

A Preliminary Comparison of Multisensory Integration in Boys with Autism Spectrum Disorder and Typically Developing Controls

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multisensory integration, responses to simultaneous multisensory auditory-somatosensory stimulation were compared to the summed unisensory auditory and somatosensory responses across three time windows (60 – 80 ms, 80 – 110 ms, and 110 – 150 ms) separately for the two groups. Statistical analyses showed multiple time windows and electrode locations where statistically significant multisensory integration occurred in typically developing children; however, no significant integration was found during any time window examined for the children with autism spectrum disorder. Additional comparison of scores on a caregiver questionnaire showed significant differences between the groups on the auditory filtering and visual/auditory sensitivity sections, and the total score.

CONCLUSION: These data support existing research indicating that sensory behavior and multisensory integration are atypical in children with autism spectrum disorder.

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Key words: Autistic disorder; Evoked potentials; Child

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ABSTRACT

AIM: Evidence is increasing that individuals with autism spectrum disorder have impairments in their ability to integrate information across different sensory modalities. To further explore this issue, event-related potentials were used to compare auditory and somatosensory processing as well as multisensory auditory-somatosensory integration for five boys ages 6 - 12 years diagnosed with autism spectrum disorder and five typically developing age- and gender-matched controls.

MATERIALS AND METHODS: Event related potentials were recorded from thirty-two scalp electrodes while participants watched a silent cartoon and three types of sensory stimulation were delivered: bilateral auditory clicks, vibro-tactile stimulation of the right palm, and both simultaneously.

RESULTS: Visual inspection of event related potential data suggests that both unisensory and multisensory processing may be atypical in the children with autism spectrum disorder. To index

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by a collection of symptoms that causes substantial social, communication, and behavioral challenges for people. Signs of ASD begin early during development and typically last throughout a person's lifetime. In the new Diagnostic and Statistical Manual, Fifth Edition (DSM-5), ASD is defined by impairments in two core domains: 1. social communication and social interaction, and 2. restricted, repetitive

patterns of behavior, interests, or activities^[1]. In practice, a clinical diagnosis of ASD involves consideration of multiple sources of information about the child, including: performance on diagnostic tests, assessment of developmental, language, communication, and adaptive functioning skills, a review of the child's medical and family history, and often other neurological tests^[2].

Prevalence estimates for ASD have increased in the last 15 years, causing ASD to become a major public health concern. These prevalence increases are thought to reflect a broadening of the concept of and diagnostic criteria for ASD as well as increased awareness and improved detection of pervasive developmental disorders at all ages and all levels of intellectual ability^[3]. A recent report by the Center for Disease Control's Autism and Developmental Disabilities Monitoring Network based on 2010 data from 11 communities in the United States indicates that ASD affects approximately 1/68 children in the U.S. aged 8 years, and that it is five times more common in boys^[4]. Although ASD affects all racial, ethnic, and socioeconomic groups, prevalence estimates and age at diagnosis vary^[4].

The impact of the new DSM 5

Each person with ASD is unique and has a highly individualized manifestation of the disorder, making diagnosis, treatment, and research difficult. Core symptoms of the disorder range from mild to severe, and the abilities of individuals with ASD vary substantially^[5-7]. In addition, documented rates of comorbidities in individuals with ASD are high^[8]. With the publication of the new DSM 5 in 2013 the diagnosis of autism has been redefined. Most importantly, several conditions that used to be diagnosed separately in the DSM IV, including: autistic disorder, childhood disintegrative disorder, pervasive developmental disorder not otherwise specified, and Asperger's syndrome are now included under the umbrella diagnosis of ASD^[1]. Discussions regarding the merits and the effects of the DSM 5 changes are ongoing^[9]. In general, individuals previously diagnosed with one of the four pervasive developmental disorders using the DSM IV are expected to also meet criteria for ASD using the DSM 5. The effect of the application of the new DSM 5 criteria, however, is not yet clear. One recent study showed that DSM 5 criteria identified over 90% of children with a DSM IV pervasive developmental disorder diagnosis^[10]. Some researchers expect that prevalence estimates for ASD will be lower with the DSM 5 compared to the DSM IV, mainly due to the increased number of criteria a person needs to meet for a diagnosis^[9,11].

