbert, 2009). Responses to faces are likely one of the best-studied examples of social communication in humans and has important roles in several domains including cognition and social processes.

Individuals with ASD have reduced interest in human faces, impaired face recognition and atypical event-related brain potentials (ERPs) to faces, indicating that face processing may be a functional marker for susceptibility to ASD (Dawson et al., 2005; Golarai, Grill-Spector, & Reiss, 2006). In typically developing individuals, the brain processes faces in a predictable manner using a consistent network of neurological pathways whose responses can be measured reliably using visually evoked ERPs. Two components of the visually evoked brain potential that are relevant to face processing are the P1 and N170. The P1, or P100, is a positive deflection that peaks between 80–100 milliseconds following a visual stimulus. The P1 signal is localized to the extrastriate cortex (Di, Martinez, Sereno, Pitzalis, & Hillyard, 2002) and the amplitude of the P1 can vary with attention, when a participant's attention is directed to the stimulus then P1 amplitude is enhanced relative to an unattended stimulus (Hileman, Henderson, Mundy, Newell, & Jaime, 2011; Hillyard, Vogel, & Luck, 1998). The second component of the ERP that is relevant to face processing is the N170, a negative deflection that peaks 170 ms after stimulus onset in the posterior temporal regions of the brain (Neuhaus, Kresse, Faja, Bernier, & Webb, 2016). When presented with an image of a whole, correctly configured face, typically developing individuals display a N170 amplitude that is stronger and lateralized to the right-hemisphere (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Munk, Hermann, El, Grant, & Hennig, 2016; Rossion, Joyce, Cottrell, & Tarr, 2003) relative to other visual stimuli including inanimate objects (Eimer, 2000; Rossion et al., 2000, 2003; Taylor, Batty, & Itier, 2004). The N170 is unaffected by the expression on the presented face (Eimer & Holmes, 2007) or the number of stimulus repetitions (Schweinberger, Pickering, Burton, & Kaufmann, 2002). For these reasons, the N170 component of the visually evoked ERP appears to represent the brain's early, pre-categorical, largely perceptual face processing (Battaglia et al., 2007). When individuals with ASD process faces, EEG studies have demonstrated that the P1 component shows increased latency (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; O'Connor, Hamm, & Kirk, 2005; Wang, Yang, Liu, Shao, & Jackson, 2017) while the N170 component has reduced amplitude, increased latency, and no apparent right hemisphere lateralization (Churches, Wheelwright, Baron-Cohen, & Ring, 2010; O'Connor et al., 2005; Hileman et al., 2011; McPartland et al., 2004, 2011; Tye et al., 2015). Thus, the phenotypic disinterest in faces that is often observed in ASD is mirrored by abnormalities in the neural response to visually presented face stimuli.

Face recognition is a highly specific and heritable cognitive ability (Wilmer et al., 2010) suggesting that genetic factors likely influence EEG responses during visual processing. Therefore, it is no surprise that studies have shown that relatives of individuals with ASD, including parents and/or siblings, demonstrate higher than normal rates of autism-related impairments including social, communication, personality, and cognitive characteristics (Landry & Chouinard, 2016), altered social/emotional processing and underlying neural circuitry (Dalton, Nacewicz, Alexander, & Davidson, 2007), and atypical EEG responses (Bosl, Tager-Flusberg, & Nelson, 2018; Dawson et al., 2005; Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012). One rationalization for this phenomenon may be that family members of an individual with ASD have a pool of autism susceptibility genes that manifest themselves as subclinical ASD traits in the parents and siblings but have accumulated in the proband to cross a threshold into a clinical diagnosis of autism (Dawson et al., 2005). Studying individuals with ASD in the context of their first-degree relatives, who have a similar genotypic profile but differ in diagnosis, may identify a link between phenotype and susceptibility genes that is specific to ASD.

Several genes with an established role in social cognitive processes and visual processing include *COMT*, *DAT1*, *SLC6A4* and *OXTR*. Both *COMT* and *DAT1* are involved in the dopaminergic system, which has an important role in cognitive processes, reward processing, and reinforcement of learning (Alcaro, Huber, & Panksepp, 2007). Importantly, dysfunction in the dopamine rewards system has been proposed to account for impairments in social motivation found in individuals with ASD (Dawson et al., 2005). Within the dopaminergic system, *COMT* is involved in catabolism of catecholamine neurotransmitters and *DAT1* clears dopamine from the synaptic cleft, both of which are key elements in regulating dopamine levels. *SLC6A4* is involved in the serotonin system, which has key roles in stress response and social cognition. The short allelic variant in the *SLC6A4* promoter (5-HTTLPR) is associated with reduced serotonin transporter activity and an increase in anxiety-related traits (Lesch et al., 1996). Recent studies by Canli et al. show that areas of the brain involved in social cognition display differential effects on activation as a function of the 5-HTTLPR genotype and stress in response to visual face stimuli (2006, Canli et al., 2005), prompting the hypothesis that dysfunction of neurons sensitive to serotonin may cause social and communication disabilities associated with ASD (Canli & Lesch, 2007). Finally, OXTR is a G-protein couple receptor for oxytocin, a neuropeptide with an important role in regulation of complex social behaviors and overcoming social stress (Heinrichs & Domes, 2008). Several single nucleotide polymorphisms (SNPs) within the OXTR gene have been associated with ASD-risk in Japanese (Liu et al., 2015), Chinese (Wu et al., 2005) and Caucasian populations (Campbell et al., 2011).

