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Review

Beyond the N1: A review of late somatosensory evoked responses in human infants

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ABSTRACT

Somatosensory evoked potentials (SEPs) have been used for decades to study the development of somatosensory processing in human infants. Research on infant SEPs has focused on the initial cortical component (N1) and its clinical utility for predicting neurological outcome in at-risk infants. However, recent studies suggest that examining the later components in the infant somatosensory evoked response will greatly advance our understanding of somatosensory processing in infancy. The purpose of this review is to synthesize the existing electroencephalography (EEG) and magnetoencephalography (MEG) studies on late somatosensory evoked responses in infants. We describe the late responses that have been reported and discuss the utility of such responses for illuminating key aspects of somatosensory processing in typical and atypical development.

1. Introduction

There is a long history of research on scalp-recorded somatosensory evoked potentials (SEPs) in human infancy. Research in this area has been driven by both theoretical and practical concerns: (a) understanding the functional integrity and maturation of the cortex in human infants and (b) the utility of SEPs for predicting outcomes in infants at risk for neurological impairment due to prematurity or birth complications (Pihko and Lauronen, 2004).

To date, studies on SEPs in infants have tended to focus on the first cortical component, which is presumed to reflect the arrival of the peripheral afferent volley at the primary somatosensory cortex (SI). In infants, the initial component following electrical stimulation of the median nerve is a negative deflection over the contralateral central area, commonly referred to as the N1. Developmental data have suggested that the N1 matures to the initial cortical response to median nerve stimulation in the adult SEP (N20) over the first few years of life (Desmedt et al., 1976; Doria-Lamba et al., 2009). A nascent N1 is detectable in most uncompromised preterm infants by the 7th gestational month, although the response is substantially longer in latency and duration compared to the response in older infants and adults (Hrbek et al., 1973; Taylor et al., 1996). The latency of this deflection decreases rapidly toward term age reaching approximately 30 ms at 39–41 weeks (Karniski et al., 1992; Taylor et al., 1996; Tombini et al., 2009). The shortening of peak latency continues gradually until 4 years of age, which has been attributed to continuing maturation of peripheral and central somatosensory pathways (Boor and Goebel, 2000; Doria-Lamba et al., 2009; Zhu et al., 1987).

Absent or delayed N1 responses in infants at term age—for example, in infants at risk for neurological deficits due to perinatal asphyxia—are predictive of unfavorable outcomes in later childhood (Kontio et al., 2013; Majnemer and Rosenblatt, 1996; Suppiej et al., 2010; Willis et al., 1989). Evidence for the prognostic value of N1 responses in at-risk infants during the preterm period is less robust, however, newer methods to optimize the recording of SEPs in preterm infants may change this picture (Vanhatalo et al., 2009).

Although the N1 has historically been studied through electroencephalographic (EEG) methods, the past decade has seen increasing use of magnetoencephalography (MEG) to examine somatosensory functions in infancy. MEG detects weak magnetic fields, which unlike electrical potentials, are minimally affected by the conductive properties of the skull and scalp. Therefore, source analysis is carried out more routinely for MEG compared to EEG.

Consistent with the first deflection in the SEP, the first component in the somatosensory evoked field (SEF) peaks at around 30 ms in sleeping newborns following electrical stimulation of the median nerve (termed the M30; Lauronen et al., 2006; Pihko et al., 2005). A similar response has been observed in the newborn SEF following tactile stimulation of the fingertip, albeit with a slightly longer latency (M60; Lauronen et

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al., 2006; Nevalainen et al., 2012; Pihko et al., 2009). Dipole source analysis of the M30 and M60 components suggests that they are generated in contralateral SI (Nevalainen et al., 2014).

Although the development of the initial cortical component in the infant somatosensory evoked response (SER – a term that we use to encompass responses recorded via EEG or MEG) has been well studied, substantially less attention has been given to longer-latency responses to somatosensory stimulation in infants. However, recent research suggests that examining later components, which are often presumed to reflect higher-level cortical processing, may advance our understanding of the early development of the somatosensory system and the utility of SERs in clinical settings. The purpose of this review is to summarize existing work on late SERs in infants in order to provide a foundation for future studies in this area. We first review the late components that are observed in the infant SER and then examine how these components have been used in clinical and theoretical research. In the last section, we discuss methodological considerations for studying late SERs in infants.

