Altered Activity of the Primary Visual Area during Gaze Processing in Individuals with High-Functioning Autistic Spectrum Disorder: A Magnetoencephalography Study

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Short title:

Altered activity of the primary visual area of autistic spectrum disorder during gaze processing

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Abstract

Background: Individuals with autistic spectrum disorder (ASD) demonstrate an impaired ability to infer the mental states of others from their gaze. Thus, investigating the relationship between ASD and eye gaze processing is crucial for understanding the neural basis of social impairments seen in individuals with ASD. In addition, characteristics of ASD are observed in more comprehensive visual perception tasks. These visual characteristics of ASD have been well-explained in terms of the atypical relationship between high and low-level gaze processing in ASD.

Method: We studied neural activity during gaze processing in individuals with ASD using magnetoencephalography, with a focus on the relationship between high and low-level gaze processing both temporally and spatially. Minimum current estimate analysis was applied to perform source analysis of magnetic responses to gaze stimuli.

Results: The source analysis showed that later activity in the primary visual area (V1) was affected by gaze direction only in the ASD group. Conversely, the right posterior superior temporal sulcus, which is a brain region that processes gaze as a social signal, in the typically developed group showed a tendency toward greater activation during direct compared with averted gaze processing.

Conclusion: These results suggest that later activity in V1 relating to gaze processing is altered or possibly enhanced in high-functioning individuals with ASD, which may underpin the social cognitive impairments in these individuals.

Key Words: Autistic spectrum disorder, Magnetoencephalography, Gaze processing, Social cognition, Minimum current estimates, Primary visual area

Introduction

Autistic spectrum disorders (ASDs) are neurodevelopmental disorders characterized by widespread abnormalities in social interactions and communication, severely restricted interests, and highly repetitive behaviors. Among the significant symptoms of ASD, an atypical pattern of eye contact is among the most distinguishable feature of the qualitative impairment in social interaction in individuals with ASD. This atypical pattern of eye contact has been reported and discussed in many clinical and experimental settings (see review [1]). Eye contact is an important platform for social interaction and communication. Thus, investigating the relationship between ASD and gaze processing associated with eye contact is crucial for understanding the neural basis of social impairments in ASD. In fact, the underlying atypical neural processing of eye gaze in individuals with ASD has been elucidated in electrophysiological studies in which stimuli consist of direct and averted gaze [2-4]. These studies have indicated that individuals with ASD show abnormal neural processing of gaze in occipital or occipitotemporal sites.

Characteristics of ASD are observed not only in gaze perception, but also in more comprehensive visual perception phenomena such as superior processing of fine detail (local structure), involving either inferior processing of overall/global structure or an ability to ignore disruptive global/contextual information, and impaired motion perception [5]. These visual perception characteristics of ASD have been addressed from the viewpoint of an atypical relationship between high and low-order cognitive processes in ASD according to two theories, the weak central coherence hypothesis (WCC) [6], and the enhanced perceptual function hypothesis (EPF) [7]. Atypical low-level processing seen in individuals with ASD is expected to have an effect on atypical gaze processing. However, to the best of our knowledge, there has been no study of early low-level visual area activity in gaze processing of individuals with ASD.

Consequently, the purpose of the present study was to examine gaze processing in individuals with ASDs in the context of the relationship between high and low processing. We used magnetoencephalography (MEG), which has advantages for investigating the signal characteristics of gaze processing (typically instantaneous and automatic), because of its superior temporal resolution. Furthermore, we performed source analysis using the minimum current estimates (MCE) method [8], which allows visualization of several separately located

sources activated simultaneously. This method enabled us to analyze brain activity involved in gaze processing both temporally and spatially. To investigate low and high–level gaze processing temporally, a time window of 50–150 ms after gaze stimulus on set was highlighted as the early time window because the event related potential (ERP) P100 component, which reflects low-level visual processing [9,10], is recorded in this time window. Conversely, the time window of 250–350 ms was adopted as the late time window, because the N270 component has been reported to be sensitive to gaze direction in typically developing children, and to show differences between children with and without ASD in a previous ERP study [3]. In addition, a previous ERP study on normal adults reported that the P300 component was also sensitive to gaze contact [11]. To investigate low and high–level brain activity involved in gaze processing spatially, we selected three areas of brain; primary visual area (V1), posterior superior temporal sulcus (pSTS), and fusiform gyrus (FG). The pSTS region is reported to be strongly involved in processing gaze and other biological motion [12-16]. In particular, viewing gaze activation of the posterior STS is thought to be related to higher-order social processes, such as intentionality conveyed by gaze, rather than the visual analysis of gaze alone [9,17]. In addition, neuroimaging studies have reported that patients with ASD exhibit structural abnormalities in the STS [18-20], and functional abnormalities of STS are associated with mentalizing [21] and gaze-related task performance [22]. The FG is the most studied brain region involved in face perception [23-25], and some studies have reported modulations of FG activity by gaze direction [17,26]. In addition, hypoactivation of the FG in ASDs has also been consistently reported [27-29]. In this study, we wanted to clarify atypical brain activity of ASD associated with gaze processing from a standpoint of the relationship between high and low processing, both temporally and spatially.

