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Affective and non-affective touch evoke differential brain responses in 2-month-old infants

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ABSTRACT

Caressing touch is an effective way to communicate emotions and to create social bonds. It is also one of the key mediators of early parental bonding. The caresses are generally thought to represent a social form of touching and indeed, slow, gentle brushing is encoded in specialized peripheral nerve fibers, the C-tactile (CT) afferents. In adults, areas such as the posterior insula and superior temporal sulcus are activated by affective, slow stroking touch but not by fast stroking stimulation. However, whether these areas are activated in infants, after social tactile stimulation, is unknown.

In this study, we compared the total hemoglobin responses measured with diffuse optical tomography (DOT) in the left hemisphere following slow and fast stroking touch stimulation in 16 2-month-old infants. We compared slow stroking (optimal CT afferent stimulation) to fast stroking (non-optimal CT stimulation). Activated regions were delineated using two methods: one based on contrast between the two conditions, and the other based on voxel-based statistical significance of the difference between the two conditions. The first method showed a single activation cluster in the temporal cortex with center of gravity in the middle temporal gyrus where the total hemoglobin increased after the slow stroking relative to the fast stroking ($p = 0.04$ uncorrected). The second method revealed a cluster in the insula with an increase in total hemoglobin in the insular cortex in response to slow stroking relative to fast stroking ($p = 0.0005$ uncorrected; $p = 0.04$ corrected for multiple comparisons).

These activation clusters encompass areas that are involved in processing of affective, slow stroking touch in the adult brain. We conclude that the infant brain shows a pronounced and adult-like response to slow stroking touch compared to fast stroking touch in the insular cortex but the expected response in the primary somatosensory cortex was not found at this age. The results imply that emotionally valent touch is encoded in the brain in adult-like manner already soon after birth and this suggests a potential for involvement of touch in bonding with the caretaker.

Introduction

Touch between individuals is a part of social interaction; it communicates emotions and creates social bonds (Hertenstein et al., 2006; Morrison et al., 2010). Touch is also an important factor for normal

development, both for humans and animals (Field, 2002; Barnett, 2005). In the classical work by Harlow in the 1950's, rhesus monkey infants were kept isolated from their mothers. The infant monkey preferred clinging to a soft mother surrogate compared to a surrogate made of wire (Harlow, 1958). This behavior was observed regardless of which of the

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surrogate mothers that was providing food and was interpreted as a preference for “contact comfort”. For humans, deprivation of social contact, including tactile interaction as seen in some orphanages, affects the intellectual, physical, behavioral and social-emotional development (MacLean, 2003) as well as the sensory modulation capacities (Wilbarger et al., 2010).

On the other hand, adding touch in health care settings has been found to be beneficial. Preterm infants who receive stroking touch massage gain more weight and spend less time in the hospital compared to controls (Vickers et al., 2009). Passive touch, as in skin-to-skin care of neonates has positive effects on physiological parameters such as the heart rate, respiratory rate and oxygen saturation (Bergman et al., 2004). Further, mother-infant attachment increases with skin-to-skin care in comparison with newborns receiving conventional neonatal care (Conde-Agudelo and Díaz-Rossello, 2014). Touch intervention in neonatal care has also been shown to have long-term implications. A study by Feldman et al. (2014) showed that children who received skin-to-skin care as neonates had attenuated stress response and better cognitive control at 10 years of age (Feldman et al., 2014).

There is reason to believe that the affective and social aspects of touch are processed by a specialized sensory nerve system, which differs in peripheral and central pathways from discriminative touch processing. Touch to the human hairy skin is detected by two types of afferent nerve fibers; A β afferents and C-tactile (CT) afferents. A β afferents are myelinated, thick afferents that convey the discriminative properties of touch, whereas the CT afferents, which are unmyelinated and thin, contribute to the affective components of the touch (Vallbo et al., 1999; McGlone et al., 2014). CT afferents are preferentially activated by touch that mimics typical human to human caressing, i.e. light pressure, skin temperature and slow stroking velocities between 1 and 10 cm/s (Ackerley et al., 2014). In addition, the firing frequency of the CT afferents positively correlates with the degree of perceived pleasantness of stroking stimulation (Löken et al., 2009). Affective touch has been defined as tactile processing with a hedonic or emotional component (Morrison, 2016) and CT fibers are likely to convey this component (Olausson et al., 2002; McGlone et al., 2014). While slow stroking of velocities between 1 and 10 cm/s activates CT afferents optimally, faster stroking evokes less CT activity and more A β afferent signaling (Löken et al., 2009).

Brain regions involved in processing affective, slow stroking, touch in adults include the secondary somatosensory cortex (S2), insular cortex, insular operculum, temporoparietal junction, superior temporal sulcus (STS), amygdala, striatum, orbitofrontal cortex and pregenual anterior cingulate cortex (Olausson et al., 2002; Lindgren et al., 2012; Gordon et al., 2013; Voos et al., 2013; Bennett et al., 2014; Kaiser et al., 2015; Perini et al., 2015; Case et al., 2016). A recent meta-analysis further revealed that affective touch differs from discriminative touch processing with a higher likelihood of activation of the posterior insula and S2 (Morrison, 2016). Electroencephalographic (EEG) responses to pleasant and unpleasant fabrics touching the right inner forearm in adults were studied by Singh et al. (2014) who found greater mu-suppression in electrodes over the left somatosensory cortex in response to the least preferred fabric compared to the most preferred fabric as well as a right-lateralized beta-band effect in electrodes over the right temporo-parietal cortex.

The affective touch processing system is present throughout the course of adulthood (Sehlistedt et al., 2016) and there are indications that this processing system is present even in very young infants (Fairhurst et al., 2014). Already at nine months after birth, infants show differentiated physiological responses, i.e. a heart rate decrease, to slow stroking of 3 cm/s on the forearm (Fairhurst et al., 2014). Indeed, in social interactions, parents spontaneously touch their infants in a way that is optimal in activating CT afferents (Croy et al., 2016). As interpersonal touch is of high developmental importance for newborns (Field, 2002), we hypothesize that there is a cortical system in place for detecting affective touch already early in postnatal life. However, to the best of our

knowledge, it is not clear whether newborns are able to process the affective side of touch; hence if they are able to differentiate between slow and fast stroking stimulation.

We compared cortical activation following slow and fast stroking in 2-month-old infants, where the slow stroking is assumed to carry a larger affective load than the fast stroking. Brain responses were studied using high density diffuse optical tomography (HD-DOT) which is a safe, non-invasive functional imaging method based on functional near infrared spectroscopy (fNIRS). HD-DOT uses many spatially overlapping measurements with multiple source-detector distances and model based image reconstruction to provide three-dimensional images of oxygenated (HbO₂), deoxygenated (HbR), and total (HbT) hemoglobin concentration changes (Arridge, 1999; Zeff et al., 2007; Heiskala et al., 2009a, 2009b).