The inclusion of sensory symptoms in the DSM 5

Another important change in the DSM 5 is the inclusion of atypical sensory behaviors under the core domain of restricted, repetitive patterns of behaviors in criteria B4^[1]. The presence of sensory symptoms in individuals with autism has been recognized for many years and was noted in the original descriptions of autism put forward by both Kanner (1943)^[12] and Asperger (1944)^[13]. Both hypo- and hyper- sensitivity to sensory stimulation in individual modalities (e.g. vision, hearing, touch, proprioception, vestibular) are widely reported. Anecdotal reports from individuals with autism (e.g. ^[14-16]), clinical reports (e.g. ^[17,18]), studies using behavioral questionnaires (e.g. ^[9,19-25]), a meta-analysis^[26], and psychophysiology studies (e.g. ^[27-29]), collectively indicate that sensory symptoms are an important feature of autism spectrum disorder. In fact, numerous researchers argue that atypical sensory behavior should be considered a core symptom of autism^[6,9]. Examples of sensory symptoms now assessed using criteria B4 of the DSM 5 include:

attraction/aversion to texture or touch, unusual visual exploration/activity, and odd responses to sensory input (any modality)^[1]. Estimates of the prevalence of sensory symptoms in ASD range from 45-95%^[26]. In one study, Leekam and colleagues reported that over 90% of children with ASD have atypical responses to sensory stimulation, often in multiple modalities, regardless of age and IQ. In addition, unusual reactions to auditory stimulation in young children with ASD have been found to be an identifying characteristic that distinguishes them from individuals with other developmental delays^[30,31]. Although many studies have found atypical or impaired sensory processing in ASD, numerous studies have also found enhanced perceptual function at least for simple tasks in some individuals with ASD^[32,33].

ERP research

One method that has been especially useful for exploring sensory processing issues in individuals with ASD is event related potentials (ERPs). Studies of ERPs, which represent transient changes in the brain's electrical response to the presentation of a stimulus, have greatly informed our understanding of ASD. ERP studies have contributed to elucidating the sources of core impairments in ASD, such as impaired social interaction and communication, by revealing underlying deficits in unisensory processing. ERP studies in individuals with ASD suggest that impairments exist in both simple and more complex levels of sensory processing in numerous sensory modalities (see for review^[34,35]).

Auditory ERP studies

Because impairments in language and social communication are considered core deficits, numerous studies have examined auditory processing in ASD. Previous studies examining auditory ERPs in typically developing individuals using scalp recordings and simple repeated stimuli have demonstrated that the ERP waveform is composed of several reliable amplitude peaks or components, for example the P100, N100, P200 and N200^[36,37], with P and N denoting positive or negative deflections, respectively, and the number representing the approximate time following the stimulus presentation. These peaks are thought to reflect the early detection of sound at the primary cortical level. Because auditory stimulation activates numerous neural pathways, each of the components of the auditory ERP represents the activity of several distinct neural generators^[36]. Typically, the most prominent response to sound in adults is the N100^[37]. Studies in children and adolescents show considerable changes in the amplitude and latency of the auditory ERP amplitude peaks over time^[38,39]. In children 8 years of age or younger, the auditory ERP is typically dominated by the P100, but only for fast stimulus presentation rates of 1Hz or more. A small but reliable vertex N100(b) potential may reportedly be found in 5 - 7 year olds, but only with slower stimulus presentation rates, and it is not consistently present until 9 years of age or older^[38,39]. Auditory ERP studies comparing adult responses to children show that multiple components of the auditory ERP peak later in children than in adults, indicating slower processing of auditory stimuli in children. Interestingly the P200 latency reaches peak adult values by 2-3 years of age, which indicates that the neural generators of the auditory ERP have distinct maturational time courses^[38,39].

