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## BIOLOGICAL AND PHYSIOLOGICAL MARKERS OF TACTILE SENSORIAL PROCESSING IN HEALTHY NEWBORNS

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**ABSTRACT:** The main objective of this review is to provide a descriptive analysis of the biological and physiological markers of tactile sensorial processing in healthy, full-term newborns. Research articles were selected according to the following study design criteria: (a) tactile stimulation for touch sense as an independent variable; (b) having at least one biological or physiological variable as a dependent variable; and (c) the group of participants were characterized as full-term and healthy newborns; a mixed group of full-term newborns and preterm newborns; or premature newborns with appropriate-weight-for-gestational age and without clinical differences or considered to have a normal, healthy somatosensory system. Studies were then grouped according to the dependent variable type, and only those that met the aforementioned three major criteria were described. Cortisol level, growth measures, and urinary catecholamine, serotonin, and melatonin levels were reported as biological-marker candidates for tactile sensorial processing. Heart rate, body temperature, skin-conductance activity, and vagal reactivity were described as neurovegetative-marker candidates. Somatosensory evoked potentials, somatosensory evoked magnetic fields, and functional neuroimaging data also were included.

Abstracts translated in Spanish, French, German, and Japanese can be found on the abstract page of each article on Wiley Online Library at <http://wileyonlinelibrary.com/journal/imhj>.

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The study of tactile sensorial processing is evolving into a more comprehensive approach, benefitting from theoretical and methodological progress within the field of cognitive neuroscience. The integration of these levels of analysis has contributed to the understanding of how biological and physiological components of tactile sensorial processing contribute to clinical outcomes. In this article, we selectively review research that has investigated the biological and physiological markers underlying tactile sensorial processing in healthy, full-term newborns. The following keywords were searched in Pubmed and related databases Science Direct and APA: “newborn,” “neonatal,” “tactile,” “touch,” and “somatosensory.” Articles that have examined biological, physiological, and central nervous system measures (somatosensory evoked electrical markers, somatosensory evoked magnetic fields, and functional neuroimaging) as potential markers of tactile sensorial processing

in the newborn were reviewed and matched the following study design criteria: (a) tactile stimulation for touch sense as an independent variable; (b) having at least one biological or physiological variable as a dependent variable; (c) the group of participants were characterized as full-term and healthy newborns; a mixed group of full-term and preterm newborns; of premature newborns with appropriate-weight-for-gestational age and without clinical differences or considered to have a normal, healthy somatosensory system, according to the authors. Studies described in the following sections were grouped according to the dependent variable, and only those that met the three major conditions described earlier were further characterized.

### BIOLOGICAL MARKERS OF TACTILE SENSORIAL PROCESSING

Several biological variables have been reported to be sensitive to human tactile stimulation in healthy, full-term newborns, including cortisol as a biological marker of stress, anxiety, and depression (Field, Grizzle, Scafidi, & Abrams, 1996; Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007; White-Traut, Schwertz, McFarlin, & Kogan, 2009); growth measures such as weight and

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length (Field et al., 1996; Field et al., 2004; Field et al., 1986); urinary catecholamines as a measure of stress and urinary serotonin, a neurotransmitter associated with well-being (Field et al., 1996); and urinary melatonin, a hormone that plays an important role in circadian rhythms (Ferber, Laudon, Kuint, Weller, & Zisapel, 2002; Weller & Feldman, 2003). Thus, human tactile stimulation, defined as tactile/kinesthetic stimulation by massage therapy or by touch during human interaction, has been reported to be a significant variable associated with improvement in certain biological and behavioral conditions, by promoting body and mental development in healthy, full-term newborns. In fact, researchers' administration of massage therapy to healthy, full-term newborns of depressed mothers have shown immediate effects, including a decrease in salivary cortisol and crying and an increase in alert states. Long-term effects also have been reported, including weight gain, a decrease in urinary catecholamine and cortisol levels, and an increase in urinary serotonin levels.