Materials and methods

Ethics

Ethical approval was obtained from the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland. The study was performed according to the Declaration of Helsinki. Information about the experiment was given to the parents at recruitment and upon arrival to the experimental session. Parents were informed that they could terminate the experiment at any time, without having to state a reason. All parents signed an informed consent form.

Subjects and recruitment

Twenty-nine healthy infants from the FinnBrain Birth Cohort Study (www.finnbrain.fi) were recruited. Data sufficient for analysis (minimum 15 min of clean recording) was obtained from 16 of them (10 male; mean age 56 days \pm 8 SD). Exclusion from analysis was mostly due to restlessness of the infants. Prior to starting the measurements the infants were breast-fed in order to avoid hunger and to keep the infants calm during the experiment. The mother was sitting in a comfortable armchair holding the infant in her arms (Fig. 1a). The clothing on the right forearm of the infant was removed in order to allow tactile stimulation on the skin. During the experimental session the infants were allowed to drift in and out of sleep.

Tactile stimulation and paradigm

The tactile stimulation consisted of a soft goat hair paint brush that was gently stroked across the skin on the right forearm of the infant with two different velocities, 3 and 20 cm/s. In order to avoid restraining of the infants' arms, hand-held brushing was used instead of a stimulation robot. The stroking was administered in proximal-distal direction on the available part of the infant's arm, dorsal or ventral side depending on the position of the arm. The slow stroking consisted of one stroking, the fast of stroking back and forth. The stimuli were all delivered by the same experimenter. The choice of the forearm as site for the stimulation was made for several reasons. Firstly, it is available when the mother is holding her infant. Secondly, it is one of the sites where the presence of CT afferents have been confirmed, and thirdly, it is commonly used in studies of affective touch (Ackerley et al., 2014; Björnsdóttir et al., 2014; Croy et al., 2016; Kaiser et al., 2015; Löken et al., 2009). The stimuli were administered in 2-s epochs in a randomized counterbalanced order. The inter-stimulus interval (ISI) was randomized to minimize habituation (mean 31 s). The stimulation was divided into runs of 25 min each. Each run contained 20 fast and 20 slow brush stroking stimuli and each infant participated in 2 or 3 runs, without breaks between runs. All sessions were video-taped and the videos were coded after the experimental session by the experimenter. Episodes of crying and excessive movement were marked and notes were also taken on when the infant was awake and when he/she was sleeping. Electrophysiological recordings were not used as we wanted to simplify the set up and avoid procedures that might

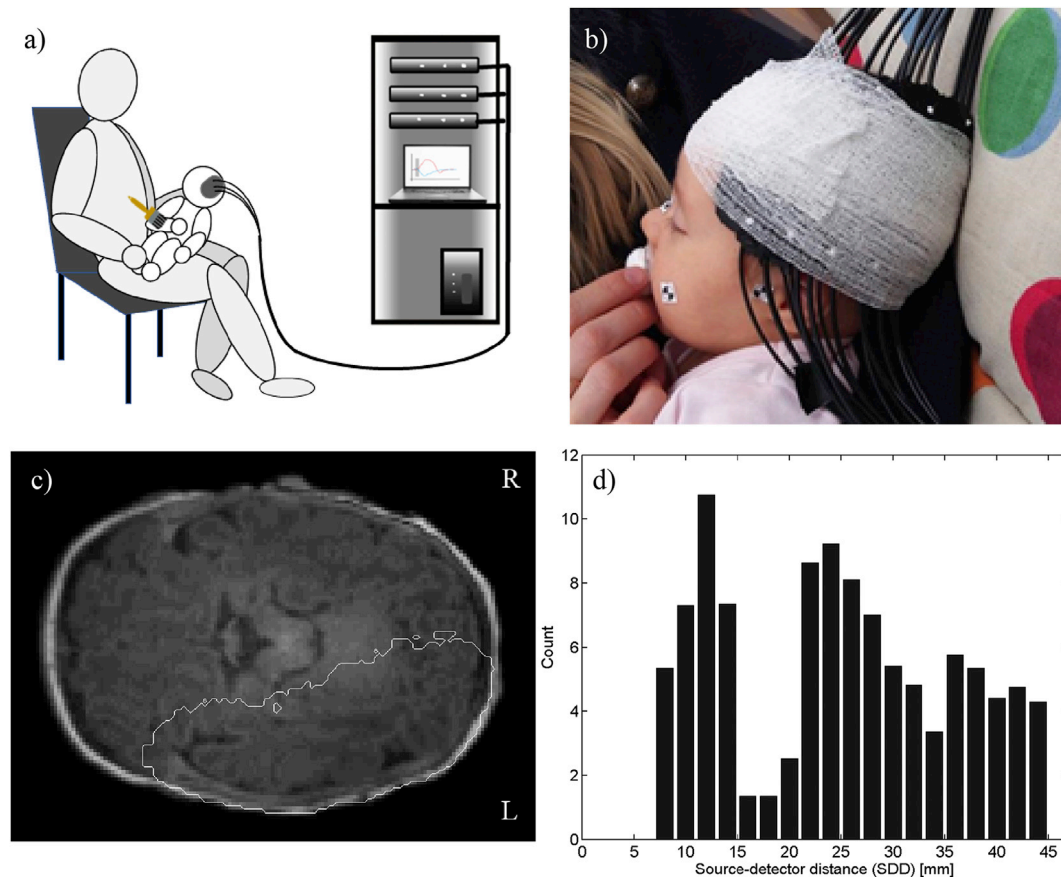


Fig. 1. a) Illustration of the measurement session with infant, mother, and instrument. b) Close-up of the HD-DOT head gear on the infants head. Also visible are stickers placed on anatomical landmarks and markers on the head gear which helped in determining the position of each source-detector pair. c) An illustration showing the approximate field of view of the imaging probe with the white contour line superimposed on an axial MR slice. d) The distribution of Euclidian source-detector distances (SDDs) used in the reconstructions.

cause discomfort to the subjects. The sleep stage could not be determined from the video. This coding of the videos was used in the averaging process, see below.