The purpose of this study was to link groups of individuals with ASD to specific genotypes in autism susceptibility genes characterized by altered performance during face processing as measured by EEG. We examined the ERPs elicited by face and object stimuli and the genotype for 7 specific polymorphisms in 50 individuals with ASD and 117 of their first-degree relatives. We hypothesized that subgroups of individuals with ASD who share a specific genetic polymorphism(s) would demonstrate differences in EEG responses during visual processing when compared with other individuals with a different phenotype and/or genotype. These differences may constitute a biomarker or endophenotype which may facilitate greater understanding of the heterogeneity underlying ASD.

Table 1
Participant characteristics for sex, age, and genotype for 7 polymorphisms in 4 genes for participants diagnosed with ASD and their first degree, unaffected relatives. Alleles that are not in Hardy-Weinberg Equilibrium (HWE: X^2, df = 1, $p < 0.05$) are designated by an asterisk.

		First degree, unaffected relatives (n = 117) †	ASD (n = 50) †
Demographics			
Sex	Male	50	38
	Female	67	12
Age (years)	Mean ± SD	37.6 ± 15.3	17.3 ± 7.0
	Range	8-67	9-48
Role in family	Parent	35M / 50F	1M / 0F
	Sibling	15M / 17F	37M / 12F
SNP Genotype			
OXTR rs7632287	G/G	28M / 38F	29M / 10F
	G/A	21M / 26F	8M / 1F
	A/A	1M / 3F	1M / 1F
	HWE	$X^2 = 1.6$, p = 0.205	$X^2 = 2.09$, p = 0.149
OXTR rs2254298	G/G	39M / 51F	33M / 9F
	G/A	10M / 15F	3M / 3F
	A/A	1M / 1F	2M / 0F
	HWE	$X^2 = 0.03$, p = 0.863	$X^2 = 5.56$, p = 0.018*
OXTR rs53576	G/G	19M / 30F	15M / 8F
	G/A	27M / 34F	20M / 2F
	A/A	4M / 3F	3M / 2F
	HWE	$X^2 = 4.54$, p = 0.033*	$X^2 = 0.01$, p = 0.938
OXTR rs1042778	G/G	20M / 21F	15M / 5F
	G/T	25M / 35F	17M / 6F
	T/T	5M / 11F	6M / 1F
	HWE	$X^2 = 0.65$, p = 0.419	$X^2 = 0.01$, p = 0.925
COMT rs4680	G/G	17M / 15F	12M / 2F
	G/A	25M / 29F	17M / 5F
	A/A	8M / 23F	9M / 5F
	HWE	$X^2 = 0.69$, p = 0.406	$X^2 = 0.72$, p = 0.396
5-HTTLPR	L/L	22M / 22F	14M / 3F
	L/S	22M / 35F	16M / 7F
	S/S	6M / 10F	8M / 2F
	HWE	$X^2 = 0.13$, p = 0.717	$X^2 = 0.19$, p = 0.663
DAT1	10/10	27M / 37F	23M / 7F
	10/9	19M / 24F	13M / 5F
	9/9	4M / 6F	2M / 0F
	HWE	$X^2 = 0.51$, p = 0.475	$X^2 = 0.12$, p = 0.729

†Sex distribution is shown as Male/Female.
*Alleles that are not in Hardy-Weinberg equilibrium.

2. Methods

2.1. Participants

Individuals diagnosed with ASD and their first-degree relatives were recruited for this study via our on-line registry at http://www.autismresearch.com. Individuals or families with ASD that were interested in autism research were directed to the on-line registry by their doctor, local autism chapter or independently. The registry collects demographic data from all potential participants including age, sex, diagnosis, contact information, etc. and formed a pool for recruitment for the study. Participants were predominately Caucasian (86.98%) but also included Black/African American (1.18%), First Nations/Indigenous (1.18%), East Indian (0.59%), and other/not specified (8.88%). Age and sex demographics of participants are summarized in Table 1.

ASD diagnosis was confirmed by clinician reports provided by the participants and validated using the Autism Diagnostic Interview-Revised and/or the Parent Pervasive Developmental Disorder Behavior Inventory. The comparison group included first-degree relatives (parents and siblings) of the ASD participants who reported that they did not have an ASD diagnosis. Informed written consent was obtained from all participants or their legal caregivers prior to the study. All experimental protocols were approved by and conducted in accordance with the Queen's University Health Sciences and Affiliated Teaching Hospitals Research

Ethics Board (HSREB#PSIY-300-09/PSIY-074-99).

2.2. ERP paradigm

2.2.1. Stimuli

To contrast response to face versus non-face stimuli, participants viewed upright images of human faces (Battaglia et al., 2005, 2007) and objects (three musical instruments) via a computer monitor. Images were black and white and standardized for size (10 cm x 20 cm), background color (black) and mean luminescence (149.6 ± 10.8 cd/m^2).