Variables associated with temperament, such as emotionality, sociability, and soothability, also have been shown to be improved following tactile stimulation (Field et al., 1996). Field et al. (2004) conducted a study with two different groups of parents being trained in massage therapy: One group applied moderate pressure, and the other applied light pressure to their newborns. The authors observed in the moderate pressure group a significant increase in orientation scores and in two growth measures (weight and length), and a decrease in excitability and depression scores on the Brazelton Neonatal Behavioral Assessment Scale (Brazelton & Nugent, 1995) (Field et al., 2004). Furthermore, when massage therapy was performed by mothers, a significant effect on melatonin secretion rhythms was observed, with the mother's cues facilitating phase adjustment of rest-activity in newborns and thereby improving the coordination of the developing circadian system (Ferber et al., 2002).

Although these studies have implied an association between massage therapy and several improvements in the development of healthy, full-term newborns, studies characterized by a detailed control of the interaction protocol have found different results. Indeed, different results were observed in a study assessing the effects of tactile-only stimulation by using a protocol that controlled the researcher's use of other interaction modalities (avoiding talking and eye contact, resulting in a loss of access to newborns' behavioral cues). Specifically, an immediate increase in salivary cortisol occurred not only in the control group (also separated from the mother and with no human social interaction) but also in the tactile-only group. However, a group receiving a 15-min multisensorial intervention (auditory, tactile, visual, and vestibular), called *ATVV Intervention* (similar to mother-infant interaction; Burns, Cunningham, White-Traut, Silvestri, & Nelson, 1994), exhibited a steady decline in salivary cortisol level. Accordingly, the authors highlighted the benefit of multisensorial intervention for reducing infant stress levels and emphasized the importance of human social contact in modeling the newborn response (White-Traut et al., 2009).

Altogether, these studies have reported results that varied according to the type of tactile stimulation provided, raising the question as to whether massage therapy intervention is truly a tactile-only procedure or is associated with a multisensorial approach, as suggested by the positive responses observed in some studies (Ferber et al., 2002; Field et al., 1996; Field et al., 2004). On the other hand, we also can question whether the increase in cortisol levels due to touch without talking and eye contact was the result of being touched or the result of an interaction that is avoidant and ambiguous, which may be more stressful than being separated for a short time from the caregiver. Moreover, the results of these studies have suggested that cortisol level, growth measures, urinary catecholamine level, urinary serotonin level, and urinary melatonin regulation rhythms are important biological markers underlying tactile stimulation processing in newborns, but only if tactile stimulation occurs in the context of mother-infant interactions. In accordance, the importance of contingent multisensory maternal/caregiver comforting behaviors in reducing infant stress has been indirectly supported (White-Traut et al., 2009).

#### *Physiological Markers of Tactile Sensorial Processing*

*Neurovegetative markers.* Mother-infant contact after birth in delivery-ward routines has been studied for its effects on newborn stress due to birth. Specifically, routine nursery procedures (handling, immobilization, and holding in arms) have been investigated using autonomic nervous system function and behavioral measures as independent variables. In general, these studies have reported that various physiological variables are differentially related with tactile stimulation processing, including heart activity (Arditi, Feldman, & Eidelman, 2006; Gray, Watt, & Blass, 2000; Porter, Wolf, & Miller, 1998), skin conductance (Hellerud & Storm, 2002; Schechter, Berde, & Yaster, 1993), and temperature during skin-to-skin contact (Bystrova, 2009; Bystrova et al., 2003).

Using crying, grimacing, and heart rate as outcome variables, Gray et al. (2000) analyzed the analgesic effect of mother contact during a heel-lance procedure. In one group, newborns were held by their mothers with whole body, skin-to-skin contact. In the second group, newborns were swaddled in a crib with no contact. Although mothers were asked to follow one of these two protocols, some of them interacted with their baby using multisensorial stimulation, namely through various comforting activities (e.g., securing contact, speaking gently to their infants, making clicking sounds). Results indicated that the outcome measures were significantly different between groups, with the skin-to-skin contact group showing less crying and grimacing and a more stable heart rate than did the group with no intervention (swaddled in crib) during the same procedure (Gray et al., 2000). In another study, two mixed groups of normal and premature newborns (with appropriate-weight-for-gestational age and without any demographic or clinical differences) were compared on the effects of handling and immobilization on heart rate, behavioral state, and facial activity responses to acute pain at three moments: baseline, a

