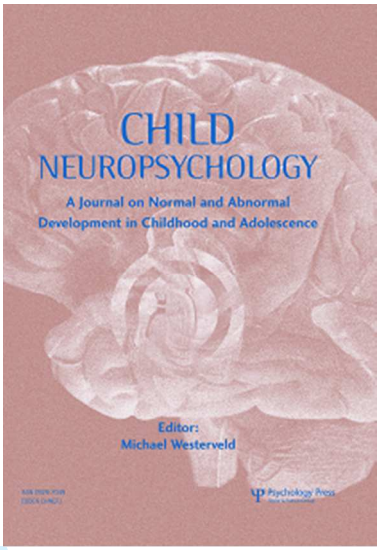

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Enhanced ERPs to Visual Stimuli in Unaffected Male Siblings of ASD Children

Gizelle Anzures[a], Louise Goyet[b], Natasa Ganea[c], & Mark H. Johnson[c]

[a]Center for Human Development, University of California, San Diego, USA

[b]Institute of Psychology, Université Paris Descartes, FR

[c]Centre for Brain and Cognitive Development, Birkbeck, University of London, UK

Corresponding Author:

Gizelle Anzures
Center for Human Development
University of California, San Diego
9500 Gilman Dr.
La Jolla, CA 92093-0115
USA

gizelle.anzures@gmail.com

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Abstract

Autism spectrum disorders are characterized by deficits in social and communication abilities. While unaffected relatives lack severe deficits, milder impairments have been reported in some first-degree relatives. The present study sought to verify whether mild deficits in face perception are evident among the unaffected younger siblings of children with ASD. Children between 6-9 years of age completed a face recognition task and a passive viewing ERP task with face and house stimuli. Sixteen children were typically developing with no family history of ASD, and 17 were unaffected children with an older sibling with ASD. Findings indicate that while unaffected siblings are comparable to controls in their face recognition abilities, unaffected male siblings in particular show relatively enhanced P100 and P100-N170 peak-to-peak amplitude responses to faces and houses. Enhanced ERPs among unaffected male siblings is discussed in relation to potential differences in neural network recruitment during visual and face processing.

Keywords: face recognition, N170, ASD, unaffected siblings, ERP

Face Perception and ASD Risk in Children

The social and communication deficits among children with autism spectrum disorders (ASD) have been found to be accompanied by atypicalities in perceiving social stimuli, such as faces (reviewed in Dawson, Webb, & McPartland, 2005a and Sasson, 2006) and biological motion (Blake, Turner, Smoski, Pozdol, & Stone, 2003; Freitag et al., 2008; Klin, Lin, Gorrindo, Ramsay, & Jones, 2009). Although impairments in processing facial expressions have also been implicated in ASD (reviewed in Harms, Martin, & Wallace, 2010), this paper will focus specifically on face identity recognition and electrophysiological responses to faces in relation to familial risk of ASD. Furthermore, while impairments in face perception among those with ASD have been widely replicated, accumulating evidence suggests that unaffected parents of children with ASD also demonstrate deficits (Baron-Cohen & Hammer, 1997; Dawson et al., 2005b; Losh & Piven, 2007; Wilson, Freeman, Brock, Burton, & Palermo, 2010a) – albeit to a much lesser degree. Thus, we sought to examine face recognition abilities and electrophysiological responses to faces among a group of unaffected younger siblings of individuals with ASD and a group of control children.

It should be noted that most studies show at least some group overlap in face recognition abilities across typically developing children and those with ASD, so that not all children with autism show impairments (Boucher & Lewis, 1992; Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998; Wilson, Brock, & Palermo, 2010b; Wilson, Palermo, Brock, & Burton, 2010c; Wolf et al., 2008). However, as a group, children with ASD tend to show reduced face recognition performance (Boucher & Lewis, 1992; Hauck, et al., 1998; Klin et al., 1999; Wilson et al., 2010b; Wilson et al., 2010c; Wolf et al., 2008). This behavioral group difference appears to be driven by a number of ways in which children with ASD differentially process face identity relative to controls. First, relative to controls, 6- to 15-year-old children with ASD likely require more time to learn the internal regions of faces (Wilson et al., 2010c). Second, children with ASD appear to weigh the mouth region more heavily than the eye region in their recognition. That is, they tend to be worse in matching the eye regions of faces (Wilson et al., 2010c; Wolf et al., 2008), but better in recognizing the mouth regions of faces (Joseph & Tanaka, 2003; Langdell, 1978). In addition, 8- to 14-year-old children with ASD tend to show holistic processing of the mouth regions, but significantly diminished holistic processing of the eye regions of faces (Joseph & Tanaka, 2003). It has been proposed that this reduced consideration of the eye region may be driven by a heightened emotional response to gaze fixation among those with ASD (Dalton et al., 2005).

Further group differences are evident at the electrophysiological level with regards to event-related potential (ERP) responses to faces. First, unlike controls, 3- to 4-year-old children with ASD fail to show different ERPs for familiar vs. unfamiliar faces – despite showing differential ERPs for familiar vs. unfamiliar objects (Dawson et al., 2002). Second, the P100 component, sensitive to low-level visual characteristics and attentional modulation (Heinze, Luck, Mangun, & Hillyard, 1990; Johannes, Münte, Heinze, & Mangun, 1995), and responsive to face orientation (Linkenkaer-Hansen et al., 1998), is larger in amplitude for inverted faces compared to upright faces in 9- to 17-year-old controls, but is comparable in amplitude for children with ASD (Hileman, Henderson, Mundy, Newell, & Jaime, 2011). Third, the N170 component, associated with the structural encoding of face stimuli and differentially responsive to face vs. non-face and inverted face categories (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 1998; Eimer, 2000a, 2000b; Rossion et al., 2000), is already lateralized in amplitude in controls during early childhood through early adolescence, but is more bilateral in distribution among children with ASD (Tye et al., 2013; Webb, Dawson, Bernier, & Panagiotides, 2006). In addition, whereas 3- to 4-year-old controls show faster N170 latencies to faces than objects, those with autism show the opposite pattern (Webb et al., 2006). Additional findings using fMRI have found group

differences in the activation of the fusiform and occipital gyri – brain structures that form part of the neural network responsible for face perception (Haist, Adamo, Han Wazny, Lee, & Stiles, 2013; Haxby, Hoffman, & Gobbini, 2000) – so that relative to controls, adolescents with ASD show decreased activation of the fusiform and right occipital gyri in response to faces (Dalton et al., 2005; Scherf, Luna, Minshew, & Behrmann, 2010), but show atypical recruitment of additional brain areas that are more associated with object processing in controls (Samson, Mottron, Soulières, & Zeffiro, 2012; Scherf et al., 2010).