2.2.2. Task description

Images of faces and objects were randomly presented to the participant until each image was presented twenty times using ePrime 1.0 software. To maintain interest, images of three different animals were interspersed throughout and participants were asked to click a button each time the image of an animal appeared. Participant response to presentation of an animal was not analyzed due to the potential bias from clicking the button. Each trial consisted of a fixation crosshair (500 ms) then stimulus image (500 ms), with a ~1000 ms interval between trials. Participants viewed 240 images (20 images of each face, musical instrument, and animal) in one continuous sitting, where the total task length was ~8 min. There was no formal training phase, but the first three trials for each stimulus was removed.

2.2.3. Data collection

We outfitted an EGI 128-channel geodesic sensor net and Net Amps 200 amplifier with impedances maintained below 30 kΩ in a dedicated room in our mobile lab. Participants were fitted with the EEG net and seated approximately 75 cm from the computer monitor delivering the stimuli. EEG was recorded continuously from the scalp at a sampling rate of 250 Hz using NetStation v4.2, referenced to vertex and filtered from 1 to 100 Hz, time constant = 1 s.

2.2.4. ERP processing

Pre-processing was conducted using NetStation's Waveform Tools. Raw recordings were filtered (bandpass: 0.3–20 Hz) and the filtered files were segmented to 200 ms before and 1000 ms after each stimulus presentation. Artifact rejection and correction was undertaken for bad channels and bad trials. Bad channels were those that showed large transients (> 100 μV) on more than 20% of the experimental trials. Channels identified as bad were replaced with the bad channel replacement tool that uses spherical spline interpretation from surrounding channels. Ocular artifact was identified using an algorithm that identified large rapid transients in the infra- and supra-orbital electrodes (blinks) and transients in the left and right external canthi (lateral eye movement). Blinks were corrected using the ocular artifact removal tool that uses a weighted linear regression to subtract the signal from the ocular channels from the cortical channels. Trials that included paroxysmal movements or that remained uninterpretable following bad channel and ocular correction were removed from the data analysis. Segments were averaged by stimulus type for each channel and subjects with fewer than 20 usable segments for both object and face stimuli were removed from further analysis (n = 68). Files were rereferenced to the average reference and exported to Matlab R2015b. Electrodes of interest (Fig. 1: left 57, 58, 64, 69; right 89, 95, 96, 100) were selected based on a review of relevant literature and by visual inspection of grand averaged data of first degree relatives for maximum N170 response to faces (Anzures, Goyet, Ganea, & Johnson, 2016; Neuhaus et al., 2016; Tye et al., 2015). Ranges were specified for each participant individually through visual inspection to coincide with time windows described previously (Anzures et al., 2016; Tye et al., 2013). The N170 peak was coded as the most negative peak in the selected range for subjects with a clear ERP. Participants that lacked clear waveforms including local min or max peaks for P100, N170, P300 and N400 based on a visual inspection were removed from further analysis (n = 2).

2.3. Genotyping

Following EEG recording, participants were asked to provide a buccal swab, saliva (Oragene, DNA Genotek) or blood sample for DNA extraction. Genotyping for *OXTR* (rs2254298, rs3576, rs7632287, rs1042778) and *COMT* (rs4680) SNPs were carried out using a validated Custom TaqMan SNP Genotyping Assay (ThermoFisher Scientific) in 384 well plates on a ViiA 7 Real-Time PCR System (ThermoFisher Scientific) as previously described (Liu et al., 2009, 2011). Genotyping of the *DAT1* VNTR polymorphism in the 3′ UTR and the 5-HTTLPR polymorphism was performed using polymerase chain reaction (PCR) as previously described for *DAT1* (Lackner, Sabbagh, Hallinan, Liu, & Holden, 2012) and 5-HTTLPR (Mundo, Walker, Tims, Macciardi, & Kennedy, 2000). The single participant with undetermined genotype for 5-HTTLPR and *DAT1* due to poor DNA quality was excluded from further analysis, the other 167 individuals (99.4%) were successfully genotyped for all markers. Participant characteristics including genotype distribution and frequency, and Hardy-Weinberg equilibrium statistics for each marker are shown in Table 1. Individuals who are homozygous for the *DAT1* 10-repeat allele have higher dopamine transporter availability (Heinz et al., 2000), lower dopamine transporter binding (Jacobsen et al., 2000) and more likely to be diagnosed as ADHD compared with carriers of the 9/9 or 9/10 alleles (Loo et al., 2003); therefore, individuals that had 9/9 or 9/10 genotypes were grouped together for all the analysis as previously described (Loo et al., 2003). Investigators were blind to individual's genotype during ERP data collection and processing.