preparatory period, and a heel-stick procedure period. The handled group underwent a series of handling and immobilization manipulations before the heel stick whereas the nonhandled group did not undergo these manipulations. In the handled group, the baseline was measured after handling and was similar to the nonhandled-group's baseline. Although an increase in mean heart rate occurred for both groups during the heel-stick procedure, the handled group exhibited a significant increase in mean heart rate and in average behavioral and facial activity when compared with the nonhandled group. Finally, the authors reported that the routine handling and immobilization increased the level of responsivity to a subsequent painful procedure (Porter et al., 1998).

The effects of human contact in a nursery context and vagal regulation on pain reactivity also have been studied: Arditi et al. (2006) performed electrocardiography (ECG) in two randomized groups of healthy newborns during three different moments: The first two data recordings were baselines; the first one (5 min) recording was obtained during sleep for both groups, and the other recording was obtained during a period in the research assistant's arms (experimental group) or in an infant seat (control group). A third ECG was performed during a heel stick for both groups. The behavioral pain reactivity was video-recorded and analyzed for facial activity, crying, and body movements. Human contact was not found to reduce the pain response, as there were no differences regarding heart rate and behavior between groups. However, an analysis of changes in the heart period and vagal tone of all participants showed significant differences between the heel-stick period and the other two moments: baseline and in the research assistant's arms or in an infant seat. Differences in vagal tone, an index of parasympathetic regulation of heart rate variability resulting from respiratory influences (respiratory sinus arrhythmia) (Porges, 1985), is associated with the ability to adapt to high-arousal events (Porges & Doussard-Roosevelt, 1997). Then, as a follow-up, the participants were regrouped according to vagal tone indices: baseline vagal tone and vagal tone withdrawal. The authors reported that the group with high reactivity (higher variability), higher baseline tone (higher frequency variability), and greater vagal withdrawal (greater frequency variability withdrawal) showed significantly more intense behavioral pain responses when compared with the group with low reactivity (Arditi et al., 2006). In an effort to study the development of stimulation responses to painful (heel stick in newborns or immunization in 3-month-olds) and to tactile (routine nursery handling in newborns), Hellerud and Storm (2002) registered plantar skin-conductance activity and behavioral state before, during, and after each procedure. Results indicated that full-term newborns' plantar skin-conductance activity and behavioral state arousal increased significantly in the pain and handling conditions. In the 3-month-old infants, the authors observed an increase in plantar skin conductance in response to pain stimulation, although no behavioral differences were evidenced for the pain or handled stimulation conditions. Moreover, behavioral state arousal was significantly less pronounced in the 3-month-old group than it was in the full-term newborn group during both types of stimulation (Hellerud & Storm, 2002).

Reactivity of newborns to different delivery-ward routines also has been assessed using temperature as a study variable. In newborns, well-regulated body temperature is an indicator of well-being; that is, when undressed, newborns undergo vascular and color changes in an effort to maintain body heat. However, temperature self-regulation is a difficult task for an undressed newborn, and depending on the duration of the experience and individual differences, this event can be quite stressful. Hence, one study assessed temperature reactivity to stress among three groups with different immediate after-birth routines: a *skin-to-skin group*, a *mother's arms group*, and a *nursery group* (in which the two latter groups were swaddled or clothed) (Bystrova et al., 2003). Results demonstrated that infants' temperature rose in the axils, back, and thigh in all groups. Furthermore, foot temperature significantly fell in the nursery group, with the greatest decrease observed in the swaddled newborn subgroup. In contrast, an increase was observed in the other two groups, especially in the skin-to-skin group. The authors hypothesized that skin-to-skin contact is a "natural way" of reversing stress-related effects on circulation that are induced during labor (Bystrova et al., 2003).