Studies examining cortical auditory ERPs in ASD show atypical amplitudes and latencies of the main components. For example, the P100 has been found to be smaller in amplitude in adults and children with ASD using EEG^[40] and MEG^[41], respectively. In addition other studies have found that the N100 amplitude is reduced

in children with ASD^[42-44]. The results for P200 are equivocal; however, the P200 was reportedly smaller in one study using click stimuli (see^[45], for review). Faster latency auditory ERP components have also been found by several researchers (see^[35], for review), highlighting the numerous differences in auditory processing that have been found between individuals with autism and typically developing individuals.

Somatosensory ERP studies

Despite the behavioral evidence for atypical somatosensory processing in ASD and the potential importance of touch for the development of social communication^[46], far fewer ERP studies have examined cortical somatosensory processing in ASD compared to auditory processing. The neural generators of the somatosensory ERP are less well understood compared to auditory ERPs; however, previous studies in typically developing individuals using scalp recordings and simple repeated stimuli also show several reliable amplitude peaks including the P100, N140, P190^[47,48]. These amplitude peaks are known to reflect detection of somatosensory stimulation at the primary cortical level. In one of very few studies specifically addressing cortical somatosensory processing in children with ASD, using MEG, Marco *et al.*, 2012 found that boys with ASD showed reduced somatosensory ERPs as early as 40 ms post-stimulation that was considered indicative of a diminished response in the primary somatosensory cortex^[35]. Using EEG, Russo *et al.*, 2010 also showed evidence indicative of reduced cortical somatosensory processing^[50]. However, a study by Kemner *et al.*, 1994, found no differences in a negative peak between 50 and 200 ms^[49].

Multisensory processing

Studies using a variety of behavioral methods indicate that individuals with ASD have impairments in their ability to process multisensory information (e.g.^[51,52]). In order to function adaptively in the environment, the brain must combine information from the separate senses in a coherent and ongoing way. This basic cortical function, referred to as multisensory integration (MSI)^[53] is considered foundational for higher level cognitive functions such as speech and communication, which are core impairments in ASD. Typically, multisensory stimuli that are coincident in space and within approximately 150 ms of each other will be integrated. In typical adults, coincident (and even spatially non-coincident auditory and somatosensory) stimuli are effortlessly integrated, leading to enhanced behavioral performance on detection, discrimination, and other perceptual tests compared to unisensory performance^[53,54].

When MSI is impaired, sensory-perceptual experiences are thought to be significantly disrupted^[55]. In fact, initial anecdotal reports from individuals with ASD suggested an impaired ability to process information in more than one sense at a time^[14,16]. In one recent perceptual study of multisensory processing, the performance of children with autism on the sound induced-flash illusion was compared to age- and IQ- matched typically developing controls^[52]. Results showed children with ASD were significantly less likely to experience the sound induced-flash illusion, which was considered indicative of less perceptual fusion in ASD, and weaker MSI. In another study manipulating the timing of the stimuli in the sound induced-flash illusion, results suggested that the “time window for integration” may be extended in individuals with ASD leading to the binding of stimuli from unrelated sources^[56].

Electrophysiology of MSI in typical development

Very few ERP studies have examined MSI in typically developing

children, and even fewer ERP studies have examined MSI in children with ASD. One study conducted in 2008 examined auditory-somatosensory MSI in typically developing children aged 6-13 years by comparing multisensory and summed unisensory ERPs using a standard method similar to the one used here^[57]. Results showed simultaneous onset auditory and somatosensory stimuli were integrated: (1) between 60-80 ms at scalp locations contralateral to the side of somatosensory stimulation; (2) between 110-150 ms ipsilateral to the side of somatosensory stimulation, and 3. between 180-220 ms over central regions bilaterally. This study extended previous work in typical adults where multiple post-stimulus time frames for auditory-somatosensory integration, beginning around 50 ms post-stimulation, were also found^[54,58].