Instrumentation and head gear

A 16-channel intensity modulated frequency-domain optical tomography system (Nissilä et al., 2005) modified with micro-electromechanical systems (MEMS) switches (Opneti Communications Co. Hong Kong, China) for faster imaging was used for cortical recordings at two wavelengths (758 nm and 824 nm; mean optical power 0.3 mW). A flexible probe constructed of optical fibers, fiber bundles and prisms embedded in a black polyvinyl siloxane support material (Accutrans Black, Ultronics/Colthane) was used, with approximate dimensions of 80 mm × 130 mm × 6 mm. The measured source-detector distances (SDD) ranged from 7 mm to 80 mm, however, in order to avoid contribution from possible light leaks on the measured signal, source-detector pairs were limited to 45 mm Euclidian distance in this study. Due to the smaller radius of curvature, higher scattering in the superficial tissue, and lower attenuation of the unmyelinated brain, it is possible to image tissues slightly deeper than would be possible in adults, in particular, in areas adjacent to pockets of cerebrospinal fluid (CSF), such as are found between the temporal and frontal lobes and the insular cortex. Combining this range of source-detector separations with a three-dimensional image reconstruction algorithm provided a degree of separation between scalp and brain physiology. The probe was attached to the left side of the infant's head, right above the ear, using a flexible, self-adherent bandage (Mollelast Haft, 6 cm width; Lohmann & Rausher, Rengsdorf, Germany). We chose the left hemisphere for study for practical reasons as the right side of the infant's cheek was then free to lean on

the mother without being obstructed by the optical fibers. Contralateral stimulation of tactile afferents was expected to cause greater responses than ipsilateral stimulation. The position of the probe was determined based on coverage of brain areas of interest, such as superior temporal sulcus (STS), and secondary somatosensory cortex (S2), as well as maximum contact with the scalp, i.e. minimum curvature. Stereo images were taken of the probe position relative to landmarks to allow subsequent co-registration (Fig. 1b). Fig. 1c shows the approximate field of view (FOV) of the measurements estimated from the reconstructed images by thresholding the grand average HbT image with the maximum value divided by 10^5 and requiring that at least five infants exceeded the threshold. The frontal/inferior tip of the STS (~2 cm) below the frontal lobe was not within the FOV of most subjects as the positioning of the probe was sometimes affected by the subject head movement during probe placement. Fig. 1d shows the histogram of the SDDs that were used in the image reconstructions.

Photogrammetry

Photogrammetry was selected as an infant-friendly method for registering the probe position with the anatomical model. Photogrammetry markers were attached on anatomical landmarks and a stereo camera system was used to acquire images of the position of the measurement probe. The stereo camera system consisted of two Olympus E-EP5 camera bodies with 25 mm f/1.4 Leica Panasonic lenses. A metal bar was used to hold the cameras in position relative to each other at a distance of approximately 26 cm from each other. Synchronized release of the two cameras was achieved by using an electrical remote release. A studio flash (Elinchrom RX400, triggered by radio transmitter) was attached to the ceiling to illuminate the room. An additional white

reflector of 100 cm diameter was positioned under the flash to prevent direct reflection of light from the ceiling. The flash provided a short pulse of sufficient quantity of light (200Ws) which permitted the use of a small aperture (f/11) to keep the whole head within the depth of field, accurate color reproduction in the images and minimized the effect of subject movement on the image sharpness. A mesh cap with colored markers at nodes was put on the head of the infant and images of the infant's head were acquired from 5 different orientations using the stereo camera system. Matching points between the corresponding images from the two component cameras were marked using a semiautomatic method and 3D coordinates for each marker were estimated. The 3D point sets from the different stereo camera orientations were co-registered using a rigid transformation, forming a 3D model of the infant's head with anatomical landmarks and probe position marked. The outer surface of the probe contained markers used to determine the position of each optode. The 3D model was used to co-register the infant data to an anatomical MR image of a representative individual (described below).

Signal processing and averaging of the optical signals

Although the frequency-domain instrument used measures of both amplitude and phase data types, in this study only the amplitude data was used for image reconstruction because of insufficient signal-to-noise of the phase at 0.3 mW source power. The signal drift caused by contact variations, sweating and instrument drift was removed by subtracting a low-pass filtered version (-3 dB cutoff frequency = 0.007 Hz) of the amplitude signal from the time course. A manually selected threshold was used to detect motion artifacts from the signal itself. The raw and filtered data were evaluated by eye to detect abrupt signal transitions in the unfiltered data and corresponding peaks in the filtered data. Using thresholds with increments of 0.5 from 2 to 8 times the standard deviation of the filtered signal, the proportion of rejected stimuli was calculated and the timing of the artifacts was visualized. The threshold was chosen so that it lead to the removal of obvious artifacts in the data but retained as much as possible of the clean signal.

In addition, epochs from the video analysis where the infant was crying or moved vigorously were excluded from the averaging. Averaging of the responses to each stimulus condition (slow and fast brushing) was carried out using finite impulse response (FIR) deconvolution. Source-detector pairs with low signal to noise ratio ($\text{SNR} \leq 3$ in the raw data) were excluded from the image reconstruction; on average, one source-detector pair was excluded based on this criterion. Additionally, three source and three detector fibers were excluded from the superior posterior corner of the probe due to concern about inconsistent contact in an area of steep curvature of the head.

Diffuse optical tomography

To generate 3D images of the hemoglobin concentration changes, a flexible high-density fiberoptic imaging probe was used together with an instrument that recorded signals with a wide range of source-detector separations (Euclidian SDDs from 7 mm to 45 mm were included in the reconstruction; see Fig. 1d), and an image reconstruction algorithm based on the perturbation Monte Carlo method. By using a high-density optode arrangement with multiple partially overlapping measurements, we can reduce variations in sensitivity across the field of view (FOV) of the imaging (Heiskala et al., 2009a) as well as between subjects. In the reconstruction, Tikhonov regularization with a Laplacian regularization matrix was used to suppress noise. Voxels that coregistered with scalp or skull voxels in the segmented MR image were excluded from cluster analysis to minimize the contribution from extracerebral physiology on the results.

A representative anatomical MR image of a 1.5-month old female infant (from the FinnBrain MRI sub-study) was manually segmented using in-house software into different tissue types (scalp and skull, cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM)). The optical parameters for each tissue type were assumed to be constant and

were taken from literature (Table 1). Light propagation was simulated using Monte Carlo and measurement sensitivity to absorption changes in each voxel was calculated. Linear image reconstruction with Laplacian regularization was used to calculate the absorption changes in each voxel at the two wavelengths used. Oxygenated and de-oxygenated hemoglobin (HbO_2 and HbR , respectively) changes were calculated from absorption changes using extinction coefficients from (Cope, 1991). The CSF was in this study modeled using weakly diffusive parameters (Custo et al., 2006). The use of an intermediate scattering coefficient for the CSF reduces the sensitivity of the resulting images to the exact position of the CSF.