Materials and Methods

Subjects

Twelve right-handed participants with ASDs (age range 19-29 years; 10 males and 2 females), and 12 right-handed typically developed (TD) participants (age range19-29 years; 10 males and 2 females) participated in the present study. All participants had a high school education at the very least. The ASD participants did not have intellectual disabilities, but had experienced episodes of social impairment in school or at workplaces. They were recruited from patient advocacy groups or from the psychiatry department of Niigata University Medical and Dental Hospital. In accordance with the DSM-IV criteria of pervasive developmental disorder (PDD) [30], a registered psychiatrist diagnosed all ASD participants as follows: autistic disorder, 2; Asperger disorder, 9; PDD not otherwise specified (PDD-NOS), 1. No ASD or TD subjects had any comorbid psychiatric illnesses or neurological disorder. All participants had normal or corrected-to-normal vision.

The Autism Spectrum Quotient (AQ, Japanese version) [31,32], and the Japanese Raven's colored progressive matrices (RCPM) [33,34] tests were administered to all subjects to assess their autistic traits and fluid intelligence, respectively. The two groups did not differ in terms of age [ASD mean = 22.5 ± 2.8 years (standard deviation; SD), TD mean = 22.5 ± 3.6 years] or RCPM score [ASD mean = 32.5 ± 2.4, TD mean = 33.7 ± 1.9]. However, there was a significant difference in AQ score between the groups [ASD mean = 27.3 ± 6.9, TD mean = 12.3 ± 4.9, t (22) = 6.12, $p < 0.001$; Student's t-test]. All participants gave their written informed consent to participate in the experiment and were paid for their participation. The experiments were performed in accordance with the Helsinki Declaration. The experiment was approved by the ethics committee of the institutional review board of Niigata University School of Medicine.

Stimuli and procedure

Stimuli (fig. 1) consisted of photographs of a young female's face with a neutral facial expression, and her head position rotated by 45 degrees from the observer. Apparent motion of the eyes [11,35] was created by consecutively presenting two stimulus photographs, which did not differ except for gaze direction, within a sufficiently short inter-stimulus interval (60 ms). The duration

of each stimulus was 500 ms. The first stimulus was a straight gaze parallel to the head orientation. The second stimulus consisted of one of three conditions. In Condition 1, eye gaze was directed to the observer. In Condition 2, eye gaze was moved upward or downward as an averted gaze. In Condition 3, eye gaze was maintained in the same direction as the first stimulus so that it appeared stationary. Conditions (35% Condition 1, 35% Condition 2, and 30% Condition 3) were randomly presented, and the number of presentations of each condition was balanced for all participants. The stimuli were presented on a non-magnetic back-projection screen placed 1.5 m in front of the participants (a visual angle of about 13° vertically and 9° horizontally for face stimuli) in an electromagnetically shielded room. The participants were asked to fix their heads, to gaze at the screen intently, and to not blink as much as possible. They were allowed to blink only during inter-stimulus intervals in the case of an intolerable situation. They were also asked to signal by slightly putting up their index finger when the model's gaze moved (i.e., when Condition 1 and Condition 2 appeared), to direct their attention to the model's gaze.

Data acquisition

Event-related magnetic field data were recorded in a magnetically shielded room with 306 channels of the Vectorview MEG system (Elekta Neuromag, Helsinki, Finland). The channels consisted of 204 planar gradiometers and 102 magnetometers. Evoked data for Conditions 1 and 2 only were obtained because our objective was to compare the direct and averted gaze. The data were sampled at 600 Hz (0.01–200 Hz passband filter). On-line averages were generated for each participant and each condition (Condition 1, Condition 2) separately between 60 ms before and 800 ms after eye movement. Specifically, time zero was the onset of the second stimulus (creating apparent gaze motion). Epochs with magnetic amplitude larger than 3000 fT/cm in any channel were rejected to exclude data with blinking/movement artifacts or other noise contamination. The recordings were continued until 60-70 artifact-free responses to each of the two conditions were obtained. Individual pre-auricular-nasion coordinates were coregistered with the device system.