Atypicalities in face perception likely extend into adulthood, so that relative to controls, adults with ASD generally show reduced face recognition performance and lack early ERP or EEG differentiation between upright and inverted faces (Grice et al., 2001; McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; Webb et al., 2012). Early ERP differentiation between upright and inverted faces are thought to occur in typically developing populations due to the disruption in face processing that inversion causes (Eimer, 2000). The lack of such ERP differentiation between upright and inverted faces suggest that individuals with ASD are likely processing upright and inverted faces in a more similar way than controls. This suggests a disruption in the typical development of face processing expertise, which is characterized by enhanced sensitivity to differences between faces in the canonical upright presentation compared to an atypical inverted presentation (Yin, 1969).

Adults with ASD also demonstrate atypical activation of the neural network associated with face processing. While group differences in fusiform and inferior occipital gyrus activation remain inconclusive, likely due to differences in task demands and variability in ASD characteristics across studies, more consistent findings allude to decreased amygdala and superior temporal sulcus activation in response to faces among adults with ASD relative to controls (Hadjikhani et al., 2004; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001). In addition to hypoactivation of particular structures critical for typical face processing, evidence of decreased functional connectivity relative to controls likely also contribute to atypical face processing (Kleinhans et al., 2008). Despite reports of hypoactivation in some brain regions among adults with ASD, there is also evidence of atypical recruitment of additional areas not typically associated with face perception in controls (Pierce et al., 2001; Samson et al., 2012).

While such atypicalities in perceiving social stimuli exist in individuals with ASD, there is accumulating evidence of behavioral and biological markers indicative of vulnerability among unaffected relatives of individuals with ASD – suggesting that cognitive and neural traits are associated with a genetic risk for ASD, irrespective of whether or not social and communication deficits are deemed to be clinical in severity. There appears to be a genetic susceptibility to milder social and communication deficits among unaffected relatives of individuals with ASD (Bolton et al., 1994; Pickles et al., 2000; Piven, Palmer, Jacobi, Childress, & Arndt, 1997). There also appears to be mild deficits in face emotion and face identity processing in this group. Relative to controls, unaffected parents of children with ASD show a decreased tendency to look at the eye region when making categorical judgments of emotion, and those with aloof personalities also show increased reliance on the mouth region in their emotion judgments (Adolphs, Spezio, Parlier, & Piven, 2008). Unaffected parents of children with ASD also tend to be worse than controls in inferring emotion based on the eye region alone (Baron-Cohen & Hammer, 1997; Losh & Piven, 2007).

With regards to processing face identity, poorer face recognition was found among 3-year-old high-risk siblings compared to controls when different photographs of familiarized faces were used during test trials (de Klerk, Gliga, Charman, Johnson, & the BASIS team, in press). Unaffected fathers

of children with ASD also tend to show lower face recognition performance relative to controls (Wilson et al., 2010a). Although unaffected mothers of children with ASD show comparable face recognition scores relative to controls, their performance on a sequential four-alternative forced choice match-to-sample task with faces has been found to be positively associated with the performance of their children with ASD (Wilson et al., 2010a). When collapsed across gender, parents of children with autism, as a group, show lower face recognition abilities relative to controls, under conditions of high memory demands, such as a 30 minute delay between the familiarization and test phases of the face recognition task (Dawson et al., 2005b). These parents also demonstrate a less lateralized N170 in response to faces, and no latency advantage in processing faces over non-face objects (Dawson et al., 2005b). Such overall findings are consistent with evidence regarding the heritability of face recognition abilities and holistic face processing in typically developing populations (Wilmer et al., 2010; Zhu et al., 2010).

Given such atypicalities in face perception among those with a high familial risk for ASD, we sought to examine face perception among unaffected first-degree relatives of individuals with ASD. We specifically examined recognition performance and electrophysiological responses to faces among children with an older sibling with ASD, but without ASD themselves. Obtaining behavioral and electrophysiological measures of face perception in this group would shed further light on the nature of atypical face perception associated with a high familial risk for ASD. Alternatively, given their unaffected status, these siblings can offer potential insight into protective factors – factors unique to this group and not found among controls or affected siblings – that may act to promote a more typical processing of faces relative to their ASD counterparts.

We also recruited controls matched in chronological age and verbal and non-verbal abilities. Participants completed the Cambridge Face Memory Test for children (CFMT-Kids) – a test designed to identify potential deficits in face recognition (Dalrymple, Gomez, & Duchaine, 2012). Participants also completed a passive viewing task with photographs of upright faces, inverted faces, and upright houses, while their evoked potentials to visual stimuli were recorded using dense array electroencephalography (EEG). We specifically examined the P100 and the N170 – components responsive to low-level visual characteristics and attentional modulation (Johannes et al., 1995), and structural encoding of visual stimuli (Bentin et al., 1996; Eimer, 1998; Eimer, 2000), respectively.

Group differences were examined for the behavioral face recognition and ERP tasks. Given the heritability of face recognition abilities and the increased genetic susceptibility to atypical face perception among unaffected first-degree relatives of individuals with ASD, it was hypothesized that unaffected high-risk siblings of individuals with ASD might show poorer face recognition abilities compared to controls. It was also expected that unaffected siblings might differ from controls in their P100 or N170 amplitude or latency responses to faces.

Methods

Participants

Children between 6 and 9 years of age were recruited to participate in the study. Sixteen children had no diagnosis or family history of ASD (M = 94.11 months, SD = 12.84 months, 6 males), and 17 children had no diagnosis of ASD, but had an older sibling with ASD (M = 98.71 months, SD = 7.91 months, 6 males). All children were recruited from a database of participants who had volunteered in past studies at the centre.

Between 5 and 7 years of age, 10 of the 17 unaffected high-risk siblings had completed the Autism Diagnostic Observation Schedule (ADOS), and their parents had completed the Social Communication Questionnaire (SCQ) and the Social Responsiveness Scale (SRS; as reported in Leonard et al., in press; see Table 1). At this time point, 4 of these unaffected siblings (3 males) met the ADOS cutoff for ASD and 1 female met the cutoff for autism, but none of them met ASD/autism cutoffs on the on the SCQ or SRS. While the ADOS is recommended for usage in conjunction with developmental history and other screening tools rather than as a stand-alone tool for diagnosis (Lord et al., 2000), cutoff scores as measured by ADOS accompanied by lack of corroborating measures indicative of autism/ASD, nonetheless, likely points to features of ASD that may be evident at sub-clinical levels. It should be noted that the present study did not discriminate between unaffected siblings who may or may not have sub-clinical levels of ASD, thereby resulting in a more variable unaffected sibling group. For one additional unaffected sibling, SCQ and SRS measures were obtained but ADOS was not completed. Currently, none of the unaffected siblings have a community diagnosis of ASD and their parents reported no current concerns regarding their children's development.