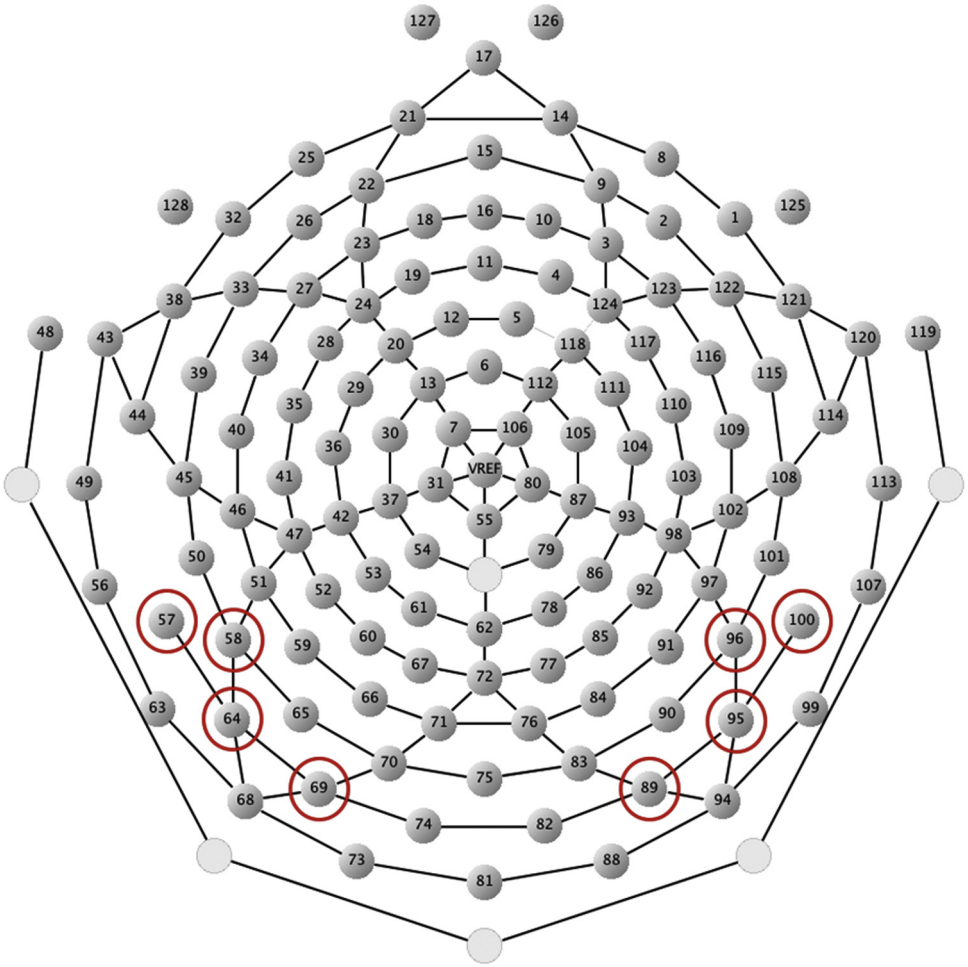

Fig. 1. EEG sensor layout showing the eight occipito-temporal electrodes used to generate grand average ERP waveforms.

2.4. Statistical analysis

We used R-studio Version 1.0.136 (R Core Team, 2017) with the *lme4* package (Bates, Maechler, Bolker, & Walker, 2015) to perform a linear mixed effects (lme) model (corrected for age of participant) with varying-intercept nested group effects for family and participant for P1 amplitude, P1 latency, N170 amplitude and N170 latency. First, we fit a null model without any variables, then sequentially fit the model with one of the following variables: group (ASD vs relatives), sex (male vs female), stimulus (face vs object), hemisphere (left vs right), *OXTR* rs7632287, *OXTR* rs2254298, *OXTR* rs53576, *OXTR* rs1042778, *COMT* rs4680, 5-HTTLPR, and *DAT1*. Each model was compared to the null model by an ANOVA test using goodness of fit as indicated by likelihood ratio tests. Variables that showed significant improvement over the null model ($p < 0.05$; FDR < 0.05) were retained in the main-effects model. Interactions were modeled by fitting the interaction of each main effect variable with each other variable and compared to the main-effects model with an ANOVA test. Interactions that showed significant improvement over the main model ($p < 0.05$; FDR < 0.05) were retained in the final model. Reported FDR values were obtained by adjusting P-values for multiple comparison using the Benjamini-Hochberg (BH) correction (Benjamini & Hochberg, 1995) method in R. We conducted a post-hoc power analysis with the pwr package in R using the general linear model function with the 11 variables, sample size of 167 individuals and alpha value of 0.05. The post-hoc analysis revealed that to reach 80% statistical power, the effect size must be greater than 0.107, which represents a medium effect based on Cohen's benchmark: small ($f_2 = 0.02$), medium ($f_2 = 0.15$), and large ($f_2 = 0.35$).

2.5. Data availability

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

Table 2
Amplitude and latency of the P1, showing the mean (M), standard error of the mean (SE) and sample size (n).