Source estimation and statistical analysis

Source modeling of the evoked magnetic field data was performed using the MCE method (Elekta Neuromag, Helsinki, Finland), which is based on the L1-norm solution [8]. The MCEs were calculated separately for each individual participant in each of the two conditions. The data were first pre-processed using the signal space projection (SSP) method to edit out the signals generated from eye movement or other external noises. Second, the data were pre-processed by filtering with a 33.4-Hz low-pass digital filter and applying a prestimulus baseline (60 ms before second stimulus onset) and a detrended baseline (500-600 ms from the second stimulus onset) to eliminate low-frequency noise. Calculations were performed from 0 to 500 ms after the second stimulus onset. A spherical head model was used to calculate MCE solutions, which were then projected onto an averaged brain surface. The sphere was centered on the base of the perpendicular from the nasion to the line joining the pre-auricular points (pre-auricular-nasion head co-ordinate system). The origin of this model was determined individually for each participant on the basis of a 3D set of T1-weighted anatomical MRIs, by fitting a sphere to the curvature of the outer surface of the brain. The 3D MRI images were acquired using a gradient-recalled (GR) sequence [repetition time (TR) = 8.28 ms; echo time (TE) = 4.2 ms; field of view (FOV) = 230×230; size = 256×256; pixel size = 0.8984×0.8984] with a Signa HDxt 1.5-T instrument (GE Healthcare UK, Chalfont St Giles, UK). The same anatomical landmarks used to create the pre-auricular-nasion head co-ordinate system were visualized in the MRI images by affixing markers to these points. A boundary element model (BEM) was used to create the source space. Electric current locations about 10 mm apart from each other were measured and locations closer than 30 mm to the center of the sphere model were excluded. After calculating the MCE, five regions of interest (ROIs) centered on V1, bilateral pSTS, and bilateral FG were selected in accord with previous studies on brain areas involved in gaze and face processing [23],[36]. ROIs were ellipsoids with the following center (c) and extent (e): V1: c = 0/–55/47, e = 35/20/25; left pSTS: c = –50/–25/50, e = 15/22/20; right pSTS: c = 50/–25/20, e = 15/22/20; left FG: c = –42/–10/25, e = 10/25/8; right FG: c = 42/–10/25, e = 10/25/8. Average amplitudes during the early time window (50-150 ms) and the late time window (250-350 ms) were recorded for each participant, in both conditions and ROIs. Average amplitudes were

analyzed using a series of three-way repeated-measures analyses of variance (ANOVA), with gaze direction (direct, averted) and time window (early, late) as the within-subject factors, and clinical group (ASD, TD) as the between-subject factor.

Results

Statistical analysis revealed significant main effects of time window. The amplitude was significantly larger in the early time window than in the late time window in V1 (9.22 ± 3.9 vs. 7.05 ± 3.9 nAm; [F(1, 22) = 5.8, p = 0.025]), whereas it was larger in the late time window than in the early time window in the left pSTS (4.37 ± 2.99 vs. 2.63 ± 1.39 nAm; [F(1, 22) = 13.4, p = 0.00014]) and in the right FG (2.12 ± 2.54 vs. 0.88 ± 0.74 nAm, [F(1, 22) = 4.82, p = 0.039]). There was a trend for an increase in amplitude in the late time window compared with the early time window in the right pSTS, but this was not significant (3.73 ± 1.64 vs. 2.91 ± 1.81 nAm; [F(1, 22) = 4.15, p = 0.054]).

In V1, there was a significant interaction between diagnostic groups and gaze direction [F(1, 44) = 6.6, p = 0.013]. Simple effect analyses showed that there was a significant simple main effect of gaze direction only in the ASD group [F(1, 44) = 5.61, p = 0.027], showing that averted gaze elicited a larger amplitude (8.58 ± 4.63 nAm) than did direct gaze (7.64 ± 3.93 nAm). Although a three-way interaction in V1 did not reach significance [F(1, 22) = 1.6, p = 0.22], there was a significant simple interaction between diagnostic groups and gaze direction [F(1, 44) = 6.62, p = 0.014] in the late time window, while the same simple interaction in the early time window did not reach significance [F(1, 44) = 0.51, p = 0.48]. The simple-simple main effect of gaze direction in the late time window in individuals in the ASD group was significant [F(1, 44) = 5.72, p = 0.021), showing that averted gaze elicited a larger amplitude (8.12 ± 5.1 nAm) than did direct gaze (6.71 ± 4 nAm). No other simple-simple main effect reached significance in V1 (fig. 2).

In both pSTS areas, no interactions or simple interactions were significant. However, a significant simple-simple main effect of gaze direction was observed in the right pSTS in the late time window of the TD group only [F(1, 44) = 4.22, p = 0.046]. Direct gaze elicited significantly larger amplitudes (4.4 ± 1.4 nAm) than did averted gaze (3.39 ± 1.6 nAm) (fig. 2).

Fig.3 and Fig.4 are examples of brain activity elicited by the gaze task revealed by MCE for each clinical group.

In the bilateral FG, no significant effects of diagnostic groups or gaze directions were found.