2. Late responses

SERs in infants have most commonly been elicited using electrical stimulation of the median nerve or punctate tactile stimulation of the fingertip or hand. Punctate tactile stimulation is often delivered using inflatable membranes driven by pulses of compressed air. When the membrane expands, it applies light pressure to a precise area of the skin surface, activating local mechanoreceptors. Electrical stimulation of the median nerve, in contrast, bypasses cutaneous receptors and results in a more complex waveform, as described below.

2.1. Median nerve stimulation

Research on late SERs to median nerve stimulation in infants has focused on the newborn EEG. These studies have reported three components following the initial N1 in the newborn SEP: A positive deflection peaking at around 60–100 ms (P1), a second negative deflection around 150 ms (N2), and a second positive component (P2) at around 250 ms (Hrbek et al., 1973; Karniski, 1992; Laget et al., 1976; Wolff et al., 1974). The P1 is only observed at the contralateral central electrode while the subsequent components are also detected at the vertex (Desmedt and Manil, 1970; Hrbek et al., 1973; Wolff et al., 1974). A few studies have reported a third negative component (N3) peaking around 300 to 450 ms (Hrbek et al., 1973; Karniski, 1992), which has been interpreted as late activation of the ipsilateral somatosensory cortex (Karniski, 1992).

Pihko et al. (2005) observed a similar waveform following median nerve stimulation in newborns using MEG. The initial cortical response (M30) was followed by deflections at 70 ms and 250 ms, which may represent the magnetic counterparts of the P1 and P2 components observed in the EEG waveform. The source of the M70 was reported to correspond to contralateral SI, while the source of the M250 was more proximal to contralateral SII.

Only a few studies have examined developmental changes in the late SERs to median nerve stimulation. In an EEG study with sleeping infants 31 to 40 weeks, Karniski (1992) reported the P1-N2-P2 sequence of peaks could be detected in even the youngest infants with the latencies of the components decreasing toward term age. The most prominent feature of the waveform was the N2 deflection, which was largest in the youngest infants and decreased in amplitude and duration with increasing age. Laget et al. (1976) reported that the latencies of the P1, N2, and P2 components continue to decrease steadily beyond term age, shortening from 101 ms, 157 ms, and 235 ms, respectively in the first postnatal month to 93 ms, 118 ms, and 180 ms at two to four months of age. Future research is needed for a better understanding of how the P1, N2, and P2 components in the infant SEP to median nerve stimulation mature beyond the first four months of life. Laget et al. (1976) included children up to 15 years of age in their study, and reported that the transition from the immature infant waveform to the adult-like response observed by 3 years of age was difficult to determine.

2.2. Tactile stimulation

Late responses to punctate tactile stimulation in newborns have been examined in a series of studies in which light taps were applied to the fingertip using inflatable membranes. These studies have consistently reported a prominent late deflection in the contralateral hemisphere peaking at 200–250 ms (see Fig. 1; Nevalainen et al., 2008a; Nevalainen et al., 2008b; Nevalainen et al., 2012; Pihko et al., 2011; Rahkonen et al., 2013). As suggested by Nevalainen et al. (2014), this late component (termed the M200) may correspond to the P2 component that peaks at around the same time in the newborn SEP to median nerve stimulation. The source of the M200 appears to correspond to the parietal-opercular area and therefore, has been hypothesized to reflect activity in the secondary somatosensory cortex (SII; Nevalainen et al., 2014; Nevalainen et al., 2008a). In adults, responses from SII are observed at around 100 ms in both the contralateral and ipsilateral hemisphere (Hari and Forss, 1999). There is some evidence that the M200 is similarly bilateral in newborns, although responses from the ipsilateral cortex are only detectable in quiet sleep (Nevalainen et al., 2008a).