Image analysis and statistical testing

The time series of reconstructed changes in total hemoglobin (HbT) concentration were smoothed using a 3D Gaussian blur operation (with a standard deviation of 1.5 mm) and averaged across all 16 subjects. The smoothing was applied to reduce the effect of coregistration errors and inter-individual differences between the positions of functional areas. To avoid introducing cross-talk between scalp and brain voxels, the smoothing was limited to gray and white brain matter voxels only. The images were analyzed by identifying regions where the fast and slow brushing produced different responses over the time window from 2 to 8 s after stimulus onset, and subjected these regions to statistical testing. The time window was selected using prior knowledge of the time course of typical hemodynamic responses to 2-s stimuli in infants. Although the duration of the hemodynamic response in infants is typically longer than in adults, we find the early part of the response to be most closely tied to the stimulus condition with less variability than the “return to baseline” phase; this may be in part due to different stages of maturation of the hemodynamic response in young infants. In this study, HbT was used as the hemodynamic parameter of primary interest as we consider it to have a more straightforward relationship with neuronal activity than HbO_2 and HbR . When regional neuronal activity increases, the neurovascular coupling causes arterioles that supply blood to that region to dilate, leading to an increase in HbT and cerebral blood flow (CBF). HbO_2 and HbR are affected both by vascular effects as well as metabolism (oxygen extraction to support tissue function), whereas oxygen metabolism has no direct effect on HbT. According to Lindauer et al. (2010), the regional coupling of blood flow to neuronal activation is independent of the level of oxygen transported to the tissue, and a shortage of oxygen is not a driving force for vasodilation during increasing neuronal activity. An increase in local neuronal activity is likely to cause arteriolar dilation as well as an increase in oxygen metabolism, leading to two processes that contribute with opposite signs to HbO_2 and HbR , resulting in potentially complex signals that are more difficult to interpret. In some of our fNIRS studies (Kotilahti et al., 2010) as well as our previous reconstructions calculated from HD-DOT data, when the analysis is limited to brain voxels, the best statistical sensitivity to differences in responses to different stimulus conditions has generally been found in the HbT parameter (Näsi et al., 2013). Because of their smaller magnitude, HbR responses are more susceptible to measurement noise than HbO_2 or HbT responses. Furthermore, in infant studies, the sign of HbR responses (as well as BOLD fMRI responses) is inconsistent across studies and sometimes also within studies. For a review of infant fNIRS responses, see e.g. Lloyd-Fox et al. (2010). The maturation of the BOLD response in infants is

Table 1

Tissue types and optical parameters used in the model. μ_s = scattering coefficient, μ_a = absorption coefficient, g = anisotropy factor, n = index of refraction.

	μ_s (mm^{-1})	μ_a (mm^{-1})	g	n
Scalp & Skull	16	0.015	0.9	1.4
CSF	0.3	0.0041	0	1.4
Gray Matter	5	0.048	0.9	1.4
White Matter	10	0.037	0.9	1.4

discussed in Kotzberg et al. (2013).

Two approaches were used to delineate the activated regions from the surrounding tissue. In the first approach, we selected the voxel with the largest difference in HbT between slow and fast stroking in the time window from 2 to 8s, grew the region by considering voxels in the 27-neighbourhood of the selected voxel and progressively included these voxels in the region if their absolute value exceeded one quarter of the maximum value. The 27-neighbourhood of a voxel includes the 27 adjacent voxels including diagonal neighbors. Alternative definitions for the cluster boundaries were also tested, and we chose this method which we felt was representative of the responses. Center of gravity for the cluster was calculated using a weighted average

$$CoG = \frac{1}{\sum_i^N [|HbT(r_i, slow) - HbT(r_i, fast)|]} \times \sum_i^N [r_i |HbT(r_i, slow) - HbT(r_i, fast)|]$$

where N = the number of voxels within the cluster and r_i are the vector coordinates for each voxel in the cluster.

In the second approach, voxels where the difference between the slow and fast conditions was statistically significantly different were included in the cluster. Three p-value thresholds were tested: 0.01, 0.02 and 0.05. At the $p < 0.01$ level, the resulting cluster volume (0.4 cm^3) was smaller than the expected smallest volume that our method can independently reconstruct ($\sim 1 \text{ cm}^3$). We considered using the canonical hemodynamic response function to determine the response amplitude as an alternative to averaging the time course from 2 to 8 s post-stimulus onset; however, both approaches resulted in a similar result at the $p < 0.01$ and 0.02 levels. At the $p < 0.05$ level, the cluster boundary was sensitive to the chosen time window and so based on these considerations we decided on an intermediate p-value threshold of 0.02 for the final testing. The center of the statistical cluster was calculated as the average of the voxel coordinates within the cluster.

Time courses for the responses to the two conditions were calculated as volume averages of the HbT responses in the cluster (Fig. 3). The final clusterwise HbT, HbR and HbO₂ values and statistical significance were evaluated by averaging the concentration values in two time windows (4–8s and 2–14s for HbT and HbO₂; 6–10s and 4–16s for HbR) and calculating the paired Student's *t*-test on the averaged values (Tables 2–4). The HbR response is delayed slightly because it is mainly venous in origin whereas the HbT and HbO₂ responses are mainly thought to arise due to arterial dilation.

When evaluating the statistical significance of imaging data, it is necessary to consider the rate of false positive discoveries in the presence of many statistical comparisons. In DOT data, multiple comparison correction is complicated by the spatial correlations due to the spatial measurement sensitivity profiles and the presence of spatiotemporal correlations in the physiology itself. To estimate the number of spatially independent regions in the statistical clustering method, we first calculated the number of source-detector pairs with separation greater than or equal to 12 mm (since the shorter source detector pairs mainly sample the superficial tissue) as $N_1 = 85$. A second estimate of the number of independent regions was obtained by calculating the volume of the gray brain matter in the studied region ($\sim 75 \text{ cm}^3$) and dividing this volume by the expected smallest volume which can be imaged independently ($\sim 1 \text{ cm}^3$) to obtain $N_2 = 75$. The 1 cm^3 estimate is realistic within the surface of the cortex but quite optimistic in deeper structures where the spatial resolution of the method becomes progressively worse. Based on these considerations we used a multiple comparison correction factor of $N = 80$ to obtain corrected p-values for the statistical clustering method.

Region-of-interest (ROI) analysis

Voxels corresponding to the representative area of the right arm of the

Table 2

HbT response magnitude averaged over 16 subjects for different conditions and the corresponding p-values in the clusters. HbT units in μM . * = $p < 0.05$ (uncorrected); ** = $p < 0.05$ (corrected for multiple comparisons with $N = 80$). Cluster 1 resides mostly in the temporal cortex (extending slightly into the insula) and is defined using the contrast-based method. Center of gravity (CoG) is defined for values in cluster 1. Cluster 2 is in the insula and is defined using the statistical method with voxelwise $p < 0.02$ for the HbT (slow) vs. HbT (fast) (two-tailed Student's *t*-test).

Condition Location	Slow HbT	Slow vs. 0 p-value	Fast HbT	Fast vs. 0 p-value	Slow – Fast HbT	Slow vs. Fast p-value
CoG of cluster 1 (4–8s) Fig. 3	3.7	0.06	−0.6	0.2	4.3	0.03*
Cluster 1 (4–8s); Fig. 2	1.7	0.09	−1.6	0.23	3.3	0.04*
Cluster 2 (4–8s) Fig. 5	0.8	0.02*	−0.9	0.01*	1.7	0.0005** Corrected 0.04**
S1 ROI (4–8s), Fig. 6	0.38	0.3	−0.03	1.0	−0.41	0.6
CoG of cluster 1 (2–14s)	3.5	0.1	−0.6	0.3	4.1	0.06
Cluster 1 average (2–14s)	1.7	0.1	−1.6	0.2	3.3	0.04*
Cluster 2 average (2–14s)	0.6	0.08	−1	0.04*	1.4	0.006*
S1 ROI (2–14s)	−0.19	0.6	0.16	0.8	−0.35	0.6

Table 3

HbR response magnitude averaged over 16 subjects for different conditions and the corresponding p-value in the clusters. HbR units in μM .