Discussion

In the present study we used MEG and source estimation by MCE analysis and obtained two major findings. First, V1 was strongly associated with early processing of gaze stimuli. The activity of the V1 in the early time window corresponds to the P100 or P1 component, which is considered to be the earliest endogenous visual ERP component, and reflects low-level visual processing [9,10]. With face stimuli, P1 reflects the first step of face processing such as the holistic processing of the face [37]. Thus, activity in V1 in the TD group may have contributed to early low-level holistic processing and may not have a major function in the discrimination of gaze direction. Second, activity in V1 was affected by gaze direction only in the ASD group, and this gaze effect in individuals with ASDs was only evident in the late time window. This result suggests that V1 activity in individuals with ASD in the late time window plays a larger part in gaze processing compared with TD individuals, which have poor selectivity to gaze direction. One of the models that account for this finding is the theory of enhanced perceptual functioning (EPF); features of which include locally oriented visual and auditory perception, enhanced low-level discrimination, and use of a more posterior network in ‘‘complex’’ visual tasks in ASD [7]. The enhanced perceptual functioning model is proposed to encompass the main differences between autistic and non-autistic social and non-social perceptual processing [7]. Findings from fMRI and PET studies [38-41] consistently indicate that individuals with ASDs display enhanced activation of visuoperceptual regions for these types of perceptual processing.

In the present study, there was gaze-sensitive activation in the right pSTS in the TD group. However, it is impossible to conclude that this activity is characteristic of TD individuals because there was no significant effect of diagnostic groups for activity in the right pSTS. The pSTS activation in response to viewing gaze could relate to higher-order social processes such as intentionality conveyed by gaze, more so than visual analysis of gaze alone [17,42]. A previous ERP study [11] using apparent motion of gaze in typically developed adults showed that the right pSTS region was significantly more active during direct compared with averted gaze processing, which is consistent with our finding of right pSTS activity in the TD group. The study concluded that direct gaze, which was a strong social signal, recruited more resources than averted gaze. Therefore, TD individuals process eye contact using the pSTS to decode gaze,

creating eye contact for social behavior and social signal. Conversely, pSTS activity in the ASD group had poor sensitivity to gaze direction in the present study. ASD individuals demonstrated an impaired ability to infer the mental states of others (e.g. intentions) from their gaze [42]. An fMRI study has reported that activity in the right STS was modulated by the context of the perceived gaze shift in TD subjects, but activity in this region was not modulated in individuals with ASD [22]. Our results, and findings from previous studies, suggest that dysfunction in the pSTS could contribute to social communication impairment of eye gaze seen in ASD. In the present study, the V1 in the ASD group was inversely more activated by averted gaze than direct gaze, which is a strong social signal, and recruited more resource compared with averted gaze in TD individuals. This result implies that ASD individuals do not process eye gaze as a social signal, but rather process it with a focus on local discrimination factors such as the position or shape of the iris and sclera, because V1 is forming an essentially local representation [5]. This prominent low-level and locally oriented visual perception within-gaze processing by ASD individuals may play a crucial role in the impaired processing of social context through gaze perception in ASD individuals.

This study had some limitations. First, minimum norm estimate analysis including MCE might show location bias toward the sensors [43]. This technical issue may cause some errors of the estimated sources. Second, Brain activities observed in the present study are not strictly specific for gaze processing because the stimuli used in the present study include other factors such as face. Therefore, the ROIs could not be selected from the present data of the brain activity. Instead, we used the predefined ROIs which were pointed to be brain areas related to gaze processing or V1 by previous studies. In addition, the coordinates of these ROIs did not reflect the previous studies because the coordinates of MCE is not compatible with others such as Talairach coordinates. Accordingly, the brain areas reported in the present study are relatively coarse, and may not be the most appropriate measures for showing activity in the gaze-relating area or V1. Third, we did not investigate whole brain area or time course in the present study. With regard to temporal dynamics, a time window of around 170 ms was not adopted in the present study, because this time window is in an intermediate position for the present study, which was designed to compare early and late time windows. A previous ERP study of gaze

processing reported a difference in N170 between ASD and TD children [2]. Therefore, the present study might fail to show a critical difference in activity during gaze processing between ASD and TD individuals.

In conclusion, the present study focused on high and low–level gaze processing, and temporally and spatially showed that later activity in V1 relating to gaze processing is altered in high-functioning individuals with ASD, which may underpin the social cognitive impairments seen in these individuals. Additional studies investigating more extensive brain area and longer time windows are needed to show differences in high-order brain regions related to gaze processing between ASD and TD individuals, in addition to the findings reported here.

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Conflict of interest: We declare that we have no conflicts of interest.

Figure Captions

Fig. 1. Illustrations of stimuli.

Gaze-change stimulus conditions generated from stimulus pairs creating three gaze direction conditions: Condition 1 (direct), Condition 2 (averted), and Condition 3 (stationary).