			P1 amplitude		P1 latency		
Sex	Stimulus	Hemisphere	M (μV)	SE	M (ms)	SE	n
Unaffected Relatives Group							
Female	Face	Left	2.06	0.2	142.78	2.5	67
		Right	2.71	0.3	142.67	1.9	67
	Object	Left	2.35	0.3	150.05	2.2	65
		Right	3.03	0.3	151.40	2.1	65
Male	Face	Left	3.00	0.3	148.09	2.6	50
		Right	3.59	0.2	149.93	2.2	50
	Object	Left	3.46	0.3	158.77	3.0	49
		Right	4.19	0.3	156.24	2.4	49
ASD Group							
Female	Face	Left	1.36	0.7	130.71	6.4	12
		Right	2.21	0.7	135.71	3.5	12
	Object	Left	1.32	0.5	152.04	6.2	12
		Right	2.92	0.7	140.04	5.0	12
Male	Face	Left	3.73	0.4	141.89	3.9	38
		Right	3.95	0.5	138.31	3.4	38
	Object	Left	4.32	0.6	157.56	3.2	35
		Right	4.11	0.5	155.16	3.8	35

3. Results

This study collected EEG data and the genotype of seven common variants for 167 participants (50 ASD and 117 first-degree unaffected relatives). The mean amplitude and latency of the P1 (Table 2) and N170 (Table 3) components of the ERP are reported for group (ASD vs relatives), brain hemispheres (left vs right), and stimulus (face vs object).

3.1. P1 amplitude

Using a lme model to fit the P1 ERP amplitude data, the final model that best described the P1 amplitude data included the main effects of sex ($\chi^2(1) = 19.451$, FDR < 0.001), hemisphere ($\chi^2(1) = 16.974$, FDR $= 0.001$) and stimulus ($\chi^2(1) = 7.167$, FDR $= 0.027$) (Supplementary Fig. S1). The model was not significantly improved by main effects of the other variables (all $\chi^2 \leq 3.375$, FDR ≥ 0.407) or interactions between the main effects and other variables (all $\chi^2 \leq 10.305$, FDR ≥ 0.074).

3.2. P1 latency

The final lme model that best fit the P1 latency ERP included main effects of stimulus ($\chi^2(1) = 78.215$, FDR < 0.001) and 5-

Table 3
Amplitude and latency of the N170 ERP showing the mean (M), standard error of the mean (SE) and sample size (n).

			N170 amplitude		N170 latency		
Sex	Stimulus	Hemisphere	M (μV)	SE	M (ms)	SE	n
Unaffected Relatives Group							
Female	Face	Left	−2.84	0.3	205.84	2.9	67
		Right	−3.74	0.3	203.93	2.0	67
	Object	Left	−1.35	0.3	218.35	3.0	65
		Right	−1.34	0.3	218.41	2.6	65
Male	Face	Left	−5.98	0.5	209.61	2.6	50
		Right	−6.52	0.5	207.61	2.3	50
	Object	Left	−2.19	0.4	225.36	3.1	49
		Right	−2.63	0.4	222.58	2.8	49
ASD group							
Female	Face	Left	−3.50	0.7	203.93	5.5	12
		Right	−4.37	1.0	197.26	6.0	12
	Object	Left	−1.77	0.8	204.26	5.7	12
		Right	−1.98	0.9	205.26	4.2	12
Male	Face	Left	−5.65	0.6	207.24	4.0	38
		Right	−6.14	0.7	208.39	4.0	38
	Object	Left	−1.41	0.5	220.40	4.7	35
		Right	−1.70	0.6	214.57	3.8	35