The differing results reported in these studies are possibly related to variations in tactile stimulation procedures. Specifically, when tactile stimulation was offered by the newborn's mother in a skin-to-skin or in-arms condition, temperature and heart rate decreased or remained stable in response to stress. When tactile stimulation was offered by nurses ("handling" or "holding in arms") with a more rigid protocol, heart rate and vagal tone increased or remained stable in response to stress. Skin-conductance activity also showed an increase in response to stress. We hypothesize that during these studies, mothers might interact with their babies, modeling tactile contact and using other interactive modalities in their behavior to respond to their baby's cues to comfort them. Indeed, researchers' flexibility on the protocol rules and acceptance of individual differences in mothers' behavior has been reported (Gray et al., 2000).

### Central Nervous System Markers

*Somatosensory evoked electrical markers.* Event-related brain potential (ERP) methodology allows for the detection of electrical brain activity on the scalp as a response to specific stimuli. The ERP waveform is represented by a series of positive (P) and negative (N) wavelike components, identified by latency and polarity. Early sensory components are generated in the brain stem or primary sensory cortices and represent how sensory information is being transmitted and processed. Longer latency ERPs are generated in associative brain areas (temporal, parietal, and frontal areas), are more variable between subjects, and are associated with higher cortical functions (Picton & Taylor, 2007).

Cortical somatosensory evoked potentials (SEPs) can be measured in newborns from the seventh gestational month. At this time, the somatosensory pathways can conduct peripheral impulses to the cortex, which is mature enough to produce responses (for a review, see Pihko & Lauronen, 2004). During early development, the greatest change in the cortical responses is the shortening of

the latencies due to an increase in the conduction velocity of the nerve impulses, resulting from the myelination and maturation of the pathways (Pihko & Lauronen, 2004). To our knowledge, SEPs obtained with normal newborns were first reported by Desmedt and Manil (1970). Peripheral somatosensory pathways have been primarily studied with electrical stimulation of the median nerve (George & Taylor, 1991; Gibson, Brezinova, & Levene, 1992; Laureau, Majnemer, Rosenblatt, & Riley, 1988; Willis, Seales, & Frazier, 1984) and often with electrical stimulation of both the median and tibial nerves (Laureau & Marlot, 1990; Zhu, Georgesco, & Cadilhac, 1987). All of these studies have evaluated early cortical response, with some also reporting spinal responses (Gibson et al., 1992; Laureau & Marlot, 1990) whereas others evaluated all cortical, spinal, and Erb's point evoked responses (Laureau et al., 1988; Willis et al., 1984). Late responses resulting from the electrical stimulation of fingers in healthy, full-term newborns also have been reported (Desmedt & Manil, 1970; Karniski, 1992; Karniski, Wyble, Lease, & Blair, 1992). SEPs also have been studied across different age groups, including not only newborns but also 13-week-olds (George & Taylor, 1991), 7-month-olds (Laureau et al., 1988), 12-month-olds (Willis et al., 1984), 16-year-olds (Zhu et al., 1987), and adults (Desmedt, Brunko, & Debecker, 1976). Finally, in one study, responses to electrical stimulation were compared for the nonrapid and rapid eye movement sleep stages and wakefulness (Desmedt & Manil, 1970). Overall, these studies have reported a consistent early cortical response that in newborns is called "N1" (equivalent to the N20 in adults).

Somatosensory evoked potentials research with healthy, full-term newborns using nonelectrical tactile stimulation was first conducted by Pihko et al. (2004). Considering that sleep stage affects electroencephalography (EEG) results, the authors assessed their effects on tactile stimulation responses using both electric potentials (SEPs) and magnetic fields [supplementary eye fields (SEFs)], measured with EEG and magnetoencephalography (MEG), respectively (Pihko et al., 2004). Tactile stimulation was mechanical and was delivered by a device that produced movements through air pressure in a plastic membrane touching the skin (tip of the index finger and/or thenar eminence). Sleep stages were determined from data analysis of EEG, MEG, ECG, and electromyography (EMG) as well as data derived from behavioral eye movement, head movement, and breathing pattern. SEP results did not allow for the evaluation of the sleep-stage effect on N1 deflection. However, the sleep stage had a significant effect on P1 and P2 at the vertex. Both were reduced in amplitude in active sleep when compared with quiet sleep in all newborns. SEF results showed a significant effect of the sleep stage in P1m and P2m, with an attenuation of amplitude in active sleep. These results were similar in waveform and latency to previous findings using electrical stimulation of the fingertips of neonates (Desmedt et al., 1976; Desmedt & Manil, 1970). Although N1 responses were observed only in active sleep in a small group of newborns, the authors noted that a gentle tactile stimulation of the index finger tip or thenar eminence elicited responses that were similar to those obtained with electrical transcutaneous stimulations: N1 and later components