Most of the participants in both groups were right-handed (n = 14 controls, n = 14 unaffected siblings). The 2 controls and 3 unaffected siblings who were left-handed showed the predominant pattern of P100 and N170 peak amplitude responses, and were thus included in the ERP analyses. ANOVAs with participant group (unaffected sibling or control) and participant gender as independent variables revealed no group differences across unaffected siblings and controls on the following measures: digit span, vocabulary, matrix reasoning, and the Wechsler Abbreviated Scale of Intelligence (WASI-II) two-subtest (i.e., vocabulary and matrix reasoning) full-scale IQ (p values > .20, see Table 2). There was no significant influence of participant gender on the matrix reasoning and the two-subtest full-scale IQ scores (p values > .20), however a significant main effect of participant gender was found in participants' digit span and vocabulary scores (p values < .01). Female participants in both the unaffected sibling and control groups scored higher on the digit span and vocabulary subtests than their male counterparts. Despite within-group gender differences, comparable measures across unaffected sibling and control participants verified that the 2 groups did not differ in short-term or working memory, or in verbal and non-verbal abilities.

Materials and Stimuli

The CFMT-Kids (Dalrymple et al., 2012) was used to examine participants' face recognition abilities. The passive viewing ERP task used 25 photographs of male adult faces and 25 photographs of female adult faces showing direct gaze. Faces were placed within an oval frame to minimize hair and facial contour cues to ensure that participants focus on the internal regions of faces. These facial photographs were presented in an upright orientation as well as in an inverted orientation during the ERP task. The ERP task also included 50 photographs of houses presented in an upright orientation only. All photographs were rendered grayscale and presented on a gray background (see Figure 1). A blank oval was used during the inter-stimulus intervals (ISIs). Median brightness levels for face, house, and ISI visual presentations were matched. Dense array HydroCel Geodesic Sensor Nets with 128 channels and Netstation 4.4.2 were used to record evoked responses to visual stimuli.

The forwards and backwards digit span from the Wechsler Intelligence Scale for Children (WISC-IV) was used to obtain measures of short-term and working memory. The vocabulary and matrix reasoning subtests of the WASI-II were used to obtain measures of verbal and non-verbal abilities, respectively. The verbal and non-verbal measures were also used to compute two-subtest full-scale IQ scores.

Procedure

Research protocols used in the current study were approved by the London – Central National Research Ethics Committee. Participants were asked to complete three main tasks: i) face recognition, ii) passive viewing ERP, and iii) memory/verbal/non-verbal tests.

Face recognition. Participants completed the CFMT-Kids – a face recognition task designed to identify face recognition deficits in children (Dalrymple et al., 2012). During the task, participants were seated approximately 40cm away from a 13.5inch laptop monitor. Each face stimulus presented subtended a visual angle of approximately 6.40° x 5.00°.

The CFMT-Kids is a computerized face recognition task comprised of 3 increasingly difficult sub-sections. Participants were told that they would be playing a face memory game on the computer and that their task would be to look carefully at the children's faces that would appear on the screen one at a time because they would later identify each face from a set of faces. The first section of the CFMT-Kids is characterized by limited memory demands. It began with practice trials during which a popular cartoon face (i.e., Bart Simpson) appeared on the screen 3 times (each presentation = 3000ms) in 3 different poses (left ¾, right ¾, and frontal) followed by 3 test trials, each showing the target face (in different poses across test trials) along with 2 distractors. Practice was followed by familiarization with 4 male target child faces. Similar to practice, each target face was presented 3 times in 3 different poses, followed by 3 test trials during which participants were asked to point to the target face presented among 2 distractors. The experimenter would press a corresponding key to move onto the next trial. Faces during the test trials remained on the screen until participants indicated their responses. No time limit was imposed during the test trials. This first section of the CFMT-Kids comprised of a total of 12 face recognition trials.

The second section of the CFMT-Kids is characterized by greater memory demands relative to the first section of the test. Participants were shown the 4 target child faces they had seen previously, but this time they were familiarized with all 4 faces (in frontal poses) simultaneously for 20 seconds. Participants were instructed to look carefully at all of the faces because they would have to later identify them from a set of faces. After familiarization, participants were given 5 test trials per target face presented in random order. In each test trial, participants were asked to point to the target face present among 2 distractors. Facial pose of the target faces varied across test trials. Again, faces during test remained on the screen until participants indicated their responses, and no time limit was imposed. This second section of the CFMT-Kids comprised of a total of 20 face recognition trials.

The third section of the CFMT-Kids is characterized by greater memory demands as well as by degraded images during test. Familiarization and test trials were identical to the second section of the CFMT-Kids, with the only differences being i) the addition of Gaussian noise to the test faces, and ii) fewer test trials (i.e., 4 test trials per target face). This third section of the CFMT-Kids comprised of a total of 16 face recognition trials.

Passive viewing ERP. Participants viewed photographs of 50 upright faces, 50 inverted faces, and 50 upright houses while EEG was recorded. Participants were seated approximately 90cm away from a 20inch monitor. Each image presented subtended a visual angle of 11.40° x 7.30°.

Images were presented in random order and each image was presented twice, for a total of 300 trials. Each image was presented for 500ms followed by an ISI that randomly varied between 800 and 1200ms. Continuous EEG was recorded with a sampling rate of 500Hz and a band-pass of 0.1 and 200Hz. During this passive viewing task, participants were videotaped so that sessions could be coded for movement artifacts.

Participants' videos during the passive viewing ERP task were coded for movement artifacts. ERP trials were excluded when participants moved, looked away from the screen, or blinked. After exclusion of trials due to movement artifacts, the number of trials used for the ERP analyses did not differ between groups (p values > .10) for upright faces (unaffected siblings: M = 59.00, SD = 19.76, controls: M = 68.00, SD = 15.77), inverted faces (unaffected siblings: M = 57.65, SD = 17.57, controls: M = 67.19, SD = 15.70), or upright houses (unaffected siblings: M = 58.53, SD = 18.43, controls: M = 67.31, SD = 15.26). Participants' EEG recordings were digitally low-pass filtered at 30Hz.

