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Infants' sex affects neural responses to affective touch in early infancy

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Abstract

Social touch is closely related to the establishment and maintenance of social bonds in humans, and the sensory brain circuit for gentle brushing is already active soon after birth. Brain development is known to be sexually dimorphic, but the potential effect of sex on brain activation to gentle touch remains unknown. Here, we examined brain activation to gentle skin stroking, a tactile stimulation that resembles affective or social touch, in term-born neonates. Eighteen infants aged 11–36 days, recruited from the FinnBrain Birth Cohort Study, were included in the study. During natural sleep, soft brush strokes were applied to the skin of the right leg during functional magnetic resonance imaging (fMRI) at 3 cm/s velocity. We examined potential differences in brain activation between males (n = 10) and females (n = 8) and found that females had larger blood oxygenation level dependent (BOLD) responses (brushing vs. rest) in bilateral orbitofrontal cortex (OFC), right ventral striatum and bilateral inferior striatum, pons, and cerebellum compared to males. Moreover, the psychophysiological interactions (PPI) analysis, setting the left and right OFC as seed regions, revealed

significant differences between males and females. Females exhibited stronger PPI connectivity between the left OFC and posterior cingulate or cuneus. Our work suggests that social touch neural responses are different in male and female neonates, which may have major ramifications for later brain, cognitive, and social development. Finally, many of the sexually dimorphic brain responses were subcortical, not captured by surface-based neuroimaging, indicating that fMRI will be a relevant technique for future studies.

KEYWORDS
developmental neuroscience, neonates, sexual dimorphism, touch

1 | INTRODUCTION

In the beginning of life, mother–infant interactions are characterized by nonverbal communication. Especially during the first year of life, one key nonverbal channel through which mothers communicate affection to their infants is touch (Field et al., 2007). It plays a key role in early affective mother–infant exchanges and lays the foundation of lifelong socioemotional wellbeing (Cekaite, 2016; Mariani Wigley, Mascheroni, Peruzzo, et al., 2021; Yoshida & Funato, 2021). Several studies have shown the importance of early physical contact, highlighting different positive neurodevelopmental outcomes, such as heart rate stabilization and arousal regulation, and decreased risk of infections, improved regulatory as well as social learning abilities (Björnsdotter et al., 2009; Croy, Drechsler, et al., 2016; Feldman et al., 2010; Mariani Wigley, Mascheroni, Fontana, et al., 2021; Tuulari et al., 2019; Van Puyvelde et al., 2019, 2021).

Studies on adults highlighted that skin stroking activates low-threshold mechanoreceptors and myelinated fast-conducting Aβ fibers. These fibers innervate the entire body, including both glabrous and hairy skin, and play a critical role in coding discriminative properties of touch such as thermal, nociceptive, chemical, and pruritic stimuli. Aβ fibers target contralateral primary (SI) and bilateral secondary (SII) somatosensory cortices (McGlone et al., 2014). Even if these fibers are not fully mature in infancy, they are capable of conveying tactile stimulation at early stages of life (Williams et al., 2015). In preterm and term-born infants, for example, a palm stimulation activates infants' postcentral gyrus (Arichi et al., 2012), while the stimulation of the plantar surface of the foot yields activations in primary sensory areas in 2-week-old infants (Williams et al., 2015).

In addition, gentle skin stoking activates a particular group of mechanosensitive neurons, the so called C-tactile (CT) fibers, which innervate exclusively hairy skin (McGlone et al., 2014). CT afferents are unmyelinated, slow conducting, and tuned to respond to specific thermomechanical properties of a tactile stimulation that resembles a caress-like touch, typically made by a human hand (ie, velocities between 1 and 10 cm/s and temperatures of 32°C). As a result, it has been hypothesized that CT-fibers encode socioaffective dimensions of touch. In the mature nervous system, gentle skin stroking evokes the activation of the posterior insular cortex, the primary target of CT-fibers (Olausson et al., 2002). More recently, insular sensitivity to gentle skin stroking has been detected also in full-term infants of 2–5 weeks of age, suggesting that the CT system functions early in infancy (Tuulari et al., 2019). However, while neural correlates of affective touch in early infancy have already been investigated (Jonsson et al., 2018; Tuulari et al., 2019), the potential effect of infants sex on brain activation remains unexplored.