Fig.2. The mean amplitudes of the ASD and TD groups in the V1 and right pSTS.

Mean (vertical bars) and standard error (vertical lines) of average amplitudes during the early time window (50-150 ms) and the late time window (250-350 ms) in both gaze conditions and ROIs among each clinical group.

* = $p < 0.05$ in simple interaction or simple-simple main effects.

ASD: autistic spectrum disorder, TD: typically developed, V1: primary visual area, pSTS: posterior superior temporal sulcus

Fig. 3. Examples of minimum current estimates for each clinical group.

Minimum current estimates of one of the autistic spectrum disorder subjects (ASD1) and one of the typically developed subjects (TD1) for the direct and averted conditions, integrated over the time windows 50-150 ms and 250-350 ms after stimulus onset (view from back right). Note the differential activation dependent on gaze direction in the primary visual area (V1; circled by white line) in ASD1, and in the right posterior superior temporal sulcus (pSTS; circled by yellow line) in TD1 at 250-350 ms.

Fig. 4. Examples of temporal source dynamics for each clinical group.

Temporal source dynamics of ASD1 (left) and TD1 (right) plotted for ROIs (V1 and right pSTS) and gaze direction. The grey blocks indicate the 250-350 ms time window.

ASD: autistic spectrum disorder, TD: typically developed, V1: primary visual area, pSTS: posterior superior temporal sulcus.

