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Research Report

An exploratory event-related potential study of multisensory integration in sensory over-responsive children

Barbara A. Brett-Green[a,b,*], Lucy J. Miller[a,b,c,d], Sarah A. Schoen[a,b,d], Darci M. Nielsen[a]

[a]Sensory Processing Disorder Foundation, Greenwood Village, CO, USA
[b]Department of Physical Medicine and Rehabilitation, University of Colorado Denver, Denver, CO, USA
[c]Department of Pediatrics, University of Colorado Denver, Denver, CO, USA
[d]Doctoral Program in Pediatrics, Rocky Mountain University of Health Professionals, Provo, Utah, USA

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ABSTRACT

Children who are over-responsive to sensation have defensive and "fight or flight" reactions to ordinary levels of sensory stimulation in the environment. Based on clinical observations, sensory over-responsivity is hypothesized to reflect atypical neural integration of sensory input. To examine a possible underlying neural mechanism of the disorder, integration of simultaneous multisensory auditory and somatosensory stimulation was studied in twenty children with sensory over-responsivity (SOR) using event-related potentials (ERPs). Three types of sensory stimuli were presented and ERPs were recorded from thirty-two scalp electrodes while participants watched a silent cartoon: bilateral auditory clicks, right somatosensory median nerve electrical pulses, or both simultaneously. The paradigm was passive; no behavioral responses were required. To examine integration, responses to simultaneous multisensory auditory–somatosensory stimulation were compared to the sum of unisensory auditory plus unisensory somatosensory responses in four time-windows: (60–80 ms, 80–110 ms, 110–150 ms, and 180–220 ms). Specific midline and lateral electrode sites were examined over scalp regions where auditory–somatosensory integration was expected based on previous studies. Midline electrode sites (Fz, Cz, and Pz) showed significant integration during two time-windows: 60–80 ms and 180–220 ms. Significant integration was also found at contralateral electrode site (C3) for the time-window between 180 and 220 ms. At ipsilateral electrode sites (C4 and CP6), no significant integration was found during any of the time-windows (i.e. the multisensory ERP was not significantly different from the summed unisensory ERP). These results demonstrate that MSI can be reliably measured in children with SOR and provide evidence that multisensory auditory–somatosensory input is integrated during both early and later stages of sensory information processing, mainly over fronto-central scalp regions.

* *Corresponding author*. Sensory Processing Disorder Foundation, 5655 South Yosemite Street, Suite 304, Greenwood Village, CO 80111, USA. Fax: +1 303 322 5550.
E-mail address: barb@indra.com (B.A. Brett-Green).

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1. Introduction

Sensory processing disorder is a heterogeneous clinical condition characterized by a range of atypical behavioral responses to ordinary sensory stimulation. Three primary patterns of the disorder with six total subtypes have been proposed (Miller et al., 2007). Patterns include sensory modulation disorder, sensory discrimination disorder, and sensory-based motor disorder. Within sensory modulation disorder the subtypes are: sensory over-responsivity, sensory under-responsivity, and sensory seeking/craving. This study specifically examines a clinical sample of children with behavioral symptoms of sensory over-responsivity.

Sensory over-responsivity (SOR) was first described by Dr. A. Jean Ayres, an occupational therapist and neuroscientist (Ayres, 1964). Descriptions of the behavioral symptoms indicate children with SOR feel over-whelmed by sensory input, and display "fight or flight" and defensive responses to one or more types of sensory stimuli not perceived as overwhelming by typically developing children. Prevalence research suggests that between 5% and 16% of school age children have negative responses to sensation that interfere with participating in daily life activities (Ahn et al., 2004; Ben-Sasson et al., 2009). Commonly reported symptoms of sensory over-responsivity include sensitivity to sound and touch (Ben-Sasson et al., 2009; Goldsmith et al., 2006). Behavioral studies suggest that over-responsiveness in the somatosensory and auditory systems is associated with emotional and psychological disorders in adults and children (Kinnealey and Fuiek, 1999; Kinnealey et al., 1995; Neal et al., 2002; Pfeiffer et al., 2005). The effects of over-responsivity can be profound, impacting a child and family's quality of life, and interfering with engagement in social interactions, participation in home and school routines, self-regulation, and self-esteem (Cohn et al., 2000; Lane, 2002). Examining the neurophysiology of sensory processing in children with SOR can help elucidate whether the behavioral symptoms of SOR have a neural basis.

Early theories describe SOR as a disorder in which sensory input is not integrated or organized appropriately in the brain to facilitate adaptive behavior (Ayres, 1972, 1979). Based on the early work of Sherrington (Sherrington, 1906; Sherrington, 1955), Ayres (1972), hypothesized that children with SOR have a deficit in inhibiting irrelevant sensory information resulting in excessive central nervous system arousal in response to typical levels of sensory stimulation (Ayres, 1972). This difficulty processing sensory input was theorized to result in a lack of development/functioning of integrative mechanisms. To date little is known about the neural mechanisms underlying SOR; however, recent advances in technology, such as high resolution recording of event-related potentials (ERPs), which can be used to accurately measure the timing of when sensory information processing is occurring in the brain, as well as provide some indication of where it is occurring, and have made it possible to examine the theoretical constructs of the neurophysiology of SOR.