Sexual dimorphism is known to affect several aspects of brain development and the maturation of the social brain. Female neonates make more eye contact (Leeb & Rejskind, 2004), are more likely to orient to faces and human voices (Connellan et al., 2000), and exhibit a better discrimination of emotional expression than males (McClure, 2000). Although some sex differences have been detected also in relation to affective touch (Björnsdotter et al., 2014; Schirmer & McGlone, 2019) (eg, females often perceive affective touch as more pleasant compared to males), the role of sex in brain processing of caress-like touch remains poorly understood, and regarding neonates, unknown. Early differences in the neural processing of a social cue, such as affective touch, may explain later-life differentiations in cognitive and social development and, therefore, call for investigation.

In light of this evidence, it emerges that caress-related neural activity plays an important role in shaping social functioning and stress regulation from the earliest moments of life. In this regard, although we have already shown that the infant's brain is responsive to affective touch soon after birth and highlighted the activation of brain regions related to CT-fibers and affective touch processing (posterior insular and somatosensory cortices) (Tuulari et al., 2019), it remains crucial to further characterize brain mechanisms related to affective touch in early infancy (Björnsdotter et al., 2014).

In the present study, we therefore, extended our previous work with infants (Tuulari et al., 2019) by exploring whether sex could affect neural responses to affective touch using fMRI to capture subcortical activations otherwise impossible to catch with surface-based neuroimaging techniques. Specifically, like in previous studies, we examined caress-like, gentle skin stroking, a type of tactile stimulation intimately associated with social interaction and affectionate touch (Croy, Geide, et al., 2016). Moreover, we conducted a psychophysiological interaction (PPI) and a seed-based connectivity (SCA) analysis in order to investigate connectivity networks related to gentle brushing.

2 | MATERIALS AND METHODS

2.1 | Participants and recruitment

Infants of families taking part in the FinnBrain Birth Cohort Study were recruited between May and December 2015 for an fMRI session through telephone calls. When the infants were aged 2–5 weeks, families were contacted to participate in the present study and interviewed by one of the authors. If at least one of the following criteria was detected in the interview, the mother infant dyad was not included in the study: occurrence of any perinatal complications with potential neurological consequences (eg, hypoxia), less than 5 points in the 5 min Apgar score, previously diagnosed central nervous system anomaly or an abnormal finding in a previous MRI scan (with clinical indications), preterm birth (delivery at less than 32 weeks of pregnancy or birth weight less than 1500 g). Demographics of mothers and infants included in the present study are reported in Table 1. Supporting Information Table S1 resumes descriptive statistics of a smaller sample size (n = 13). Data from this smaller sample size were collected between the data included in the previous study conducted by Tuulari et al. (2019) and the final sample size (n = 18). In this regard, it should be mentioned that recruitment and data collection of the present study were carried out in three stages. Results coming from the first stage (May–July) are presented in Tuulari's work (2019), results coming from the second (July–September) and third (October–December) stages are presented here. Specifically, the smaller sample size (n = 13) represents data coming from infants recruited from May to September (ie, stage 1 + stage 2) and the final sample size (n = 18) from May to December (ie, stage 1 + stage 2 + stage 3). The study protocol was conducted in accordance with the Declaration of Helsinki and it was approved by the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland. Informed written consents were obtained from parents before MRI scanning sessions.

2.2 | Tactile stimuli and experimental protocol

During MRI acquisition, a trained experimenter (author JJT) manually applied gentle brush strokes to the infants' right anterior shin region (along the tibia) in a proximal to distal direction. This site was chosen due to ease of access, as the babies were wrapped in a vacuum mattress that blocked upper extremities. Also, the investigator leaned on the scanner bed, leaning slightly toward the scanner bore, without touching the infant, while delivering the stimuli. The length of the stimulated area was measured to cover 15 cm, and brush strokes were applied at a velocity of 3 cm/s for 15 s, with randomized interstimulus intervals of 10—15 s (resulting in three strokes in one 15 s block) between the two experimental conditions (ie, stroking and no-stroking). The experimenter was guided by auditory cues delivered through the scanner's headphones. A total of 11 brushing blocks were administered.