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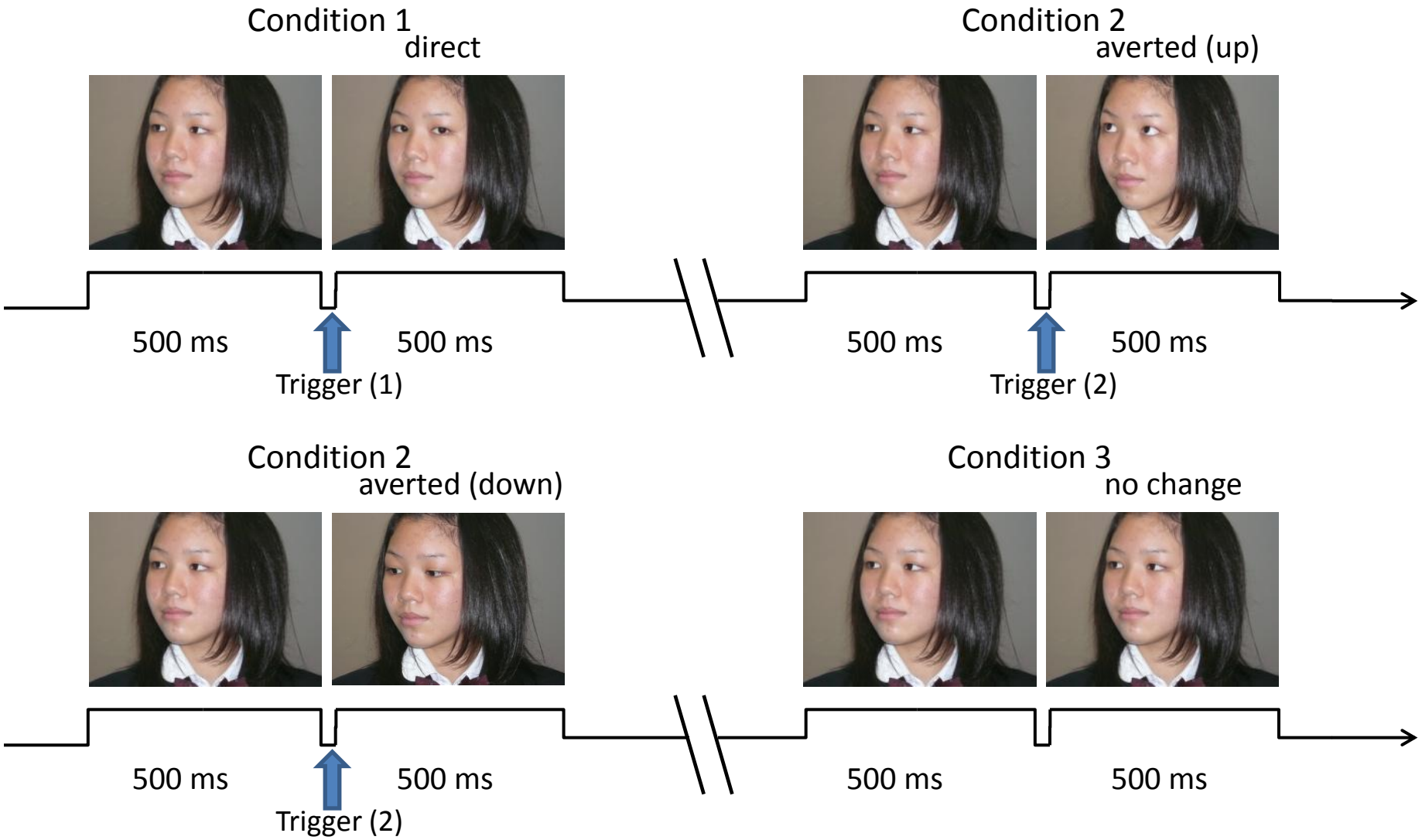
Condition 1
direct
500 ms
500 ms
Trigger (1)
Condition 2
averted (up)
500 ms
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Trigger (2)
Condition 2
averted (down)
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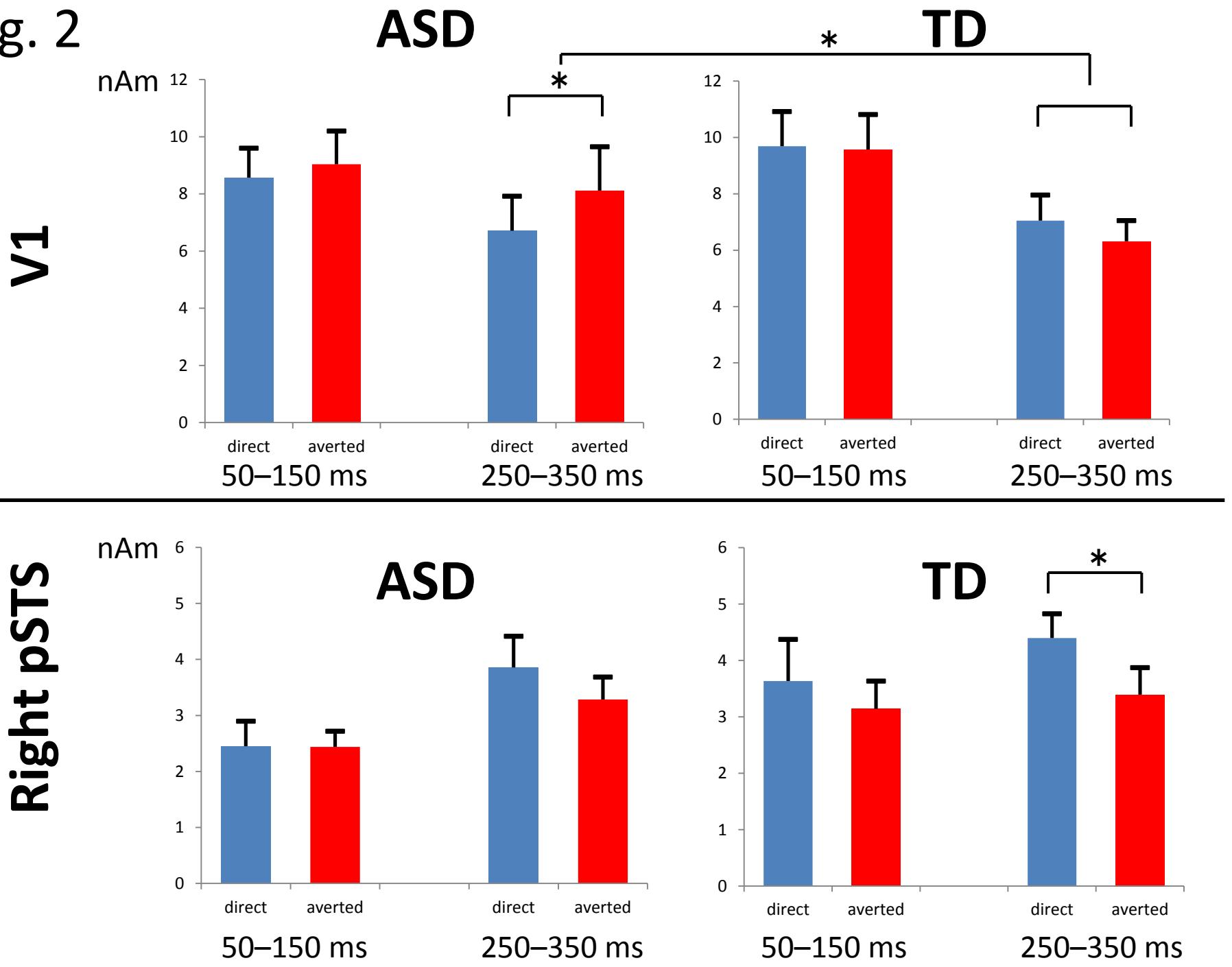
500 ms
Trigger (2)
Condition 3
no change
500 ms
500 ms

Fig. 1

Fig. 2


ASD
TD
*
*
V1
nAm
12
10
8
6
4
2
0
direct
averted
50–150 ms
250–350 ms
Right pSTS
6
5
4
3
1