Studies using ERPs report sensory processing differences in individuals with SOR consistent with Ayres' hypotheses. Kisley et al. used a gating paradigm to evaluate the degree of neural inhibition occurring in response to repetitive paired click stimulation based on a ratio of measurements of ERP amplitude peaks. They found that healthy adults with less P100 amplitude peak suppression (to the second click in a pair) reported greater symptoms of auditory SOR (Kisley et al., 2004), suggesting that poor inhibition of irrelevant sensory input is associated with over-responsivity. Similarly, in a study of children, Davies and Gavin (2007) reported less P50 gating in those diagnosed with SOR compared to typically developing controls. Other studies have also found a link between SOR and atypical sensory processing. For example, Parush et al. (1997, 2007) found that SOR in boys with ADHD is associated with larger somatosensory evoked potentials compared to typically developing boys. The few neural studies conducted on individuals with SOR employed specific paradigms using either unisensory auditory stimuli or unisensory somatosensory stimuli (Davies and Gavin, 2007; Kisley et al., 2004; Parush et al., 1997, 2007). Despite the implications of Ayres' early theory and evolving perspectives regarding the possible relevance of impaired multisensory integration to other neurobehavioral disorders, such as autism and pervasive developmental disorder (Iarocci and McDonald, 2006; Magnée et al., 2008), no study of children with symptoms of SOR has examined neural responses to simultaneous multisensory auditory and somatosensory stimulation.

A growing body of neuroscience research is examining the influence of interactions between the auditory and somatosensory systems on sensory information processing and behavior in adult humans, thus providing a foundation for extending multisensory integration (MSI) research to clinical populations. Studies using diverse methodology, including functional magnetic resonance imaging (Foxe et al., 2002; Kayser et al., 2005; Schürmann et al., 2006), electrophysiology (Foxe et al., 2000; Murray et al., 2005; Sperdin et al., 2009; Touge et al., 2008), and magnetoencephalography (Gobbelé et al., 2003; Lam et al., 1999; Lütkenhöner et al., 2002; Stephen et al., 2007) have all provided evidence demonstrating extensive neural interactions between these systems. For example, ERP studies in typical adults have consistently shown auditory–somatosensory MSI beginning around 50 ms in auditory cortical regions previously thought to be unisensory (Foxe et al., 2000; see Foxe and Schroeder, 2005; Lütkenhöner et al., 2002; Murray et al., 2005). A similar finding in typically developing children suggests that like adults, children integrate multisensory auditory–somatosensory input during multiple stages of sensory information processing (Brett-Green et al., 2008).

In the present study, high resolution ERP recordings were used to investigate auditory–somatosensory MSI in a referred sample of children clinically identified with SOR. A widely accepted method that compares ERP responses to multisensory stimulation with the sum of unisensory ERP responses was used (Di et al., 1994; see Calvert and Thesen, 2004; Foxe et al., 2000; Murray et al., 2005; see Stein and Meredith, 1993; Teder-Sälejärvi et al., 2002; Talsma and Woldorff, 2005; Giard and Peronnet, 1999). Differences between the multisensory and summed ERPs revealed using this approach are considered indicative of cortical multisensory integration occurring when the stimuli are presented simultaneously; however, it should be noted that this method is not sensitive to all areas

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where multisensory integration could occur (Foxe et al., 2000). Based on clinical observations that children with SOR have difficulty processing multiple sensations and literature suggesting that most children who are over-responsive to somatosensory stimulation are also over-responsive to auditory stimulation (Ben-Sasson et al., 2009; Goldsmith et al., 2006), we hypothesized that behavioral symptoms of SOR (e.g. defensive reactions to auditory and tactile stimulation) may be related to poor integration between these sensory systems, which would be reflected in the ERPs. While a more comprehensive study directly comparing auditory–somatosensory MSI between children with SOR and typically developing controls is in progress, here we describe an initial effort to determine the feasibility of studying auditory–somatosensory MSI in children with SOR. Our goals were to: 1. demonstrate that MSI can be reliably measured in children with SOR; 2. characterize the spatio-temporal distribution of MSI; 3. examine age effects on MSI; and, 4. generate hypotheses for future research.

2. Results

2.1. *Unisensory and multisensory ERPs: visual inspection*

Grand averaged unisensory auditory, unisensory somatosensory, and multisensory auditory–somatosensory ERPs are shown superimposed for select electrode sites (Fig. 1). These electrode sites, located at midline scalp locations (Fz, Cz, and Pz), contralateral to the side of somatosensory stimulation (C3 and CP5), and ipsilateral to the side of somatosensory stimulation (C4 and CP6), represent the locations at which MSI was examined.

The auditory ERP exhibited a sequence of ERP amplitude peaks with grand averaged peak latencies at electrode site Fz as follows: P100 at 85 ms, N100 at 122 ms, and P200 at 155 ms, respectively. The somatosensory ERP had amplitude peaks with grand average P100, N100, and P200 peak latencies at contralateral electrode site C3 of 95 ms, 145 ms, and 200 ms,