A few studies have examined late responses in older infants using a similar means of punctate tactile stimulation. As in the work with newborns, these studies have focused on a single late deflection in the SER waveform. In a MEG study with sedated infants between 6–8 and 11–21 months of age, Gondo et al. (2001) documented a late component peaking around 120 ms in response to light taps applied to the tip of the thumb and ring finger. The latency of this component was comparable between the younger and older infants, although the amplitude was substantially larger in the older group. More recently, Saby et al. (2015) reported a prominent deflection at around 175 ms in the SEP of awake 7-month-olds in response to tactile stimulation of the hands and also of the feet. Future research is needed to clarify how the late responses reported in these studies with older infants relate to the late response observed in the newborn SER as measured by MEG (i.e., M200). Considering the latency of the responses may be affected by precise characteristics of the tactile stimulus (e.g., pressure of the taps) as well as vigilance state (e.g., sleeping versus awake), a developmental study applying the same methods with infants of different ages would be particularly informative for advancing our understanding of how late responses to tactile stimulation mature over infancy.

A relatively more complex waveform was reported by a recent EEG study in which vibrotactile stimulation (200 ms duration) was applied to the palms of awake infants between 6 and 10 months of age. Unlike

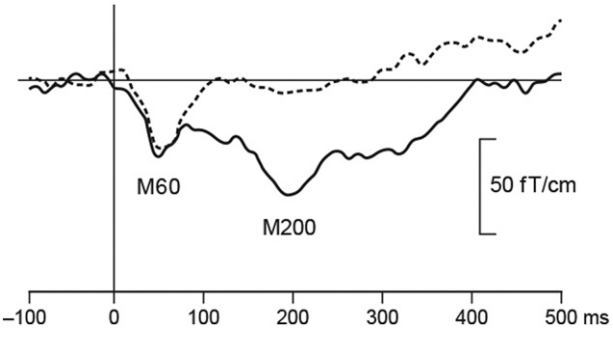

Fig. 1. SEF waveforms at one gradiometer channel for a representative newborn showing the M60 and M200 components elicited by tactile stimulation of the fingertip. Waveforms are shown for quiet sleep (solid line) and active sleep (dashed line).
Adapted from Pihko et al. (2011).

the other studies on tactile stimulation that reported one main late deflection, Rigato et al. (2014) observed a series of positive and negative deflections over the contralateral central area within 700 ms following stimulus onset. The difference between this waveform and the others described above may be related to the intensity and duration of the vibrotactile stimulus, which lasted longer than the punctate taps employed by the other groups.

3. Applications of research on late responses

In examining late SERs, the studies described above have provided novel insights into the development of somatosensory cortical processes, setting the stage for future research in this area. Similar to the literature on the N1, some of this work has been aimed at developing prognostic tools for newborns at increased risk for neurological impairment. Other studies have addressed theoretical questions about brain-behavior associations in early development.

3.1. Clinical applications

There is interest in the utility of SERs for predicting neurodevelopmental outcomes in at-risk newborns so that appropriate interventions can begin as early as possible. Thus far, research on the prognostic value of SERs in at-risk newborns has focused on the first cortical response (i.e., the N1) in order to assess the functional integrity of the connections from the periphery to the somatosensory cortex (for review, see Majnemer and Rosenblatt, 1996). However, it has become clear that other measures are needed to identify infants with disturbances in higher-level somatosensory processing who may experience adverse neurodevelopmental outcomes despite having normal early responses. To examine whether late responses may be useful in this respect, Rahkonen et al. (2013) recorded SEFs to tactile stimulation of the fingertip from extremely preterm infants (born < 28 weeks) at term-equivalent age (range: 37–44 weeks gestational age) and examined neurological outcome at 2 years of age. Although the first cortical component at around 60 ms was present in all of the preterm infants when tested at ~40 weeks gestational age, the M200 response was only observed in 21 out of 30 infants. Compared to the preterm infants who had typical M200 responses, those with absent M200 responses had poorer neurodevelopmental outcomes at 2 years of age as indexed by lower scores on the Griffiths Mental Development Scales.