Condition Location	Slow HbR	Slow vs. 0 p-value	Fast HbR	Fast vs. 0 p-value	Slow – Fast HbR	Slow vs. Fast p-value
CoG of cluster 1 (6–10s)	−2.3	0.2	0.5	0.2	−2.8	0.09
Cluster 1 average (6–10s)	−1.3	0.1	0.9	0.3	−2.2	0.07
Insula average (6–10s)	−0.04	0.8	0.33	0.2	−0.37	0.2
S1 ROI (6–10s)	−0.86	0.1	−0.07	0.9	−0.79	0.4
CoG of cluster 1 (4–16s)	−1.7	0.1	0.4	0.2	−2.1	0.07
Cluster 1 average (4–16s)	−1.0	0.1	0.8	0.4	−1.8	0.1
Cluster 2 average (4–16s)	−0.3	0.3	0.6	0.3	−0.8	0.1
S1 ROI (4–16s)	−0.7	0.08	−0.1	0.8	−0.6	0.4

primary somatosensory cortex (S1) were labeled as a separate region of interest (ROI). The region was determined using prior knowledge from literature and confirmed with studies of older subjects. The mean value of the HbT, HbR and HbO₂ within the S1 ROI were calculated and given in Tables 2–4.

Results

From the photogrammetry, we measured the distance between the left and right preauricular points and found the mean \pm standard deviation to be $100 \text{ mm} \pm 4 \text{ mm}$ (range 96–109 mm); estimated the distance between nasion and inion as $140 \text{ mm} \pm 3 \text{ mm}$ (range 134–147 mm) and the circumference of the head (HC) as $384 \text{ mm} \pm 10 \text{ mm}$ (range 367–403 mm). In the successful experiments, an average of 67 stimuli was presented and 36% of them were rejected from the averaging process mostly due to infant movement. The infants slept 50% of the measurement time, on average. 63% of stimuli presented in awake periods and 15% of stimuli presented during the infant's sleep periods were rejected.

Table 4

HbO₂ response magnitude averaged over 16 subjects for different conditions and the corresponding p-value in the clusters. HbO₂ units in μM .

Condition Location	Slow HbO ₂	Slow vs. 0 p-value	Fast HbO ₂	Fast vs. 0 p-value	Slow – Fast HbO ₂	Slow vs. Fast p-value
CoG of cluster 1 (4–8s)	5.2	0.05*	–1.0	0.2	6.3	0.02*
Cluster 1 average (4–8s)	2.5	0.1	–2.3	0.3	4.7	0.07
Cluster 2 average (4–8s)	1.1	0.02*	–1.4	0.04*	2.5	0.002*
S1 ROI (4–8s)	0.4	0.5	–0.0	1.0	0.4	0.6
CoG of cluster 1 (2–14s)	5.0	0.08	–1.0	0.2	6.0	0.04*
Cluster 1 average (2–14s)	2.6	0.1	–2.3	0.2	4.9	0.05
Cluster 2 average (2–14s)	0.9	0.08	–1.5	0.07	2.3	0.01*
S1 ROI (2–14s)	0.6	0.2	0.3	0.7	0.3	0.7

During awake periods, movement was typically spread out in time and we did not observe concentration of artifacts around transitions between awake and sleeping periods. Using contrast-based clustering. We located one contiguous region in the temporal cortex with a significant HbT difference ($p = 0.04$; paired Student's *t*-test) for slow (3 cm/s) compared to fast (20 cm/s) stroking. The cluster volume was 14 cm³. We designate this region Cluster 1. No additional clusters were found which satisfied the threshold. The adult MNI coordinates, identified using the AAL atlas, for the center of gravity of the cluster are approximately $x = -52$, $y = 0$, $z = -21$, which is located in the middle temporal gyrus. The cluster expands to the STS, parietal operculum and toward the insular cortex (Fig. 2).

The time course of the response in the center of gravity of Cluster 1 is shown in Fig. 3. Following the slow stroking, there was an increase in HbT that peaked around 8 s after stimulus onset. In contrast, after fast stroking stimulation, a slight decrease in HbT was observed.

As we cannot distinguish perfectly between the surface of the cortex and extracerebral tissue due to the limited resolution of the 3D reconstruction, we chose to use the center of gravity of cluster 1 instead of the spatial average to calculate the time courses in Fig. 3. This highlights the responses in a location which is safely within the brain, in the middle of the cluster, thus minimizing possible superficial contamination. To