P1 and P2. Moreover, sleep stages were associated with different effects on information processing in the somatosensory modality.

Consequently, understanding these effects in healthy newborns could be an important approach for assessing abnormalities in the brain functions of at-risk infants for developmental abnormalities (Pihko et al., 2004). Despite these findings, Nevalainen et al. (2008) showed different results on the effects of the sleep stage that will be further discussed in the next subsection on the evoked magnetic field markers.

In addition to the newborn's neurodevelopmental level, there are several variables that could affect SEP results and must be addressed. First, a greater number of traces can be related to smaller SEP responses; namely, fatigue related to immaturity or habituation to stimuli. In addition, in psychophysiological research, the filter-setting choice is an important issue that must be carefully acknowledged. Indeed, the most recommended filter for clinical studies is the high-pass filter; however, at higher settings, this filter attenuates late-latency responses and thus limits the appearance of these components. Finally, since 1967, sleep stage has been known to play a determinant role in tactile stimulation heart rate responses (Lewis, Bartels, & Goldberg, 1967). This variable also can have a prominent effect on evoked responses: The earlier N1 response is better recorded in active sleep whereas the later positive responses are better observed in quiet sleep. Therefore, the monitoring of the sleep stages is recommended in SEP studies (for a review, see Pihko & Lauronen, 2004) since the waveform with an early N1 and later P1 and P2 components is considered the temporal electrical brain response marker of tactile sensorial processing in newborns.

*Somatosensory evoked magnetic fields markers.* Multichannel MEG is a reference-free method that does not require precision in electrode placement, like ERP, and provides a detailed picture of the field distribution associated with each SEP waveform component (Lauronen et al., 2006). This methodology also has been applied to the study of evoked responses to tactile stimulation (Lauronen et al., 2006; Nevalainen et al., 2008; Pihko et al., 2004; Pihko, Nevalainen, Stephen, Okada, & Lauronen, 2009) and is an important resource in the characterization of cortical generators underlying SEFs elicited by tactile stimulation.

Lauronen et al. (2006) conducted an MEG study to characterize the cortical generators of the N1 and subsequent responses in healthy human newborns. In addition, they studied the maturation process of tactile processing by analyzing evoked responses to tactile stimulation (electrical and tactile) of the index finger in newborns, 6-month-olds babies, and adults. Electrical stimulation was applied to the left median nerve at the wrist of 12 newborns. Tactile stimulation also was applied to the tip of the left index finger to 20 newborns (including 6 from the first group of 12), five 6-month-olds, and 10 adults. Tactile stimulation and sleep-stage characterization followed the same procedures as those described in previous studies (Pihko et al., 2004). Tactile evoked responses were recorded from 20 newborns (15 during both sleep stages, 1 only during active sleep, and 4 only during quiet sleep). Results have shown that the first major response to tactile stimulation in