Building on these findings, Nevalainen et al. (2015) demonstrated that evaluating M200 responses at term-equivalent age may help to identify extremely preterm infants who have adverse neurodevelopmental outcomes that may be missed by a neonatal neurological examination. Of the extremely preterm infants in this study who had an unfavorable neurological outcome (complex minor neurological dysfunction or cerebral palsy) at 2 years of age, only 50% of them had been identified as abnormal on a neonatal neurological examination. However, combining the neonatal neurological examination with evaluation of the M200 response at term-equivalent age increased the detection rate to 80%.

Nevalainen et al. (2015) also reported that M200-like responses could be recorded in preterm infants at term-equivalent age using EEG. SEPs to median nerve stimulation were recorded from a subset of preterm infants who had shown detectable M200 responses in their MEG recordings. Based on the known field patterns underlying the M200 response from studies with healthy term newborns (Nevalainen et al., 2008a; Nevalainen et al., 2012; Pihko et al., 2005), similar responses were considered to be present in the SEP if there was a late negative response around 200 ms at temporoparietal electrodes with the signal referenced to Cz. M200-like responses were visible in the SEP response for 4/4 infants following stimulation of the right median nerve and 4/6 infants following stimulation of the left median nerve. Given EEG systems are portable and more widely available than MEG scanners, the finding that EEG may be used for assessing higher-level cortical processes in at risk infants will support the opportunity for this work to be applied more readily in clinical settings (see also Zafeiriou and Vargiami, 2015).

3.2. Effects of sensorimotor experience

Research with older infants has demonstrated that examining late SERs may also be useful for elucidating how somatosensory processing is influenced by sensorimotor experience. In a MEG study with infants 6–21 months of age, Gondo et al. (2001) compared SEFs to tactile stimulation of the thumb and ring finger in infants in the palmar grasp (range 6–8 months) versus pincer grip (range 11–21 months) stages of grasp development. The main difference between the resulting waveforms for the two groups was a significantly larger late component for stimulation of the thumb in the pincer-grasping infants. The transition from the palmar grasp to the pincer grasp involves a substantial increase in the use of the thumb, thus the authors suggested that the larger late response in the pincer group might be explained by more sensorimotor experience using their thumb. Importantly, no group differences were found as a function of age/experience in the amplitude of the late response to stimulation of the ring finger, which plays little role in the pincer grasp.

Rigato et al. (2014) also suggested that differences in somatosensory responses between younger and older infants could be related to changes in sensorimotor experience. It is known from work with adults that the somatosensory evoked response is modulated by the posture of the arms (Heed and Röder, 2010; Rigato et al., 2013; Soto-Faraco and Azañón, 2013). This modulation may reflect the combination of information about the location of stimulation on the body with information about the location of that body part in external space. To examine the origins of postural modulation of somatosensory information, Rigato et al. (2014) presented vibrotactile stimuli (200 ms duration) to the palms of 6.5-, 8-, and 10-month-old infants while their arms were held in either a crossed or an uncrossed posture. For the 6.5-month-olds, there were no differences in the SEP waveforms for the crossed and uncrossed postures. By 10 months, there was a significant difference in the waveforms, as indicated by a larger positivity from around 60 ms to 220 ms for the crossed condition. An increased positivity was also observed in the crossed-arms condition at 8 months, but only in a subset of infants who had produced spontaneous reaches across the midline in a preceding behavioral task. The authors suggested that infants' increasing experience moving their arms across the midline might contribute to the shift in postural effects on the SEP from 6.5 to 10 months of age.

3.3. Infant body maps

Another line of developmental research suggests that late SERs may be useful for studying the ontogenesis of *infant body maps* in SI (Marshall and Meltzoff, 2015; Saby et al., 2015). This work builds on an established literature with adults demonstrating the utility of SERs for non-invasively examining somatotopic representations of the body surface in the somatosensory cortex (Hari et al., 1993; Hari et al., 1984; Heed and Röder, 2010; Nakamura et al., 1998). These studies with adults have shown that the evoked responses to stimulation of various body parts are spatially distributed along the postcentral gyrus in accordance with the somatosensory homunculus described using intracranial stimulation (e.g., Penfield and Rasmussen, 1950).