Participants' P100 and N170 responses to visual stimuli were examined. The P100 is an early visually evoked potential, which peaks at approximately 100ms post-stimulus onset and is sensitive to low-level stimulus characteristics (e.g., luminance) and spatial attention to stimuli in typical adults (Heinze et al., 1990; Johannes et al., 1995). The N170 is another visually evoked potential, which peaks at approximately 170ms post-stimulus onset and is associated with the early structural encoding of face stimuli and is differentially responsive to face vs. non-face and inverted face categories in typical adults (Bentin et al., 1996; Eimer, 1998; Eimer, 2000a, 2000b; Rossion et al., 2000). These visually evoked potentials have been found to change across development. The P100 latency and amplitude decrease from childhood to adulthood (Itier & Taylor, 2004a; Taylor, Batty, & Itier, 2004; Taylor, Edmonds, McCarthy, & Allison, 2001). The N170 latency also decreases with age, but generally increases in amplitude from childhood to adulthood (Itier & Taylor, 2004a; Taylor et al., 2004; Taylor, McCarthy, Saliba, & Degiovanni, 1999).

Occipital and posterior temporal and parietal electrodes were used to examine the P100 (see Figure 2), and posterior temporal and parietal electrodes were used to examine the N170 (see Figure 3). These electrodes were chosen based on visual inspection of the P100 and N170 components across unaffected high-risk siblings and low-risk controls. These electrodes also overlap with those used to examine the P100 and N170 in past studies with a similar age group of children and face stimuli (Itier & Taylor, 2004a, Itier & Taylor, 2004b). To capture the components for all participants, we used a time window of 70-180ms post-stimulus onset for the P100 component, and a time window of 150-290ms post-stimulus onset for the N170 component. For both components, a period of 100ms immediately prior to stimulus onset was used for baseline correction. P100 and N170 peak amplitude and latency were examined within each participant group. Multiple comparisons in all analyses were subject to sequential Bonferroni corrections.

Memory/verbal/non-verbal tests. Participants completed the forwards and backwards digit span from the WISC-IV, and the vocabulary and matrix reasoning subtests of the WASI-II.

Results

Preliminary analyses on participants' total CFMT recognition scores, as well as scores on each subsection of the test, revealed no main effect or interactions with participant gender (p values > .05). Face recognition scores were, thus, collapsed across participant gender, and independent-samples t-tests were conducted with participant group (unaffected siblings or controls) as the independent variable and

participants' face recognition scores as the dependent variable. Results revealed no significant group differences in overall face recognition abilities ($p > .20$, see Figure 4). There were also no significant group differences in each subsection of the CFMT-Kids (p values $> .20$, see Figure 4). Thus, unaffected high-risk siblings and low-risk controls were comparable in their face recognition abilities under circumstances of limited memory demands (test immediately after familiarization), relatively greater memory demands (delay between familiarization and test), and greater memory demands combined with noisy test images.

P100 amplitude. A 3 (stimulus category: upright faces, inverted faces, houses) x 2 (hemisphere) x 2 (participant group: unaffected sibling, control) x 2 (participant gender) ANOVA was conducted with P100 peak amplitudes as the dependent variable. The analysis revealed a significant main effect of stimulus category, $F(2, 47) = 47.85$, $p < .001$, partial $\eta^2 = .62$, so that houses elicited a more positive P100 peak amplitude than upright and inverted faces (p values $< .001$), and inverted faces, in turn, elicited a more positive P100 peak amplitude than upright faces ($p < .001$). The significant main effect of hemisphere, $F(1, 29) = 35.12$, $p < .001$, partial $\eta^2 = .55$, showed that a more positive P100 peak amplitude in the right than in the left hemisphere. A significant interaction between stimulus category and hemisphere, $F(2, 58) = 4.15$, $p < .05$, partial $\eta^2 = .13$, showed that the main effects described above holds for each hemisphere, but that the differentiation between houses and inverted faces was more pronounced in the right than in the left hemisphere ($p = .001$). There was also a significant interaction between participant group and participant gender, $F(1, 29) = 7.02$, $p < .05$, partial $\eta^2 = .20$, which showed that while unaffected sibling and control female participants were comparable in their P100 peak amplitude responses ($p > .10$), unaffected male siblings showed significantly larger P100 amplitude responses compared to their control male counterparts, $F(1, 10) = 5.71$, $p < .05$, partial $\eta^2 = .36$ (see Figure 2). The remaining main effects and interactions were not significant (p values $> .20$).

P100 latency. A 3 (stimulus category: upright faces, inverted faces, houses) x 2 (hemisphere) x 2 (participant group: unaffected sibling, control) x 2 (participant gender) ANOVA was conducted with P100 peak latency as the dependent variable. The significant main effect of stimulus category, $F(2, 58) = 4.82$, $p < .05$, partial $\eta^2 = .14$, showed faster P100 peak latency responses to upright faces than inverted faces ($p < .01$). There was also a trend towards faster P100 peak latency responses to upright faces than houses that did not survive the Bonferroni correction with the adjusted alpha at .03 ($p = .05$). Inverted faces and houses were comparable in P100 peak latency ($p > .05$). The remaining main effects and interactions were not significant (p values $> .10$).

N170 amplitude. To control for any influence of the P100 on the N170, peak-to-peak amplitude differences between participants' P100 and N170 responses were calculated and used as the dependent variable in a 5 (electrode) x 3 (stimulus category: upright faces, inverted faces, houses) x 2 (hemisphere) x 2 (participant group: unaffected sibling, control) x 2 (participant gender) ANOVA. The significant main effect of electrode, $F(3, 82) = 64.34$, $p < .001$, partial $\eta^2 = .69$, revealed larger peak-to-peak amplitudes as electrode placement became more posterior and medial (p values $\leq .001$). The significant main effect of stimulus category, $F(2, 58) = 15.87$, $p < .001$, partial $\eta^2 = .35$, revealed larger peak-to-peak amplitudes for upright and inverted faces than for houses (p values $< .001$), and comparable peak-to-peak amplitudes for upright and inverted faces ($p > .20$). The significant main effect of hemisphere, $F(1, 29) = 36.91$, $p < .001$, partial $\eta^2 = .56$, showed larger peak-to-peak amplitudes in the right than in the left hemisphere. The significant main effect of participant group, $F(1, 29) = 12.51$, $p = .001$, partial $\eta^2 = .31$, showed larger peak-to-peak amplitudes in unaffected siblings than in controls, and the significant main effect of participant gender, $F(1, 29) = 4.03$, $p = .05$, partial $\eta^2 = .12$, showed larger

peak-to-peak amplitudes in males than in females. However, these main effects were subsumed by a number of significant interactions.