2.3 | Tactile MRI scanning visits

Families were received at the Medical Imaging Center of Hospital District of Southwest Finland by a trained radiographer and the researchers. Before the MRI, the scanning protocol was revised with the parents, and the absence of safety risks (eg, pacemakers, inner ear implants, or other metals parts) was confirmed by the personnel. Infants were then fed with breast or bottle milk to get them asleep and gently swaddled into a vacuum mattress. All infants were provided with customized hearing protection, as well as the parents, as they stayed in the scanning room throughout the whole experimental session. If a baby did not fall asleep or wake up during the scan, the session was ended. The whole procedure was carefully observed by the personnel from the control room through a window, and a loudspeaker was set up to allow the staff to hear if the baby should have woken up. All scans took place between the afternoon and early evening hours. After the scan, families were given a small present as a thank you for participating. No anesthetics were used. Each set of structural images was checked by an experienced neuroradiologist for possible pathological signs. In the case of a pathological finding, the families were referred to a child neurologist and a neurological check-up at age 6—8 months. In the current sample, one participant had incidental findings (minor hemorrhages) that were deemed irrelevant by the radiologist and assured to be outside the cerebral tissues during data processing (not confounding the analysis). Also, this infant did not exhibit developmental problems at the check-up. Radiology reports were delivered to the researchers, who then communicated them to the family within 1—4 weeks of the scans.

2.4 | MRI acquisition

MRI scans were conducted on a Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany). A 12-element Head Matrix coil allowed the use of the Generalized Autocalibrating Partially Parallel Acquisition technique to accelerate acquisitions (PAT factor of 2 was used). Sequence parameters of the 2D Dual Echo TSE (Turbo Spin Echo) sequence were optimized so that "whisper" gradient mode could be used in order to reduce acoustic noise during the scan. Slice thickness was 1 mm in order to acquire isotropic 1.0 × 1.0 × 1.0 mm voxels. TR time of 12,070 ms and effective TE times of 13 and 102 ms were used to produce both PD-weighted and T2-weighted images from the same acquisition. The total number of slices was 128. T1-weighted 3D MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) sequence with isotropic 1.0 × 1.0 × 1.0 mm voxels was used for anatomical imaging as well. The sequences included DTI imaging (details not reported here). Functional MRI consisted of 120 volumes with voxel size of 3.0 × 3.0 × 3.0 mm, TR 3000 ms, TE 30 ms, flip angle of 80° and 42 axial slices without gaps. Prior to fMRI acquisition, all infants had slept during the 45–50 min required for structural scanning. The total duration of the complete scanning protocol did not exceed 60 min.

TABLE 1 Demographics of mothers and infants.

	Males (n = 10)			Females (n = 8)				
	Mean	SD	Range	Mean	SD	Range	*t*	*p*
Infant characteristics								
Gestation age (weeks)	39.69	.90	38.14–41.14	40.30	1.01	39–42	−1.366	.191
Birth weight (grams)	3665.5	323.08	3105–4050	3579.5	391.66	3085–4395	.565	.580
Apgar minute 1	8.20	2.098	3–9	8.88	.354	3–9	−.895	.384
Apgar minute 5	9.10	.568	8–10	9.13	.641	8–10	−.088	.931
Age at scan from birth (days)	23.40	1.01	11–36	26.75	6.36	19–40	−.960	.351
Sociodemographic variables								
Maternal age (years)	29.60	5.06	34.0–37.5	29.63	4.57	24–36	−.011	.991
Maternal BMI	27.19	5.03	21.26–34.42	26.29	3.55	21.05–33.06	.424	.678
Frequencies								
Ethnicity (Caucasian/Non-Caucasian)	10/0			8/0				
Maternal Education (1 = High school graduate or lower; 2 = College degree; 3 = University degree)	2/2/6			4/3/1				
Family SES (1 = < 500; 2 = 501–1000; 3 = 1001–1500; 4 = 1501–2000; 5 = 2001–2500; 6 = 2501–3000; 7 = 3001–3500; 8 = 3501–4000; 9 = > 4000)	1/0/1/5/3/0/0/0/0			1/1/0/5/0/0/0/1/0				
Maternal smoking during pregnancy (yes/no)	0/10			1/7				
Maternal use of illicit substances during pregnancy (yes/no)	0/10			0/8				
Maternal emotional state								
EPDS score	3.10	2.33	0–7	3.62	4.34	0–11	−.329	.746
SCL score	3.80	3.01	0–10	1.87	2.64	0–8	1.421	.174

Note. BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale (Cox et al., 1987); SES, socioeconomic status assessed via the Hollingshead (1978); SCL, The Symptom Checklist (Derogatis & Unger, 2010).