Although most work with infants has tended to stimulate only one body part (e.g., median nerve or fingertip), Saby et al. (2015) examined the scalp distribution of SEPs to punctate tactile stimuli that were delivered to both hands and both feet of 7-month-old infants. The SEP was characterized by a large positive component that peaked around 175 ms and was organized somatotopically across central electrode sites. Specifically, the amplitude of this component for left and right hand stimulation was greater at the contralateral central electrode

(C4 or C3, respectively) than at the midline central electrode (Cz). The opposite pattern was obtained for stimulation of the feet, with greater peak amplitude at Cz than at C3 and C4 (see Fig. 2).

The findings from Saby et al. (2015) provide good evidence that stimulation of relatively distant body parts (hands versus feet) is associated with a somatotopic SEP response pattern. Studies employing MEG in combination with source analysis would be useful for delineating a more fine-grained map of the infant somatosensory cortex and examining how this map is shaped by body growth, experience, and developments in behavioral abilities. The feasibility of infant MEG for examining such questions is supported by MEG studies with adults that have revealed changes in somatotopic maps following training or injury (Elbert et al., 1995; Liu and Ioannides, 2004; Mogilner et al., 1993; Weiss et al., 2000). Although questions regarding the ontogenesis of body representations could also be addressed using the initial (N1) component, the prominence of the later response makes it an ideal candidate for future studies in this area. In addition to elucidating the ontogenesis of somatotopy, studying infant body maps has the potential to provide insights into the role of body representations in infant imitation and social-cognitive development (Marshall and Meltzoff, 2015; Meltzoff and Moore, 1997).

4. Other considerations

Both early and late components of the infant SER are sensitive to changes in procedural variables including filter settings and interstimulus interval (ISI) as well as factors related to infant state (e.g., sleep stage). Below, we offer some methodological suggestions for future developmental studies on late components in the SER.

4.1. Filter settings

Many studies on the infant N1 component have employed a high-pass filter of 5 or 30 Hz (George and Taylor, 1991; Doria-Lamba et al., 2009; Zhu et al., 1987). Although the use of an increased high-pass filter cutoff (e.g., 30 Hz) is well suited for studying the early, fast components in the SER, it may attenuate or even abolish the later responses, which generally occur at slower frequencies (Pihko and Lauronen, 2004). In order to detect the later components, a high-pass filter of 1 Hz or below should be used. Most of the studies on late components described in this review used a high-pass filter of 0.03 Hz, 0.1 Hz or 1 Hz.

4.2. Interstimulus interval

Changes in the ISI are also known to influence the infant SER, particularly the later components. In an EEG study with sleeping newborns, Desmedt and Manil (1970) reported the late positive components following median nerve stimulation were smaller in amplitude with an ISI of 4 s compared to 8 s. More recent work has shown that the newborn M200 following tactile stimulation is attenuated with an ISI of 0.5 s compared to 2 and 4 s, and is completely absent at the shorter interval in some infants (Nevalainen et al., 2008a). Although the amplitude was numerically largest when the ISI was 4 s, the difference in M200 amplitude between 2 and 4 s was not statistically significant. Based on these results, Nevalainen et al. (2008a) recommended an ISI of 2 s for studies with newborns in order to maximize trial numbers without distorting the late components. It is possible that an ISI of <2 s may be suitable for older infants, but no study to date has examined the effect of ISI on late components beyond the neonatal period. In their study with infants 6–21 months of age, Gondo et al. (2001) were able to

