Universidade do Minho
Escola de Psicologia

Helga Filipa de Oliveira Miguel

Touch processing and social-emotional development - neural and behavioral correlates

junho de 2017

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UMinho | 2017

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Tese de Doutoramento em Psicologia Básica

Trabalho efetuado sob a orientação da
Professora Doutora Adriana da Conceição Soares Sampaio
e do
Professor Doutor Óscar Filipe Coelho Neves Gonçalves

junho de 2017

DECLARAÇÃO

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Título da Tese: Touch processing and social-emotional development - neural and behavioral correlates.

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Ano de conclusão: 2017

Designação do Doutoramento: Psicologia Básica

DE ACORDO COM A LEGISLAÇÃO EM VIGOR, NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTA TESE.

Universidade do Minho, 22 de junho de 2017

Assinatura:



STATEMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity, and confirm I have not used plagiarism or any form of falsification of the results.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

Universidade do Minho, junho de 2017

Assinatura: 

Acknowledgments

This dissertation is a result of a wise decision to leave Lisbon and head to the north of Portugal, where I found a truly inspiring and motivating environment to pursue a PhD degree. I want to thank Professor Adriana Sampaio for accepting to be my mentor, and for guiding me throughout my research interests. Your discrete and attentive attitude promoted a great learning environment, and provided the support I needed to pursue such an ambitious project. You are a bright researcher, and I am very grateful to have worked with you. I also want to thank Professor Óscar Gonçalves for being such an inspiring and motivating mentor. Seating in your classes and participating in the lab meeting was a joy, and a motivation to accomplish my goals as a PhD student. I am really happy I did the PhD under your supervision.

I would like to thank Professor Charles Nelson (Laboratories of Cognitive Neuroscience, Boston´s Children Hospital, Boston) for the opportunity to spend a period in his lab, through which I learned how to set up a "baby lab" and carry out a project with families and infants. I am very grateful for the stimulating environment and for the group of scholars I met. A special thanks to Alissa Westerlund, who involved me in many lab activities as she could during my stay, and to Katherine Perdue, for guiding me throughout my first steps on fNIRS.

Many thanks to the Neuropsychophysiology Lab fellows and friends. It was very nice to be part of this stimulating and fun team for the past five years. A special thanks to my dear and nice friend Catarina Fernandes, always ready to help, who made me feel welcomed when I first arrived to the Lab; to funny and meticulous Sara Cruz, with whom I share the passion for infancy, thank you for your valuable input and discussions; to Ana Ganho, bright researcher/clinician and mother of 3, who helped cope with the family- work balance every time I thought I was struggling; and finally, to Sónia Sousa, my companion in the journey of the PhD "marathon". It was great to have you as a friend and colleague, and to share the achievements and struggles of the PhD process with you, in a daily basis. Thank you all for the friendship, I am very happy I met you in this journey.

To Marta Alves and Tiago Ferreira, thank you for the time dedicated to the project and for the responsibility and professionalism demonstrated since we first met. I was lucky to have you as my research assistants. A special thanks to Marta, for all the Saturdays spent in the Lab. I would also like to acknowledge Isabel Lisboa, Sara Cruz and Eugénia Fernandes for their help

with data collection, and Carla Barros for the time spent working with me on Matlab Scripts. Your help was precious!

To Ana Luis Carmo and Paula Serrano, thank you for the clinical discussions on sensory processing, which kept reminding me the reason I was interested in pursuing a PhD in the first place. It is great to have such amazing occupational therapists as colleagues and friends.

Thank you to all the daycares, institutions and clinics from Braga that allowed me to advertise the study. Many thanks to Fátima Monteiro, who enthusiastically recruited families to participate in the study. And thank you from the bottom of my heart to all the families that agreed to join the study. I had the pleasure to meet great moms and dads who abdicated from their time to have their babies take part in the study, and I am really thankful for that.

To my family and friends, that although were kilometers away, were always present and supportive. To my dear parents, for their dedication and encouragement to all projects that I embrace, thank you. Special thanks to my mother and my mother in law that were always available when I was not, and took such good care of my baby.

And finally, my dear husband and daughter, thank you so much for your patience and resilience during this journey. To Pedro, my companion and friend, my role model in persistence and hard work, I have no words for your support. Thank you so much for believing in me, and to pushing me forward. I look forward to the next adventure together. Sofia, my funny and happy little girl, thank you for making motherhood such a joy. Holding you in my arms made me experience the power that *touch* conveys, and I am very grateful for that. I love you both.

FUNDING: This study was supported by the Portuguese Science Foundation through an individual doctoral grant to Helga Miguel (SFRH/BD/86694/2012). The work was conducted at Psychology Research Center (UID/PSI/01662/2013), University of Minho, and supported by the Portuguese Science Foundation and the Portuguese Ministry of Science, Technology and Higher Education through national funds (PSI/01662) and co-financed by FEDER through COMPETE2020 under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-007653).

Touch processing and social-emotional development – neural and behavioral correlates

Abstract

Touch is a sensory modality used in the context of affiliative behaviors and social interactions, thought to have preceded more advanced forms of social-emotional competencies as language or emotional expressions. It has been proposed that a specific group of tactile fibers (CT afferents) are likely to mediate this affective-motivational component of touch, but the role of these fibers, particularly during the first year of life is still uncertain. Moreover, the importance of touch has been demonstrated in studies of disorders that lack social-emotional reciprocity, namely autism spectrum disorder (ASD), but the relative contribution of the tactile domain to the core symptoms of the disorder remains to be understood. The aim of this dissertation was to examine touch processing at a brain and behavior level, and contribute to a better understanding of this sensory domain to social-emotional development.

In the first study (Chapter 2) I examined brain responses for affective and discriminative touch in 7-month-old infants using functional near infrared spectroscopy (fNIRS). Specifically, I used a paradigm including the sensory-discriminative and affective-motivational aspects of touch, and recorded hemodynamic activity in two main regions of interest, the somatosensory cortex and the pSTS. The results showed that 7-month-old infants process both affective and discriminative components of touch in the somatosensory cortex, but that the right temporal region is not yet recruited at this age to process affective touch, similarly to children and adults. In the second study (Chapter 3) I examined the developmental trajectory of brain activity to affective touch, by following longitudinally infants from 7 to 12 months of age. The paradigm and regions of interest were the same as described earlier. This study showed that touch processing for discriminative and affective domains undergoes a developmental shift from 7 to 12 months of age, at a brain level. At 12-months of age, infants presented a significant increase in hemodynamic activity in channels placed over the temporal region for affective touch, compared to 7-month-olds. In the following study (Chapter 4), I investigate whether this shift at 12 months of age was associated with infant's behavioral differences to tactile sensory stimuli, by measuring negative emotional responses to touch - sensory over responsiveness (SOR). The findings from this study suggest that the emergence of brain activity in the temporal region to affective touch is modulated by individual differences in affective reaction towards touch. Finally, in the last study

(Chapter 5) I test the relation between tactile processing patterns and social problems in a sample of children and adolescents with ASD. I found that atypical touch processing is related with core symptoms in ASD, supporting that touch processing plays an important role in social-reciprocity in this population. These findings combined suggest that touch processing contributes to social-emotional development, and might have important implications for the understanding of neurodevelopment disorders, namely ASD.

Processamento do toque e desenvolvimento sócio- emocional – correlatos neuronais e comportamentais

Resumo

O toque é uma modalidade sensorial usada no contexto de comportamentos afiliativos e interações sociais, que se julga ter precedido formas mais avançadas de competências sócio-emocionais, como por exemplo a linguagem ou expressões emocionais. Tem sido proposto na literatura que um grupo específico de fibras táteis (fibras CT) é provavelmente responsável por mediar esta componente afetivo-motivacional do toque, mas a função destas fibras, principalmente durante o primeiro ano de vida, é ainda incerta. A importância do toque tem sido demonstrada em estudos de desordens de neurodesenvolvimento que apresentam um compromisso na reciprocidade sócio-emocional, nomeadamente na perturbação do espetro do autismo (PEA), mas a contribuição do processamento sensorial do toque para os sintomas apresentados por indivíduos com a desordem continua por explicar. O objetivo desta dissertação foi estudar o processamento do toque a nível cerebral e comportamental, e contribuir para uma melhor compreensão deste domínio sensorial para o desenvolvimento sócio-emocional.

No primeiro estudo (**Capítulo 2**) examinei a resposta cerebral ao toque afetivo e discriminativo em bebés de 7 meses de idade, utilizando espectroscopia funcional por infravermelhos (fNIRS). Especificamente, foi testado um paradigma que incluía as dimensões sensório-discriminativa e afetivo-motivacional do toque, e registada a atividade hemodinâmica do cérebro em duas regiões de interesse, o córtex somatosensorial e o sulco temporal superior posterior. Os resultados demonstraram que os bebés de 7 meses de idade processam ambos tipos de toque no córtex somatosensorial, mas que a região temporal não é ainda recrutada nesta idade para processar o toque afetivo, à semelhança de crianças e adultos. No segundo estudo (**Capítulo 3**) examinou-se a trajetória desenvolvimental da resposta cerebral ao toque afetivo, através do estudo longitudinal dos bebés dos 7 aos 12 meses de idade. O paradigma e regiões de interesse foram as mesmas descritas anteriormente. Este estudo demonstrou que os domínios discriminativos e afetivos do toque estão sujeitos a uma mudança desenvolvimental dos 7 aos 12 meses de idade, ao nível dos mecanismos neuronais. Aos 12 meses de idade, os bebés apresentaram um aumento significativo na resposta hemodinâmica nos canais localizados sobre a região temporal para o toque afetivo, comparado com bebés de 7 meses. No estudo

seguinte (**Capítulo 4**), foi investigada a relação entre a mudança ao nível do processamento cerebral observada aos 12 meses e as diferenças individuais na resposta comportamental ao estímulo tátil, através da avaliação de respostas emocionais negativas ao toque – hiperresponsividade ao toque (SOR). Os resultados deste estudo sugerem que atividade cerebral na região temporal em resposta ao toque afetivo é modulado por diferenças individuais na reação afetiva ao toque. Finalmente, no último estudo (**Capitulo 5**) é testada a relação entre padrões de processamento tátil e problemas socias numa amostra de crianças e adolescentes com PEA. Encontrou-se que o processamento tátil atípico está relacionado com sintomas/ critérios de inclusão nas PEA, sugerindo que o processamento tátil tem um papel importante na reciprocidade social nesta população. Num todo, estes resultados sugerem que o processamento do toque contribui para o desenvolvimento sócio-emocional, e pode ter implicações importantes para a compreensão de desordens de neurodesenvolvimento, nomeadamente as PEA.

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Chapter 1. General Introduction

Touch is the first sensory system to develop *in utero* (Montagu, 1986), with behavioral responses to touch observed as early as 7 weeks' gestation when the fetus moves following a touch in the lips (Hooker, 1943, 1952). Around 12 weeks of gestation grasping and rooting reflexes emerge (Fifer & Moon, 2003; Humphrey, 1964) and not long after that, patterns of inter-twin contact such as head to head, head to arm and arm to head contact are observed in twin pregnancies (Sasaki, Yanagihara, Naitoh, & Hata, 2010). The spatial and temporal characteristics of movements from 22-week gestation fetus (Kurjak et al., 2003; Kurjak et al., 2005; Zoia et al., 2007) suggest an advanced level of motor planning, and maturation of the foetal central nervous system, specifically, the system that is responsible for the process of touch (somatosensory system). Interestingly, observation of twin-pregnancies suggest that the actions observed in the womb between the foetuses are not accidental (Castiello et al., 2010). In particular, during the second semester of gestation, twin foetuses seem to plan and execute more movements specifically aimed at the co-twin, rather than self-directed actions, suggesting that the foetuses are already "*socially wired to touch* " (Castiello et al., 2010).