2.5 | Plan of analysis

In the present study, to further explore the neural correlates of caress-like touch and related potential sex differences, we conducted a standard preprocessing pipeline. The images of this first-level analysis were then used for the second-level group statistics. First, we ran a one-sample *t*-test, to test the effect of gentle stroking stimulation in the whole sample (N = 18) and then a two-sample *t*-test to explore potential differences between infant males (N = 10) and females (N = 8). Finally, we conducted a PPIs and a SCA analysis to investigate connectivity networks related to gentle brushing. Following the procedure suggested by Gerchen et al. (2021), we have computed and reported maps of Hedge's g for the results obtained from the sample (N = 18) (Gerchen et al., 2021). All the models were tested in a smaller group (N = 13), which is part of the whole sample (N = 18), to test the same models in slightly different samples and see if results would change. Results from the smaller sample (N = 13) are reported in Supporting Information. Data from this smaller sample size were collected between the data included in the previous study conducted by Tuulari et al. (2019) and the final sample size (N = 18) presented here. In the following paragraphs, each analysis step is explained in detail.

2.5.1 | Data preprocessing and statistical analyses

Preprocessing and statistical analyses were conducted using SPM12 (http://www.l.ion.ucl.ac.uk/spm/software/spm12/). Functional data preprocessing included slice time correction, realignment to the

first volume, and spatial normalization to the University of North Carolina at Chapel Hill neonate atlas (Shi et al., 2011). Motion artifacts were examined using the Artifact Detection Toolbox (http://www.nitrc.org/projects/artifact_detect/). Volumes where the global signal deviated more than two standard deviations from the mean signal or where the difference in motion between two neighboring volumes exceeded 1 mm were classified as outlier volumes. Subjects were excluded if the number of outliers in the fMRI data exceeded 30% of either rest or brushing blocks. The stimuli were modeled as one predictor convolved with the standard SPM12 hemodynamic response function. A fixed-effects general linear model (GLM) analysis, including motion parameters and outlier volumes as regressors of no interest, was performed in each individual infant. The images of this first-level analysis were then used for the second-level group statistics in a new GLM. First, we ran a one-sample *t*-test, controlling for infants' gestational weeks and age at scan from birth, to test the effect of gentle stroking stimulation in the whole sample (N = 18). An a priori primary threshold for voxel-level statistical significance was set to $p < .01$ and results were FDR corrected at the cluster level (pFDR < .05), and a secondary threshold was set at $p < .05$, FDR corrected at the cluster level.

All the models were tested with the same thresholds also in a smaller group (N = 13), which is part of the whole sample (N = 18), and related results are reported in Supporting Information.

2.5.2 | PPIs in the GLM

PPI analysis reveals changes in the connectivity between brain regions as a function of psychological context. Specifically, PPI captures context-dependent connectivity between a source region with any possible target region(s). This means that PPI reveals which regions have similar activity patterns with the source region as a function of a specific contrast and thus shows task-dependent interactions between functional brain systems.

Source regions for PPI analysis were selected from our previous results. Two spherical 5-mm regions of interest (ROIs) were drawn at left orbitofrontal cortex (left-OFC) and right orbitofrontal cortex (right-OFC) locations in brushing minus resting contrast to further delineate connectivity changes. The time series for each participant was computed by using the first eigenvariate from all voxel time series in the defined ROIs, and deconvolved using the PPI-deconvolution parameter defaults in SPM12 (Gitelman et al., 2003). The PPI term was then calculated as the element-by-element product of the ROIs in "neuronal time series" and a vector coding for the selected contrast (1 for brushing and −1 for resting tasks). This product was then reconvolved by the canonical hemodynamic response function.

First-level PPIs were run to generate SPM contrast images similar to the first-level GLM model, and these contrast images were analyzed and thresholded in the second-level model. An a priori primary threshold for voxel-level statistical significance was set to $p < .01$ and results were FDR corrected at the cluster level (pFDR < .05), and a secondary threshold was set at $p < .05$, FDR corrected at the cluster level.