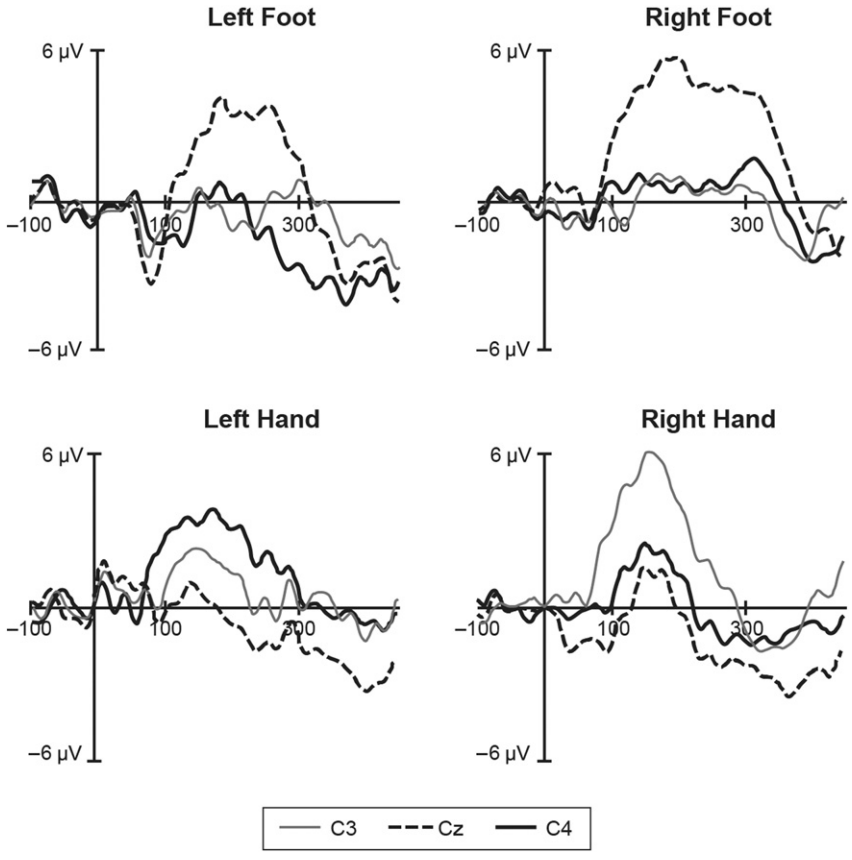

Fig. 2. SEP waveforms from Saby et al. (2015) showing somatosensory evoked potentials elicited by tactile stimulation of 7-month-old infants' hands and feet. The resulting waveform was characterized by a large positive component peaking around 175 ms that was organized somatotopically over central electrode sites. For left and right foot stimulation, peak amplitude was greatest at the midline central electrode (Cz). For left and right hand stimulation, amplitude was greatest at the contralateral central electrode (C4 and C3, respectively).

record late responses with a comparatively shorter ISI of 900 to 1100 ms.

4.3. Sleep stage

It is important to monitor sleep stage when recording SERs because sleep can have strong effects on the resulting waveform. Most studies on somatosensory responses in neonates have been carried out during sleep. Those that have compared responses across sleep stages have found that the earliest components can be measured similarly in active (REM) and quiet (non-REM) sleep, whereas the later components are more prominent in quiet sleep. For instance, in their study with term newborns, Nevalainen et al. (2012) observed a clear M200 response in 90% of infants during quiet sleep, but in only 50% of infants during active sleep. Other studies with newborns have also reported diminished late responses in active versus quiet sleep (see Fig. 1; Desmedt and Manil, 1970; Pihko et al., 2011; Pihko et al., 2004).

The finding of enhanced late responses during quiet sleep in newborns contrasts with the pattern observed in adults, which is that late responses are diminished or absent during stage II sleep (Kakigi et al., 2003; Kitamura et al., 1996). This distinction may reflect a developmental difference in the function of non-REM sleep between newborns and adults. Indeed, there is some evidence from the animal literature to support the idea that the function of sleep stages may change over development (Mirmiran et al., 2003). Comparable work with human infants is limited, although future studies on late SERs in infants could contribute to this discussion.

The existing studies that have compared responses across sleep stages have been carried out with newborns, thus it is not yet known if quiet sleep has the same effect on late components in older infants as it does in newborns. Importantly, the studies of Rigato et al. (2014) and Saby et al. (2015) demonstrate that prominent late components can be detected in awake infants of this age.