There was a significant interaction between participant group and participant gender, $F(1, 29) = 8.18$, $p < .01$, partial $\eta^2 = .22$, which showed that while unaffected sibling and control female participants were comparable in their peak-to-peak amplitudes ($p > .20$), unaffected male siblings showed significantly larger amplitudes relative to their control male counterparts, $F(1, 10) = 35.94$, $p < .001$, partial $\eta^2 = .78$ (see Figure 3). A significant interaction between electrode and participant group ($p < .001$) was subsumed by a significant interaction between electrode, participant group, and participant gender, $F(4, 116) = 8.68$, $p < .001$, partial $\eta^2 = .23$. Follow-up analyses showed no significant electrode x participant group interaction among female participants ($p > .20$), but a significant interaction among male participants, $F(4, 40) = 20.86$, $p < .001$, partial $\eta^2 = .68$. Unaffected male siblings showed significantly larger peak-to-peak amplitudes than their control male counterparts in 4 of the 5 electrode placements (p values $< .01$).

A significant interaction between electrode and hemisphere ($p < .05$) was subsumed by a significant interaction between electrode, hemisphere, and participant gender, $F(4, 116) = 2.62$, $p < .04$, partial $\eta^2 = .08$. Follow-up analyses revealed a significant interaction between electrode and participant gender for the left hemisphere, $F(4, 124) = 2.54$, $p < .05$, partial $\eta^2 = .08$, but not for the right hemisphere ($p > .20$). In the left hemisphere, male participants showed larger peak-to-peak amplitudes than females in 1 of the 5 electrodes ($p < .01$). However, this effect may be driven by the enhanced peak-to-peak amplitudes among unaffected male siblings.

There was also a significant interaction between electrode and stimulus category ($p < .01$) that was subsumed by a significant interaction between electrode, stimulus category, and hemisphere, $F(5, 136) = 2.84$, $p < .05$, partial $\eta^2 = .09$. Follow-up analyses showed larger peak-to-peak amplitudes in the right than in the left hemisphere for all 5 electrode placements (p values $\leq .001$). Three (59/91, 65/90, 63/99) of the 5 electrode placements also showed larger peak-to-peak amplitudes for upright and inverted faces than houses (p values $< .01$), and comparable amplitudes for upright and inverted faces (p values $> .20$). The remaining electrode placements showed different patterns of responses to stimulus categories across the two hemispheres. For electrode pair 58/96, both hemispheres showed larger peak-to-peak amplitudes for upright and inverted faces than houses (p values $< .001$), and larger peak-to-peak amplitudes for inverted faces than upright faces ($p = .05$) in the left hemisphere, but comparable amplitudes for upright and inverted faces in the right hemisphere ($p > .20$). For electrode pair 64/95, larger peak-to-peak amplitudes were elicited by inverted faces than upright faces and houses (p values $< .001$, and comparable amplitudes were elicited by upright faces and houses ($p > .10$) in the left hemisphere. Larger peak-to-peak amplitudes were elicited by upright and inverted faces than houses (p values $< .01$), and comparable amplitudes were elicited by upright and inverted faces ($p > .20$) in the right hemisphere.

N170 latency. A 3 (stimulus category: upright faces, inverted faces, houses) x 2 (hemisphere) x 2 (participant group: unaffected sibling, control) x 2 (participant gender) ANOVA with N170 peak latency as the dependent variable revealed no significant main effects or interactions (p values $\geq .10$).

ERP responses and face recognition abilities. Pearson correlations were conducted between ERP responses to upright faces and face recognition scores for each participant gender in the control and unaffected sibling groups. Results revealed no significant correlations between any of the ERP responses

to upright faces (P100 amplitude, P100-N170 peak-to-peak amplitude, and P100 and N170 latencies) and total/individual CFMT subset scores (all p values > adjusted Bonferroni correction of .01).

Unaffected sibling sample. As noted earlier, approximately 2 years before the present study, 5 of the 17 siblings met criteria for either autism or ASD on the ADOS, but none met cutoff on the SCQ or SRS, and none went on to acquire a community diagnosis of autism or ASD. However, additional analyses were conducted excluding these 5 siblings to verify the validity of the results from the entire sample of unaffected siblings. Similar to the results with the entire unaffected sibling sample, when the 5 siblings were excluded from the analyses, the unaffected siblings were comparable to control children with regards to short-term and working memory, vocabulary, non-verbal reasoning (p values > .10), and face recognition abilities (total CFMT score and individual subsections, p values > .20). There was also a trend towards significantly larger P100 peak amplitudes among unaffected male siblings compared to male controls with the smaller unaffected sibling sample (p = .06). Faster P100 latency for upright faces compared to inverted faces was replicated with the smaller sibling sample (p < .01), and the trend towards a faster P100 latency for upright faces than houses that did not survive the Bonferroni correction in the previous analysis (p = .05) was significant with the smaller sibling sample size (p = .02).

With the smaller sibling sample, all significant main effects previously found in the analysis on peak-to-peak amplitude were replicated except for the effect of participant gender (p > .05). All significant two-way interactions were replicated, including the interaction between participant group and participant gender showing larger peak-to-peak amplitudes among unaffected male siblings compared to male controls (p < .001). All significant three-way interactions were also replicated except for the interaction between electrode, hemisphere, and participant gender (p > .20). All post-hoc results for the interaction between electrode, stimulus category, and hemisphere were replicated except that for electrode pair 58/96, the larger peak-to-peak amplitude for upright faces compared to houses in the left hemisphere was only a trend (p = .07), and for electrode pair 65/90, there was a significant interaction between electrode and hemisphere (p = .05), so that the effect of stimulus category was only significant in the left hemisphere. As with the larger sample of unaffected siblings, analysis of participants' N170 peak latencies showed no significant main effects or interactions (p values > .10). Finally, similar to the larger sample, there were no significant correlations between ERP responses to upright faces and face recognition scores in the smaller sample of unaffected sibling (all p values > adjusted Bonferroni correction of .01).

Discussion

Contrary to our predictions, unaffected siblings showed comparable face recognition abilities relative to controls. Unaffected female siblings were also comparable to female controls with regards to P100 and P100-N170 peak-to-peak amplitude and latency responses. While unaffected male siblings showed ERP latency responses comparable to male controls, they also showed enhanced P100 and P100-N170 peak-to-peak amplitude responses. This gender difference in atypical amplitude responses found only in unaffected male siblings is consistent with the notion of a female protective effect against ASD, so that males likely require fewer familial risk factors to reach an impairment threshold (Robinson, Lichtenstein, Anckarsäter, Happé, & Ronald, 2013). Unaffected male siblings' atypically enhanced ERP amplitude responses were evident for both face and house stimuli, suggesting that the enhanced response was not specific to social stimuli, but rather a general characteristic of their processing of visual stimuli.