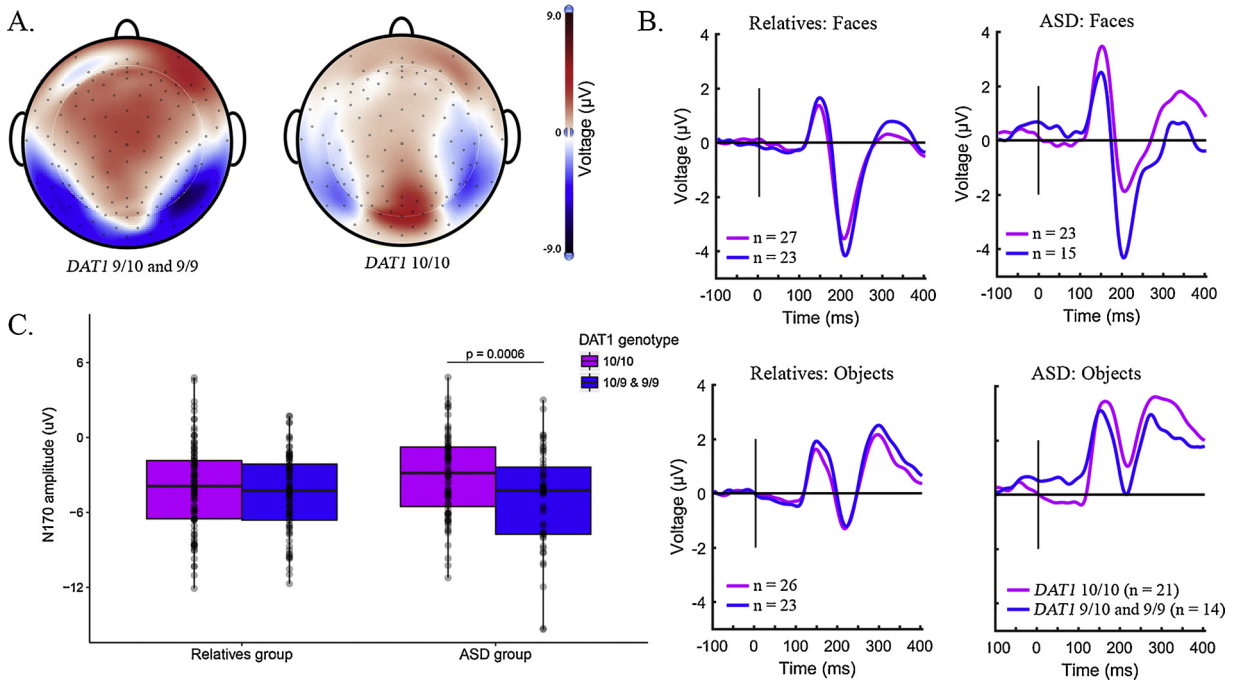

Fig. 2. N170 amplitude is correlated with *DAT1* genotype in male participants with ASD. A. Scalp distribution shows different signal strength and distribution between ASD males carrying *DAT1* 10/10 (n = 23) and *DAT1* 9/9 or 9/10 (n = 15) genotypes in response to face stimulus. B. The average wave scan for males with ASD and their unaffected male relatives presented with face and object stimuli shows reduced N170 ERP in ASD individuals carrying the *DAT1* 10/10 allele. C. Male participants with ASD and homozygous 10/10 for the *DAT1* locus demonstrate significantly reduced N170 amplitude compared with ASD males carrying a *DAT1* 9-repeat allele (group**DAT1* interaction: F(1,340) = 6.304, p = 0.013, Tukey p adj = 0.0006).

HTTLPR genotype (χ^2 (1) = 7.665, FDR = 0.031) using the S allele as a dominant risk allele (Supplementary Fig. S2). The model was not significantly improved by main effects of the other variables (all $\chi^2 \leq 5.564$, FDR ≥ 0.067) or by interactions between the main effects and other variables (all $\chi^2 \leq 9.496$, FDR ≥ 0.055).

3.3. N170 amplitude

The final lme model to best fit the N170 ERP amplitude data included main effects of sex (χ^2 (1) = 21.008, FDR < 0.001) and stimulus (χ^2 (1) = 224.9, FDR < 0.001) and the interactions of sex:stimulus (χ^2 (1) = 34.974, FDR < 0.001) and *DAT1*:stimulus (χ^2 (2) = 11.967, FDR = 0.024) using the 10-repeat allele as a recessive risk allele for *DAT1* (Supplementary Fig. S3). The main effect of *DAT1* (χ^2 (1) = 5.569, p = 0.018, FDR = 0.067) and the interaction between *DAT1*:sex (χ^2 (2) = 7.4752, p = 0.024, FDR = 0.113) were also significant before the BH correction. The model was not significantly improved by main effects of the other variables (all $\chi^2 \leq 4.066$, FDR ≥ 0.12) or other interactions between the main effects and variables (all $\chi^2 \leq 5.81$, FDR ≥ 0.173).

Since sex had a significant interaction with stimulus and an interaction that approached significance with *DAT1*, a lme model was conducted separately for each sex and group (male relatives, female relatives, ASD males and ASD females), using individual as the varying-intercept group effects. Stimulus had a main effect in each model (all $\chi^2 \geq 12.154$, FDR ≤ 0.001), but *DAT1* only had a significant main effect in the ASD male model (χ^2 = 6.798, FDR = 0.015; other models $\chi^2 \leq 2.422$, FDR ≥ 0.159). The ERP scalp distribution demonstrated that following the presentation of a face, males with ASD and 10/10 for *DAT1* show reduced N170 waveform signal strength and distribution across the posterior of the brain than males with ASD and carrying one or two 9-repeat alleles in the *DAT1* gene (Fig. 2A). A two-way ANOVA was run on the 38 male participants with ASD and 50 male relatives to further examine the effect of group and *DAT1* genotype on N170 amplitude across stimulus and hemisphere. There was a main effect of *DAT1* genotype (F(1,340) = 9.763, p = 0.002) and a significant interaction between the effect of group and *DAT1* genotype on N170 amplitude (F(1,340) = 6.304, p = 0.013). A Tukey Post Hoc test identified a significant difference in N170 amplitude between males with ASD carrying 10/10 allele of *DAT1* compared to males with ASD carrying at least one copy of the 9-repeat allele of *DAT1* (p adj = 0.0006) across stimulus, but no difference between male relatives with different *DAT1* genotypes was observed (p adj = 0.867). (Fig. 2B and C). A post-hoc power analysis using the pwr.f2.test function in the pwr package demonstrated sufficient power to detect changes due to the interaction between diagnosis group and *DAT1* genotype in the male participants (α = 0.05, effect size = 0.1362). A similar two-way ANOVA on 12 female participants with ASD and 67 female relatives did not demonstrate any changes in N170 amplitude due to group or *DAT1* genotype (all F(1,308) ≤ 1.788, p ≥ 0.182).