newborns was M60 (“M” referring to collection via MEG), and the equivalent current dipole (ECD) analysis showed a neural current flow with a direction from the posterior to the anterior regions of the brain. This field pattern was considered consistent with a neuronal current directed from deep cortical layers toward superficial layers within area 3b in the posterior bank of the central sulcus. No significant differences were found in ECD source location (SI cortex) or in orientation between median nerve stimulation and tactile stimulation for the 5 newborns who were in both experiments (Lauronen et al., 2006). Furthermore, to identify the cortical generators underlying the neonatal SEFs elicited by tactile stimulation of the contra- and ipsilateral index fingers, Nevalainen et al. (2008) studied a group of 21 newborns using the previously reported tactile stimulation technique (Pihko et al., 2004). In this study, cortical activity was recorded from the right hemisphere during natural sleep. Eleven newborns were stimulated in the contralateral (left) index finger with three different interstimulus intervals (ISIs = 0.5, 2, and 4 s), in separate runs, and 10 other newborns were stimulated with a constant ISI of 2 s and with the contra- and ipsilateral (right) index fingers being stimulated one at a time. The sleep stages were monitored with EEG, electrooculography, and behavioral coding. All newborns showed contralateral responses, with two significantly different deflections being found: M60 and M200 in both sleep stages (quiet sleep and active sleep). Contrary to previous work using waveform analysis (Pihko et al., 2004), sleep stages did not affect M60 when analysis was carried out using ECDs. The source location of the M60 corresponded to the contralateral SI cortex (primary cortex) while the M200 source was inferior and lateral to the M60 source, suggesting an SII (secondary cortex) generator. Ipsilateral responses were significantly different from contralateral responses, showing longer latencies. The ipsilateral SI cortex and the ipsilateral SII cortex were activated in some newborns, with the latter being described for the first time in newborns. The M60 was not affected by ISI whereas the M200 was significantly attenuated with 0.5-s ISI. The authors suggested the use of the 2-s ISI for studying both M60 and M200 SEF responses and that SI and SII (contra and ipsilateral) play an important role in somatosensory processing in neonates (Nevalainen et al., 2008). In a recent study, SEFs to tactile stimulation of the left index finger were measured from the contralateral somatosensory cortex with MEG in newborns, 6-month-olds, 12- to 18-month-olds, 1½- to 6-year-olds, and adults in awake and sleep states (Pihko et al., 2009). The results showed an M60 response (U-shaped) in newborns that shifted to a W-shaped response around 6 months of age. By 2 years of age, the M30 and M50 responses were an adultlike response, suggesting that the most significant maturation of cortical responses occurs within the first 2 years of life. The ECDs of M60 and M30 showed a neural current flow with a direction from the posterior to the anterior regions of the brain, and the ECDs of M50 showed a neural current flow with a direction from the anterior to the posterior regions of the brain. Furthermore, the MRI of 1 newborn showed the location of the M60 ECD in the posterior bank of the central sulcus. Finally, these maturational changes were independent of vigilance state (Pihko et al., 2009).

Despite the need to carry out future studies for more robust conclusions, these later studies have suggested consistent brain magnetic field markers to tactile stimulation of the index finger; namely, a first response M60 with an ECD from the posterior to the anterior regions that is generated in the SI cortex.

*Neuroimaging markers [functional magnetic resonance imaging (fMRI) and resting functional connectivity (rfc-MRI)].* fMRI studies using tactile stimulation paradigms in newborns are sparse. Erberich et al. (2006) analyzed whether lateralization systems were established in the area of the pre- and postcentral gyrus (BA4, 3a, 3b) in a group of preterm and full-term newborns (mean postconceptional age = 42 weeks), sedated and with clinical MRI indication, but without evidence of anatomic or pathologic abnormalities in somatosensory areas. The MRI and the fMRI were acquired using an MR-compatible incubator with a built-in radiofrequency head coil that was optimized for the neonatal brain volume, specially developed for neonates and used for the first time in a study of preterm neonates (Erberich, Friedlich, Seri, Nelson, & Bluml, 2003). The full-term newborns were stimulated in a passive task performed separately on the left and the right hands with a rubber ball (30 ml) placed and fixed in the palm. The ball was inflated, provoking pressure on the palm and opening it (passive extension), and deflated, alleviating the pressure and resulting in the flexion of the fingers (similar to grasping). Results showed that passive stimulation of coetaneous and proprioceptive receptors in newborns’ hands resulted in a significant bilateral activation of the cortex and thalamus in the majority of the newborns. While there was a contralateral predominance, it was not significant. This slight advantage of contralateral dominance suggested that the lateralization of the somatosensory system is not specialized between midgestation and early postnatal life but instead develops after birth. The authors demonstrated that complete lateralization is not yet accomplished by 38 to 49 weeks postconceptional age, suggesting that lateralization or refinement of the sensorimotor pathways must occur in the postneonatal period (Erberich et al., 2006). This proposal has not been supported by subsequent research. Specifically, a recent study was conducted in a group of 13 preterm infants, 19 ex-preterm infants who were scanned at term-corrected gestational age, and 8 healthy, full-term control infants using a synchronized tactile and proprioceptive stimulus developed for fMRI (Arichi et al., 2010). The somatosensory stimulus was a balloon placed in the right hand controlled by software on a standard PC that was connected to the MRI scanner. This study reported consistent activation following somatosensory stimulation in both preterm and term newborns. Positive blood oxygen level dependent (BOLD) activation in the contralateral primary somatosensory cortex (Arichi et al., 2010) suggested that hemispheric lateralization of the somatosensory system occurs earlier. In agreement, other studies using different methodology (MEG) evidenced contralateral activation to touch-only passive stimulation in a group of healthy, full-term newborns (Lauronen et al., 2006; Nevalainen et al., 2008; Pihko et al., 2009).