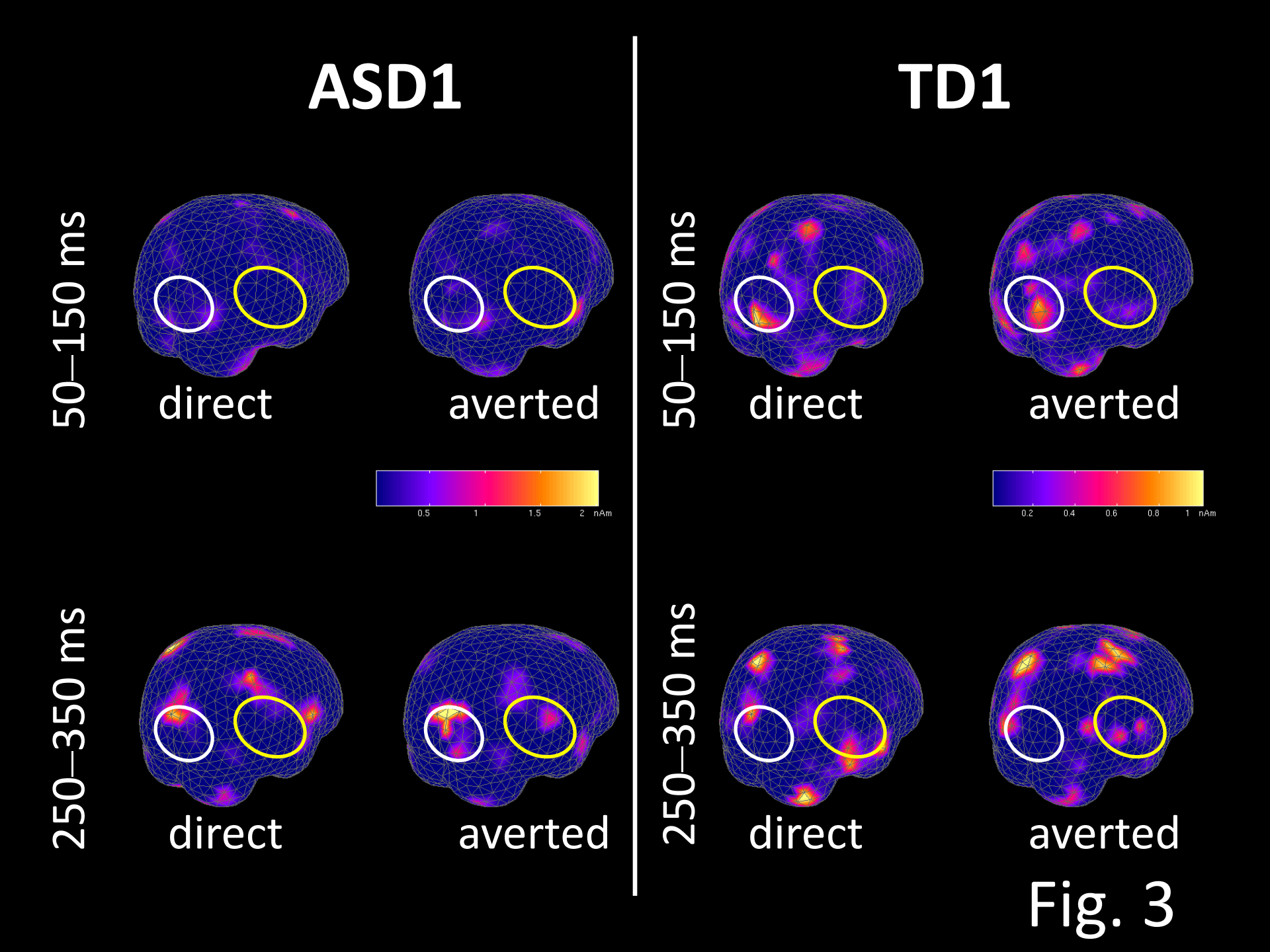
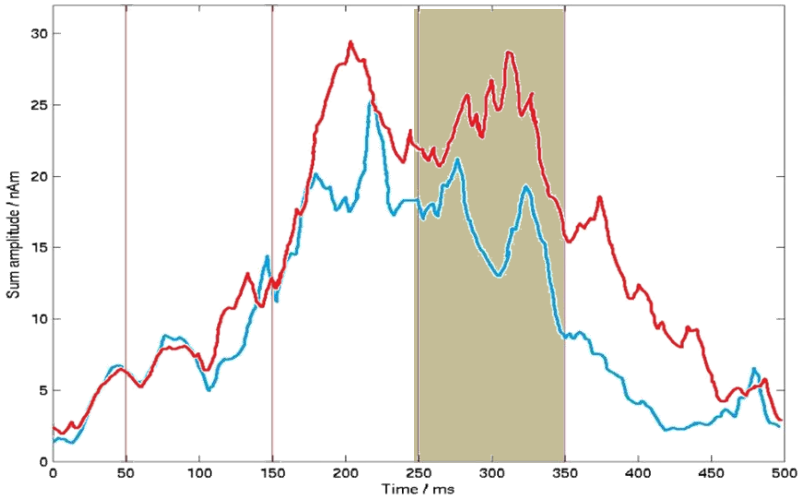