Not only touch (cutaneous sensitivity) is the first system to develop, it is also one of the most developed sensory systems at birth. Compared with other sensory modalities, namely vision and audition, touch receptors mature and are functionally developed, earlier *in utero* (Bremner & Spence, 2017; Gallace & Spence, 2010). Therefore, it is not surprising that touch has been acknowledged as the primary channel of communication between the mother and the newborn (Barnett, 2005; Field, 2001, 2010). The importance of touch for nurturing behavior and well-being of the off-spring was first addressed by the classic work of Harlow (Harlow & Harlow, 1962). He removed infant monkeys from their mothers and assigned them to either a soft terrycloth surrogate mother, or wire surrogate mother, who also provided food. The infant monkeys preferred the contact comfort offered by the terrycloth mother, over the nursing provided by the wire mother. Moreover, when exposed to a stress condition, the infant monkeys consistently searched for the soft surrogate mother compared with the wire one. This was the first report, although controversial, highlighting the importance of comforting touch to psychological well-being in non-human primates. In human infants, the importance of nurturing touch derives mainly from studies on early deprivation, including infants from depressed mothers (Herrera, Reissland, & Shepherd, 2004; Moszkowski et al., 2009), and interventions, such as

infant massage (Diego et al., 2007; Field et al., 2008; Field, Diego, Hernandez-Reif, Deeds, & Figueiredo, 2006) or *kangaroo* mother care (Charpak & Ruiz, 2016; Feldman, Eidelman, Sirota, & Weller, 2002; Feldman, Weller, Sirota, & Eidelman, 2002).

Touch is the prevalent mode of communication and regulation in the mother- infant dyad (Hertenstein, 2002; Jean & Stack, 2012; Jean, Stack, & Fogel, 2009), with estimates of touching behaviors up to 82% of the time during an interaction. Across the first year of life, the amount of touch the mother uses in the interaction with her infant decreases (Ferber, Feldman, & Makhoul, 2008; Jean et al., 2009). Specifically, in the second semester of life, as the infant develops motor skills and becomes more independent, mothers seem to rely less on proximal physical cues (Ferber et al., 2008; Jean et al., 2009). Nevertheless, the amount of affectionate touch they use in the interaction (but not stimulating or instrumental) predicts dyadic reciprocity, suggesting that even if it less frequent, it is still important for the mother-infant communication system (Ferber et al., 2008). Furthermore, when mother-infant interaction is disrupted, as for example following the still face paradigm, mothers use more nurturing touch to sooth their infant, suggesting that nurturing touch helps re-engaging and co-regulating the stressed infant (Jean & Stack, 2012; Mantis, Stack, Ng, Serbin, & Schwartzman, 2014). Altogether, these results suggest touch is a key sensory modality early in life. Comfort touch seems to be critical for infants thrive and social-emotional development. But how is touch processed to create this sense of affiliation and pleasantness? Is touch from a tap in the shoulder processed the same way as a caress from a mother to her infant? Touch (or cutaneous sensitivity) is part of a broader system, denominated *somatosensory system*, responsible to process, not only cutaneous sensitivity but also proprioception (sense responsible for limb position and muscle force). To better understand how hedonic experience of touch is processed, it is important to start by describing the organization of the somatosensory system, specifically, the cutaneous senses.

Somatosensory system is constituted by peripheral afferent nerve fibers and receptors that provide the central nervous system (CNS) information about proprioception and cutaneous sensitivity (Kandel, Schawartz, & Jessell, 2000). Proprioception refers to information from limb position and muscles, that the central nervous system uses to plan and monitor movements of the body, in a coordinated and smooth fashion. Cutaneous information is sent to central nervous system by a variety of tactile receptors that process touch, temperature, itch and pain (Abraira & Ginty, 2013) Discriminative touch encompasses the perception of pressure, vibration, slip and texture, critical to inform about the localization and encoding of a stimulus. These low-threshold

mechanoreceptors (LTMs), present in the skin and joints, are innervated by myelinated Aβ fibers that conduct high-speed impulses (50m/s) and sub serve discriminative functions as, for example, handling objects or explore surfaces (Abraira & Ginty, 2013). What we know about the tactile modality originates primarily from primate research on the digits, where there is a high density of this mechanoreceptors (Mountcastle, 2005). The skin of the hand palm (and also sole of the foot) denominated glabrous skin, has a proportionally high number of LTM receptors, compared with the hairy skin (non-glabrous), allowing a precise and skilled manipulation of objects, and exploration of surfaces. LTM receptors include slow adapting type 1 (SA1), slow adapting type 2 (SA2), rapidly adapting (RA) and Pacinian units, which transduce distinct aspects of a mechanical stimuli, sent by nerve impulses by Aβ fibers. SA1 receptor consist of Merkel disc, responsible to transduce contact, sustained pressure and texture; SA2 refer to Ruffini corpuscle that transduces contact, displacement and skin stretch; RA receptors are associated with Meissner and Pacinian corpuscles, which respond best to mechanical stimulus that include movement (Kandel et al., 2000). Although each has a specific role, they complement each other to create a perception of touch (Mountcastle, 2005). These impulses travel via dorsal root ganglion to the dorsal horn of the spinal cord and then up to the medulla, where they cross and synapse at the ventral posterolateral nucleus of the thalamus. From the thalamus, the information is sent to its last target, the somatosensory cortex (Kandel et al., 2000). LTM are innervated by myelinated Aβ fibers, which allow fast conduction of the stimuli. This is an important condition for detecting and discriminating rapidly external stimuli in the environment, which is why this system is suggested to be a "first system", important for survival purposes. Cutaneous information regarding temperature, pain and itch are processed by another category of fibers, namely Aδ and C fibers.

Research on the sense of touch has focused mostly on Aβ fibers and, consequently, on the discriminative role of touch (Mountcastle, 2005). However, cutaneous information is also mediated by slow conducting fibers, has been associated with the valence of a stimulus, which is thought to have an important role in social behavior (McGlone, Vallbo, Olausson, Loken, & Wessberg, 2007; McGlone, Wessberg, & Olausson, 2014; Morrison, Loken, & Olausson, 2010). The finding that mammals, such as cats and monkeys, present a more primitive system constituted by low-threshold mechanoreceptors (CLTMs in animals) (Bessou, Burgess, Perl, & Taylor, 1971; Kumazawa & Perl, 1977; Zotterman, 1939) present in hairy skin, but that are not nociceptive or pruritic in nature, lead to the examination of this system in humans. C-tactile fibers

(CT afferents) were first identified in humans using microneurography (Johansson, Trulsson, Olsson, & Westberg, 1988; Nordin, 1990), a technique that consists of measuring post-ganglionic sympathetic neural activity of the skin, which allows to isolate single axons and determine single unit receptive fields and perceptive effects. Results showed that majority of mechanoreceptive afferents were slowly adapting with small and well defined receptive fields but that were not similar to typical Pacinian-corpuscle afferents. CT afferents have been measured in the forearm (Vallbo, Olausson, & Wessberg, 1999) and leg (Edin, 2001), but their activity was never recorded in glabrous skin. Although it was long recognized that these low-threshold afferents were involved in transduction of low-threshold receptors in mammals (Zotterman, 1939), in humans CT fibers were understood as part of the broader C-fiber group, thought to transduce tickle sensations (McGlone et al., 2007) or processing of interoceptive signals (McGlone et al., 2014).

CT afferents are unmyelinated, slow conducting, and low-threshold mechanoreceptive fibers that carry signals from hairy skin. These fibers seem to be especially sensitive to a range of stroking speeds, with strokes consistent with social caress (1-10 cm/s) resulting in greater CT firing. In contrast, fibers fire less when the skin is stroked at faster or lower speeds (Loken, Wessberg, Morrison, McGlone, & Olausson, 2009; Nordin, 1990). Moreover, intermediate brushing velocities are perceived as more pleasant (Loken et al., 2009). CT fibers respond best to low indentation forces in the range of 0.3 – 2.5 mM, and present higher impulse rates (50-100 s^{-1}) to soft stimuli, as a water color brush, suggesting their role in coding innocuous stimuli (Vallbo et al., 1999). In contrast, they fail to detect pin-pick stimuli and smooth-probe stimuli, demonstrating that they are poor in discriminating features of objects, contrary to Aβ fibers. (Vallbo et al., 1999). Another feature of CT afferents is that they are sensitive to temperature (Ackerley et al., 2014), firing preferably to stimuli delivered at a neutral skin temperature, compared with cooler or warmer stimuli. In addition, firing at a neutral temperature, but not cooler or warmer temperatures, is correlated with how pleasant one feels the stimuli (Ackerley et al., 2014). However, there are also reports showing that CT fibers fire in response to skin cooling but not noxious heat (Nordin, 1990),what suggests some heterogeneity in the distribution and function of these fibers.

Since CT afferents share the same sensory pathway than other cutaneous fibers (Aβ), it is great challenge to draw conclusions on CT stimulation exclusively. Research involving patients with a rare neuropathy that lack Aβ afferents (do not have touch sensation) as a result of a rare

disorder on nerve cell bodies of primary sensory neurons, have contributed for a better understanding of the role of CT afferents (Olausson et al., 2008; Olausson et al., 2002; Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). When stimulated with a soft brush in glabrous (hand palm) versus non-glabrous skin (forearm and hand dorsum) these patients mislocalize the stimuli in areas lacking CT afferents, but are able to detect brush stroking in hairy skin. Moreover, they report that the sensation elicited by CT stimulation is pleasant. Stimulation CT afferents also elicits a robust sympathetic sudomotor skin response (Olausson et al., 2008), suggesting that although none of the patients presented any touch sensations (which is consistent with the idea that CT afferents do not contribute to the discriminative dimension of touch) the autonomic responses suggest that CT may have autonomic consequences. All the characteristics of CT fibers, including poor localization, sympathetic responses, slow speed of conduction, and association with valence of stimulation reinforce that this category of fibers contribute to the motivational-affective dimension of touch, which is thought to have an important role in social behavior (McGlone et al., 2007; McGlone et al., 2014; Morrison et al., 2010).

The study of these patients also allowed the first reports on the brain mechanisms to process CT afferents. Whereas in healthy subject's brush stroking on hairy skin results in activation of contralateral primary somatosensory cortex (S1) and secondary somatosensory cortex (S2), patients with neuropathy lack activation in these primary sensory regions. Instead, stimulation of CT fibers resulted in activation of the posterior insula (Olausson et al., 2002), an important region to process not only sensory and visceral information (Augustine, 1985, 1996), but also emotional states and self-awareness (Craig, 2011). Moreover, similarly to healthy subjects, patients with neuropathy presented a somatotopic organization within the insular cortex, suggesting that CT afferents do indeed project to social-emotional regions of the brain (Bjornsdotter, Loken, Olausson, Vallbo, & Wessberg, 2009), consistent with the affective-motivational role purposed for the CT system (Morrison et al., 2010).

Since these initial reports on the cortical processing of CT afferents, many other studies have now looked at the brain mechanisms to process affective touch. Beyond the insula, which is considered a prime candidate for the cortical processing of the CT afferents (Morrison, 2016), a network including right posterior superior temporal sulcus (pSTS), the medial prefrontal cortex (mPFC) and dorsal anterior cingulate cortex (dACC) is consistently involved in CT processing (Bennett, Bolling, Anderson, Pelphrey, & Kaiser, 2014; Bjornsdotter, Gordon, Pelphrey, Olausson, & Kaiser, 2014; Gordon et al., 2013). The involvement of brain regions implicated in socio-

emotional processes namely theory of mind, socioemotional processing and social perception, in the process of CT afferents, highlight the importance of this fibers in the context of social interactions and affiliative behaviors (McGlone et al., 2007; McGlone et al., 2014). However, although touch plays an important role early in infancy, the brain response to affective touch in earlier stages of development is still poorly understood.

Very few studies have been conducted in the developmental trajectory of affective touch, but the conclusions suggest that the network including the posterior insula, pSTS, medial prefrontal cortex, dACC, and also primary sensory-regions as S1 and S2 are already in place during childhood (5 years old and beyond) during affective touch paradigms (Bjornsdotter et al., 2014; Van de Winckel et al., 2013). In younger ages, one of the few studies that looked at brain activity in response to different types of touch using functional near infra-red spectroscopy (fNIRS) (Kida & Shinohara, 2013), found that 10 month old-infants but not 3- or 6- month-olds presented brain activation in the anterior prefrontal cortex to affective touch but not to discriminative touch. This suggests that the social-brain network to affective touch might be in place in infancy, but probably only emerges in the second semester of the first year. Other study (Fairhurst, Loken, & Grossmann, 2014) measured the heart-rate in a sample of 9-month-old infants in response to different brush velocities. The authors found that the velocity closest to CT- targeted touch resulted in a decrease of arousal, but faster and slower velocities did not. Together, these findings suggest that sensitivity to affective touch probably emerges between 7 and 9 months of age, but very few is still known about the emergence and trajectory of affective touch processing in the first year of life.