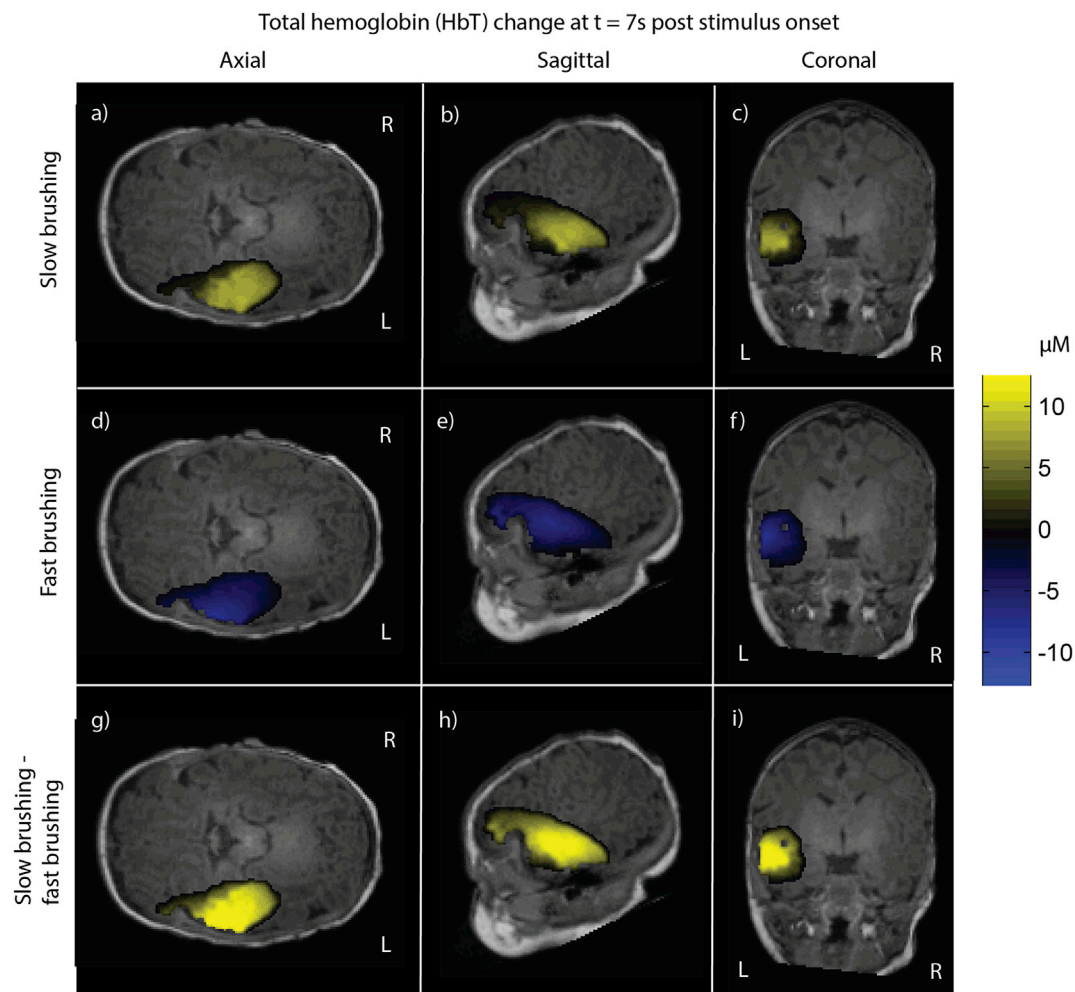


Fig. 2. (Color) Total hemoglobin change in response to slow brushing (3 cm/s) (panels a–c), fast brushing (20 cm/s) of the right arm (panels d–f), and the difference between the two conditions (panels g–i) at 7s post stimulus onset. The boundary of the region shown in color was defined according to the contrast based clustering method, and is superimposed on a single T1 MR image. The slices intersect the center of gravity of the difference between the two conditions. The color map shows positive changes in HbT relative to baseline in yellow and negative changes in HbT in blue. The baseline was set according to values obtained in the interval from –1s to 0s prior to stimulus onset. The probe was attached to the left side of the infant's head, just above the ear, covering mainly temporal and parietal areas over an area of $8 \times 13\text{ cm}$.

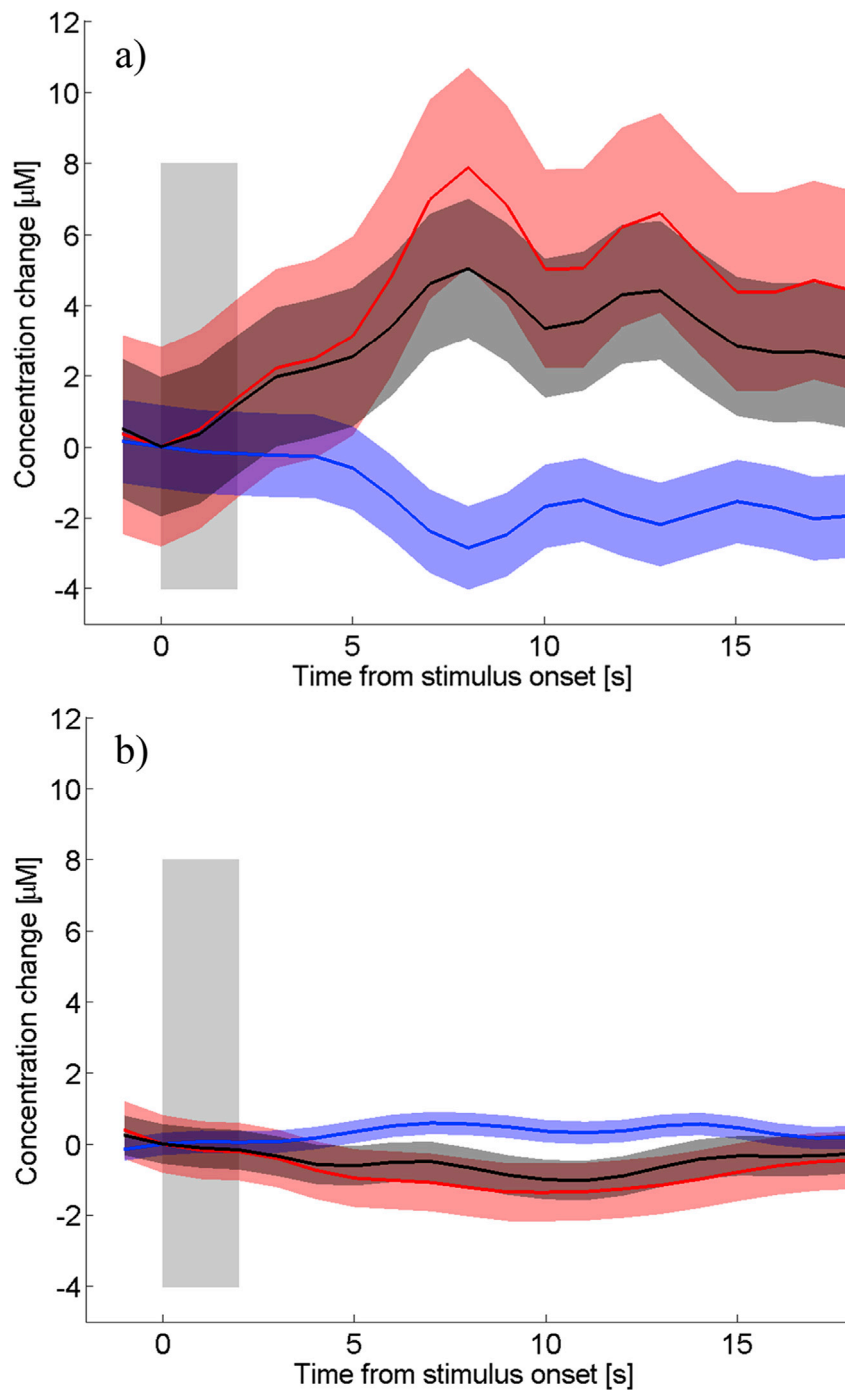


Fig. 3. (Color) Time course of HbT (black line with gray shading), HbR (blue) and HbO₂ (red) in response to (a) slow and (b) fast brushing at the estimated center of gravity (CoG) of the response. The shading indicates standard error mean (SEM). The stimulus was presented from 0s to 2s (vertical gray bar).

illustrate the responses as a function of depth, we look at a cylindrical cross-section of the tissue from the outer surface of the scalp through the center of gravity of the cluster, up to a depth of 30 mm. Fig. 4 shows the mean and SEM of the HbT responses as a function of distance from the outer surface of the scalp, each point was calculated by averaging the response in a disc of 20 mm radius around the center axis and within the time interval from 2 to 8s post stimulus onset. It can be seen that the response to fast stimulation is centered more superficially (peaking at depth 9.5 mm) than the response to slow stimulation (peaking at 14.5 mm) and not statistically different from zero at any depth. The maximum of the difference between slow and fast responses is at depth 12.5 mm. The response to slow stimulation is centered more deeply and

is statistically significantly greater than zero at depth ≥ 18 mm and greater than the fast response at depth ≥ 17 mm (two-tailed Student's *t*-test). Although the magnitude of the response to fast stimulation in this cylindrical cross-section is comparable to the magnitude of the response to slow stimulation, there is more variability in the former across subjects. The insular cortex starts at a depth of approximately 20 mm, according to the MRI. Due to head growth between 1.5 months and 2 months of age, we expect the insula in two month olds to be approximately 1.4 mm deeper, on average, than shown in the MRI, i.e., it would start at approximately 22 mm. In this analysis of statistical significance in a cylindrical cross-section, the activation appears in both temporal and insular cortices. However, voxel-wise statistical testing, as used in