In 2011, Brandwein and colleagues systematically examined audio-visual MSI in typically developing children aged 7-16 years, and 13 young adults using ERPs as well as behavioral measures. The participants were divided into 4 age groups (7-9, 10-12, 13-16, and adults) to assess developmental changes^[59]. Multisensory and summed unisensory ERPs were compared during several time intervals and across several scalp regions. This study showed that the brain processes underlying audio-visual MSI continued to mature into at least middle childhood. In addition, changes in these processes during the time frame of the auditory N100 were related to a gradual fine tuning in the ability to benefit behaviorally from multisensory stimulation in terms of reaction time. These results support a connection between neurophysiology and behavior, and suggest ongoing plasticity in the brain circuitry underlying MSI.

Electrophysiology of MSI in ASD

In one of the first ERP studies of MSI in children with ASD, Brandwein *et al.*, 2013 examined the development of audio-visual integration in children with ASD aged 7-16 years^[43]. This study found differences between multisensory and summed ERPs indicative of MSI for both typically developing children and children with ASD prior to 100 ms. This study also found MSI between 100 and 120 ms for the two typically developing age groups (7-10, 11-16), but not for the ASD group. During the second time frame examined between 180 and 210 ms, both the typically developing and ASD groups showed evidence of MSI. This study also found that children with ASD showed considerably less behavioral facilitation of reaction time with multisensory stimulation compared to typically developing children. Exploratory topographic analyses further suggested that children with ASD may rely on different cortical networks during early multisensory processing than typically developing children. In addition in another recent study of audio-visual ERPs, Brandwein and colleagues found significant associations between auditory processing, MSI, and symptom severity in ASD^[44].

Although the majority of ERP studies of MSI in ASD examine auditory-visual integration, one study has examined auditory-somatosensory integration^[50]. Similar to the present study, Russo *et al.* 2010 examined unisensory auditory and unisensory somatosensory ERPs, and multisensory auditory-somatosensory MSI in a group of children with ASD aged 6-16 years (including autism, Asperger’s and PDD-NOS diagnoses) compared to typically developed age, and IQ- matched controls. ERPs elicited by unisensory auditory and somatosensory stimulation were reportedly highly similar in morphology for the two groups; however, decreased amplitudes were noted for the ASD group beginning at 100 ms for auditory stimulation and 70 ms for somatosensory stimulation. Furthermore, comparing multisensory and summed

unisensory ERPs to index MSI, differences were revealed between the groups that appeared around 175 ms, and were indicative of MSI occurring in the typically developing children, but not in the children with ASD. MSI was essentially absent until approximately 310 ms in the children with ASD and was determined to be less extensive overall compared to the typically developing children.

The present preliminary ERP investigation examined unisensory auditory and somatosensory processing, and auditory-somatosensory MSI in a small group of boys with ASD and a small group of typically developing age- and gender-matched controls. A passive paradigm was used that required no behavioral response on the part of the participant. To evaluate MSI, a standard method of comparing multisensory and summed unisensory responses widely reported in the literature was used (e.g.^[50,54,57,58,60-63]). Statistically significant differences found between the multisensory and summed unisensory responses were considered indicative of MSI. The primary goals of this study were to replicate the results of a previous study demonstrating MSI in typically developing children and to explore whether or not children with ASD showed a similar spatio-temporal pattern of auditory-somatosensory MSI.