In sum, the literature suggests that CT afferents are a strong candidate mediating interpersonal communication and social behavior, since early stages of development. Particularly, the sense of touch (affective touch) seems to be intrinsically related with social cognition, and our ability to bond with others (Dunbar, 1998; Hertenstein, Verkamp, Kerestes, & Holmes, 2006). In populations that lack social and emotional reciprocity, namely autism spectrum disorders (Kaiser et al., 2016) and in healthy adults who present autistic traits (Bennett et al., 2014; Voos, Pelphrey, & Kaiser, 2013) studies have shown that the processing of CT fibers is different than healthy controls. An emerging body research has now been looking at touch processing in the population with ASD to better understand if tactile processing is contributing to the impaired social-communicative skills presented by this population, and consequently to its phenotype

(Cascio et al., 2012; Green et al., 2015; Green, Hernandez, Bowman, Bookheimer, & Dapretto, 2017; Kaiser et al., 2016).

Interestingly, reports on atypical sensory features to tactile stimuli have long been recognized in ASD population, but had never gained the attention of the scientific community compared with visual or auditory modalities (Bremner & Spence, 2017; Marco, Hinkley, Hill, & Nagarajan, 2011). Within the sensory domains, impaired responses to tactile stimulation are one of the most reported (Hilton et al., 2010; Lane, Young, Baker, & Angley, 2010), and symptoms include for example atypical sensory responses to textures, preoccupations with sensory features of objects, and problems habituating to prior sensory experiences. In addition, children with ASD show significantly more defensive reactions and lower pleasantness ratings to tactile stimuli than typically developing children (Tomchek & Dunn, 2007). These symptoms have been reported in 85% to 95% of children with ASD (Kientz & Dunn, 1997; Puts, Wodka, Tommerdahl, Mostofsky, & Edden, 2014; Rogers & Ozonoff, 2005; Tomchek & Dunn, 2007). Although the majority of these findings are based on parent reports, atypical touch processing has also been examined using psychophysical studies (Blakemore et al., 2006; Cascio et al., 2008; Guclu, Tanidir, Mukaddes, & Unal, 2007) and more recently neuroimaging studies (Cascio et al., 2012; Green et al., 2015; Kaiser et al., 2015).

While studies on the discriminative component of touch (vibro-tactile discrimination, contact detection, texture classification) yield some contradictory findings, with some studies suggesting that individuals with ASD present distinct thresholds than typically developing controls for some frequencies of vibro-tactile stimuli (Blakemore et al., 2006; Cascio et al., 2008) and others failing to find differences (Guclu et al., 2007), the findings regarding the affective component of touch are more consistent (Cascio, Lorenzi, & Baranek, 2016; Cascio et al., 2012; Kaiser et al., 2016).Children, adolescents and adults with ASD seem to present diminished brain activation to pleasant and neutral stimuli in the network involved in social-emotional processing (Kaiser et al., 2016), and increased brain activation in similar regions to unpleasant stimuli (Cascio et al., 2012; Green et al., 2015).Activity in primary (S1) and secondary somatosensory cortex (S2) following tactile stimuli seems also to differ in individuals with ASD, with reports of enhanced response in S1 for brush stroking in the palm of the hand (non- CT targeted) (Kaiser et al., 2016), and aversive tactile stimuli applied to the inner arm (Green et al., 2015), suggesting a cortical hyper-reactivity/ failure to habituate to sensory stimuli in this individuals. Moreover, within the ASD spectrum, the individuals who present greater aversive behaviors toward tactile

stimuli, known as sensory over-responsivity (SOR), present increased brain response to aversive stimuli in both regions(Green et al., 2015). The relation between affective touch and behavioral responses toward social and emotional reward have also been examined in healthy subjects, and the conclusions are consistent: the more autistic traits an individual presents, the fewer brain activity is present in social-brain regions following affective touch stimulation (Bennett et al., 2014; Voos et al., 2013). In addition to this findings, few studies have also suggested a relation between specific patterns of touch processing with core deficits of ASD, including social deficits (Foss-Feig, Heacock, & Cascio, 2012) and repetitive behaviors (Baranek, Foster, & Berkson, 1997), suggesting the involvement of touch processing in the ASD phenotype.

The *sense of touch* seems to constitute a fundamental foundation for affiliative behaviors and social-emotional development. Particularly, the CT system seems to constitute a strong candidate to mediate this relation. Despite the fact that touch is the primary channel of communication since we are born, it is currently not known whether this affective-motivational dimension of touch is present in infancy, and how it evolves during the first year of life. Moreover, if the CT system is present in infancy, does it differ based on the infant´s behaviors toward tactile stimuli? Finally, in this dissertation we were interested in understanding the contribution of distinct touch patterns to social behaviors in ASD: does the way children and adolescents process touch have an impact in the way they relate to each other? Therefore, the aim of this thesis is to answer these questions by: 1) studying a group of typically developing infants in their second semester of life (7-month-olds), and follow them longitudinally at 12 months of age; 2) studying a group of children and adolescents with ASD and relate their individual touch patterns toward tactile stimuli with atypical social behaviors.

Organization of the thesis

This thesis examines brain and behavioral mechanisms of touch processing, and how these relate to social-emotional development. In this first chapter (chapter 1), touch processing is characterized in the framework of infant development. Distinct domains of touch are described, with an emphasis in affective touch, namely its physiological and neural mechanisms. In addition, the importance of affective touch is examined in the context of social-emotional development, specifically how it might be involved in ASD phenotype.

In the chapter 2, the brain mechanisms to process affective and discriminative touch in a sample of 35 7-month-old infants will be explored. This study is an important first step to

characterize cortical responses to touch stimuli using functional near infrared spectroscopy. To this end, brain activation was recorded using functional near infrared spectroscopy (fNIRS) in somatosensory and temporal regions, during a paradigm using sensory- discriminative and affective-motivational stimuli.

In the chapter 3, we will do a follow up of the same infants at 12 months of age (N=25) to understand if this process undergoes a developmental change. To accomplish this, we will use fNIRS to record brain activation in somatosensory and temporal regions, using the same sensory-discriminative and affective-motivational stimuli as in Chapter 2.

In the chapter 4, the relation between brain activation to affective touch and individual patterns of aversive sensory processing to tactile stimuli will be examined. To this purpose, brain responses to affective and discriminative touch will be recorded using fNIRS a in social-emotional region of the brain (posterior superior temporal sulcus) in 12-month-old infants (n=25). In addition, mothers will complete a questionnaire regarding everyday-behaviors of their infants towards tactile stimuli.

In the chapter 5, in order to understand the role of touch processing and impaired social reciprocity, we will examine the relation between tactile processing patterns and social problems in a sample of 44 children and adolescents with ASD. Autism severity, social problems and touch processing will be examined by parent report.

Finally, in the chapter 6, I will do an overall discussion of the 4 experimental chapters. I will examine the finding from each study and will consider touch processing as a potential biomarker to the study of social-emotional development in infants with typical and atypical development.

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Chapter 2. Brain mechanisms for processing discriminative and affective touch in 7-month-old infants

A version of this Chapter is currently under review in Developmental Cognitive Neuroscience

Brain mechanisms for processing discriminative and affective touch in 7-month-old infants

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Abstract

Affective touch has been linked to affiliative behavior in early stages of infant development, but its underlying brain mechanisms are poorly understood. In children, adolescents and adults, affective touch seems to activate a brain network responsible for processing social-emotional stimuli including the posterior superior temporal sulcus (pSTS). **Purpose:** This study used fNIRS (functional near-infrared spectroscopy) to examine affective and discriminative touch in 7- month-old infants (n=35). **Methods:** Infants were given discriminative and affective stimuli to the forearm for 10 seconds followed by 20 seconds of a rest period while watching a silent movie. Brain activation (oxy-hemoglobin and deoxy-hemoglobin concentration) was registered in somatosensory and temporal regions. **Results:** A pattern of increase in oxy-hemoglobin and decrease in deoxy-hemoglobin was observed only in the somatosensory region. **Conclusion:** Seven-month-olds show a similar pattern of brain activation in the somatosensory cortex for both discriminative and affective touch, but no activation was found pSTS for either type of touch. In contrast to findings with young children, adolescents and adults, our results suggest that 7-month-old infants do not yet recruit socio-emotional brain areas to process affective touch.

Keywords: affective touch; brain development; fNIRS; infancy

Introduction

Skin is the largest of our sensory systems and touch is the first sensory system to develop in the utero (Field, 2001; Montagu, 1986). Skin touch had been acknowledged as the major communication channel between the mother and the newborn (Barnett, 2005; Field, 2001, 2010), playing a core role on attachment processes (Hertenstein, Verkamp, Kerestes, & Holmes, 2006).

Studies on touch deprivation have found that infants from depressed mothers, who reported decreased touching, exhibit more self-touch behaviors when compared to infants whose mothers reported higher levels of touching (Herrera, Reissland, & Shepherd, 2004). Another study found that infants who received less touch tended to fall back more on touching behaviors such as grabbing, patting or pulling, when exposed to stressful situations (Moszkowski et al., 2009). On the other hand, a few studies have analyzed the benefits of touching in early development. For example, some studies tested the cumulative effect of touch using standard care methods for newborns such as the *kangaroo mother care* (Charpak & Ruiz, 2016; Feldman, Eidelman, Sirota, & Weller, 2002; Feldman, Weller, Sirota, & Eidelman, 2002). Specifically, evidence suggests that benefits of touch include several gains such as reduced weight/height, reduced rates of infection or hypothermia, and a reduction on the risk for premature mortality (Conde-Agudelo & Diaz-Rossello, 2016). Touch has also been shown to be related to positive neurodevelopmental outcomes such as better sleep-wake cycles, arousal modulation and sustained exploration in the post-partum period (Feldman, Weller, et al., 2002), as well as long term effects in stress response, organized sleep and cognitive control (Feldman, Rosenthal, & Eidelman, 2014).

Research on the sense of touch has focused mostly on a class of receptors responsible for transducing information regarding pressure/vibration, temperature, itch and pain. These low-threshold mechanoreceptors (LTMs), present in the skin and joints, are innervated by myelinated Aβ fibers that conduct high-speed impulses (50m/s) and sub serve discriminative functions as, for example, handling objects or explore surfaces (McGlone, Vallbo, Olausson, Loken, & Wessberg, 2007; McGlone, Wessberg, & Olausson, 2014). This system is faster and responsible for detecting and discriminating external stimuli, which we need for survival. However, the finding that mammals, such as cats and monkeys, present a more primitive system constituted by unmyelinated low-threshold mechanoreceptors (C tactile - CT afferents) present in hairy skin, led

some researchers to test this mechanism in humans (Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). The research with adults showed that CT fibers are poor in the processing of discriminative components of touch (linked instead to myelinated Aβ fibers), such as vibration and force/pressure (H. Olausson et al., 2008; Olausson et al., 2002). They are, however, quite effective coding low-velocity/force stroking movements, with maximum firing at velocities between 1 -10 cm^{-1}, which is consistent with the human caress speed (Essick et al., 2010; Loken, Wessberg, Morrison, McGlone, & Olausson, 2009; Olausson et al., 2010). Considering these properties, it has been hypothesized CT fibers might be tuned to affiliative behaviors or affective touch present in mammals, including mother and infant.

Neuroimaging studies conducted with adults have shown that CT afferents activate a particular network of brain regions including the posterior insula, posterior superior temporal cortex (pSTS), medial prefrontal cortex and dorsal anterior cingulate cortex (dACC) (Gordon et al., 2013; Olausson et al., 2002; H. W. Olausson et al., 2008; Voos, Pelphrey, & Kaiser, 2013). According to recent studies, this network is already in place during childhood, with 5-year-olds showing similar activations as adolescents and adults in pSTS in response to affective touch (Bjornsdotter, Gordon, Pelphrey, Olausson, & Kaiser, 2014; Van de Winckel et al., 2013).