3.4. N170 latency

Finally, the lme model that best fit the N170 ERP latency data included only the main effects of stimulus ($\chi^2 = 92.722$, FDR < 0.001) (Supplementary Fig. S4). The model was not significantly improved by the other main effects ($\chi^2 \leq 3.522$, FDR ≥ 0.39) or by interactions between stimulus and the other variables ($\chi^2 \leq 6.544$, FDR ≥ 0.379).

4. Discussion

This study collected genotypic and electrophysiological data from individuals with ASD and their undiagnosed relatives to identify potential genotype-phenotype interactions that may contribute to clinical ASD. When considering main effects of stimulus, brain hemisphere and diagnosis group, our results support well-documented characteristics of the N170 waveform including reduced latency and increased amplitude in response to faces compared with objects (Eimer, 2000; Munk et al., 2016; Rossion et al., 2000, 2003; Taylor et al., 2004) (Supplementary Figs. S3 and S4). Another hallmark characteristic of the N170 waveform in typically developed individuals, right hemisphere lateralization in response to faces, was not detected in either the ASD group (O'Connor et al., 2005; Churches et al., 2010) or their relatives (Webb, Dawson, Bernier, & Panagiotides, 2006). The lack of significant differences in ERP response between diagnosis groups and the absence of the right hemisphere lateralization in response to faces support the broader autism phenotype (BAP) model that relatives of individuals with ASD possess subclinical autistic traits which may be related to genetic susceptibility factors (Bernier, Gerdts, Munson, Dawson, & Estes, 2012; Bora, Aydin, Sarac, Kadak, & Kose, 2017; Dawson et al., 2005; Gerdts & Bernier, 2011; Gerdts, Bernier, Dawson, & Estes, 2013; Pisula & Ziegart-Sadowska, 2015). Social interaction requires a high level of cognitive ability to interpret both verbal and non-verbal cues (Harvey & Penn, 2010), and individuals with ASD typically have deficits in several social behaviors including language processing, executive functioning, social reward and face processing (Dawson et al., 2005). As each individual with ASD carries their own landscape of susceptibility genes, environmental risk factors and phenotypic characteristics, identification of subgroups of individuals with ASD sharing biomarkers or endophenotypes will facilitate a better understanding of the heterogeneity underlying ASD.

When considering main effects of the sex of the participant, our results show that males had a significantly larger amplitude in both the P1 and N170 ERPs compared with female participants. Previous studies have reported sex differences in the occipito-temporal response to facial processing, but the nature of these differences have not been consistent (Proverbio, Brignone, Matarazzo, Del, & Zani, 2006; Proverbio, Brignone, Matarazzo, Del, & Zani, 2006; Proverbio, Riva, Martin, & Zani, 2010; Wang, Kitayama, & Han, 2011). Coffman et al. (Coffman, Anderson, Naples, & McPartland, 2015) demonstrated that P1 amplitude is reduced in females with ASD compared with males with ASD due to reduced specialization and more severely compromised social information processing. However, as the study did not include typically developing individuals it cannot be concluded if this was a characteristic of females with ASD or of all females. This variability highlights the importance of considering and controlling group effects (sex, family) and participant effects (age, variability between participants) on the recorded ERP and the need for larger and balanced numbers of male and female participants in future studies (Neuhaus et al., 2016).

We tested 7 markers in 4 genes including *COMT*, *DAT1*, *OXTR* and the 5-HTTLPR region upstream of *SLC6A4*. Our results showed a significant effect of the 5-HTTLPR genotype on P1 latency, where individuals with the S/S or S/L genotype, across group, sex and stimulus, had slower P1 ERP than individuals carrying the L/L genotype (Supplementary Fig. S2). The primary function of the serotonin transporter in the central nervous system is to capture serotonin from the synaptic cleft for transport into the pre-synaptic terminal for re-utilization, making the transporter an important regulator of serotonergic neurotransmission (Lee et al., 2011). Several brain regions associated with social behavior show differential effects on activation as a function of 5-HTTLPR genotype (Canli et al., 2005; 2006), leading Canli & Lesch (Canli & Lesch, 2007) to speculate that interaction between 5-HTTLPR gene and environmental stress may cause dysfunction in specific groups of neurons (mirror and Von Economo) causing social and communication disabilities associated with autistic syndromes. Further investigation is required to determine if the correlation between the 5-HTTLPR polymorphism and EEG response is observed outside of the ASD and BAP communities.