2.5.3 | Seed-based connectivity analysis (SCA)

The SCA analyses were performed with FSL tools with identical preprocessing and nuisance regression as for previous analyses (see above). As for the PPI analysis, two different seed ROIs were defined by a 2.5-mm radius sphere generated in FSL's (Jenkinson et al., 2012) FSLeyes, corresponding to the location (left-OFC and right-OFC) of our previous result in the UNC neonate template space. SCA maps were then generated using FSL v6.0 fMRI expert analysis tool (FEAT) (Woolrich et al., 2001). Average time series from the seed ROIs were extracted using the "fslmeants" command and a first-level FEAT analysis was run to assess the brain regions that had activity correlated to the mean left-OFC and right-OFC activity separately. The resulting *z*-score maps for each participant were then normalized to UNC template space, and group-level statistical analyses, testing differences between males and females, were conducted in SPM12. An a priori primary threshold for voxel-level statistical significance was set to $p < .01$ and results were FDR corrected at the cluster level (pFDR < .05), and a secondary threshold was set at $p < .05$, FDR corrected at the cluster level.

3 | RESULTS

3.1 | Participants and motion

A total of 26 parents gave informed consent on behalf of their infants for the participation in the present study. Scan sessions failed for three infants. Excessive motion in five infants rendered the data unusable, leaving data from 18 infants. Infant characteristics are reported in Table 1.

In Supporting Information, demographics of infants and families of the smaller sample (N = 13) are reported in Table S1.

3.2 | Main effects of stroking and sex differences

Across the whole group (N = 18), gentle skin stroking evoked neural activation in bilateral somatosensory, bilateral insular, middle cingulate, and precuneus cortices and bilateral cerebellar vermis as compared to conditions without stimulus (Figure 1). Our results expectedly resemble brain activation maps reported previously by Tuulari et al. (2019), highlighting the activation of the two brain regions known to be the main targets of CT fibers. Supporting Information Figure S4 shows maps of Hedge's g for the activations shown in Figure 1. Moreover, similar activity patterns resulted considering the smaller sample (N = 13) (Supporting Information Figure S1).

Regarding sex differences, compared to males (N = 10), females (N = 8) exhibited stronger blood oxygenation level dependent (BOLD)

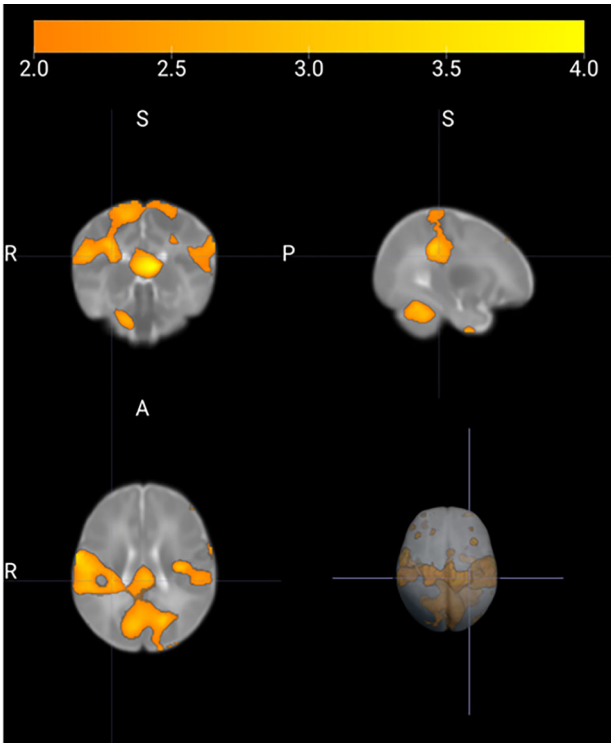

FIGURE 1 Neural activation to gentle touch (compared to rest) in 18 term-born neonates during natural sleep. *Note*. Brain activation images ($p < .05$ threshold; FDR-corrected at cluster level) are displayed in coronal, sagittal, axial, and multiplanar slices on the UNC neonate template. Color bars represent T-scores.

increases in the bilateral OFC, right ventral and bilateral inferior striatum, pons, and cerebellum, at a statistical threshold of $p = .01$, FDR-corrected at the cluster level (Figure 2a). Including the model maternal BMI, depressive and anxiety scores did not change the results at uncorrected $p < .05$. Supporting Information Figure S5 shows maps of Hedge's g for the activations shown in Figure 2a. Supporting Information Figure S2 represents differences between males and females in the smaller sample (N = 13).