Although touch plays an important role early in infancy, the brain response to touch in infants is still poorly understood. This limited research can be partially justified by the lack of feasible neuroimaging techniques that could be used in infants (Lloyd-Fox, Blasi, & Elwell, 2010). The emergence of functional near-infrared spectroscopy (fNIRS), has open the opportunity for studying brain's haemodynamic activity in response to target stimuli under less controlled environments (Lloyd-Fox, Papademetriou, et al., 2014; Lloyd-Fox, Szeplaki-Kollod, Yin, & Csibra, 2015). Only a few studies have used fNIRS to better understand cortical brain activity in response to sensory stimulation (Altvater-Mackensen & Grossmann, 2016; Karen et al., 2008) and to our knowledge, only one study has looked at the effects of discriminative and affective touch among infants (i.e., 3-, 6- and 10 months of age) (Kida & Shinohara, 2013b). It showed that 10-month-old-infants but not younger infants present activation in anterior prefrontal cortex to affective touch, suggesting that the period between 6 and 10 months is critical for the development of the social-network involved in the processing of affective touch. However, this study left an important gap: both of the administered stimuli (discriminative and affective) were given to the palm of the hand (glabrous skin), a region lacking CT afferents, and therefore, it limited the conclusions

about brain responses to affective touch on the CT targeted areas. Additionally, the study was restricted only to one region of interest (anterior prefrontal cortex) and no conclusion can be made regarding if other regions are recruited at this age.

The literature suggests that affective touch, in both children and adults, activates key-nodes of the social brain, namely, the posterior insula, pSTS, medial prefrontal cortex and dACC (Bjornsdotter et al., 2014; Gordon et al., 2013; Olausson et al., 2008; Olausson et al., 2002; Voos et al., 2013). However, in infants, the research is very scarce, with only one study pointing to 10 months of age as the earlier age at which affective touch is processed in social areas of the brain. In the present study, we intend to examine the brain mechanisms for processing affective and discriminative touch in 7-month-old infants using fNIRS. To do so, we will use a paradigm that targets both the CT afferents (affective touch) and the Aβ fibers (discriminative touch), and use 2 distinct regions of interest: the pSTS and the somatosensory cortex. We choose 7-month old infants to fill the gap in the literature and because it is around this age that core social behaviors emerge, namely, discrimination of emotional displays (Leppanen & Nelson, 2006, 2009) and attachment (Zeanah, Berlin, & Boris, 2011). Regarding the ROI, we choose to look at the somatosensory region as the primary sensory region, and the temporal region as the "social" region. Brain activity in the somatosensory region has been recorded previously following tactile stimulation in infants (Verriotis et al., 2016); and the temporal region, namely the pSTS, has shown to be activated following affective touch in adults (Bennett, Bolling, Anderson, Pelphrey, & Kaiser, 2014).

We hypothesized that 7-month-old infants would present increased oxy-hemodynamic response in the somatosensory region to both affective and discriminative stimuli. In addition, increased oxy-hemodynamic response to affective touch would also occur in adult-like areas, namely the pSTS.

Methods

Participants

Thirty-five 7-month-old infants were included in the study (mean age 228.77 ± 89.19, range 214 -244; 14 females). All infants but one were born full term (mean time in weeks 39.07 ± 1.22, range 36.6-41) with normal birth weight (> 2500 g, with the exception of one infant who

weighted 2350g), and had no reported hearing problem or neurological conditions. Fourteen additional infants were tested but excluded due to fussiness (n=2) or not having the minimum number of 3 good trials to be included (n=12). Total attrition rate was 28.57%. Infant demographics and developmental data are shown in **Table 1**.

Infants were recruited in early parenting classes, social networks and daycare centers. Mothers signed informed consent prior to the start of the experiment. The experimental protocol was approved by local Ethics Committee.

Table 1. Sample demographics.

Characterization of the sample
Number of infants - 35
Age at birth (weeks) - 39.07± 1.22 (36.6 - 41)
Age at study (days) - 228.77 ± 9.20 (214 - 244)
Female infants -14
Weight at birth (g) - 3384.24 ± 459.59 (2350 - 4390)
Height at birth (cm) - 48.90 ± 2.64 (43- 54
Cesarean deliveries - 7 (20%)
Apgar 1 - 9.33 ± 1.10 (5 - 10)
Apgar 10 - 9.96 ± .19 (9 - 10)

Stimuli

Two types of stimuli were used: affective and discriminative touch. The affective stimuli consisted of touching the infants with a 7 cm wide watercolor brush (Bennett et al., 2014; Kaiser et al., 2016) and the discriminative stimuli with a squared-shape piece of wood 2 x2 cm (Kida & Shinohara, 2013b). *Affective* stimuli were slow strokes (8cm/s) of the watercolor brush, administered in a proximal-distal direction by a trained experimenter. This velocity was used in previous experiments and it has been shown to target CT fibers (Loken et al., 2009). Manual

administration of the affective stimuli has been previously validated in contrast with automatic stimulation by a robot (Triscoli, Olausson, Sailer, Ignell, & Croy, 2013). *Discriminative* stimuli consisted of applying touches with the wood-block in the dorsal forearm in a proximal-distal direction for the same period of time. To include the same the area of contact of the brush, the wood-block was applied 3 times for every second (between 21 and 24 stimuli applied).

Both discriminative and affective stimuli were delivered to the right dorsal forearm of the infant (bare arm) in a within subject block design procedure. There were two alternating blocks of each experimental condition (affective, discriminative), of 8 trials each (Bennett et al., 2014), that were counterbalanced between the subjects. One trial consisted of 10 seconds of stimulation followed by a baseline period of 20 seconds of rest. Baseline stimuli (rest) consisted of a silent movie (czech cartoon Krtecek) (Fairhurst et al. 2014) that played continuously throughout the session. See **Fig. 1** for schematic representation of the paradigm.

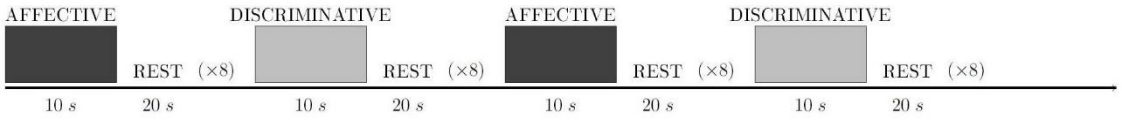


Figure 1. Experimental design. Each block consisted of a tactile stimulus delivered for 10 seconds, followed by 20 seconds of rest, repeated 8 times. There was a total of 2 blocks per condition (2 affective + 2 discriminative). Presentation of the experimental conditions was randomized.

NIRS recording

Hemodynamic responses were recorded using the UCL – fNIRS topography system (Everdell et al. 2005) with 12 sources and 6 detectors. This system uses 2 continuous wavelengths of source light at 780 and 850 nm to make spectroscopic measurements. Data were sampled every 100 ms (10 Hz) (for a detailed description of fNIRS methodology see Lloyd-Fox et al. 2010).

NIRS data was recorded from 18 channels, 9 placed over the left somatosensory region and 9 placed over right temporal region (See Figure 2). The NIRS probe was customized for this experiment using an elastic cap (Easy Cap), with reference to the 10-5 system (See **Figure 2**) (Jurcak, Tsuzuki, & Dan, 2007). Inter-optode distance was 22 mm in the temporal region (except for the two longest channels that crossed the middle of the array, around 45mm) and between 40 and 45 mm in the parietal region. Before the experiment, measurements of head circumference (44.16 cm ± 1.17) and nasion-inion (28.84 ± 2.74 cm) were taken to align the headgear with the 10-5 system. The cap, adjusted for head circumference, was placed centrally in the top of Cz, with channel 11 (correspondent to TP8) placed above the peri-auricular point.

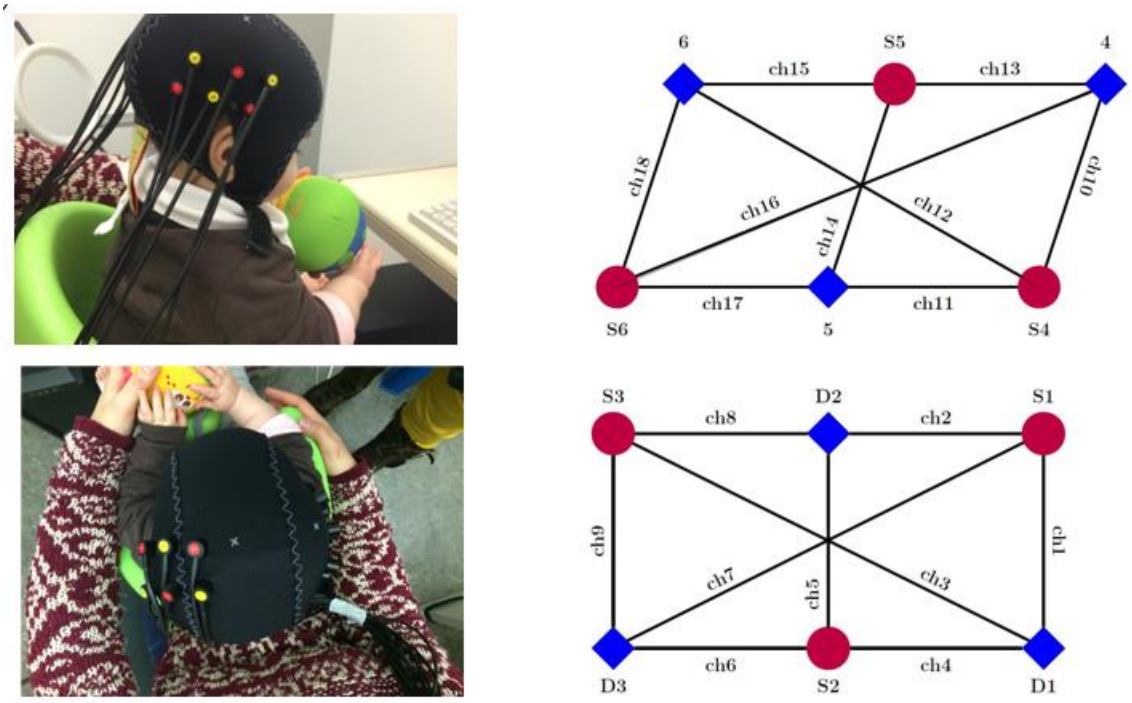


Figure 2. fNIRS probe. NIRS data was recorded from eighteen channels, 9 placed over right temporal region. (top left panel) and 9 placed over the left somatosensory region (bottom left panel). Red circles represent sources and blue squares represent detectors. The NIRS probe was customized to this experiment using an elastic cap (Easy Cap), with reference to the 10-5 system.

Procedure

Infants were allowed to familiarize with the setting for about 10 minutes, while the mother completed the consent form and the experimenter the demographic questionnaire. While infants were held in their mother´s lap, head measurements were taken. Following head

measurements, the infant was given toys to play with, to direct his/her attention away while the cap was being placed. The baby was then seated in a baby seat (Jelly Mom baby chair) to avoid physical contact with the mother, and the silent movie started being displayed (Czech cartoon Krtecek as in Fairhurst et al. 2014).

The infant was seated at approximately 70 cm from a computer screen (screen size: 53*30). The experimenter sat in the right back hand side of the infant and parent, administered the stimuli and re-directed the infant's attention to the screen when needed. No visual contact took place between the experimenter and the infant during the course of the experiment. Parents were instructed to avoid any interaction with the infant, unless he/she became fussy. The experiment took place in a dimmed-light room to avoid light-interference. Breaks were introduced when needed to keep the infant involved throughout the experiment. The experiment ended when the infant completed the 4 blocks (16 minutes) or when he/she became fussy. All the sessions were videotaped for offline coding.

Data Processing and Analysis

Concentration changes in oxy-hemoglobin (**HbO_2**) and deoxy-hemoglobin (**Hbb**) (μmol) were used as indicators of hemodynamic activity. For each participant, the video of the experimental session was coded offline by an observer who was blind to the inclusion criteria. Each participant did a maximum of 16 trials per experimental condition. Participants were only included if they completed at least 3 good quality trials (Lloyd-Fox, Wu, Richards, Elwell, & Johnson, 2015). Specifically, we considered a good quality trial when the following conditions were met: the infant did not move the arm in any direction while the stimulus was being administered; the infant was not looking at the experimenter or the mother while the stimulus was being administered; the infant did not touch the experimenter or the mother while the stimulus was being delivered. Infants completed an average of 6.65 ± 3.06 affective trials (range 3 -14) and 7.25 ± 2.82 (3- 17) discriminative trials. No statistical difference was found for number of trials completed ($\chi^2 = 119.79$, $p = 0.09$).