More importantly, this study attempts to link groups of individuals with ASD to specific genotypes in autism susceptibility genes characterized by reduced performance during face processing as measured by EEG. We found that males with ASD and homozygous for the 10-repeat allele for *DAT1* demonstrated reduced N170 amplitude to both faces and objects compared with ASD males with a 9-repeat allele; while male relatives demonstrated no difference in N170 amplitude as a result of *DAT1* genotype. These results suggest that this group of males with ASD may have accumulated genetic variants (including *DAT1*) which affect similar pathways and result in decreased performance during visual processing. *DAT1* primarily functions in the brain for reuptake of dopamine, and individuals that are homozygous for the 10-repeat *DAT1* allele have increased levels of the dopamine transporter in the brain resulting in relative hypodopaminergia (Kirley et al., 2002). The mechanism underlying the dopamine hypothesis of ASD proposes that dopamine dysregulation causes a failure to register social experiences as rewarding, resulting in reduced motivation to seek social interaction and failure to develop social abilities, which results in the persistent deficits in social interactions and communication (Paval, 2017) often seen in individuals with ASD. The dopaminergic neurons in the ventral tegmental area of the brain form the mesocorticolimbic circuit which is involved in high-order brain functions including the reward system (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Paval, 2017). Dopamine dysregulation due to hypodopaminergia from high *DAT1* activity, or aberrant *DAT1* function due to *de novo* genetic variants (Bowton et al., 2014; Cartier et al., 2015; Hamilton et al., 2013) may contribute to the failure of individuals with ASD to register social experiences as rewarding.

Methylphenidate (MPH) is a central nervous system stimulant commonly used to treat individuals with ADHD or ADHD symptoms in individuals with ASD because MPH is known to inhibit the dopamine transporter (Volkow et al., 1998) and ameliorates a *DAT1*-

mediated hypodopaminergic state (Bellgrove et al., 2005). As this report demonstrates that the high-activity allele of *DAT1* may be associated with altered EEG signal in visual processing, further study into the use of MPH to treat ASD symptoms in certain cases of ASD, namely males that are homozygous for the 10-repeat allele for *DAT1*, may be warranted. Not all individuals carrying two copies of the 10 repeat *DAT1* allele demonstrated altered visual processing likely due to the epistatic component of genetic risk (Dreher et al., 2009) that contributes to the heterogeneity underlying ASD. The female participants of this study do not show significant difference in ERP waveform due to *DAT1* genotype. Females with ASD often require a higher burden of ASD associated genetic variants (Goin-Kochel, Abbacchi, & Constantino, 2007; Werling & Geschwind, 2015) and may have different neurocognitive correlates and endophenotypes than males (Rhodes, Jeffery, Taylor, & Ewing, 2013), which may explain the observed sex differences. In addition, there were only 12 females with ASD in this study, which severely limits our ability to describe the effect of sex on visual processing in individuals with ASD, particularly those that are homozygous for the 10-repeat allele in *DAT1*.

The *COMT* or *OXTR* polymorphisms included in this study did not have any significant effect on visual processing in the neural response of ASD individuals or their relatives. Some genotypes did not meet Hardy-Weinberg equilibrium (*OXTR* rs53576, *OXTR* rs2254298), and others were rare (homozygous for A in *OXTR* rs2254298) indicating that the sample size may not be large enough to detect whether these genetic markers interact with EEG response. Furthermore, the post-hoc power analysis demonstrated the power of this study was limited to medium effect sizes, so to capture small effects of genetic markers on EEG responses would require much larger studies.

A significant barrier to research involving human participants is the requirement that participants must dedicate time and effort to attend the lab and perform required tests. The number of participants, including individuals with ASD together with their siblings and both parents recruited in this EEG study, was enabled using our mobile lab, allowing our researchers to travel to various cities and bring the test equipment to the participant. However, a drawback to the mobile lab was the environmental noise and vibration from the generator running the EEG equipment and the absence of radio-frequency shielded room. The increased background noise resulted in a considerable number of samples being removed during ERP processing due to limited usable segments and unclear waveforms. The sample groups used in this project contain deficits that may limit the detectable results. Distribution of age and sex are not consistent between the ASD group and the first-degree relatives group due to inherent differences between groups. The participants with ASD are obviously younger than their parents and ASD prevalence is four-fold higher in males than females. Conversely, the group containing parents is older and gender biased towards females as more mothers than fathers participated in the study. Furthermore, the lack of an external control group prevented determination of ASD-risk of the variants since we don't know how the genetic variants affects neural processing in healthy, unrelated individuals.

In conclusion, this study suggests an interaction between males with ASD and *DAT1* genotype which can be quantified as a reduction in N170 amplitude of the ERP waveform during face processing. It is likely that ASD individuals have accumulated multiple autism susceptibility genes that are dispersed between other family members and contribute to subclinical autism phenotypic characteristics in the family members, but synergistically cross the diagnostic threshold for autism in the proband. Homozygosity of the high activity, 10-repeat *DAT1* allele may constitute one such autism risk factor. Identifying ASD functional markers and grouping individuals with shared genetic biomarkers or endophenotypes may facilitate greater understanding of the heterogeneity underlying ASD leading to improved diagnosis and treatment of ASD.

Author contributions

Data acquisition: SW, JWK, MH; Analysis and interpretation of data: CS, MS, SW; Statistical analysis: CS; Genotyping: AM; Drafting of the manuscript: CS; Review of the manuscript: all authors; Study concept, design and supervision: XL

Competing interests

The authors declare no competing interests.

Acknowledgments

We thank all the families for their participation in this study. This work was supported by Ongwanada Special Operating Research Fund for the genetic study of autism and related disorders (XL) and private donations.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rasd.2018.12.003.

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