METHODS

Participants

Five children with ASD and five typically developing children, between the ages of 6 to 12 years participated in this study (mean age ASD = 10.18, SD = 1.73; mean age typically developing = 10.36, SD = 1.95; $p = 0.9$). Participant's parents/legal guardians provided written consent using procedures that were approved by the university institutional review board for human subjects research. Of the five participants with autism, parents reported on a demographics form DSM IV diagnoses including: autism (two participants), high functioning autism (two participants), and Asperger's syndrome (one participant). Reported comorbidities included seizure disorder (1 participant, no seizures in 4 years), learning disabilities, speech difficulties, motor problems, ADHD, allergies, and asthma. Exclusion criteria for typically developing children included any report of a previous psychological or neurological diagnosis.

Instruments

Three types of sensory stimulation were presented and ERPs were recorded while participants watched a silent movie: bilateral auditory clicks (80 dB, 3 ms duration) delivered via earphones (Etymotic Research, Inc. (ER-1), somatosensory vibro-tactile pulses (138 Hz, 20 ms) delivered to the right palm (Johnson Kinetics, Inc.), or simultaneous onset auditory and somatosensory stimulation as described. One hundred of each type of stimulus was delivered in a pseudo-random order, with an average inter-stimulus interval of 4 s (range = 3-5 s). The paradigm was passive; no behavioral responses were required of the participants. Participants were instructed to watch the video and ignore sensory stimulation.

A 32-channel BioSemi Active Two EEG system (Coretech Solution, Willmington, NC, US) with electrodes positioned according to the American Electroencephalographic Society Guideline (1994) was used for continuous EEG recording. The Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode were used as the reference and ground, respectively (see: <http://www.biosemi.com/faq/cms&drl.htm>.) Recordings were digitally sampled at 1024 Hz. Off-line data reduction using Brain Vision Analyzer software (Brain Products GmbH, Munich, DE) included re-referencing to an average of the

two earlobes, filtering (0.1-100 Hz; roll-off=12 dB/octave), and segmenting ERPs. Segments were 200 ms pre-stimulus (baseline) to 400 ms post-stimulus. Trials with blinks/large eye movements greater than 150 mV based on vertical and horizontal electro-oculograms and trials with other artifacts greater than 150 mV were rejected. The following averaged ERPs were generated for each participant: 1. auditory, 2. somatosensory, 3. multisensory (simultaneous auditory and somatosensory), 4. summed (unisensory auditory plus unisensory somatosensory), and 5. difference (the averaged summed unisensory ERPs subtracted from the averaged multisensory ERPs). The accepted number of segments for the auditory, somatosensory and multisensory ERPs for typically developing children was 83.5, 84.5, 82.2 respectively, and 71.2, 68.8, 72.8, respectively for the ASD group.

Matlab (Mathworks) was used to measure average amplitudes for multisensory and summed unisensory ERPs at 8 electrode sites (Fz, Cz, C3, C4, CP1, CP2, CP5, CP6). These sites corresponded to scalp regions where ERPs elicited by auditory, somatosensory and multisensory were expected, and where auditory-somatosensory MSI was found in previous studies^[57,58,60]. Averaged amplitudes were calculated for three time windows: 60-80 ms, 80-110 ms, and 110-150 ms) by deriving an area measure between each ERP waveform and the 0 microvolts baseline. The time windows evaluated were selected based on the approximate timing of the amplitude peaks of the multisensory ERPs at electrode site Cz in a previous study of typically developing children^[57].

The Short Sensory Profile questionnaire^[64] was administered to parents/legal guardians of the participants to assess sensory-related behaviors. The Short Sensory Profile uses a five-point Likert scale (1 = never, 5 = always). The extent to which participants' sensory preferences were typical or atypical was calculated by reverse-scoring each item (i.e. a response of 5 received a score of 1, and so on); a low total for a section was more atypical, and a high total was more typical.