Hemodynamic activity data was processed using HOMER2 (Huppert, Diamond, Franceschini, & Boas, 2009), a MATLAB (The MathWorks, Inc., Natick, MA, USA) software package. The attenuated light intensities measured by the detecting optodes were converted to

optical density units and assessed for movement artifact using Principal Component Analysis (PCA) set at 0.9. (Cooper et al., 2012). Since we only included trials in which the infant was not moving the arm, rejecting trials is a preferable method than correction approaches as for example wavelet motion correction. Data were then low- pass filtered at 0.5 Hz (Lloyd-Fox, Szeplaki-Kollod, et al., 2015) and used to calculate the change in concentration of the hemoglobin chromophore according with the modified Beer-Lambert Law (Delpy et al. 1988) assuming a pathlenght factor of 5.13 (Duncan et al. 1995). Traces were segmented into 30 second epochs, starting 2 seconds prior to each stimulus. Baseline corresponded to the mean time from -2 to 0, as in previous fNIRS studies (Ravicz, Perdue, Westerlund, Vanderwert, & Nelson, 2015). Following visual inspection of the data, we decided to remove the 4 long channels (s-d distance 40 and 45 mm, channels 3, 7, 12 and 16) as we confirmed that their response was too weak compared with the other channels, and could add error to the results.

Statistical analysis was performed using SAS (Statistical Analysis Software) 9.4v. Grand average haemodynamic response (μm) was calculated for the two conditions (affective and discriminative). For each channel, the maximum change in HbO_2 (increase in chromophore concentration) and/or **Hbb** (decrease in chromophore concentration) in response to each experimental condition were assessed relative to baseline using a linear mixed-model. Significant increase in HbO_2 and significant decrease in **Hbb** have been considered as indicators of cortical activation in NIRS studies with infants (Lloyd-Fox et al., 2010), but because most of the changes observed were in HbO_2, the following analyses focused on this chromophore. After visual inspection of the grand mean concentration changes of each chromophore for each condition, we realized the discriminative stimuli resulted in earlier hemodynamic responses than the affective. Therefore, and to include the maximum signal changes of both stimuli, three time windows were determined for the analyzes: t1 = 10 to 15 seconds; t2= 15-25 seconds, and t3= 25 to 28 seconds. Variable *time* was dummy coded to capture non-linear relation over time. We used a linear mixed-model to test the differences between condition (2) and time (3) by channel on HbO_2 activity.

Results

Discriminative touch. To assess the response to discriminative touch on all individual channels, the discriminative condition (wood block) was analyzed relative to baseline

(silent movie). This analysis revealed significant hemodynamic increases in HbO2 centered over the somatosensory cortex for channel 1 at time 1 (t (102) = 3.86, $p <$ 0.001) and time 2 (t (102) = 2.45, $p = 0.016$); for channel 2 at time 1 (t (102) = 3.04, $p = 0.003$) and time 2 (t (102) = 1.97, $p = 0.051$); and for channel 5 at time 1 (t (102) = 2.18, $p = 0.032$. Over the temporal region/ area correspondent to the STS, there was a significant hemodynamic increase of HbO2 at time 1 for channel 13 (t (102) = 2.60, p = 0.010. (**Table 2**). Hemodynamic response function for discriminative touch in channel 1 is illustrated in **Figure 3**.

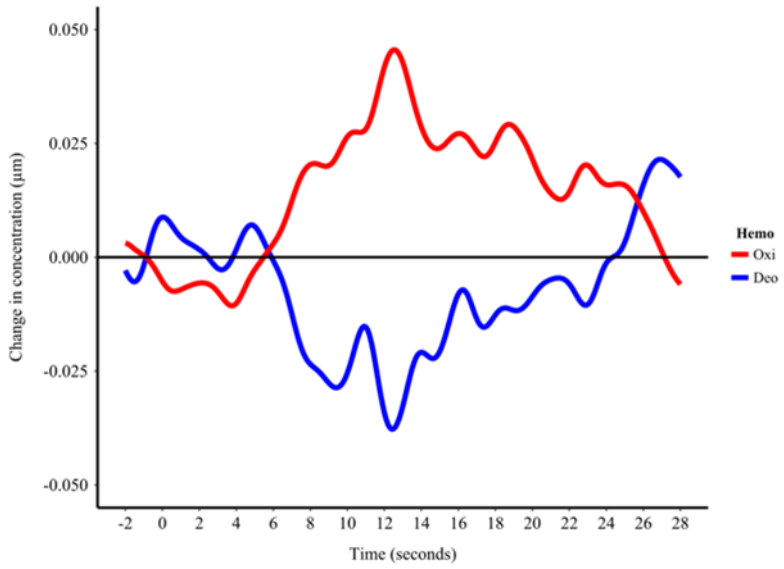


Figure 3. Hemodynamic response function for discriminative touch in channel 1.

Table 2. Contrasts for discriminative and affective stimuli for measures of HbO2.

Discriminative > Baseline					Affective > Baseline				
Channel	Time Window	β	SE	*p* value	Channel	Time Window	β	SE	*p* value
1	1	0.034	0.009	< 0.001	1	2	0.021	0.011	0.051
	2	0.021	0.009	0.016					
2	1	0.049	0.016	0.003					
	2	0.031	0.016	0.051	Discriminative > Affective				
5	1	0.026	0.012	0.031	2	1	0.064	0.024	0.009
						2	0.055	0.024	0.026
13	1	0.035	0.014	0.010	5	1	0.033	0.014	0.019

* time window 1: 10 - 15 seconds; time window 2: 15-25 seconds;

*channels 1, 2, and 5 are located in somatosensory region; channel 13 is located in temporal region.

* β value refers to relative hemodynamic change; SE refers to standard error.

Affective touch. Hemodynamic response for the affective stimuli resulted from the contrast between the affective stimuli (brush) relative to baseline. Analysis from all the individual channels revealed a significant hemodynamic increase in HbO_2 over the somatosensory cortex for channel 1 at time 2 (t (102) = 1.97, $p = 0.051$). Over the temporal region / area correspondent to the STS there was no significant hemodynamic response. (**Table 2**). Hemodynamic response function for affective touch in channel 1 is illustrated in **Figure 4**.

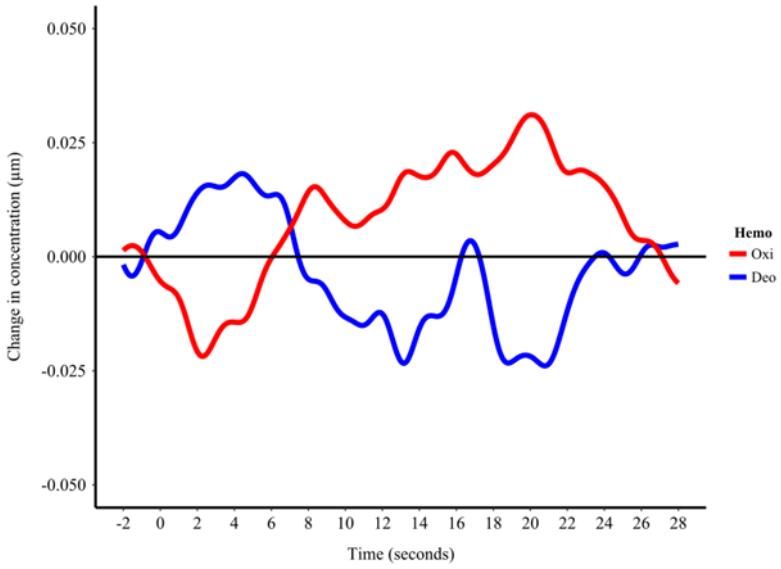


Figure 4. Hemodynamic response function for affective touch in channel 1.

Effect of condition and time. To compare the effect of each condition within the two regions, we performed a linear mixed model for the channels that previously presented a significant hemodynamic response against baseline. For the discriminative > affective contrast in channels placed over the somatosensory region, channel 2 showed greater activation for discriminative stimuli compared to affective stimuli at time 1 (M = 0.064, SE = 0.024; t (170) = 2.64, $p = 0.009$) and time 2 (M = 0.055, SE = 0.024; t (170) = 2.25, $p = 0.026$); and channel 5 at time 1 (M= 0.033, SE = 0.014; t (172) = 2.36, $p = 0.019$). No significant change was found for channels placed over the temporal region. In addition, the affective > discriminative contrast did not reveal any significant results in somatosensory and temporal region.

Discussion

This study examined brain responses for affective and discriminative touch in 7-month-old infants. As hypothesized, results showed that 7-month-old infants process both affective and discriminative components of touch in the somatosensory cortex. However, results did not support our second hypothesis that affective touch would further activate the right temporal region in infants, specifically the posterior STS, a critical region associated with social cognition (Bennett et al., 2014; Bjornsdotter et al., 2014). Both the activation of somatosensory region and lack of activation of the temporal regions seem to be unique patterns in the age cohort, suggesting that brain activation to affective touch follows a specific developmental trajectory.

In fact, no hemodynamic response function was found in any of the channels that have an approximate location to pSTS in response to the affective stimuli. These findings are similar to the study from Kida and Shinoara (2013a), that found no activation of other social-related brain regions such as the anterior prefrontal cortex to a pleasant stimulus in contrast to discriminative stimulus among 3 and 6-month old infants. Instead, this study found that the anterior prefrontal cortex activation was only present at 10-months old (Kida & Shinohara, 2013a). To the best our knowledge no other study has looked at cortical response trajectories for affective touch during infancy; however, the combined findings of our study with Kida & Shinohara (2013b) suggests that activation in response to affective touch in the temporal region does not occur until after the age of 7 months. One further study that has looked at physiological responses to affective touch in 9-month-olds, confirmed that infants are sensitive to affective touch at this age (Fairhurst, Loken, & Grossmann, 2014). Fairhurst et al. (2014) replicated findings from adult experiments (Loken et al., 2009) by showing that infants presented a decrease in heart rate to the medium velocity, compared to slower or faster velocities of touch, meaning that the medium velocity (CT optimal velocity) best leads to an increased parasympathetic activity which reflects a decrease in arousal. In our study we used brush stroking to elicit stimulation of CT afferents as used in the literature (Bennett et al., 2014; Bjornsdotter et al., 2014; Olausson et al., 2002), but it could be that in young ages the stimulation needs to occur at human harm skin temperature (32°) (Ackerley et al., 2014), a condition that has been found to best activate CT system. The temperature could represent the necessary condition to promote the sense of interpersonal touch and affiliative behavior, hypothesized to be dependent on the CT system. Another possible explanation is aligned with social- cognitive development at this age. Although infants are tuned to stimuli with social relevance since they are born (Johnson, 2005; Johnson, Dziurawiec, Ellis, &

Morton, 1991), and at 7 months of age already show the ability to discriminate emotions (Leppanen, Moulson, Vogel-Farley, & Nelson, 2007) and are sensitive to ostensive signals (Senju & Csibra, 2008), it is not until 9 months that they start presenting a group of core social behaviors like joint attention, social referencing, and implicit mental state attribution (Carpenter, Nagell, & Tomasello, 1998; Striano & Reid, 2006). Please see Happé and Frith (2014) for a review on the neurodevelopmental trajectory of social cognition (Happe & Frith, 2014). It could be that processing of "social" touch accompanies this trajectory, and the STS is only recruited at later stages of development.

Another important finding of this study was that both affective and discriminative components of touch elicited activation on contralateral somatosensory cortex. This finding goes along with other fNIRS studies, reporting activations in contralateral somatosensory region in response to non-noxious tactile stimuli in infants aged 0-19 days (Verriotis et al., 2016), but the cortical response to touch with this type of stimuli has been reported in infants as young as 28 weeks gestation (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006). Ours is, nevertheless, the first study reporting activation of the somatosensory cortex, not only to discriminative, but also in response to affective stimuli in infants. This demonstrates that infants as early as 7 months of age already process affective touch in contralateral primary somatosensory cortex (SI), similarly to children, adolescents (Bjornsdotter et al., 2014), and adults (Gordon et al., 2013; Kaiser et al., 2016; Morrison, 2016).

We also found that within the somatosensory region, the discriminative stimuli resulted in an increased hemodynamic response and in a greater number of activated channels compared to affective stimuli. This is unexpected because affective and discriminative touch share a common pathway – lemniscal pathway, responsible for carrying information from low-threshold mechanoreceptors with large myelinated (Aβ) afferents that conduct impulses relative to stimuli discrimination/detection, independent of site of stimulation or stimulus type. The majority of neuroimaging studies with adults look specifically to one or other stimuli separately, preventing the direct comparison between these different stimuli. However, a recent study by Morrison (2016) used an activation likelihood estimate (ALE) meta-analysis to compare both stimuli and concluded that although the affective and discriminative touch activations overlap in primary and secondary cortices, the activation likelihood between the two is distinct: primary somatosensory cortices (SI) are more likely to be activated for discriminative touch, and posterior insula more

likely activated for affective touch (Morrison, 2016). This means that although there might be a dissociation for affective and discriminative touch in some brain regions, the two kinds of touch share somatosensory co-activations.