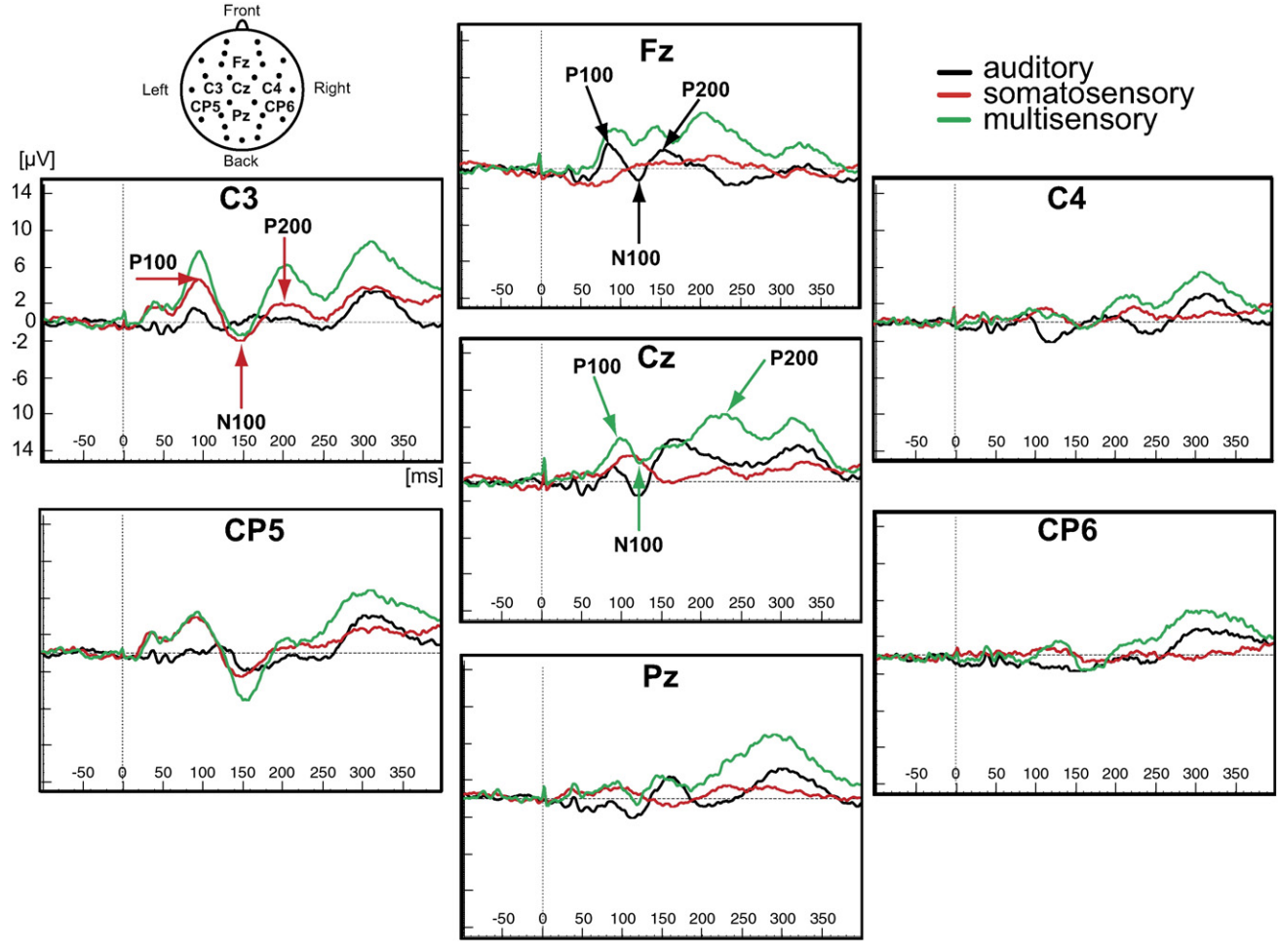

Fig. 1 – Event-related potentials (ERPs). The grand averages of event-related potentials for auditory (black strokes), somatosensory (red strokes) and multisensory auditory–somatosensory stimulation (green strokes) are shown for a sample of 20 children with the sensory over-responsive (SOR) subtype of sensory processing disorder. The schematic (top left) depicts a top view of the electrode cap and the electrode sites for which the data is shown. The ERPs are shown for midline electrode sites (Fz, Cz, and Pz), and electrode sites that are contralateral (C3 and CP5) and ipsilateral (C4 and CP6) to the side of somatosensory (right median nerve) stimulation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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respectively. Multisensory auditory–somatosensory stimulation evoked ERP amplitude peaks with the following peak latencies at electrode site Cz: P100 at 95 ms, N100 at 120 ms, and P200 at 225 ms. In general, the polarities of the multisensory amplitude peaks were more positive than for either unisensory response. Note that the amplitude and latency of ERP amplitude peaks vary depending on electrode location.

2.2. *Multisensory vs. summed unisensory ERPs: visual inspection*

Clear differences between the ERP amplitude peaks elicited by multisensory stimulation and the peaks of summed unisensory ERPs were strongly suggestive of MSI (Fig. 2). For example, substantial amplitude differences were apparent at electrode site Fz, beginning around 40 ms that continued for the remainder of the 400 ms recording epoch, with the multisensory P100, N100, and P200 amplitude peaks having larger positive polarities. Another notable difference was at electrode site Cz, where the multisensory P200 was larger in amplitude and peaked later than the summed unisensory ERPs. Large differences in the P200 amplitude of multisensory and summed unisensory ERPs also occurred at electrode site C3. Differences at electrode site Pz were mainly after 200 ms. Differences between the multisensory and summed ERP amplitude peaks at electrode sites CP5, C4, and CP6 appeared minimal. In general, multisensory ERP amplitude peaks had polarities across the entire recording epoch that were more positive compared to summed ERP amplitude peaks.

2.3. *MSI: statistical analyses*

2.3.1. *Midline MSI (Fz, Cz, and Pz)*

Repeated measures 2-way analysis of variance (ANOVA) with factors of stimulus type (multisensory, summed) and electrode site (Fz, Cz, and Pz), calculated for each of the four time-windows, found a significant main effect of stimulus type for the earliest time-window (60–80 ms), with multisensory responses being larger in amplitude (more positive) than the summed unisensory amplitude peaks ($F(1,19)=6.12$, $p=0.02$). In addition, a significant interaction was found during this time-window ($F(2,34)=3.47$, $p=0.04$). Partial eta squares were