These different results regarding newborns’ maturity/immaturity in somatosensory system lateralization in response to passive

stimulation of the hand (Erberich et al., 2006) are possibly related to the varying methodologies used in different studies; namely, time resolution and synchronization of the stimulus. For example, MEGs are time-accurate when compared with fMRI techniques. Furthermore, the use of different neuroimaging methods and clinical participant conditions as well as stimulation experiences during pregnancy and after birth that were not fully described also potentially may impact the results. Consistent findings using different methodologies have suggested that healthy newborns have mature nervous pathways and a primary somatosensory cortex and thus a contralateral response to tactile stimulation similar to that observed in adults. Although more studies are required to pursue this issue, positive BOLD activation in the contralateral primary somatosensory cortex is a potential neuroimaging marker for tactile processing.

Finally, rfc-MRI studies also have reported an increase in the percent of brain volume that showed rfc in the sensorimotor area in children (neonates and 1- and 2-year-olds). The temporal and spatial pattern of rfc in healthy babies between 2 weeks and 2 years of age was assessed in a study conducted by Lin et al. (2008). The rfc-MRI was performed in 38 neonates (2–4 weeks of age), twenty-six 1-year-olds, and twenty-one 2-year-olds during natural sleep. To identify regions with high temporal correlation, mean signal intensity of the primary motor, sensory, and visual cortices in each hemisphere was used to perform correlational analysis, voxel by voxel, throughout the entire brain. The percentage brain volume of rfc continued to increase from 2 weeks to 2 years. The percentage brain volume that showed rfc in the sensorimotor area was significantly larger than that in visual areas for 2-week-old neonates and 1-year-old children, but not for 2-year-old children, suggesting that rfc in the sensorimotor area precedes the rfc in the visual areas, becoming comparable at 2 years of age. Finally, the strength of rfc continued to increase from 2 weeks to 2 years of age and was similar for both sensorimotor and visual areas for all age groups, suggesting a dissociation between percentage brain volume and the strength of cortical rfc (Lin et al., 2008).

These functional neuroimaging studies provide important and valuable information regarding somatosensory maturational process and its relation with tactile processing; however, some of these studies have used sedation and, for ethical reasons, this represents a limitation in research with healthy infants. Although the Lin et al. (2008) study does not allow for the identification of the neural correlates of tactile stimulation processing, it is a good illustration of how we can use neuroimaging techniques with healthy, full-term newborns without sedation.

## DISCUSSION

In our review, we found two distinct approaches to tactile sensorial processing research with healthy, full-term newborns: (a) tactile sensorial processing in the context of human interaction using biological and autonomic physiological variables and (b) understanding somatosensory system activity that results from tactile stimulation using central nervous system physiological variables.