The enhanced amplitude responses in unaffected male siblings may be indicative of recruitment of greater neural resources that they may require to process visual stimuli. This would be in line with findings from a meta-analysis showing that in response to visual stimuli (faces, objects, words), children and adults with ASD show overall greater activation in posterior cortical regions relative to controls (Samson et al., 2012). With regards to specific responses to face stimuli, children and adults with ASD also show greater activation of occipital and temporal areas relative to controls – suggesting they recruit a face processing network that is larger than that found in controls and subsuming areas typically associated with object processing in controls (Samson et al., 2012). Such recruitment of a larger neural network to process visual stimuli may be compensatory and potentially driven by structural atypicalities found in the temporal neocortex of children with autism (Stoner et al., 2014). Structural MRI should clarify whether unaffected male siblings are also more likely to share some of these structural atypicalities.

However, unlike children with ASD, the unaffected male siblings in the present study showed typical patterns of ERP differentiation across face and non-face stimuli and across upright and inverted faces. Perhaps the strategy they use to process faces is comparable to controls despite their recruitment of a larger neural network. Future investigations should examine processing of the eye and mouth regions of faces, and use fMRI methodology, to verify whether unaffected male siblings use a similar strategy to process faces as controls while recruiting a relatively larger neural network.

It should be noted that the present study has a number of limitations. One limitation is the small sample size. Future studies should, therefore, verify the generalizability of these results. However, it should be noted that the effect sizes of the group differences for male participants in the present study were very large (partial η^2 for P100 amplitude = .36 and partial η^2 for P100-N170 peak-to-peak amplitude = .76). Additional limitations of this study are the lack of ADOS/SCQ/SRS measures for all unaffected siblings, and thereby the lack of differentiation among the unaffected siblings based on sub-clinical levels of symptoms characterizing ASD. Such differentiation would help to identify behavioral and electrophysiological responses associated with the behavioral characteristics of ASD from responses associated with genetic susceptibility to the disorder. A recent study has indeed found distinct neurophysiological responses to faces across unaffected adults with no family history of ASD, unaffected adults who display social aloofness and have a child with ASD, and unaffected adults who are not socially aloof but have a child with ASD (Yucel et al., in press).

While past studies with high-risk 3-year-olds and unaffected adults with children with ASD have found mild face recognition deficits (Dawson et al., 2005b; de Klerk et al., in press; Wilson et al., 2010a), the present study found comparable face recognition abilities in a group of 6- to 9-year-old controls and unaffected siblings. A more difficult face recognition task may possibly elicit a group difference – although this would suggest recognition deficits relative to controls only under extremely difficult face recognition conditions. Alternatively, children during middle childhood may be able to compensate for any mild behavioral and/or neural atypicalities that would otherwise lead to mild deficits in face recognition. However, such compensatory processes may not be sufficient to maintain comparable face recognition in the long-term as controls continue to develop more sophisticated face recognition abilities, whereas unaffected adults with a family risk for ASD show poorer abilities (Dawson et al., 2005b; Wilson et al., 2010a). Findings from the present study suggest that unaffected children with a family risk for ASD show face recognition abilities and underlying neural processes that overlaps in most ways with controls, but unaffected male siblings may be more vulnerable to development of mild impairments as evidenced by their atypical enhanced responses to visual stimuli. Further studies examining children with ASD, unaffected siblings, and controls should shed additional

light on the behavioral and neural risk factors that impede the development of optimal face processing abilities. This would help to identify potential interventions that can improve such abilities, which may, in turn, have beneficial effects on the development of social and communication skills.

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Table 1

Average Raw Scores on Social and Communication Measures for Unaffected Siblings

	n	*M* (*SD*)
Social Responsiveness Scale (SRS)	11	19.18 (12.54)
Social Communication Questionnaires (SCQ)	11	2.55 (2.95)
Autism Diagnostic Observation Schedule (ADOS)		
Communication		
Module 3 (Austism cut-off = 3, Spectrum cut-off = 2)	8	1.50 (0.93)
Module 2 (Austism cut-off = 5, Spectrum cut-off = 3)	2	2.50 (0.71)
Reciprocal Social Interaction		
Module 3 (Austism cut-off = 6, Spectrum cut-off = 4)	8	4.88 (3.40)
Module 2 (Austism cut-off = 6, Spectrum cut-off = 4)	2	5.50 (2.12)
Stereotyped Behaviors and Restricted Interests		
Module 3	8	0.63 (1.19)
Module 2	2	1.00 (1.41)

Table 2

Average Group Performances on Memory, Verbal, and Non-verbal Tests

	Controls	Unaffected Siblings
Test	*M* (*SD*)	*M* (*SD*)
Digit Span	10.63 (2.73)	9.29 (3.08)
Vocabulary (*T* Score)	58.75 (10.14)	54.06 (9.83)
Matrix Reasoning (*T* Score)	58.69 (9.79)	54.18 (12.16)
WASI-II FSIQ-2	115.06 (13.16)	107.18 (16.19)

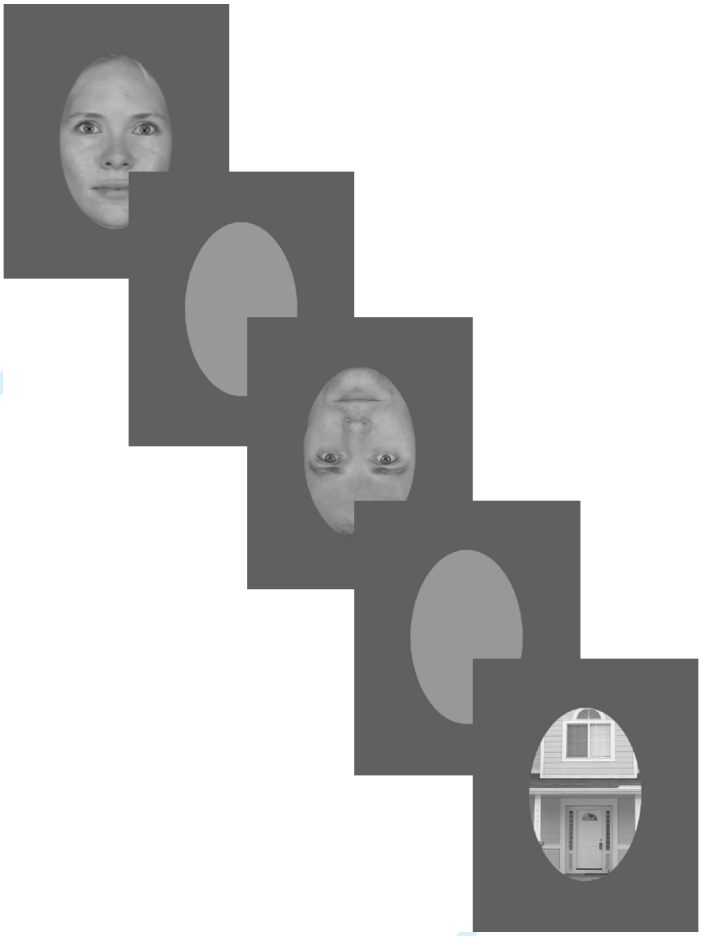

Figure 1. Examples of stimuli used in the ERP task.