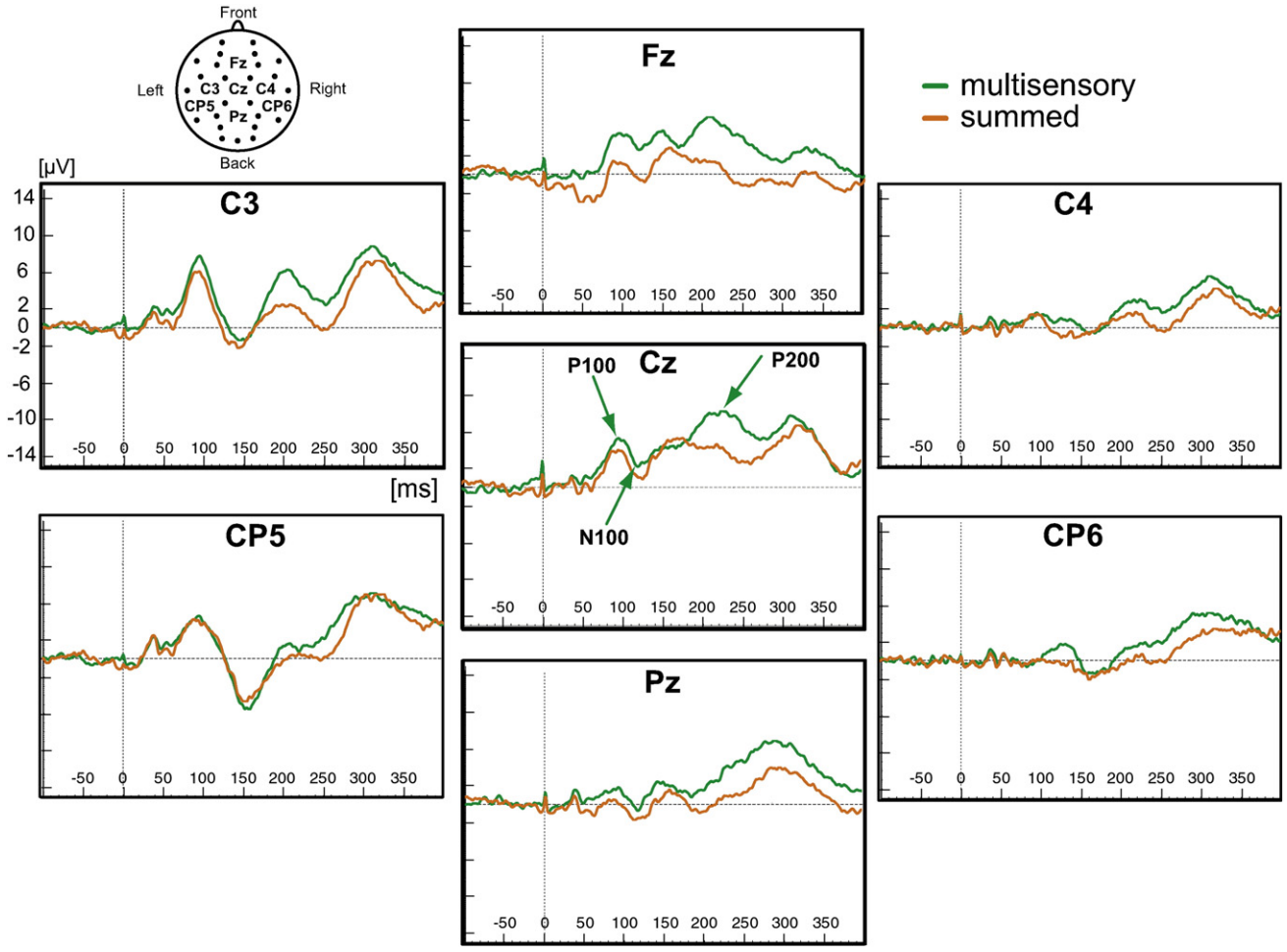

Fig. 2 – Multisensory vs. summed ERPs. The grand average ERPs are shown for the seven electrode sites (Fz, Cz, Pz, C3, CP5, C4, and CP6) identified in the top left schematic. Multisensory ERPs (green traces) are superimposed on the summed unisensory auditory and somatosensory ERPs (orange traces). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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moderate: 0.24 and 0.15, respectively, suggesting that the main effect contributes more to the statistical model than did the interaction.

A significant main effect of stimulus type was also found for the last time-window (180–220 ms) with the multisensory amplitude peaks being larger (more positive) than the summed amplitude peaks at all three electrode sites ($F(1,19)=4.68$, $p=0.04$). Partial eta squared was moderate (0.20). Statistical results were consistent with topographical difference wave maps showing a unique multisensory activity between 60 and 80 ms over electrode site Fz, and between 180 and 220 ms over electrode sites Fz and Cz (Fig. 3). No significant main effect of stimulus type or interaction was found for the other two time-windows between 80 and 110 ms and 110 and 150 ms.

2.3.2. *Contralateral MSI (C3 and CP5)*

Repeated measures 2-way ANOVAs with factors of stimulus type (multisensory, summed) and electrode site (C3 and CP5) showed no significant main effect of stimulus type for any of the time-windows. However, an interaction between stimulus type and electrode site was found for the 180–220 time-window ($F(1,19)=5.67$, $p=0.03$). Responses to multisensory stimulation during this time-window were larger (more positive) in amplitude at electrode site C3 ($p=0.01$) compared to the summed ERP (Fig. 2). Effect size estimated by partial eta squared for the interaction was moderate (0.23). The interaction was consistent with topographical difference wave maps that showed unique multisensory activity over electrode site C3, but not CP5, during the last time-window between 180 and 220 ms (Fig. 3).