In the first approach, we found the following biological marker candidates: cortisol level decrease, growth measures increase, urinary catecholamine level decrease, urinary serotonin level increase, and urinary melatonin regulation rhythms. However, we also observed that a careful analysis of the stimulation procedures must be taken into account. Indeed, a deeper analysis of the procedures used in tactile/kinesthetic stimulation (massage therapy) showed that touch (pressure), temperature (heat), proprioceptive, and vestibular stimulation were used. It remains unclear whether (although it is quite likely) visual and auditory stimulation also were incorporated and thus accounted for the obtained results; namely, if the procedure involved a maternal interaction style in which mothers either used different stimulation modalities or modulated their behavior to their baby's cues.

In addition, in studies that have evaluated autonomic physiological variables, the following marker candidates were identified: heart rate, body temperature, skin-conductance activity, and vagal reactivity. Two comments should be made concerning the results reported in these studies. First, tactile stimulation can be experienced as pleasant or unpleasant. When tactile stimulation was offered by the mother in a cuddling mode, decreasing or non-increasing newborn stress (measured by heart rate and body temperature) was observed; however, when tactile stimulation was offered by others by handling or holding in their arms, there was an increase in the stress response (evaluated through vagal reactivity or measured by skin-conductance activity). Second, these marker candidates are stress-related markers that seem sensitive to the effects of tactile stimulation in the newborn, of which the most robust and widely studied is vagal reactivity as a marker for emotional regulation (Beauchaine, 2001). Although we did not find any study reporting the effects of touch stimulation on plasma levels of cholecystokinin and opioids in healthy, full-term newborns, we hypothesize that they may be hypotactic marker candidates. These two neuropeptides have been reported as having a mediating role on emotion and behavior regulation in studies with infant rats, lambs, and premature human infants, demonstrating that they underlie physiological mechanisms of self-regulation (Weller & Feldman, 2003).

Regarding central nervous system markers, a more precise description of the stimuli and procedures was provided. Specifically, we evidenced that they were not offered in the context of any human interaction but were true tactile-only stimuli (touch–pressure). All of the studies that have used SEPs and SEFs (developed from the initial work of Pihko et al., 2004) showed solid and consistent results. In the work developed by this team, we found the most unambiguous markers: the SEPs waveform with N1–P1–P2 components and SEF M60 with ECD from posterior to anterior regions, generated in the primary cortex (Nevalainen et al., 2008; Pihko et al., 2004). These markers were found in healthy, full-term newborns and also were found to change along the infant developmental process.

Although the fMRI study using tactile stimulation reported interesting results, it must be interpreted with caution because all participants were in a clinical condition (Erberich et al., 2006).

Nevertheless, the positive BOLD activation in the contralateral primary somatosensory cortex may be considered as a neuroimaging marker candidate for healthy newborns (Arichi et al., 2010). Finally, results of the rfc-MRI study suggest that rfc in the sensorimotor area precedes the rfc in the visual area from 2 weeks to 1 year, which seems to confirm the maturation of the somatosensory cortex. The three central nervous system marker candidates are compatible with the hypothesis that during fetal growth, tactile stimulation processing develops more strongly than do other sensorial modalities, although through a second tactile system of unmyelinated low-threshold C-afferents (Bystrova, 2009). These findings confirm that newborns have the capacity to benefit from tactile-sense stimulation in human contact. Results that have shown a developmental pattern of the responses (Lauronen et al., 2006; Lin et al., 2008; Pihko et al., 2009) also help us to understand the role of mother's cuddling in the regulation of healthy newborns, suggesting that the environmental experience plays an important role in cortical development during the first 2 years of life.

We suggest that future studies should consider the effect of other interaction modalities during tactile stimulation, replicate previous SEFs with newborns while awake (Lauronen et al., 2006; Pihko et al., 2009), use gentle pressure (Kawohl et al., 2007), synchronized stimulation (Arichi et al., 2010), and neonatal head coil and compatible incubator in an fMRI setting (Erberich et al., 2003). Finally, greater knowledge of the neural correlates underlying sensorial processing in newborns and infants provides a valuable tool for studying individual differences that have been identified in clinical settings.

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