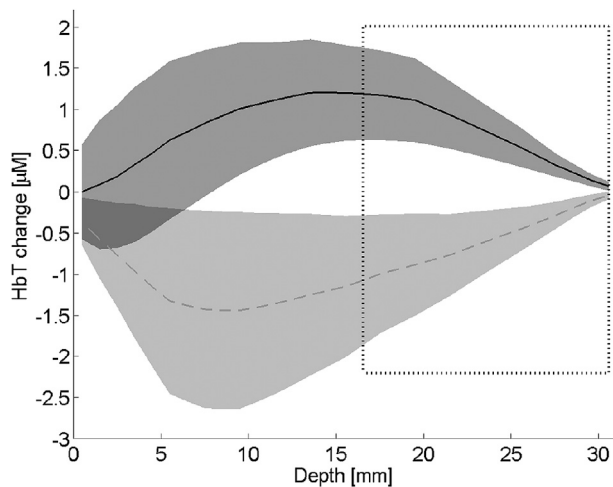


Fig. 4. The HbT response to slow (solid black line with dark gray shading) and fast stimulation (dashed ‘-’ light gray line with light gray shading) as a function of depth within a cylindrical section of 20 mm radius and 25 mm length through the center of gravity of the cluster shown in Fig. 2. The response is averaged within each disc of voxels of 20 mm radius and within the time interval from 2 to 8 s post stimulus onset. The dotted rectangle indicates depth range for which the HbT response to slow brushing differs significantly from the response to fast brushing ($p < 0.05$; two-tailed Student's t -test).

analysis approach 2, places the source more firmly in the insula.

The region obtained using the statistical clustering method (Cluster 2), illustrating the most statistically significant difference between slow and fast stroking, is located in the insula and is shown in Fig. 5 for $p < 0.01$ (solid yellow area) and $p < 0.05$ (contour). The intermediate $p < 0.02$ threshold was used to calculate the statistics for Cluster 2 in Tables 2–4, chosen as described in Section 2.8. Within this region, the average HbT response to slow stroking was statistically significantly greater than the response to fast stroking ($p = 0.04$, corrected for multiple comparisons with $N = 80$) in the shorter time window from 4 to 8 s. The activated region at the $p < 0.02$ voxelwise level was 1.1 cm^3 in volume, and at $p < 0.05$ level, 4.7 cm^3 .

As a reference we studied the representative area of the arm in the primary somatosensory cortex using ROI analysis. The time course of the HbT response in the S1 ROI is given in Fig. 6. No statistically significant response or difference was found in this region, suggesting that either the cortical neuronal processing of touch or the mechanism for the hemodynamic response may not be fully mature in this region at the age of two months.

The results averaged within both clusters, as well as the S1 ROI are summarized in Table 2. Deoxy- and oxyhemoglobin concentration changes and corresponding p -values for the previously defined clusters are given in Tables 3 and 4

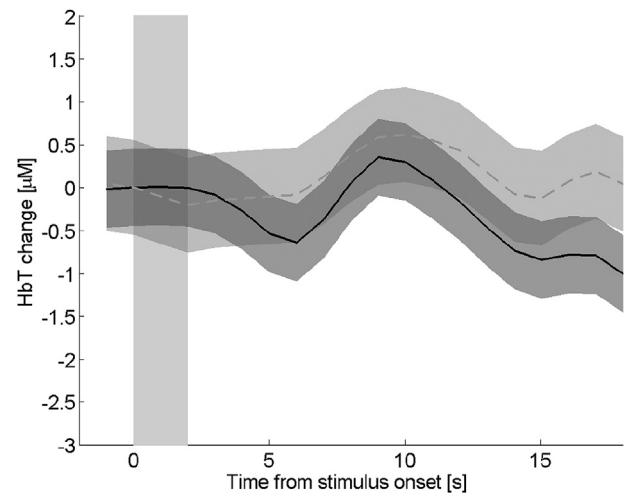


Fig. 6. Time course of the HbT response to slow (solid black line with dark gray shading) and fast (dashed light gray line with light gray shading) brushing in the S1 ROI. The shading indicates standard error mean (SEM). The stimulus was presented from 0 s to 2 s (vertical gray bar).

Discussion

In the current study, we showed that 2-month old infants have different and stronger cortical activation in response to slow stroking (optimal in activating CT afferents), compared to fast stroking (CT afferent non-optimal) touch in the insular cortex and temporal lobe. At birth, the nervous system of the infant is immature since the myelination process is not finished (Eyre, 1992; Deoni et al., 2011), which means that the discriminative sense of touch probably lacks the specificity it has in adults. However, the unmyelinated system, which is evolutionarily older and encompasses temperature, pain and CT afferents (Uvnäs-Moberg, 2012), may already be in place. CT afferents have been proposed to be a part of the social communication system in humans and detect emotional components of touch in adults, and they show the greatest activation for caress-like stimulation (Olausson et al., 2002; Löken et al., 2009). The presented results suggest that the affective touch system is functional and able to distinguish between affective and non-affective touch already in early postnatal life. The sensitivity of the imaging method used is greater to changes in superficial parts of the cortex than deeper areas which makes it perhaps more striking that the statistical significance of the difference to slow and fast brushing is greater in the insula than in the temporal cortex. This may indicate that the discrimination between affective and non-affective touch in the insula may be mature at an earlier age than areas in the temporal cortex, or the responses in the temporal cortex may simply have greater inter-subject variability. The smaller magnitude of the response in the insula compared to temporal cortex is likely due to the partial volume effect.

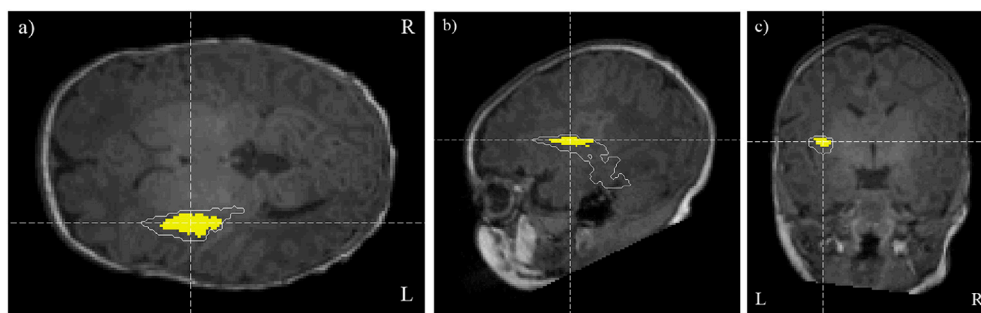


Fig. 5. Region showing statistical significance of the differences between the responses to the slow and fast stimulation within the time interval from 2 to 8 s at the $p < 0.01$ level. The center of the region is at a depth of 24 mm from the surface of the scalp and its location corresponds to MNI coordinates $-x = 35$, $y = -10$ and $x = 15$ in the adult template brain (manual search). The gray contour line corresponds to $p = 0.05$.