Running head: ERPS IN UNAFFECTED SIBLINGS OF ASD CHILDREN

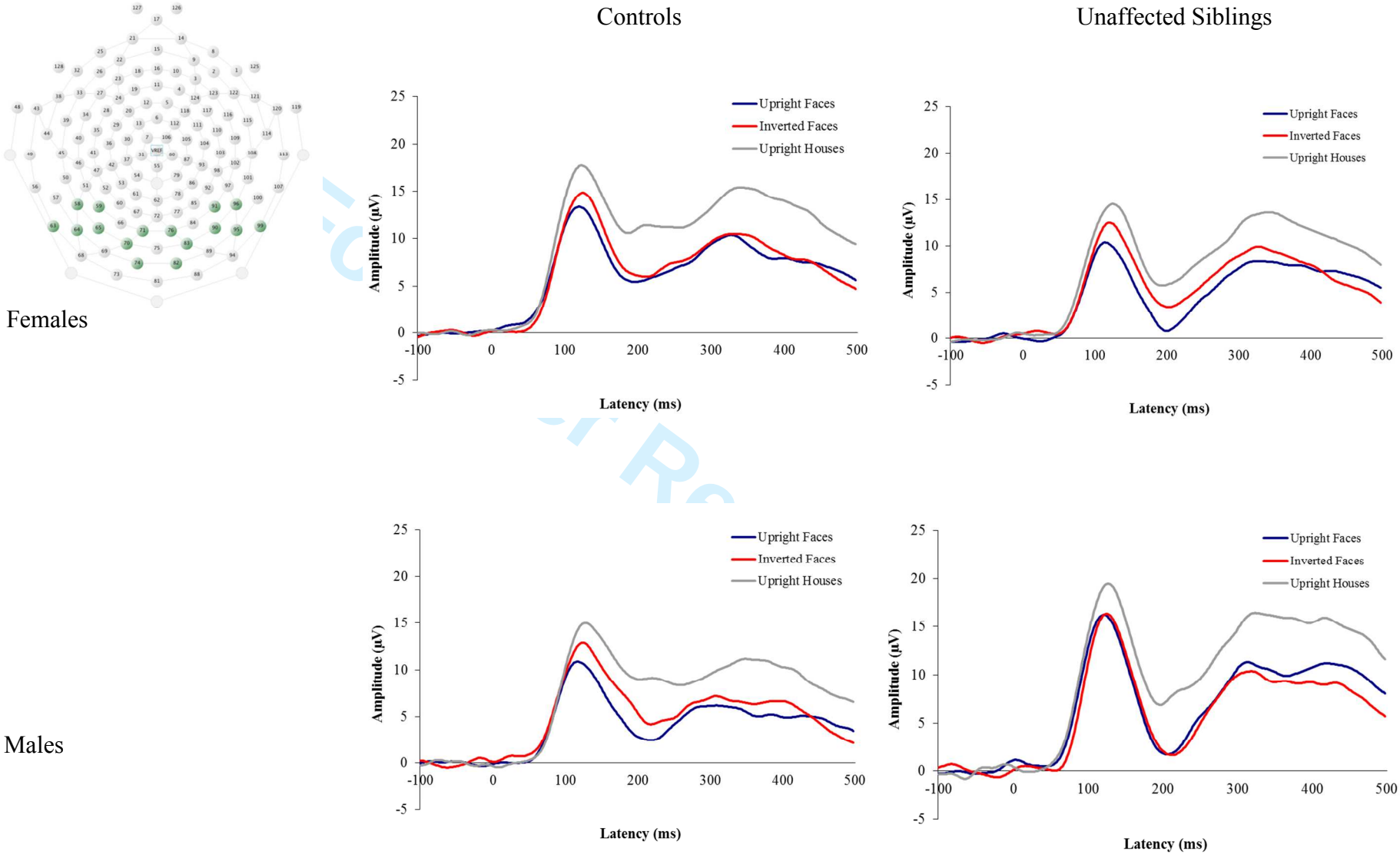

Figure 2. Occipital and posterior temporal and parietal electrodes used to examine the P100 (top left). Unaffected female siblings were comparable to female controls, but unaffected males showed larger P100 amplitude responses relative to controls.