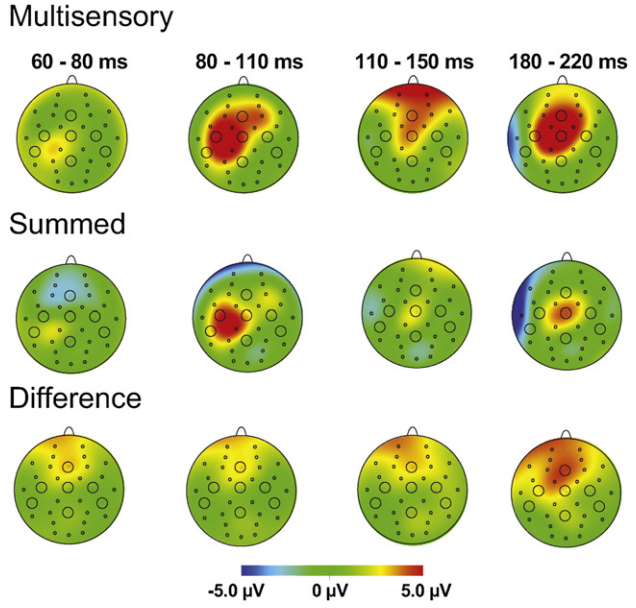

Fig. 3 – Topographical voltage maps. Spline-interpolated voltage maps of the spatio-temporal distribution of grand average multisensory, summed and difference responses across the scalp are displayed for four time-windows: 60–80 ms, 80–110 ms, 110–150 ms, and 180–220 ms. The ranges of voltages are shown in the key on the bottom. Difference maps show that fronto-central scalp regions are differentially activated by multisensory stimulation.

2.3.3. *Ipsilateral MSI (C4 and CP6)*

Repeated measures 2-way ANOVAs with factors of stimulus type (multisensory, summed) and electrode site (C4 and CP6) found no significant main effect of stimulus type or interaction for any time-window. These findings were consistent with topographical difference wave maps showing no unique multisensory activity over ipsilateral scalp electrode sites (Fig. 3).

2.4. *MSI: topographical maps*

Topographical maps showed the spatio-temporal distribution of multisensory responses across the entire scalp for each of the four time-windows (Fig. 3). Positive polarity multisensory activity between 60 and 80 ms was centered over post-central electrode sites contralateral to the side of somatosensory stimulation. From 80 to 110 ms, positive contralateral activity became stronger and spread towards the midline; positive frontal activity developed. Between 110 and 150 ms, positive activity was stronger at frontal and midline electrode sites. For the 180 to 220 ms time-window, frontal, midline, and central electrode sites showed strong positive activity, and negative activity developed over the left temporal region.

Topographical maps for the summed ERPs showed a different spatio-temporal distribution compared to topographical maps of multisensory responses (Fig. 3). Between 60 and 80 ms, the map of the summed unisensory responses showed weaker positive activity over contralateral electrode sites than with simultaneous multisensory stimulation. In addition, negative polarity activity was apparent at frontal electrode sites in the summed unisensory map that was not seen with multisensory stimulation. For the time-window between 80 and 110 ms, positive activity over contralateral electrode sites became stronger, but did not extend to frontal electrode sites as seen with multisensory stimulation; negative activity spread frontally. At 110–150 ms, the summed map did not show the strong positive activity at frontal and midline electrode sites that was evident in the multisensory map. Instead of positive activity, weak negative activity was distributed over parieto-occipital and left temporal electrode sites. For the time-window between 180 and 220 ms, positive activity at electrode site Cz in the summed ERP became stronger, but was still weaker than activity in this location during the multisensory response. Finally, the negative left temporal activity present during the 180–220 ms time-window was stronger for the summed response than for multisensory response.

Where and when the cortex was differentially activated during multisensory stimulation was readily observed in topographical difference wave maps generated by subtracting the summed unisensory responses from the multisensory response (Fig. 3). Across the four time-windows, the focus of unique activation with multisensory stimulation was primarily in fronto-central cortical regions.

2.5. *Age effects*

Correlations between age (in months) and the averaged amplitude of the multisensory ERPs were tested for the four time-windows at select electrode sites (Fz, Cz, Pz, C3, CP5, C4, and CP6). Correlation values ranged from −0.37 (Fz during the

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110–150 ms time-window) to 0.23 (CP6 during the 60–80 ms time-window); all were non-significant.

3. Discussion

This study characterizes cortical MSI between audition and somatosensation in a clinical sample of children with SOR based on a standard method of significant differences between multisensory ERPs and summed unisensory ERPs (Giard and Peronnet, 1999; Stein and Meredith, 1993). The principal findings were: 1. significant MSI at midline electrode sites (Fz, Cz, and Pz) between 60 and 80 ms and 180 and 220 ms; 2. significant MSI at contralateral electrode site C3 between 180 and 220 ms; and, 3. no significant MSI at ipsilateral electrode sites (C4, and CP6) for any time-window.

3.1. *Unisensory and multisensory ERPs*

Unisensory auditory and unisensory somatosensory P100, N100, and P200 ERP amplitude peaks commonly identified in ERP studies were also identified in children with SOR (Luck, 2005; Regan, 1989). The spatio-temporal distribution for unisensory auditory and somatosensory ERPs was consistent with previously reported results (Näätänen and Picton, 1987). In addition, ERP components were identified for multisensory responses that were approximately consistent with previous studies (Brett-Green et al., 2008; Foxe et al. 2000; Murray et al., 2005). However, possible differences in unisensory and multisensory ERPs that could contribute in part to the sensory-related behavioral problems seen in children with SOR should be further examined.

3.2. *MSI effects*

A focus of recent multisensory ERP research has been to examine the spatial and temporal distributions of cortical auditory–somatosensory MSI in typical adults (Foxe et al., 2000; Murray et al., 2005; Sperdin et al. 2009; Touge et al., 2008). In this study, significant MSI was found at midline (fronto-central) electrode sites between 60 and 80 ms and between 180 and 220 ms in children with SOR. Significant MSI at midline electrode sites between 180 and 220 ms in children with SOR is consistent with auditory–somatosensory MSI at midline electrode sites described in previous studies (Brett-Green et al., 2008; Murray et al., 2005). However, finding MSI between 60 and 80 ms at midline electrode sites was unexpected. Studies in adults consistently show early auditory–somatosensory MSI (prior to 50 ms) localized contralateral to the side of somatosensory stimulation (see Foxe and Schroeder, 2005; Murray et al., 2005). This early MSI in adults is attributed to activation in a subregion of the auditory cortex along the posterior superior temporal plane (Foxe et al., 2002). The results presented here suggest that early contralateral integration attributed to the posterior auditory cortex may not occur in children with SOR, but that instead midline (fronto-central) electrode sites are activated. Accordingly, the automatic association of causally related sensory inputs that typically occurs at an early sensory-perceptual stage of sensory information processing may not function properly in children with SOR. The midline pattern of activation seen here suggests that different neural generators may be activated at a very early stage of sensory information processing in children with SOR than in typically developing individuals. One possibility is that multisensory stimulation may activate a higher-level system in frontal cortex that involves attention and cognitive processing, rather than the automatic integration of multisensory stimuli observed in typically developing adults in auditory cortex. Early midline rather than contralateral MSI may be related to the difficulty children with SOR have automatically processing ordinary multisensory stimulation in the environment.