Interestingly, there was some variability associated with the timing of the activation pattern for affective and discriminative touch. The peak of the activation of oxy-hemoglobin in the somatosensory cortex associated with discriminative touch occurred between 10 and 15 seconds and for affective touch occurred later, between 15 and 25 seconds. No other study has looked at this region for affective touch, and the study that examined affective touch in infants did not report peak activation (Kida & Shinohara, 2013a). In adult´s studies, affective touch in the pSTS peaks between 8.4 and 9.7 seconds (Bennett et al., 2014) for a stimulus presented for 6 seconds. Our paradigm was slightly different, as we presented the stimuli for 10 seconds, what can contribute for the differences found between our study and Bennett et al (2014). Another possible explanation for the differences in latency is the developmental trajectory between infancy and adulthood, as the hemodynamic response to visual, auditory and tactile (pain) seems to become more rapid with age (Lloyd-Fox et al., 2016; Slater et al., 2006). For discriminative touch, most activations occurred earlier, between 10 and 15 seconds (although, some channels also presented activation between 15 and 25 seconds). This replicates other studies using a exclusively tactile paradigm (Verriotis et al., 2016) or sensorimotor paradigm combining touch and movement (Kusaka et al., 2011) that have also found hemodynamic changes in the same time window 15-25 seconds for optodes placed over the somatosensory region. Furthermore, our differential temporal responses for discriminative and affective touch go along with the hypothesis that these two kinds of touch are sub-served by distinct fibers – one myelinated, faster and responsible for the discriminative aspects of touch, and the other unmyelinated, slower, with less importance for human survival; it is likely that the timing of processing at the cortical level is different between the two, being the discriminative processed faster (Loken et al., 2009; McGlone et al., 2014; Morrison, Loken, & Olausson, 2010).

An unexpected result was the hemodynamic response to discriminative touch in an optode placed over the temporal region (channel 13) that showed activation between 10 and 15 seconds. Although this region was not expected to target a response to discriminative touch, its location is close to temporo-parietal region (Lloyd-Fox, Richards, et al., 2014) where the secondary somatosensory cortex is located, and it is likely that this region is also sensitive to

discriminative touch (Morrison, 2016). Also, other discriminative stimuli, namely vibrotactile stimuli, is known to activate the temporal lobe (Beauchamp, Yasar, Frye, & Ro, 2008; Davidovic, Jonsson, Olausson, & Bjornsdotter, 2016) what suggests that the region is not only sensitive to affective touch.

In addition, there were also a time and channel interaction worth mentioning. For one channel placed over the somatosensory cortex, no differences were found between the two types of stimuli confirming that the primary somatosensory cortex processes both kinds of stimuli (Morrison, 2016). However, for two other channels placed in the same region, discriminative touch resulted in greater activation compared with affective touch, between 10 and 25 seconds, which was probably related with a deactivation observed for the affective touch. Finally, the lack of differences between stimuli in the channels placed over the temporal region, reinforces that at this age is possible that tactile stimuli are mainly processed in primary sensory regions.

To the best of our knowledge this is the first study looking at the differential effects of discriminative and affective touch in infants. However, several methodological constraints are worth mentioning. The use of different types of stimulation (brush and wood block) might have led to different volumes of touch. However, we defined the same touch contact' time per stimuli for both brush and wood block. Another important challenge was the selection of the baseline stimuli. We used a silent video as a baseline that was previously used in a touch paradigm with infants (Fairhurst et al., 2014). Although this is not a true baseline, it is a type of stimuli that captures infant's attention and increases the quiet period during data collection, improving the signal to noise ratio and the number of trials included. Future studies should test different visual/sound stimuli (e.g., sound movies instead of silent movies for example) and see how these interfere with the hemodynamic responses and to what extent can be considered reasonable for baseline control. Although our design minimized exclusion and non-compliance with the protocol, there was still a few number of participants that were not included in the final sample due to fussiness or for not having a minimum number of good trials. Future studies need to address if non-compliant infants constitute a specific cohort with a typical activation profile that differs from the compliant sample.

The role of touch for mammal's survival is undeniable. Touch is a very important modality for affiliative behaviors and dyadic reciprocity between caregiver and offspring. Innumerous studies have documented the role of touch in humans, with behavioral and

physiological findings on the positive effects of touch in the newborn (premature and full term), however little is known about what happens at the brain level when infants are subject to different kinds of tactile stimulation. This study contributed to a better understating of the brain mechanisms among 7-month-olds when processing affective and discriminative touch. Future studies should include a broader age-range and longitudinal designs, including observational measures, to understand how brain responses to affective touch relate to individual infant differences and maternal care in infancy. Such studies can contribute to a better understanding of how affective touch is linked to social-emotional development in infancy and childhood, and ultimately contribute to a better understanding of some neurodevelopmental disorders, namely autism spectrum disorder.

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Funding: This study was supported by the Portuguese Science Foundation through an individual doctoral grant to Helga Miguel (SFRH/BD/86694/2012). The work was conducted at Psychology Research Center (UID/PSI/01662/2013), University of Minho, and supported by the Portuguese Science Foundation and the Portuguese Ministry of Science, Technology and Higher Education through national funds (PSI/01662) and co-financed by FEDER through COMPETE2020 under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-007653).

Conflict of interest: The authors declare they have no conflict of interest.

Chapter 3. When the brain starts discriminating affective touch: A longitudinal study between 7 and 12-month-old infants

A version of this Chapter is currently submitted to Psychological Science

When the brain starts discriminating affective touch: A longitudinal study between 7 and 12-month-old infants

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Abstract

The affective-motivational component of touch has been shown to activate the social- brain network, including the posterior superior temporal sulcus (pSTS). Despite the widely accepted importance of touch in early development, very few is known about the neural mechanisms of affective touch processing during the first year of life. **Purpose:** The objective of the present study was to analyze brain response to affective and discriminative touch in a sample of 7-month-old-infants (N= 35) who were followed longitudinally at 12 months-of-age (N= 25). **Methods:** Infants were given affective touch (slow strokes of brush stimulation) and discriminative touch (wood block) to the bare forearm for 10 seconds, followed by 20 seconds of rest. Brain response, as assessed by near infra-red spectroscopy (fNIRS) was recorded by optodes placed over the contralateral somatosensory cortex and ipsilateral temporal region. **Results:** Seven-month-olds presented a pattern of brain activation for affective and discriminative stimuli in optodes placed over the somatosensory region, but no activation was recorded in optodes placed in the temporal region. At 12-months of age, infants presented a significant increase in hemodynamic activity in optodes placed over the temporal region for affective touch, compared to 7-month-olds. Moreover, brain activity over the somatosensory cortex for discriminative touch resulted in activation of a greater number of optodes compared with 12-month-olds. **Conclusion:** Our study presents evidence of a developmental trajectory for distinct aspects of touch brain processing in the first year of life. Although somatosensory cortex shared activation for discriminative and affective stimuli in both ages, brain activity in 7-month-olds seem to be larger for sensory-discriminative stimuli, whereas 12-month-olds presented a robust brain activation in the temporal region for affective touch.

Keywords: affective touch; developmental trajectory; brain development; fNIRS

Introduction

Touch is one of the most developed sensory systems at birth. Behavioral responses to touch can be observed as early as 7 weeks' gestation when the fetus moves after being touched in the lips (Hooker, 1952), or a few weeks later when the grasping and rooting reflexes emerge (Fifer & Moon, 2003; Humphrey, 1964). Compared with other sensory modalities, namely vision and audition, touch receptors mature and are functionally developed earlier than other senses in the womb (Bremner & Spence, 2017; Gallace & Spence, 2010). Touch is the primary channel of communication between the mother and the newborn (Field, 2001; Hertenstein, Verkamp, Kerestes, & Holmes, 2006), conveying soothing and comfort during the first months of life (Jean & Stack, 2012; Jean, Stack, & Fogel, 2009). However, contrasting with the centrality of touch early on development, very little is known about how the brain processes touch during infancy.

Cutaneous information is sent to the central nervous system by a variety of tactile receptors. Low-threshold mechanoreceptors (LTMs) transduce information regarding properties of touch that include pressure, vibration, slip and texture, and are instrumental to perform discriminative functions in everyday life as for example handling objects and use tools (c.f., Abraira & Ginty, 2013; McGlone, Vallbo, Olausson, Loken and Wessberg, 2007; McGlone, Wessberg and Olausson, 2014). These receptors are innervated by myelinated Aβ fibers that enable fast conduction of the nerve impulses, needed to quickly detect, discriminate and identify external stimuli (McGlone, Wessberg and Olausson, 2014). LTMs are present in the entire body, but especially dense in the glabrous skin of the hand, particularly the digits (Kandel, Schawartz, & Jessell, 2000; Mountcastle, 2005). C low-threshold mechanoreceptors (C-tactile afferents or CTs), present only in hairy skin, are responsible to transduce information regarding slow touch (Abraira & Ginty, 2013). Microneurography experiments in humans have shown that these fibers are maximally activated by stimuli that move slowly, with maximum firing at velocities between 1 - 10 cm^{-1} (Essick et al., 2010; Loken, Wessberg, Morrison, McGlone, & Olausson, 2009; Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). CT fibers are related with stimulus (pleasantness/ unpleasantness) valence encoding, with an important role in social behavior (Morrison, Loken, & Olausson, 2010). In contrast with the abundant research regarding the discriminative touch, only recently affective touch mediated by CT fibers started gaining attention in neuroscience research.

In adults, affective touch activates a brain network that includes the posterior insula, posterior superior temporal cortex (pSTS), medial prefrontal cortex (mPFC) and dorsal anterior cingulate cortex (dACC) along with the primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) (Gordon et al., 2013; Olausson et al., 2002; Olausson et al., 2008; Voos, Pelphrey, & Kaiser, 2013). Neuropathy patients who lack Aβ afferents (i.e., not able to sense that they were touched) pure CT stimulation evoked activation in the dorsal posterior insular cortex but not the somatosensory areas S1 and S2. In contrast, pure Aβ-fiber stimulation (glabrous skin in healthy controls), activated S1 and S2 as did combined stimulation of Aβ and CT stimulation to the forearm. These findings suggest that CT system does not provide discriminative aspects of touch, and probably has distinct connections to cortical areas (Olausson et al. 2002; Olausson et al. 2008).

The few studies about the developmental trajectory of affective touch suggest that an extensive brain network including the posterior insula, pSTS, medial prefrontal cortex, dACC, and also S1 and S2, are already in place during childhood during touch processing tasks (Bjornsdotter, Gordon, Pelphrey, Olausson, & Kaiser, 2014; Van de Winckel et al., 2013). Additionally, there is evidence that the S2 continues to mature with age (Bjornsdotter et al., 2014). In infants, the only study looking at brain activity in response to different types of touch (affective versus discriminative) using functional near infra-red spectroscopy (fNIRS) (Kida & Shinohara, 2013b) found that 10 month old-infants, but not 3- or 6- month-olds, showed an activation of the anterior prefrontal cortex to affective touch but not to discriminative touch. This suggests that the social-brain network to affective touch might be in place in infancy, and probably emerges in the second semester of the first year. Nevertheless, the few number of fNIRS channels used in this study did not allow measuring activity in cortical regions also known to be involved in processing of affective touch, such as the pSTS. Furthermore, the experimental paradigm consisted in the palm of the hand stimulation (lacking hairy skin) and not targeting CT fibers (Bennett, Bolling, Anderson, Pelphrey, & Kaiser, 2014; Bjornsdotter et al., 2014; Gordon et al., 2013).

In the study presented in Chapter 2, we found that a sample of 7-month-olds, showed activation of the somatosensory cortex, but not pSTS, in response to affective touch (Miguel, Lisboa, Gonçalves & Sampaio, 2017a). In this study, infants received affective and discriminative stimuli in their dorsal forearm, and brain activity was measured using fNIRS in a primary sensory

region (somatosensory cortex) that processes both affective and discriminative stimuli, and in an association area (pSTS) known to process affective touch. Interestingly, infants presented greater hemodynamic function in optodes placed over the somatosensory region for the two types of stimuli, but no activation was found over the pSTS.