4.4. Movement

Another factor that may influence infant SERs is body movement. This topic has not been directly addressed in the infant literature, but it is known from EEG and MEG studies with adults that short-latency responses are attenuated by limb movement occurring during or just prior to stimulation of the median nerve (Cheron and Borenstein, 1991; Huttunen and Homberg, 1991; Rushton et al., 1981; Wasaka et al., 2003). Although movement attenuates the short-latency components, other work suggests long-latency components are enhanced during movement and contraction of the stimulated limb (Huttunen et al., 1996; Lin et al., 2000; Nakata et al., 2003). These "gating" effects of movement on the early and late SERs are only observed when the subject moves the stimulated limb: Moving the contralateral limb or another distant body part has little or no effect (Cohen and Starr, 1987; Nakata et al., 2003; Tapia et al., 1987).

The potential for movement to affect SERs is particularly relevant when studying waking infants. One approach to this issue is to review contemporaneous video records of test sessions and exclude all trials containing any detectable movement by the infant, but this could lead to an unfavorable reduction in trial count. Another option is to remove certain types of movement, which was the approach employed by Saby et al. (2015) in their study of awake 7-month-old infants. In this study, the specific time window surrounding each punctate tactile stimulus was coded as containing (i) large/repetitive, (ii) small, or (iii) no movements by the infant. Small movements were found to have minimal effect on the SEPs and therefore only trials containing large/repetitive movements were excluded from the main analysis.

Future research will be helpful in establishing best practices for managing the influence of movement on SERs in awake infants. Although some insights can be drawn from adult work, it is difficult to make rigorous comparisons because the attended, directed movements used in adult studies differ from the spontaneous movements produced by infants. In addition to informing methods, future studies could examine possible ontogenetic differences in the effects of movement on SERs in infants and adults. Examining such potential developmental differences may be useful for informing the understanding of how sensorimotor integration develops.

5. Conclusions

The continued examination of late SERs has the potential to expand our understanding of cortical functioning in early human development. Because much of the existing literature on infant SERs has focused on the initial component (N1), many theoretical and methodological issues regarding the late responses remain unexplored. One open question concerns ontogenetic changes of the late components in the first months and years of life. Longitudinal studies akin to those that have been carried out on the N1 (Doria-Lamba et al., 2009; Zhu et al., 1987) are needed. In addition, with the exception of the M200 in newborns, the cortical generators of the late components in infants are poorly understood. MEG studies on late SERs with infants of different ages will be valuable for addressing these open questions. Advances in MEG technologies including continuous head-position monitoring (Taulu et al., 2005) and whole-head child sized systems (Johnson et al., 2010; Roberts et al., 2014) will support future MEG research with pediatric populations, including infants.

MEG studies on the neural generators of late SERs in infants will also be useful for determining whether areas outside SI and SII are involved in infant somatosensory processing and how connectivity between these areas changes over development. MEG and functional magnetic resonance imaging (fMRI) studies with adults have identified an extended network of areas activated by somatosensory stimulation that includes the posterior parietal cortex and other areas (Bardouille and Ross, 2008; Porro et al., 2004). Although some work has attempted using fMRI to study tactile stimulation in infants (Arichi et al., 2012; Williams et al., 2015), MEG and EEG are likely to remain the main techniques for examining somatosensory processing in infancy due the methodological challenges of fMRI research with this age group.

Future work on late SERs has the potential to inform both theoretical and applied questions. Neuroplasticity in early human development is a topic of intense interest (e.g., Meltzoff et al., 2009). Infancy is an ideal time to address plasticity in the somatosensory system and the effects of sensorimotor experiences considering the rapid motor skill changes during this period. Other research could utilize late SERs to examine ontogenetic changes in how the brain integrates somatosensory information across body parts (e.g., left and right hands) and with other sensory modalities (e.g., vision). In addition to furthering our understanding of typical development, research on the M200 component has suggested that late SERs may be useful for predicting neurological outcomes of preterm and other at-risk infants. Another potential application of late SERs is to examine somatosensory processing abnormalities in neurodevelopmental disorders such as autism spectrum disorder (Cascio, 2010).

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