3.3 | Psychophysiological interactions

Task-related connectivity via PPI analysis revealed that females had stronger functional connectivity between the left OFC and bilateral somatosensory cortex, bilateral middle cingulate cortex and precuneus, and compared to males (Figure 2b). Gestational weeks and age at scan from birth did not differ between groups (see Table 1), nevertheless second-level PPI models were not controlled for the effects of these two variables. Supporting Information Figure S6 shows maps of Hedge's g for the activations shown in Figure 2b. Results of left-OFC connectivity networks in the smaller sample (N = 13) partially resemble results obtained from the whole sample and are reported in Supporting Information, Figure S3. Considering right-OFC as the seed region, no significant results emerged in the whole sample (N = 18) and in the smaller sample (N = 13).

3.4 | Seed-based connectivity analysis

The between-group comparison with a statistical threshold set at $p < .05$ and FDR-corrected, revealed no significant resting-state connectivity networks considering left-OFC and right-OFC between males (N = 10) and females (N = 8). Similarly, the between-group comparison with the same threshold did not revealed significant results considering both ROIs in the smaller sample (N = 13).

4 | DISCUSSION

In the present study, we examined the neural correlates to gentle skin stroking of hairy skin in early infancy. We found neural activity patterns similar to Tuulari et al. (2019) and different brain responses between males and females. Specifically, compared to males, females exhibited stronger neural activation in bilateral OFC, right ventral striatum and bilateral inferior striatum, pons and cerebellum. Moreover, exploratory PPI analysis revealed differences in males and females in task-dependent functional connectivity, considering left-OFC as seed region. Between-group comparisons revealed that females had stronger functional connectivity between the left-OFC and the bilateral somatosensory cortex, cingulate cortex, and precuneus. Our findings highlight a sexually dimorphic development of neural processing of affective touch.

In the sexual differentiation of the human brain, different factors (eg, genetic, hormonal, environment) interact with each other, resulting in a variety of anatomical and functional brain differences between the two sexes (Proverbio, 2021). Pre- and postnatal differences in testosterone concentration between males and females, for example, have been found to affect brain physiology, also modulating dendritic growth, brain receptors, neurogenesis, and gliogenesis (McCarthy et al., 2012). As a result, differences in brain activity and functional connectivity patterns could be explained as a result of sexual dimorphic development.

In this regard, our results show that, while gentle brush stimulation evokes the activation of different brain areas known to be related to neural processing of affective touch, sex differentiation addresses different brain regions. Specifically, in the whole sample (N = 18) and in the smaller one (N = 13), gentle brushing evoked the activation of somatosensory and insular cortices, the two brain regions known as main targets of CT-fibers and a stronger neural activation in bilateral OFC in females (Björnsdotter et al., 2009, 2014; Tuulari et al., 2019). A significant activation of OFC is corroborated by several previous studies conducted with adults that outlined that gentle touch that activates this region in addition to the posterior insular and somatosensory cortices (Lamm et al., 2015; McGlone et al., 2012). Moreover, in adults, the activation of OFC correlates with the subjective pleasantness of touch as well as with rewarding stimuli from different modalities (Kringelbach, 2005; Rolls et al., 2003). We also found a stronger activation in ventral striatum cortices that has already been found in response to gentle touch in adolescents (May et al., 2014). OFC and ventral striatum cortices are key components of the brain's reward circuit.