Statistical analyses

To analyze MSI, the average amplitudes of multisensory ERPs were compared to the average amplitudes of the corresponding summed unisensory responses across the post-stimulus time windows (60-80 ms, 80-110 ms, 110-150 ms) at 8 electrode sites. MSI was examined statistically for each group separately using within subjects, repeated measures, two-way (stimulus type by electrode site) analysis of variance (ANOVA) for each time window. The stimulus types were multisensory and summed unisensory ERPs. The electrode sites represented scalp regions that were contralateral (C3, CP1, CP5), midline (Fz, Cz), and ipsilateral (C4, CP2, CP6) to the side of vibro-tactile stimulation of the right palm. Alpha levels were set at $p < 0.05$ for each statistical test. A Greenhouse-Geisser correction was used to determine significance if the assumption of sphericity was violated. Statistically significant differences between the average amplitude of multisensory ERPs and the average amplitude of summed unisensory ERPs were considered indicative of MSI.

A mixed model repeated measures ANOVA was used to analyze overall between group differences on the Short Sensory Profile. A Greenhouse-Geisser correction was used to determine significance if the assumption of sphericity was violated. One way ANOVAs with a factor of group were used to further examine differences between children with ASD and typically developing children on eight sections of the Short Sensory Profile and the total score. Alpha levels were set at $p < 0.05$ for each statistical test.

RESULTS

Unisensory and Multisensory ERPs: visual inspection

Grand averaged auditory (red traces), somatosensory (green traces), and multisensory auditory-somatosensory ERPs (black traces) were superimposed at select electrode sites for typically developing children (Figure 1) and children with ASD (Figure 2). The electrode sites, identified with open circles on a schematic of an electrode cap, corresponded to midline scalp locations (Fz, Cz), and locations contralateral (C3, CP1, CP5) and ipsilateral (C4, CP2, CP6) to the side of vibro-tactile stimulation of the right palm, and represent the locations at which MSI was examined statistically. Bilateral auditory click stimulation, vibro-tactile stimulation of the right palm, and simultaneous multisensory stimulation each elicited a unique spatio-temporal distribution of ERP amplitude peaks that were evident across multiple electrode sites for both the typically developing children and the children with ASD; however, visual inspection of the unisensory and multisensory data revealed possible differences between the groups.

Grand averaged auditory, somatosensory, and multisensory ERPs superimposed for the typically developing children (black traces) and the children with ASD (grey traces) at a smaller subset of electrode sites allowed for a more detailed comparison of the data (Figure 3). The grand averaged auditory P100, N100b, and P200 peak latencies recorded for typically developing children at electrode site Fz were at approximately 76 ms, 102 ms, and 129 ms, respectively (Figure 3A). Although the children with ASD showed similar auditory ERP latencies and morphologies, a decreased N100b amplitude peak was noted for the ASD group at electrode

site Fz compared to the typically developing group. Furthermore, at electrode site Cz, decreased auditory N100b and P200 amplitude peaks were noted for the children with ASD compared to the typically developing children.

Grand averaged somatosensory ERP amplitude peaks were superimposed for the two sets of children at contralateral and ipsilateral electrode sites C3 and C4, respectively, (Figure 3B). Somatosensory responses were clearly strongest contralateral to the side of stimulation for the typically developing children; however, this was less clear for the children with ASD. Peak latencies at contralateral electrode site C3 for the typically developing group were: P100 (108 ms), N145 (162 ms), and P190 (223 ms). Similar latency and morphology ERP components were recorded for the children with ASD; however, the typically developing somatosensory ERP remained mostly positive in polarity, and was dominated by positive amplitude peaks (P100, P190), while the ASD response remained mainly negative in polarity and was dominated by the N145. Although the N145 amplitude peak for the ASD group was more negative (larger in amplitude) relative to the N145 for the typically developing children, prior to the N145, the somatosensory ERP for children with ASD was weak. In addition, at electrode site C4 ipsilateral to the side of somatosensory stimulation, the somatosensory ERP was somewhat dissimilar between the groups. For the ASD group, a prolonged negative amplitude peak beginning around 110 ms post-stimulation was apparent that overlapped with the timing of the N145 at electrode site C3. Instead, for the typically developing group, the ipsilateral somatosensory ERP N145 at electrode site C4, was delayed relative to the N145 at electrode site C3.