Although children with SOR did not exhibit MSI during the first three time-windows contralateral to the side of somatosensory stimulation, contralateral integration was found at 180–220 ms, specifically at electrode site C3. MSI at time points later than 50 ms post-stimulation and contralateral to the side of somatosensory stimulation has been found in numerous studies in adults (Foxe et al., 2000; Gobbelé et al., 2003; Lam et al., 1999; Lütkenhöner et al., 2002; Murray et al., 2005; Touge et al., 2008) and in typically developing children (Brett-Green et al., 2008). For example, auditory–somatosensory MSI has been observed in contralateral posterior parietal cortex between 75 and 85 ms (Gobbelé et al., 2003), and in contralateral secondary somatosensory cortex between 50 and 170, 105 and 130, and 140 and 220 ms post-stimulus (Gobbelé et al., 2003; Lütkenhöner et al., 2002; Touge et al., 2008). One possibility is that later contralateral integration in children with SOR is similar to typically developing individuals. However, a visual inspection of the spatio-temporal distribution of auditory–somatosensory MSI across the cortex as seen in the topographic difference wave maps for children with SOR (see Fig. 3) suggests that MSI found during the 180–220 ms time-window may represent ongoing activation of the same midline generators that were active during early integration, rather than representing subsequent activation of a separate contralateral neural generator. Although specific analyses of neural generators were not conducted here, this appears to be an important area for further studies.

Children with SOR did not show evidence of integration ipsilateral to the side of somatosensory stimulation during any of the time-windows. Adult studies reporting MSI in the hemisphere ipsilateral to the side of somatosensory stimulation found, in general, that initial integration in the ipsilateral hemisphere begins later than contralateral integration (after 70 ms) and originates in the secondary somatosensory cortex (Lam et al., 1999; Lütkenhöner et al., 2002; Touge et al., 2008). However, these studies also reported more inter-individual variability in ipsilateral compared to contralateral MSI (Lam et al., 1999; Lütkenhöner et al., 2002; Touge et al., 2008). Although the stimulation parameters used in this study (bilateral auditory stimulation delivered to the ears and unilateral somatosensory stimulation delivered to the wrist) are capable of eliciting ipsilateral integration in typically developing individuals (Brett-Green et al., 2008; Lütkenhöner et al., 2002; Touge et al., 2008), this was not the case for children with SOR. Since the ability to detect ipsilateral integration may be highly susceptible to individual variability further studies with an increased number of subjects are essential to determine if the lack of

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ipsilateral integration is a reliable finding in children with SOR.

Another focus of current multisensory research examines the temporal profile of MSI at the neural level in the cat superior colliculus model (see Rowland and Stein, 2008). This research shows that multisensory interactions in individual neurons evolve over the duration of a response and have a complex temporal profile. An initial response enhancement occurs, with multisensory stimulation eliciting faster and more robust responses compared to unisensory responses from the onset. Furthermore, multisensory enhancement is accelerated at the beginning of the response (within the first 40 ms) and is superadditive, while the second half of the response was roughly equivalent to what was predicted by summing the unisensory responses. This research highlights that different processes underlie MSI at different points during the response in individual neurons. The temporal profiles of the ERPs measured in this study similarly represent a complex amalgamation of neurophysiological processes and computations that contribute to multisensory ERPs being superadditive, additive, or subadditive over their duration. This research supports our findings of significant multisensory integration during certain time-windows at certain electrode locations, as well as our findings showing time-windows and locations where multisensory responses were not significantly different from the summed unisensory responses.

The results of this study show that it is feasible to study young children with SOR using a standard multisensory paradigm (Giard and Peronnet, 1999; see Stein and Meredith, 1993). The multisensory effects obtained are suggestive that the activation and coordination of the multiple neural generators involved in auditory–somatosensory MSI may be different in children with SOR than in typically developing individuals. However, in order for any definitive conclusions to be made, a more comprehensive comparison of unisensory ERPs, multisensory ERPs, and MSI in a larger age-, gender-, and IQ-matched sample of children with SOR and typically developing children is required.

3.3. *Multisensory ERP age correlations*

No correlations were found between age (in months) and the average amplitude of multisensory ERPs at select electrode sites during the four time-windows. This finding is consistent with our previous findings in typically developing children (Brett-Green et al., 2008). Possible explanations for a lack of age effect on average multisensory ERP amplitudes in typically developing children, which may also apply in this study were previously considered in detail (Brett-Green et al., 2008). Other neurophysiologic and behavioral studies in humans and animals (Lewkowicz and Kraebel, 2004; Lickliter and Bahrick, 2004; Sperdin et al., 2009; Stein et al., 2009; Wallace et al., 2006) using different methodologies have clearly shown that MSI undergoes significant developmental changes early in life and may not fully mature in children until the age of 8 years (Ernst, 2008). Since the range of ages in the current study was 5 to 13 years, it is possible that there were both immature and mature patterns of MSI in the sample that interfered with finding age effects.