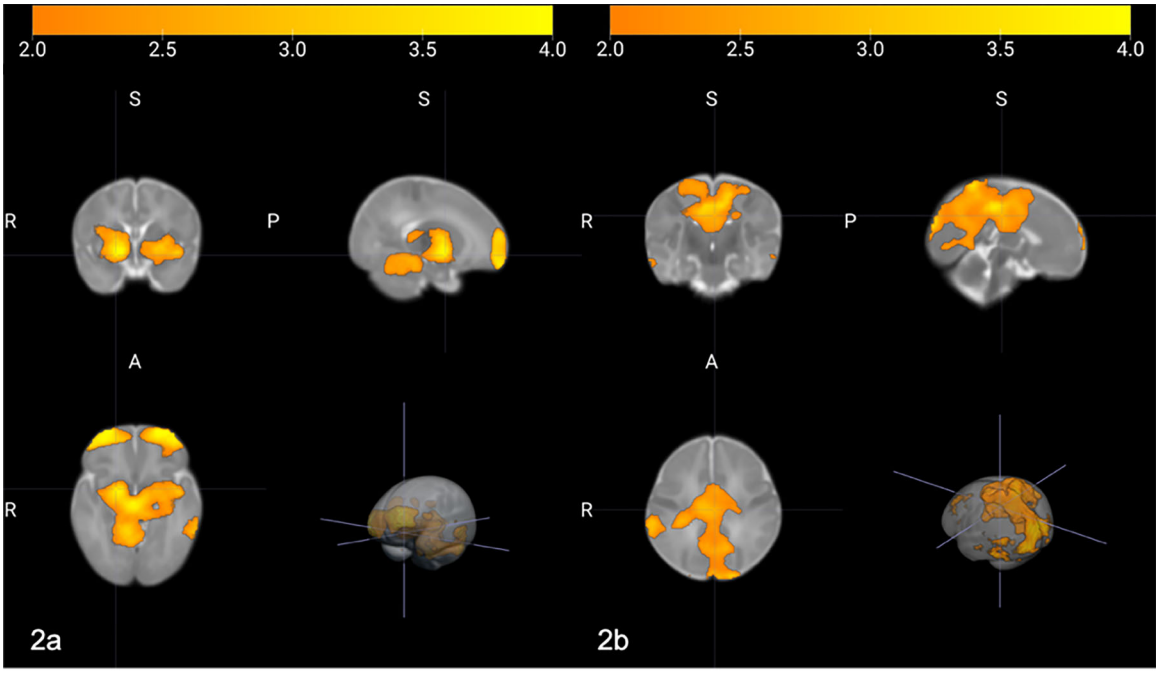

FIGURE 2 Differences between males and females. a. Differences in brain activations (brushing > rest) between males and females ($p < .01$ threshold; FDR-corrected). Females exhibited stronger neural activation to gentle-skin stroking in bilateral-OFC, right ventral and bilateral inferior striatum, pons and cerebellum. (b) Differences in PPI connectivity networks ($p < .01$ threshold; FDR-corrected). Females exhibited stronger PPI connectivity networks between left-OFC and bilateral somatosensory, bilateral middle cingulate and precuneus cortices compared to males. Color bars represent T-scores. Images of brain activation are displayed in coronal, sagittal, axial, and multiplanar slices on the UNC neonate template.

As CT fibers encode the reward value associated with close physical contact, one could speculate that affective touch could be a more rewarding stimulus for females and that this result could be related to the stronger "social attitude" often linked to the female sex since early infancy (Connellan et al., 2000; Leeb & Rejskind, 2004; McClure, 2000; Mutlu et al., 2013).

Concerning PPI analysis, which captures context-dependent connectivity between a source region and any possible target region(s), we revealed in females a widespread functional connectivity between the left-OFC (ie, source region) and the bilateral somatosensory cortex, cingulate cortex, and precuneus. In other words, PPI revealed that bilateral somatosensory cortex, cingulate cortex, and precuneus have similar activity patterns with OCF (ie, our source region) as a function of brushing versus resting contrast. The components of the human posterior medial cortex, the posterior cingulate cortex (PCC), and precuneus have been implicated in different tasks such as attention, memory, emotion, self-relevance detection, and reward evaluation, and are considered key hubs of the default-mode network (DMN). Interestingly, while the DMN in adults consists of two major rich-club hubs, such as the medial-PFC and the PCC, previous studies with infants have outlined that posterior regions of the DMN (ie, the PCC) are predominant at early stages of life (Xiao et al., 2016). Thus, our results are in line with previous studies highlighting connectivity patterns related to the PCC and precuneus in infancy (Xiao et al., 2016) but also link those to OFC activation.