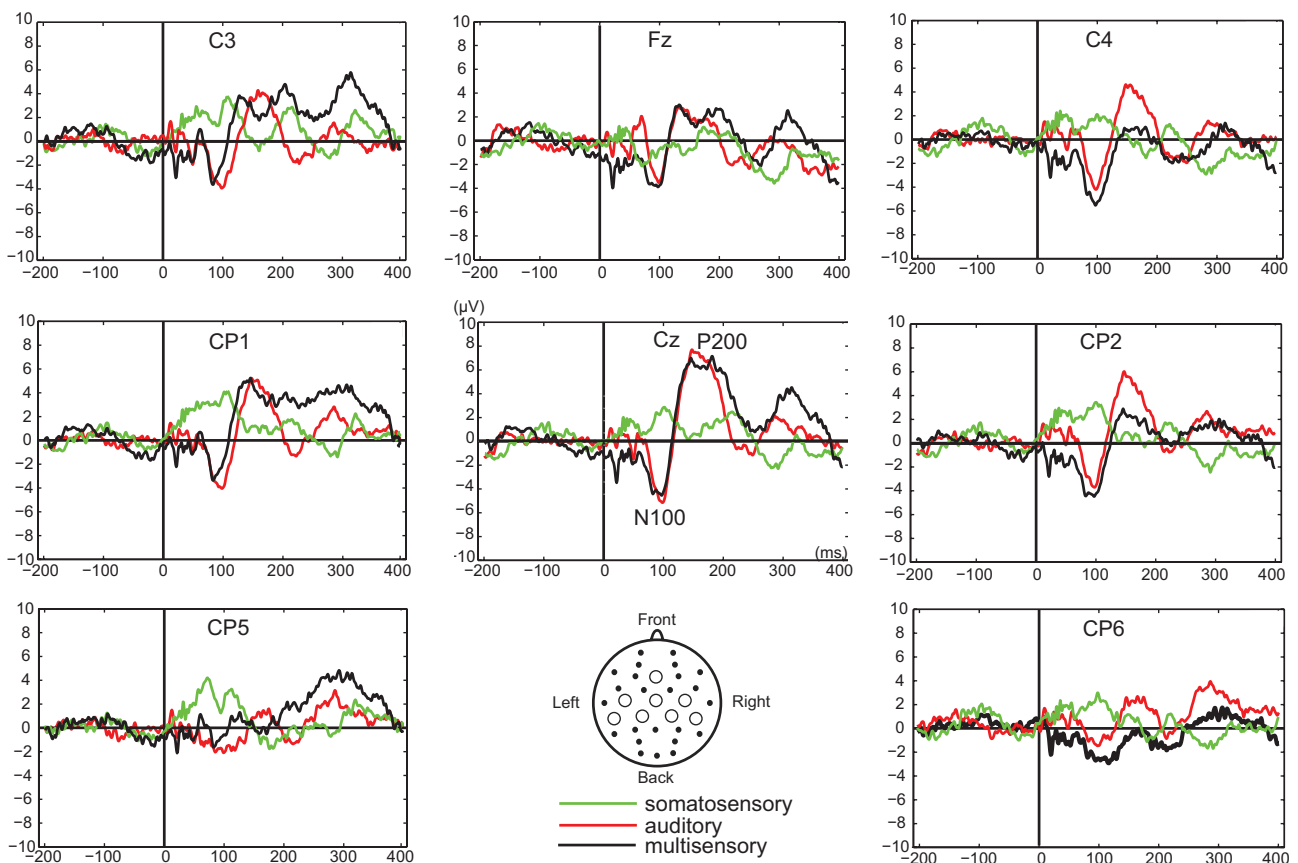


Figure 1 Grand average auditory (red), somatosensory (green), and multisensory auditory-somatosensory (black) ERPs recorded from five typically developing.