In addition, early life experiences are known to affect the development of MSI (Wallace and Stein, 2007). The experience of sensation in children with SOR is different compared to typically developing children, and this may impact the development of MSI. Consequently, in order to better understand possible variations in the development of MSI, additional studies with a large age-stratified sample and comparisons of MSI in children with SOR and typically developing controls are essential.

3.4. *Limitations*

The goals of an initial exploratory study were met, including demonstrating the feasibility of studying MSI in children who are over-responsive to sensory stimuli and characterizing the spatio-temporal distribution of auditory–somatosensory MSI. However, a number of limitations that reflect our caution in interpreting the results are noted: 1. no control group was employed in this study; 2. despite efforts to select a homogeneous sample of SOR children, the sample is heterogeneous, with comorbid diagnoses present and two children on medication; and, 3. although multiple statistical comparisons were made for the different groups of electrode sites and time-windows examined, the significance level of $p<0.05$ was applied to all the individual ANOVAs and correlations without a correction for multiple comparisons. Due to limitations of the study, interpretation of results must be viewed as descriptive and useful for hypothesis generation, rather than conclusive.

In addition, certain methodological issues recognized in previous MSI literature must be considered. First, Teder-Sälejärvi et al. (2002), pointed out that difference analysis methodology may produce spurious results. The stated issue is the possible miscalculation of integration based on the contribution to the difference equation from anticipatory slow waves that could occur with stimulus expectation (see also Gondan et al., 2007). Presumably, the potential for this type of miscalculation is minimal in the present study since the ISI was randomly varied between 3 and 5 s, thus minimizing anticipation. A second issue is the modality shift effect (Gondan et al., 2007). This effect was found to influence audio-visual MSI at around 150 ms post-stimulation. It is noteworthy that the modality shift effect was identified in a multisensory paradigm that included a simple target detection task requiring attention. The influence of the modality shift effect on MSI in a purely passive paradigm, like the one used in this study is unclear. Third, a consequence of using a passive experimental paradigm as used in this study is that the participant's attention, which can effect auditory–somatosensory MSI (see Eimer and Driver, 2001), was not overtly controlled. To minimize possible attention effects on auditory–somatosensory MSI, subjects were instructed to ignore the sensory stimuli and instead watch a silent movie that was being shown during ERP recording. An assumption is made that because the visual stimulation is ongoing and not time-locked that its contribution to the average ERP measurements is minimal. However, the effect of viewing the silent movie on auditory–somatosensory MSI is unknown. Fourth, because a passive paradigm with no behavioral component was used, the functional consequences of MSI cannot be directly

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determined. Finally, the inability to set the intensity of median nerve stimulation to 200% of threshold for all individuals likely affected individual MSI. Studies are ongoing addressing these issues which will optimize MSI research in children with SOR and other neurobehavioral disorders.

4. Conclusion

This study reports on auditory–somatosensory MSI in a population of school-aged children clinically identified with SOR. Evidence for MSI was found based on significant differences between responses to multisensory stimulation and summed unisensory responses. In particular, MSI was found in midline (fronto-central) cortical regions between 60 and 80 ms and 180 and 220 ms, and in contralateral cortical regions between 180 and 220 ms. No significant ipsilateral MSI was found for children with SOR during any of the four time-windows. Replication of the findings presented in this report with a larger sample compared to age-, gender-, and IQ-matched typically developing controls is needed to confirm and extend these preliminary conclusions. Further research examining whether behavioral over-responsivity to auditory and somatosensory stimulation and the apparent atypical integration of multisensory input are related in children with SOR is ongoing. It is possible that atypical MSI may contribute to the sensory symptoms and daily life challenges experienced by children with SOR. These challenges have a profound effect on reducing successful participation at home, school, and in community environments for children with SOR.

5. Experimental procedures

5.1. *Participants*

Twenty child volunteers (17 males), ages 5 to 13 years (M=8.59, SD=2.14) participated in this study. Participants were referred from the Sensory Therapies And Research (STAR) Center, an occupational therapy clinic in Greenwood Village, CO. Participants and/or their parent provided written consent, using procedures approved by the Institutional Review Board of the University of Colorado Denver. Subjects were selected for participation based on a global clinical impression of SOR following a comprehensive assessment by certified occupational therapists with specialized training in identifying symptoms of SOR. More specifically, clinicians were asked to refer children that had severe symptoms of auditory and/or somatosensory over-responsivity that interfered with their ability to participate in daily life activities. Additional inclusion criteria were based on Short Sensory Profile (McIntosh et al., 1999) and Sensory Over-Responsivity Scale (Schoen et al., 2008) scores. Excluded from participation were children with: genetic or medical conditions (e.g., mental retardation, seizures), severe mental health conditions (e.g., psychosis), or significant developmental disorders (e.g., autism spectrum disorders, pervasive developmental disorders).

Out of twenty children included in this study, 5 had a clinical diagnosis of attention deficit/hyperactivity disorder (ADHD). Out of the five children with attention deficit/hyperactivity disorder, one had a comorbid diagnosis of bipolar disorder, and was being treated with risperidone; the second had a comorbid diagnosis of general anxiety disorder, but was not on any medications; the third was being treated with Ritalin; and the other two children had no other diagnoses, and were not on any medications. It is not uncommon for children referred to Occupational Therapy for sensory problems to have previous diagnosis of attention deficit/hyperactivity disorder or anxiety disorder, and shown no improvement with traditional pharmacological intervention.