ASD1
TD1
50–150 ms
250–350 ms
direct
averted
direct
averted
direct
averted
direct
averted
0.5
1
1.5
2
nAm
0.2
0.4
0.6
0.8
1
nAm

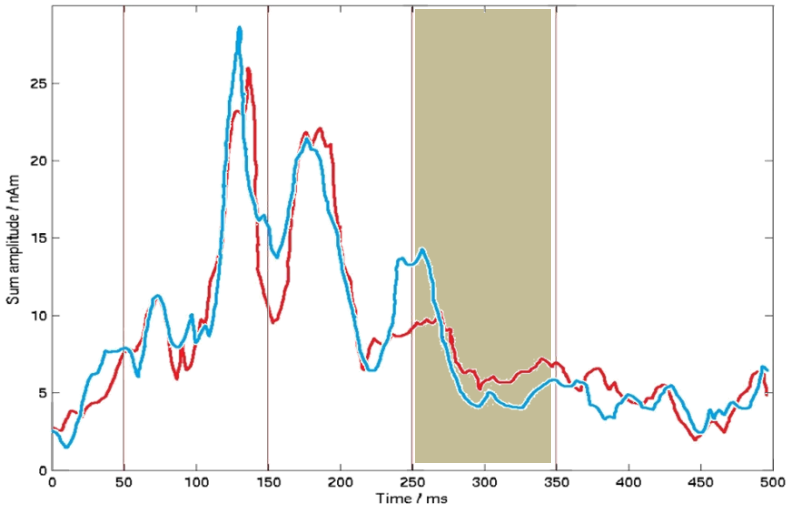
Fig. 3

ASD1

TD1

V1

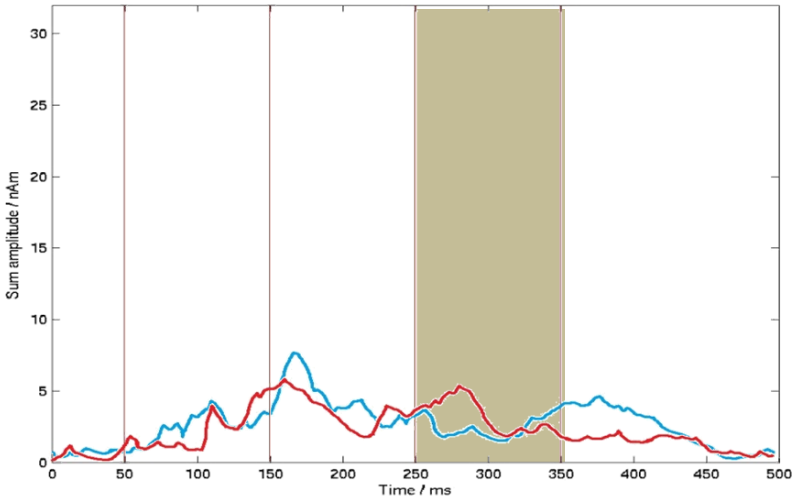




direct

averted

Right pSTS



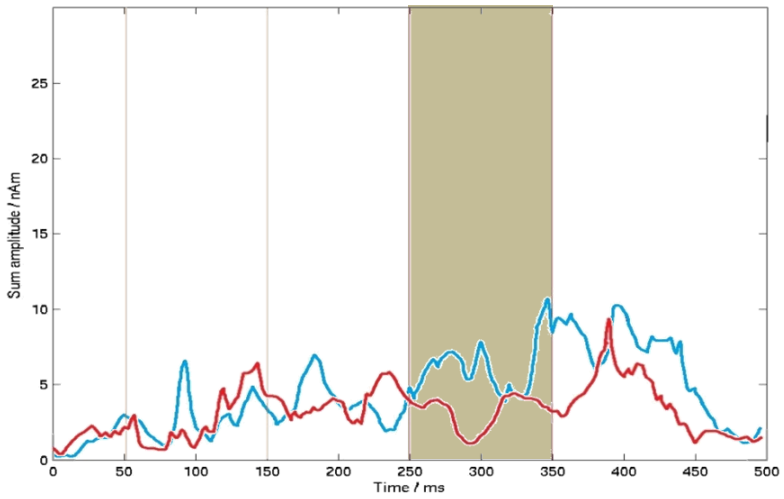


Fig. 4