During the second semester of life the infant goes through important social-emotional changes. It is around 7 months of age that important social behaviors emerge, such as gaze following (Tomasello, Carpenter, & Liszkowski, 2007) and emotional face processing (Leppanen & Nelson, 2009). Given the lack of brain response to affective touch in social-emotional regions in 7-month-olds and the maturation evidenced beyond this age, it may be important to study how the infant brain evolves in processing discriminative and affective touch after 7 months. In the present study, we select a group of 7 month-infants and followed them longitudinally at 12 months-of-age, in order to understand how the brain evolves in response to affective touch. fNIRS was used to measure brain activity in response CT stimulation (affective touch) and Aβ stimulation (discriminative touch), looking at 2 distinct regions of interest, the pSTS (brain region associated with earlier processing of social cues as biological motion, face or voice processing) and the somatosensory cortex (i.e., primary sensory region). We hypothesized that both 7 and 12-month-old infants would present brain activity in the somatosensory cortex, for discriminative and affective touch. Additionally, we also hypothesized increased activity for affective touch in pSTS for 12-month-olds but not for 7-month-olds.

Methods

Participants

Infants were recruited from local parenting classes, social networks and daycare centers. At 7 months of age 35 infants were included in the study (mean age 228.77 ± 89.19 days, range 214 -244; 14 females). All infants but one was born full term (mean time in weeks 39.07 ± 1.22, range 36.6-41) with normal birth weight (> 2750 g, with the exception of one infant who weighted 2350g). Fourteen additional infants were tested but excluded due to fussiness (n=2) or not having the minimum number of 3 good trials to be included (n=12). At 12 months of age 25 infants were included in the study (same infants) (mean age 387.15 ± 9.33 days, range 372 – 406). All infants were born full-term with normal birth weight (> 2750 g, with the exception of one infant who weighted 2420g). Twenty additional infants were tested but excluded due to fussiness

(n=4), not having the minimum number of 3 good trials to be included (n=7), motion artifact and/or noisy data (n=7) and experimental error (n=2). In addition, 9 infants missed the follow up visit. Fifteen infants were tested in both moments. Total attrition rate was 29% for the 7 month-olds and 45% for the 12 month-olds, which is comparable to other NIRS studies in infancy (Lloyd-Fox, Szeplaki-Kollod, Yin, & Csibra, 2015). Infant demographics and developmental data are shown in **Table 3**. Mothers signed informed consent prior to the start of the experiment. The experimental protocol was approved by the local Ethics Committee.

Table 3. Sample demographics.

Characterization of the sample	7 months	12 months
Number of infants	35	25
Age at birth (weeks)	39.07 ± 1.22 (36.6 - 41)	39.167 ± 1.167 (37 - 41)
Age at study (days)	228.77 ± 9.20 (214 - 244)	387.15 ± 9.33 (372 - 406)
Female infants	14	11
Weight at birth (g)	3384.24 ± 459.59 (2350 - 4390)	3245.96 ± 457.27 (2420 - 4390)
Height at birth (cm)	48.90 ± 2.64 (43 - 54)	48.58 ±1.51 (44 - 52.90)
Cesarean deliveries	7 (20%)	8 (32%)
Apgar 1	9.33 ± 1.10 (5 - 10)	9.33 ± .96 (6 -10)
Apgar10	9.96 ± .19 (9 - 10)	9.96 ± .20 (9-10)

Stimuli

Two stimuli were used to represent the affective and discriminative dimensions of touch. The affective stimuli consisted of a 7 cm wide watercolor brush (Bennett et al., 2014; Kaiser et al., 2016) and the discriminative stimuli a squared-shape piece of wood 2 x 2 cm (Kida & Shinohara, 2013a). Affective stimuli comprised slow strokes (8cm/s) of the watercolor brush, administered in a proximal-distal direction by a trained experimenter (Triscoli, Olausson, Sailer, Ignell, & Croy, 2013). This velocity was used in previous experiments and it has been shown to target CT fibers (Loken et al., 2009). Discriminative stimuli consisted of applying touches with the wood-block in the dorsal forearm in a proximal-distal direction for the same period of time. To comprise the same the distance of the brush, the wood-block was applied 3 times for every second (between 21 and 24 stimuli applied).

Both discriminative and affective stimuli were delivered to the right dorsal forearm of the infant (bare arm) in a within subject block design procedure resulting in two alternating blocks of each experimental condition (affective, discriminative), of 8 trials each (Bennett et al., 2014). One trial consisted of 10 seconds of stimulation followed by a baseline period of 20 seconds of rest. Stimuli were presented in an alternating way. Baseline stimuli (rest) consisted of a silent movie (czech cartoon Krtecek) that played continuously throughout the session and simultaneously with the task as used previously in research (Fairhurst et al. 2014). See **Figure. 5** for schematic representation of the paradigm.

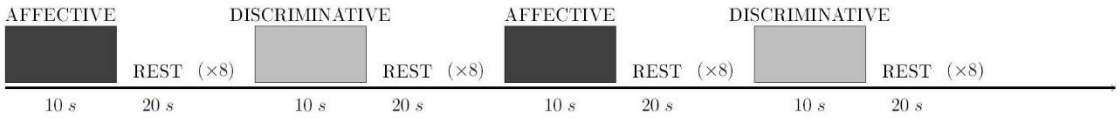


Figure 5. Experimental design. Each block consisted of a tactile stimulus delivered for 10 seconds, followed by 20 seconds of rest, repeated 8 times. There was a total of 2 blocks per condition (2 affective + 2 discriminative).

NIRS recording

Hemodynamic responses were recorded using the UCL – fNIRS topography system (Everdell et al. 2005) with 12 sources and 6 detectors, using 2 continuous wavelengths of source light at 780 and 850 nm. Data were sampled every 100 ms (10 Hz) (for a detailed description of fNIRS methodology see Lloyd-Fox et al. 2010).

NIRS data was recorded from 18 channels, 9 placed over the left somatosensory region and 9 placed over right pSTS (See **Figure 6**). The NIRS probe was customized for this experiment using an elastic cap (Easy Cap), with reference to the 10-5 system (See **Figure 6**)(Jurcak, Tsuzuki, & Dan, 2007). Depending on the head circumference at 7- and at 12-months of age, caps for different head-circumferences were used (44 and 46 cm). Inter-optode distance was 22 mm in the pSTS region (except for the two longest channels that crossed the middle of the array, around 45mm) and between 40 and 45 mm in the somatosensory region. Before the experiment, measurements of head circumference and nasion-inion were taken to align the headgear with the 10-5 system (see **Table 3** for head measurements). The cap was placed centrally in the top of Cz, with channel 11 (correspondent to TP8) placed above the peri-auricular point.

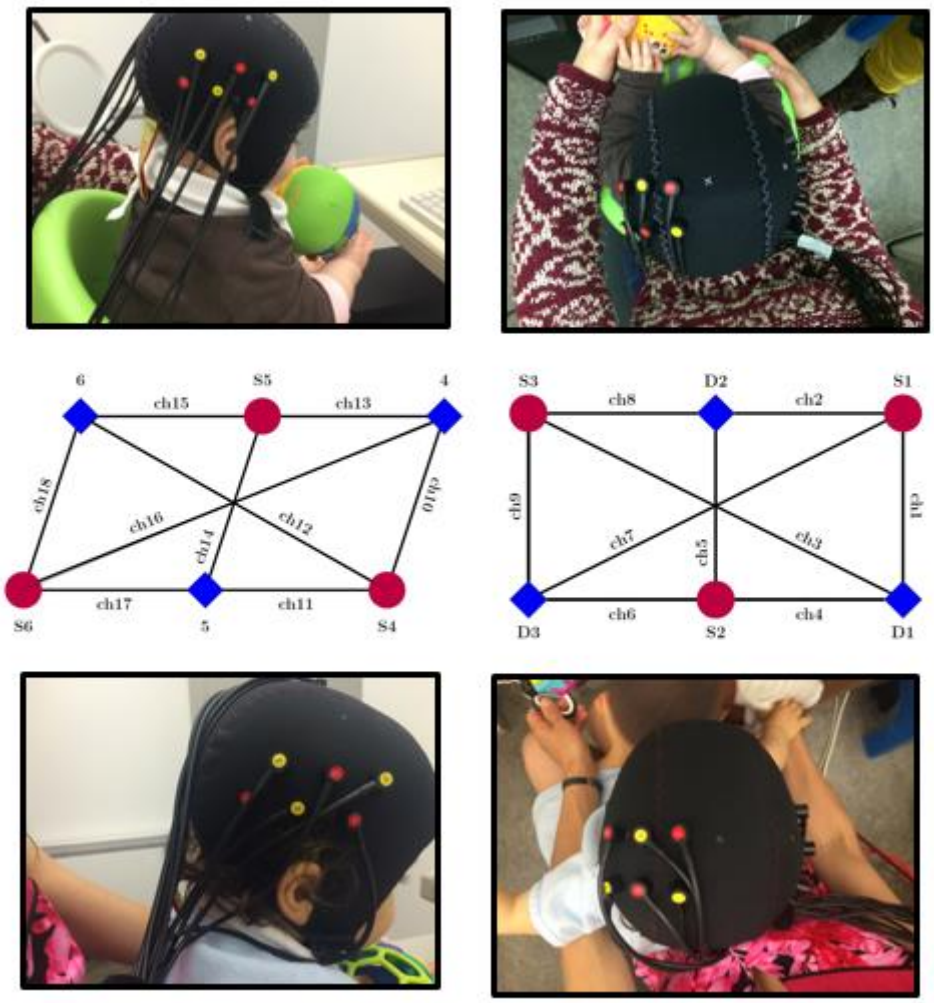


Figure 6. fNIRS probe. NIRS data was recorded from eighteen channels, 9 placed over right pSTS (left panel) and 9 placed over the left somatosensory region (right panel). The top panel refers to the fNIRS headgear on a 7-month-old and the bottom panel on a 12-month-old. Red circles represent sources and blue squares represent detectors. The NIRS probe was customized to this experiment using an elastic cap (Easy Cap), with reference to the 10-5 system.

Procedure

While the mother completed the consent form and the experimenter did the demographic questionnaire, infants were allowed to familiarize with the setting and play with toys in the experimenter room. In the meantime, infants were held in their mother´s lap and head measurements were taken. An experimenter continued to play with the infant to direct his/her attention away while the cap was being placed. The baby was then seated in a baby seat (Jelly

Mom baby chair) to avoid physical contact with the mother, and the silent movie started being displayed (Czech cartoon Krtecek as in Fairhurst et al. 2014).

The infant was seated at approximately 70 cm from a computer screen (screen size: 53*30). The experimenter sat in the right back hand side of the infant and parent, administered the stimuli and re-directed the infant's attention to the screen when needed. No visual contact took place between the experimenter and the infant during the course of the experiment. Parents were instructed to avoid any interaction with the infant, unless he/she became fussy. The experiment took place in a dimmed-light room to avoid light-interference. Breaks were introduced when needed to keep the infant involved throughout the experiment. The experiment ended when the infant completed the 4 blocks (16 minutes) or when he/she became fussy. All the sessions were videotaped for offline coding.

Data Processing and Analysis

The videos from the individual sessions were coded offline, by an observer who was blind to the inclusion criteria. Each participant did a maximum of 16 trials per experimental condition. Participants were only included if they completed at least 3 good quality trials (Lloyd-Fox, Wu, Richards, Elwell, & Johnson, 2015). To be considered a good trial the following criteria needed to be met: (1) the infant did not move the arm in any direction while the stimulus was being administered; (2) the infant was not looking at the experimenter or the mother while the stimulus was being administered; (3) the infant did not touch the experimenter or the mother while the stimulus was being delivered. Seven-month-olds completed an average of 6.65 ± 3.06 affective trials (range 3 -14) and 7.25 ± 2.82 (3- 17) discriminative trials; 12-month-olds completed an average of 6.68 ± 2.15 affective trials (range 4 -13) and 6.32 ± 2.52 (3- 12) discriminative trials. No statistical difference was found for the number of trials completed at 7 (χ^2 = 119.79, p = 0.09) nor at 12 months of age (χ^{2-} 31.39, p = 0. 885).