Finally, the left OFC has been identified as a key hub in sensory integration. Neurophysiological recordings in nonhuman primates, and neuroimaging studies in humans have found that the OFC is activated by auditory, gustatory, olfactory, somatosensory, and visual inputs. As already mentioned, gentle skin stroking also activates Aβ fibers, which target contralateral primary (SI) and bilateral secondary (SII) somatosensory cortices (McGlone et al., 2014). It would be tempting to conclude that the synchronous activation of the left OFC and somatosensory cortices are implicated in encoding the sensory value of affective touch. However, in the early stages of life, brain networks likely have different functions as compared to the corresponding networks in older infants or adults, which complicate the interpretation (Power et al., 2010).

Before concluding, the present findings have to be considered in light of the following limitations: first, despite previous studies showing detectable responses to a range of sensory stimuli in sleeping infants (Graham et al., 2015; Williams et al., 2015); it is unclear if and how sleep affects brain processing of tactile stimuli. Second, the sample size of the present study was relatively small, although within the range of previously published fMRI activation studies (Graham et al., 2015). Third, despite the manual application dominates fMRI studies of affective touch in adults (Björnsdotter et al., 2009, 2014; Gordon et al., 2013; Morrison et al., 2011; Olausson et al., 2008), it added a source of uncontrolled variability (eg, the pressure put into the brushing) within and between participants. Fourth, we used an echo time of 30 ms, whereas recent research in infant neuroimaging shows that longer echo times (~50 ms) substantially improve sensitivity (Gursul et al., 2018). Fifth, given the highly limited fMRI time allowed by the Ethics Committee (6 min) in combination with the high risk of data loss due to motion, we

opted for the collection of robust main effect of slow skin stroking with no control condition. Future studies are encouraged to include a control condition (eg, fast stroking) to determine whether the observed effects are selective to slow skin stroking. Sixth, in this study, we did not collect data with respect to touch experienced from birth to the time of the scan. Since it has been shown that maternal touch behavior might be different toward male and female infants (Fausto-Sterling et al., 2015), we defer to future studies the possibility of including the amount of touch experienced from birth to MRI acquisition. It should be emphasized, however, that studies conducted on this topic have so far included infants significantly older than those included in the present study (Fausto-Sterling et al., 2015; Hsu & Fogel, 2003). It is presumable, therefore, that in infants as young as those included in the present study (ie, 1–4 weeks of age), this potential effect may have little impact. Finally, the current sample is cross-sectional and does not address brain developmental trajectories; future follow-up studies within the FinnBrain Birth Cohort Study may allow for clarification of the maturation of sensory processing in further detail, as well as its practical implications for child development.

5 | CONCLUSIONS

The present study highlighted a sexual dimorphism in the neonatal neural processing of affective touch, a social cue known to play a key role in the early foundation of lifelong socioemotional wellbeing. Early sexually dimorphic brain development may support marked diversities in reproductive, parental, and social behavior later in life. As many of the observed brain responses to affective touch were subcortical, further fMRI studies, including additional tactile stimuli and longitudinal designs, are required to assess the sex-specificity of neural responses to socioaffective tactile stimulation and its implications for child development.

AUTHOR CONTRIBUTIONS

JJT, NMS, and JS collected the imaging data; JJT, MB, LK, HK conceptualized the study; JJT, JS, and MB designed the study and developed the fMRI paradigm; ILCMW, JJT performed statistical analysis and wrote the original draft; ILCMW, JJT, MB contributed to fMRI data preprocessing; LK, HK founded the FinnBrain project and provided the infrastructure and funding for carrying out the study; JJT supervised the creation of the manuscript with oversight and leadership responsibility for the research activity planning and execution. All authors critically revised and accepted the manuscript it in its final form.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets presented in this article cannot be shared publicly. As at the time of writing, the ethics committee decision and local legislation do not allow the open sharing of neuroimaging data. Requests to access the datasets should be directed to the corresponding author and are possible via formal procedures for data sharing.

DATA SHARING

Finnish legislation and our Ethical permission do not allow open sharing of the data. Data sharing is possible via formal data sharing agreements. The interested investigators are asked to contact the Principal Investigators of the FinnBrain Birth Cohort study https://sites.utu.fi/finnbrain/en/contact/

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