5.2. *Instrumentation*

The Short Sensory Profile is a 38-item parent report screening instrument that evaluates a child's behaviors related to sensory processing across seven subtests (tactile sensitivity, taste/smell sensitivity, movement sensitivity, under-responsive/seeks sensation, auditory filtering, low energy/weak, and visual/auditory sensitivity) (McIntosh et al., 1999). This instrument was developed as a research tool from items on the norm-referenced Sensory Profile (Dunn, 1997). The reliability of the Short Sensory Profile=0.90 and discriminant validity is greater than 95% (McIntosh et al., 1999). Sample items rated for frequency of the observed behavior include: 1. tactile sensitivity item — avoids going barefoot, especially in the sand or grass; and, 2. auditory sensitivity item — responds negatively to unexpected or loud noises (vacuum cleaner, dog barking, and hair dryer).

The Sensory Over-Responsivity Scales measure includes a clinical assessment and a parent report of responses to sensory experiences in 7 sensory domains (Schoen et al., 2008). Only the parent report measure was used in this study. Preliminary results of reliability and validity on two independent samples showed moderate to strong internal reliability (0.66–0.96) and strong discriminant validity ($p<0.01$).

All children in this study met the following inclusion criteria 1. scoring less than −2.0 SD on the auditory and/or somatosensory subtests of the Short Sensory Profile (McIntosh et al., 1999), and/or, 2. judgment of auditory and/or somatosensory over-responsivity on the Sensory Over-Responsivity Scales parent report (Schoen et al., 2008). Using subtests of the Short Sensory Profile and/or the Sensory Over-Responsivity Scales to define inclusion criteria ensured a substantial level of homogeneity amongst the participants in terms of their parents' perceptions of symptoms of auditory and/or somatosensory over-responsivity.

5.3. *Sensory stimulation*

Participants watched a cartoon (*A Grand Day Out with Wallace and Gromit*) without sound for approximately 30 min during the ERP recording, while three types of stimulation were presented: 1) click sounds (80 dB SPL, 3 ms duration) delivered binaurally via earphones (Etymotic Research, Inc. (ER-1), Elk Grove Village, IL, USA); 2) constant current pulses delivered to the median nerve (0.35–3.00 mA, 400 μs) via a bar electrode placed approximately 2 cm proximal to the right wrist; and, 3) simultaneous onset of auditory and somatosensory stimulation as described in 1 and 2 above. Each type of stimulus was delivered one-hundred times

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in a pseudo-random order with an average inter-stimulus interval of 4 s (range 3–5 s). The paradigm used was passive (i.e. no behavioral responses were requested of the participant). Participants were instructed to watch the cartoon and ignore the stimulation.

To determine the appropriate intensity of median nerve stimulation for each participant, a threshold for detection was found by presenting current pulses that were stepped-up from zero in 0.10 mA increments until the participant reported a tingling feeling near their wrist. The mean threshold across participants was 0.85 mA. Ideally the current was set to 200% of the threshold but this was decreased as necessary to a tolerance level of the participant. Eight of the twenty participants required some adjustment to the stimulation level. Mean testing intensity across participants was 1.32 mA.

5.4. *Data acquisition and reduction*

A 32 channel BioSemi ActiveTwo system (Cortech Solutions, Willmington, NC, US) with electrodes positioned according to the American Electroencephalographic Society Guidelines (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 for a detailed explanation of this method). This configuration of reference and ground reportedly sets up a feedback loop that drives the average potential across the electrode array to the amplifier to zero (De Santis et al., 2007). 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 100 ms pre-stimulus (baseline) to 400 ms post-stimulus. Trials with blinks/large eye movements greater than 100 mV based on vertical and horizontal electro-oculograms and trials with other artifacts greater than 100 mV were rejected. The following averaged ERPs were generated for each participant: 1) auditory, 2) somatosensory, 3) multisensory (simultaneous auditory and somatosensory), 4) summed auditory plus somatosensory, and 5) difference (the average of the summed unisensory responses subtracted from the average of the multisensory responses). The accepted number of segments across stimulus types ranged from 37.3 to 90.3 trials (M = 56.9). The average number of accepted segments for the auditory, somatosensory, and multisensory ERPs was: 56.4, 59.8 and 53.3, respectively.

ERPScore (Segalowitz, 1999) was used to create and score averaged amplitudes for the multisensory and summed responses at seven electrode sites (Fz, Cz, Pz, C3, CP5, C4, and CP6). These sites corresponded to scalp regions where ERP responses to auditory, somatosensory and multisensory stimulation are expected, and where auditory–somatosensory MSI was found in previous studies (Brett-Green et al., 2008; Foxe et al., 2000). Both midline and lateral electrode sites were included to facilitate the possibility of finding age effects (Picton et al., 2000). Averaged amplitudes were calculated for four time-windows: (60–80 ms, 80–110 ms, 110–150 ms and 180–220 ms) by deriving an area measure between each ERP waveform and the 0 μV baseline. The earliest time-window evaluated between 60 and 80 ms was related to the falling phase of the P50 ERP component. The three additional time-windows evaluated between 80 and 110 ms, 110 and 150 ms and 180 and 220 ms correspond approximately to the timing of the P100, N100, P200 multisensory amplitude peaks in typically developing children, respectively (Brett-Green et al., 2008).

Spline-interpolated voltage maps were used to visually analyze the spatio-temporal scalp distributions of multisensory, summed, and difference ERPs.

5.5. *Statistical analyses*

MSI was examined statistically 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, and the electrode sites for one ANOVA were Fz, Cz and Pz. Two additional within subjects, repeated measures, two-way ANOVAs were used to examine MSI in contralateral and ipsilateral hemispheres. Factors were stimulus type (multisensory and summed), and contralateral (C3 and CP5), or ipsilateral (C4 and CP6) electrode sites. Alpha level was set at $p < 0.05$ for all statistical tests. A Greenhouse–Geisser correction was used to determine significance when the assumption of sphericity was violated.

To evaluate whether significant age effects were present in the data Pearson product moment correlations were calculated for age (in months) and averaged amplitudes of the multisensory ERP at the seven electrode sites (Fz, Cz, Pz, C3, CP5, C4, and CP6), for each of the four time-windows.

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