Furthermore the region-of-interest (ROI) analysis did not show a response in the primary somatosensory cortex (S1) which suggests that the hemodynamic response to touch in the representative area of the arm in S1 is not yet mature at two months of age. Nevalainen et al. (2008) reported evoked magnetic fields to tactile stimulation of the index finger in healthy newborn infants in S1 and S2 using magnetoencephalography (MEG). However, that study used glabrous skin as opposed to hairy skin used in the current study. Furthermore, MEG records electrophysiological signals whereas the current study reports hemodynamic responses.

In this study, for the contrast between slow and fast stroking stimulation, the center of gravity of the difference between HbT responses to slow and fast stimulation is approximately located in the anterior part of middle temporal gyrus, expanding to the superior temporal sulcus, parietal operculum and toward the insular cortex. The largest statistical difference between slow and fast stroking is located in the insula. The activated regions found in the present study coincide with areas that are activated by affective stroking touch in adults, such as S2, posterior insula and STS (Olausson et al., 2002; Gordon et al., 2013; Voos et al., 2013; Bennett et al., 2014; Kaiser et al., 2015). Interestingly, the cortical activation cluster found in the current study further overlaps with areas that process emotional speech in naturally sleeping 3–7 month old infants as shown in an fMRI study (Blasi et al., 2011) and with areas shown, using fNIRS, to process socially relevant visual stimuli at 5 months of age (Lloyd-Fox et al., 2009). A recent study by Brauer et al. (2016) showed that the frequency of maternal touch predicted the resting state activity in the right pSTS in 5 year old children. They further found that connectivity of areas in the “social brain” differed between children who received high and low frequency of maternal touch (Brauer et al., 2016). Taken together, these studies, including ours, indicate that infants possess a brain network which reacts to social stimuli of different modalities.

The response to slow stroking resides deeper in the cortex than the response to fast stroking. Negative HbT responses may be due to reduced level of neuronal activity, or ‘deactivation’ in the region. Stimuli which are emotionally meaningful, such as affective touch, may cause increased neuronal activity in areas responsible for emotional processing whereas stimuli to which the infant is indifferent, may cause a decrease in activity in these areas, which would lead to the pattern observed. It is also possible that a component of the response to fast stroking originates from superficial tissue and is partially reconstructed on the cortical surface due to the limited depth resolution of the method and the effect of regularization. Removing global systemic effects using superficial signal regression (SSR) did not change the results perceptibly, which supports the idea that the negative response to fast stroking is mostly cortical in origin. Studies in rats have demonstrated that the negative changes in hemodynamic response (as seen using optical imaging, laser Doppler flowmetry, or fMRI BOLD) noted in cortical regions following tactile stimulation corresponded well with decreases in neuronal activation (using multi-unit recording; Boorman et al., 2010; Yin et al., 2011).

A limitation of the study is the field of view (FOV) and positioning of the probe on the infant's head. Obviously, responses to the stimuli in the parts of the brain outside the FOV of the probe, i.e. the ipsilateral cortex, orbitofrontal cortex, anterior tip of the temporal cortex as well as deeper brain structures, remain unknown. Although the primary somatosensory cortex was not fully within the FOV of the probe, the representative area of the arm was within the FOV and did not show a statistically significant response. This suggests that the hemodynamic response to cortical primary somatosensory processing of touch may not yet be fully mature at two months of age. The stimulus presentation in our study was adopted to the special requirements of infants. Instead of a robot, a trained experimenter delivered the stimuli using a hand-held brush. The difference between brushing administered by a human compared to a robotic device has been shown not to influence how the touch is perceived in adults (Tricoli et al., 2013). In infants, a stimulus that is as close to naturally

occurring stimuli is preferred for ethical and practical reasons. The duration of stimulus epoch (2 s) was selected so that the two velocities could be administered in a controlled and reproducible manner while being short enough that a sufficient number of stimuli could be presented for averaging. When comparing results between studies, it is important to consider the differences in touch presentation as well as the stimulus duration as parameters that may influence results. In contrast to the studies on adults, the infant subjects in the present study slept 50% of the time during the measurements. Infants are known to process sensory information in both active and quiet sleep (Desmedt and Manil, 1970; Kotilahti et al., 2005; Pihko, 2004). Since we found activation in areas that coincide with the results from other studies with socially relevant stimuli both in sleeping and awake infants (Lloyd-Fox et al., 2009; Blasi et al., 2011), we conclude that emotional or social information in the infant brain are processed also during sleep.

We used two different methods to delineate the source of the activity in the brain; contrast-based clustering and a statistical method based on testing the voxelwise statistical significance and analyzing the contiguous regions found as units. DOT with 3D image reconstruction and the statistical clustering method turned out to be more powerful than expected, allowing us to localize the primary source of the differing responses to slow and fast brushing in the insular cortex. Further development of instrumentation and data analysis techniques is likely to allow the analysis of data from individual subjects to evaluate the maturation of the affective touch response as well as other parts of the cerebral cortex. In young infants, study of most areas of the cerebral cortex seems possible due to the more permissive optical properties as well as regions of CSF that permit the light to reach deeper regions and return to detectors; however, the immature hemodynamic response poses its own challenges. Accurate modeling of light transport is particularly important in the vicinity of areas of CSF, to correctly localize activated areas in deeper parts of the cortex. In older children and in adults, however, we think the DOT method in its current state of development is limited to the more superficial parts of the cerebral cortex. In terms of instrument development, we regard wireless technology with large-area semiconductor detectors placed directly on the scalp to be the next major breakthrough in infant DOT, as a system without optical fibers is likely to have fewer issues with motion artifacts.

Conclusion

In this study we compared cortical activation using DOT in 2 month-old infants following stroking touch. We found that already at this early age, the brain is processing slow, affective touch and fast, non-affective touch differently. Human newborns are extremely dependent on their caregivers and early formation of an attachment is critical for survival. Infants are able to sense the presence of other humans by auditory (Blasi et al., 2011) and olfactory cues (Porter and Winberg, 1999). Our study suggests that the infant brain additionally possesses a specialized system which enables them to distinguish affective from non-affective tactile cues already two months after birth. This highlights the importance of affective touch early in life and could add important implications for the care of newborn babies under both normal and more special circumstances such as preterm care and care in cases of mothers suffering post-partum depression where interaction with the newborn is sometimes compromised (Feldman and Eidelman, 2007). Further studies are needed to clarify the developmental specificities, and neural network for this system, in health and disease.

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