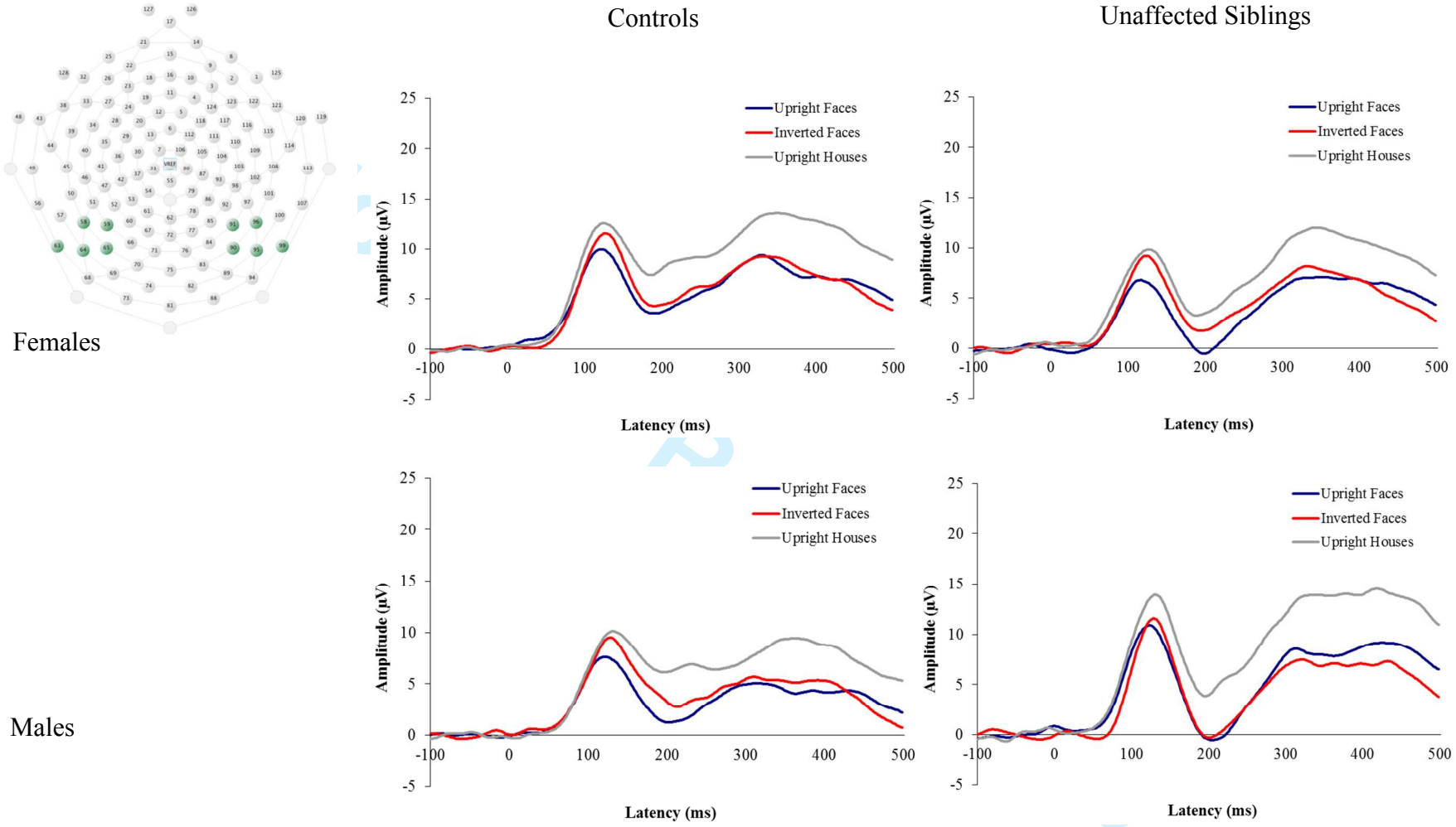

Figure 3. Posterior temporal and parietal electrodes used to examine the N170 (top left). Unaffected female siblings were comparable to female controls, but unaffected males showed larger P100-N170 peak-to-peak amplitude responses relative to controls.

Running head: ERPS IN UNAFFECTED SIBLINGS OF ASD CHILDREN

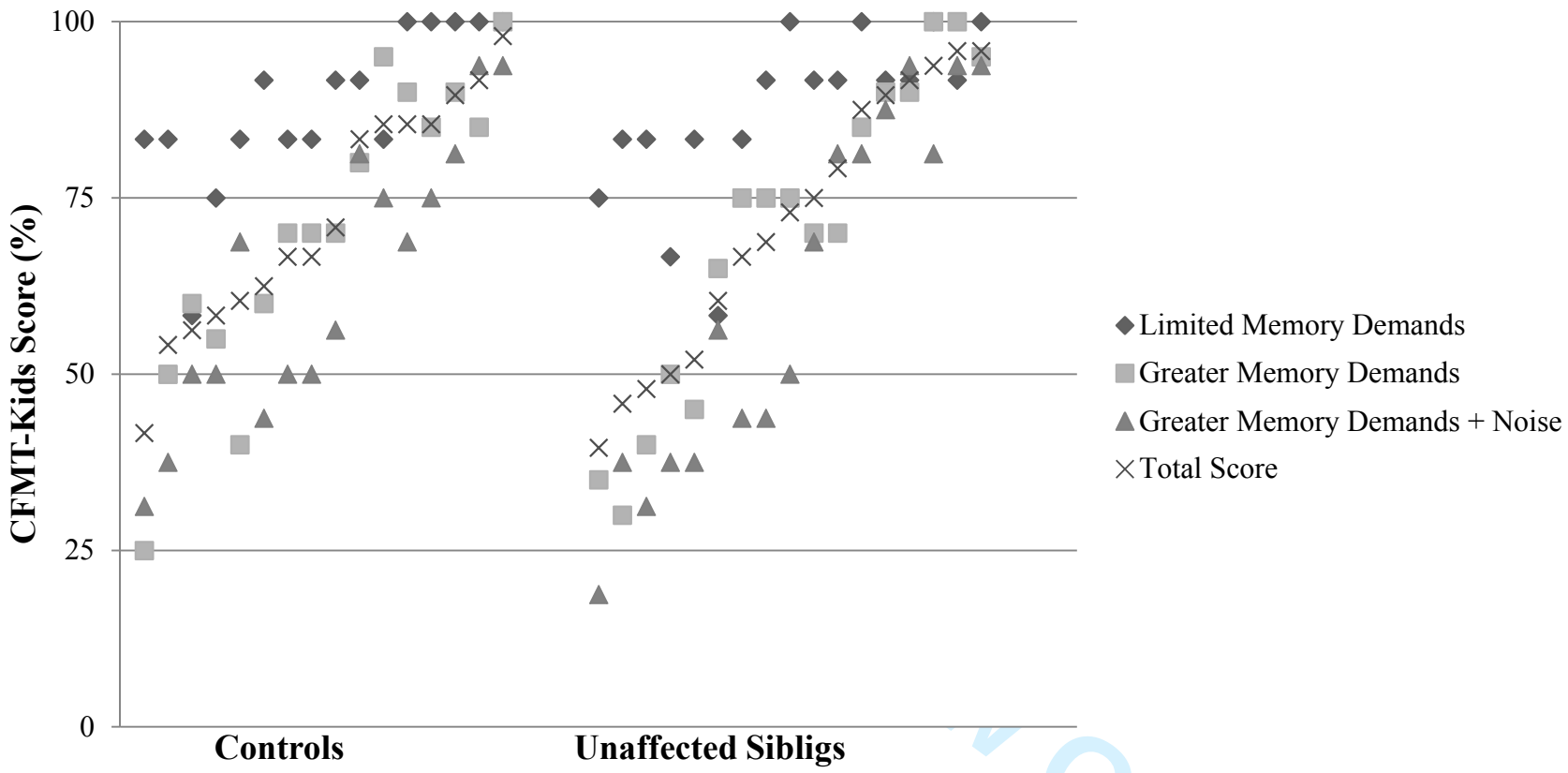

Figure 4. Face recognition scores for each control and unaffected sibling participant.