Hemodynamic activity data was processed using HOMER2 (Huppert, Diamond, Franceschini, & Boas, 2009), a MATLAB (The MathWorks, Inc., Natick, MA, USA) software package. The attenuated light intensities measured by the detecting optodes were converted to optical density units and assessed for movement artifact using Principal Component Analysis (PCA) set at 0.9. (Cooper et al., 2012). Both a significant increase in oxy- hemoglobin (HbO_2) or a

decrease in deoxy-hemoglobin (**Hbb**) are accepted as indicators of hemodynamic activity, but according with the preliminary analysis the majority of concentration changes were seen for HbO_2, and we used only this chromophore as indicator of hemodynamic activity (Lloyd-Fox et al., 2016). Since we only included trials in which the infant was not moving the arm, rejecting trials (PCA) is a preferable method than correction (e.g., wavelet motion correction). Data were then low- pass filtered at .5 (Lloyd-Fox, Szeplaki-Kollod, et al., 2015) and used to calculate the change in concentration of the hemoglobin chromophore according with the modified Beer-Lambert Law (Delpy et al., 1988) assuming a pathlenght factor of 5.13 (Duncan et al., 1995). Traces were segmented into 30 second epochs, starting 2 seconds prior to each stimulus. Baseline corresponded to the mean time from -2 to 0, as in previous fNIRS studies (Ravicz, Perdue, Westerlund, Vanderwert, & Nelson, 2015).

Statistical analysis was performed using SAS (Statistical Analysis Software) 9.4v. Grand average haemodynamic response (μm) was calculated for the two conditions (affective and discriminative). For each channel, the maximum change in HbO_2 (increase in chromophore concentration) in response to each experimental condition was assessed relative to baseline using a mixed-effect regression model. After visual inspection of the grand mean concentration changes of each chromophore for each condition, we realized there were differences in the latency of the response in the two age groups. Therefore, and to include the maximum signal changes of both stimuli, five time windows were determined for the analyzes: t1 = 0 to 5 seconds; t2= 5 to 10 seconds; t3: 10 to 15 seconds; t4: 15 to 20 seconds and t5: 20 to 25 seconds. Variable *time* was dummy coded to capture non-linear relation over time. This preliminary analysis allowed to determine that the long-channels (diagonal channels 3, 7, 12 and 16 in Fig. 2) resulted in noisy data, and therefore were excluded from the analysis. A mixed-effect regression model was then performed for each of the remaining 14 channels, for the touch condition (2: affective and discriminative), time block (1 to 5 intervals) and age (2: 7 and 12 months).

Results

We first describe the results separately for 7 and 12-month-old infants (discriminative and affective touch against baseline). We then present the contrasts between the two conditions

for the 12-month-old infants (contrasts between conditions for the 7-month-olds are presented in Chapter 2) and finally the contrasts between two age groups for the two conditions.

Effects of condition against baseline

Seven-month-old infants

Discriminative touch. To assess the response to discriminative stimuli for each channel, brain's hemodynamic response to the discriminative condition (wood block) was analyzed relative to baseline (silent movie). This analysis revealed significant increase in HbO2 centered over the somatosensory region for channel 1 at time 3 (t (1, 205) = 12.91, p = 0.0004) and 4 (t (1, 205) = 7.21, p = 0.008), channel 2 at time 3 (t (1, 205) = 6.52, p = 0.011) and channel 5 at time 3 (t (1, 205) = 4.56, p = 0.034. Marginally significant increases were found for channel 8 at time 3 (t (1, 205) = 3.04, p = 0.08). Over the pSTS region, discriminative touch elicited a significant increase in channel 13 at times 2 (t (1, 205) = 9.84, p = 0.002) and 3 (t (1, 205) = 15.75, p < 0.001), and in channel 15 at time 2 (t (1, 205) = 8.65, p = 0.004) and 3 (t (1, 205) = 5.07, p = 0.025).

Affective touch. Hemodynamic response for the affective stimuli resulted from the contrast between the affective stimuli (brush) relative to baseline. Analysis for each channel revealed significant hemodynamic increase in HbO2 for channel 1 at times 4 (t (1, 205) = 5.88, p = 0.016) and 5 (t (1, 205) = 4.50, p = 0.035).

Twelve-month-old infants

Discriminative touch. For discriminative touch, there was a significant hemodynamic increase in HbO2 centered over the somatosensory region for channel 6 at times 2 (t (145) = 2.25, p = 0.025) and 3 (t (145) = 2.15, p = 0.033). In addition, marginally significant hemodynamic increases in HbO2 were found for channels 4 (t (145) = p = 0.06) and 5 (t (145) = 3.25, p = 0.070) at time 3. Over the pSTS region there was a significant hemodynamic increase of HbO2 at time 4 for channel 17 (t (145) = 4.04, p = 0.040).

Affective touch. Hemodynamic response for the affective stimuli showed a significant hemodynamic HbO2 increase in channel 1 at time 4 (t (145) = 4.82, p = 0.029), in channel 2 at time 3 (t (145) = 7.33, p = 0.007) and 4 (t (145) = 3.83, p = 0.052), and

in channel 9 at time 4 (t (145) = 11.70, $p < 0.001$). In addition, marginally significant hemodynamic increases in HbO2 were found in channel 1 at time 3 (t (145) = 2.92, $p = 0.089$) and in channel 9 at time 5 (t (145) = 3.17, $p = 0.079$). Over the PSTS region there was a significant hemodynamic increase of HbO2 for channel 10 at time 2 (t (145) =5.13, $p = 0.025$) and 3 (t (145) =9.39, $p = 0.003$), channel 11 at time 1 (t (145) = 5.26, $p = 0.023$), channel 13 at time 3 (t (145) = 10.08, $p = 0.002$) and 4 (t (145) = 4.69, $p = 0.032$), channel 14 at time 4 (t (145) = 5.86, $p = 0.017$), and channel 15 at time 3 (t (145) = 6.60, $p = 0.011$) and 4 (t (145) = 5.51, $p = 0.020$). In addition, marginally significant responses were also found for channel 11 at time 2 (t (145) = 3.62, $p = 0.060$).

Effect of condition and block. For the discriminative > affective contrast in channels placed over the somatosensory region, channel 6 showed greater activation for discriminative stimuli compared to affective stimuli at times 2 (M = 0.044, SE = 0.012; t (304) = 3.77, $p < 0.01$) and 3 (M = 0.030, SE = 0.012; t (304) = 2.59, $p = 0.01$). For the affective > discriminative contrast in channels placed over the somatosensory region, channel 9 showed greater activation for affective stimuli compared with discriminative stimuli at time 4 (M= 0.048, SE = 0.013; t (188) = 3.85, $p < 0.01$). In the pSTS region, affective touch resulted in a greater activation for channel 10 at time 3 (M= 0.037, SE = 0.017; t (304) = 2.18, $p= 0.03$), channel 14 at time 4 (M= 0.038, SE = 0.011; t (188) = 3.35, $p < 0.001$), channel 15 at time 4 (M= 0.050, SE = 0.016; t (188) = 3.15, $p = 0.01$) and channel 17 at time 3 (M= 0.038, SE = 0.011; t (188) = 3.35, $p < 0.001$) and 4 (M= 0.038, SE = 0.011; t (188) = 3.35, $p < 0.001$). In addition, marginally significant activation was found for channel 15 at time 3 (M= 0.039, SE = 0.016; t (304) = 2.42, $p = 0.070$). See **Table 4** for significant Hbo_2 contrasts.

Table 4. Significant HbO2 responses to the different contrasts between discriminative and affective touch at 12M.

Discriminative > Affective					Affective> Discriminative				
Channel	Time Window	β	SE	*p* value	Channel	Time Window	β	SE	*p* value
6	2	0.044	0.012	< 0.010	9	4	0.048	0.013	< 0.001
	3	0.030	0.012	0.010					
					10	3	0.037	0.017	0.030
					14	4	0.038	0.011	<0.001
					15	4	0.050	0.016	0.010
					17	3	0.038	0.011	<0.001
						4	0.038	0.011	<0.001

* time window 1: 0-5 seconds; time window 2: 5- 10 seconds; time window 3: 10 - 15 seconds; time window 4: 15-20 seconds.
*channels 6 and 9 are located in somatosensory region; channels 10, 14, 17 e 17 are located in temporal region.

Effect of age, condition and block.

For the contrast discriminative 7M > discriminative 12M a significant increased hemodynamic activation was found in channel 2 at times 3 (M= 0.056, SE = 0.024; t (536) = 2.38, *p*= 0.018) and 4 (M= 0.053, SE = 0.024; t (536) = 2.25, *p*= 0.025), channel 5 at time 4 (M= 0.033, SE = 0.016; t (536) = 1.98, *p*= 0.05), channel 8 at time 3 (M= 0.035, SE = 0.015; t (412) = 2.35, *p*= 0.019), and channel 13 at time 2 (M= 0.035, SE = 0.014; t (536) = 1.94, *p*= 0.053). Marginally significant results were found for channel 8 at time 2 (M= 0.033, SE = 0.015; t (412) = 2.27, *p*= 0.088). No significant differences were found for the contrast for affective 7M > affective 12M.

For the contrast discriminative 12M > discriminative 7M a significant increased activation was found in channel 6 at time 1 (M= 0.022, SE = 0.010; t (304) = 2.01, *p*= 0.045), channel 14 at time 5 (M= 0.036, SE = 0.014; t (420) = 2.52, *p*= 0.012), and channel 17 at times 4 (M= 0.055, SE = 0.020; t (306) = 2.66, *p*= 0.008) and 5 (M= 0.046, SE = 0.018; t (306) = 2.54, *p*= 0.012). The contrast affective 12M > affective 7M resulted in a significant increase of hemodynamic activity for channel 8 at time 4 (M= 0.033, SE = 0.015; t (412) = 2.26, *p*= 0.025), channel 10 at time 3 (M= 0.046, SE = 0.019; t (536) = 2.39, *p*= 0.017); channel 11 at times 1 (M= 0.058 SE = 0.024; t (304) = 2.41, *p*= 0.016) and 2 (M= 0.056 SE = 0.024; t (304) = 2.33, *p*= 0.020), channel 14 at time 3 (M= 0.035 SE = 0.015; t (420) = 2.41, *p*= 0.017) and 4 (M= 0.051 SE = 0.015; t (420) = 3.52, $p < 0.001$), channel 15 at times 3 (M= 0.039 SE = 0.018; t (536) = 2.21, *p*= 0.027) and 4 (M= 0.042 SE = 0.018; t (536) = 2.38, *p*= 0.017).

Marginally significant activation was found for channels 4 at time 5 (M= 0.026, SE = 0.014; t (536) = 1.76, *p*= 0.079); channel 10 at time 3 (M= 0.035, SE = 0.019; t (536) = 1.88, *p*= 0.061) and channel 17 at time 5 (M= 0.033 SE = 0.018; t (306) = 1.85, *p*= 0.067). See **Table 5** significant for channel-by-channel contrasts between 7 and 12-month-olds. **Figure 7** displays the hemodynamic response function for the 7 and 12-month-olds, for the 2 conditions, in channels placed in the somatosensory and temporal regions.

Table 5. Significant HbO2 responses to discriminative and affective touch between 7M and 12M.

Discriminative 7M > Discriminative 12M					Affective 7M > Affective 12M				
Channel	Time Window	β	SE	*p* value	Channel	Time Window	β	SE	*p* value
2	3	0.056	0.024	0.018	non-significant results				
	4	0.053	0.024	0.025					
5	3	0.033	0.016	0.050					
8	3	0.035	0.015	0.019					
13	2	0.035	0.014	0.053					

Discriminative 12M > Discriminative 7M					Affective 12M > Affective 7M				
Channel	Time Window	β	SE	*p* value	Channel	Time Window	β	SE	*p* value
6	1	0.022	0.01	0.045	8	4	0.033	0.015	0.025
14	5	0.036	0.014	0.012	10	3	0.046	0.019	0.017
17	4	0.055	0.02	0.008	11	1	0.058	0.024	0.016
	5	0.046	0.018	0.012		2	0.056	0.024	0.02
					14	3	0.035	0.015	0.017
						4	0.051	0.015	<0.001
					15	3	0.039	0.018	0.027
						4	0.042	0.018	0.017

* time window 1: 0-5 seconds; time window 2: 5- 10 seconds; time window 3: 10 - 15 seconds; time window 4: 15-20 seconds. *channels 6 and 9 are located in somatosensory region; channels 10, 14, 17 e 17 are located in temporal region.

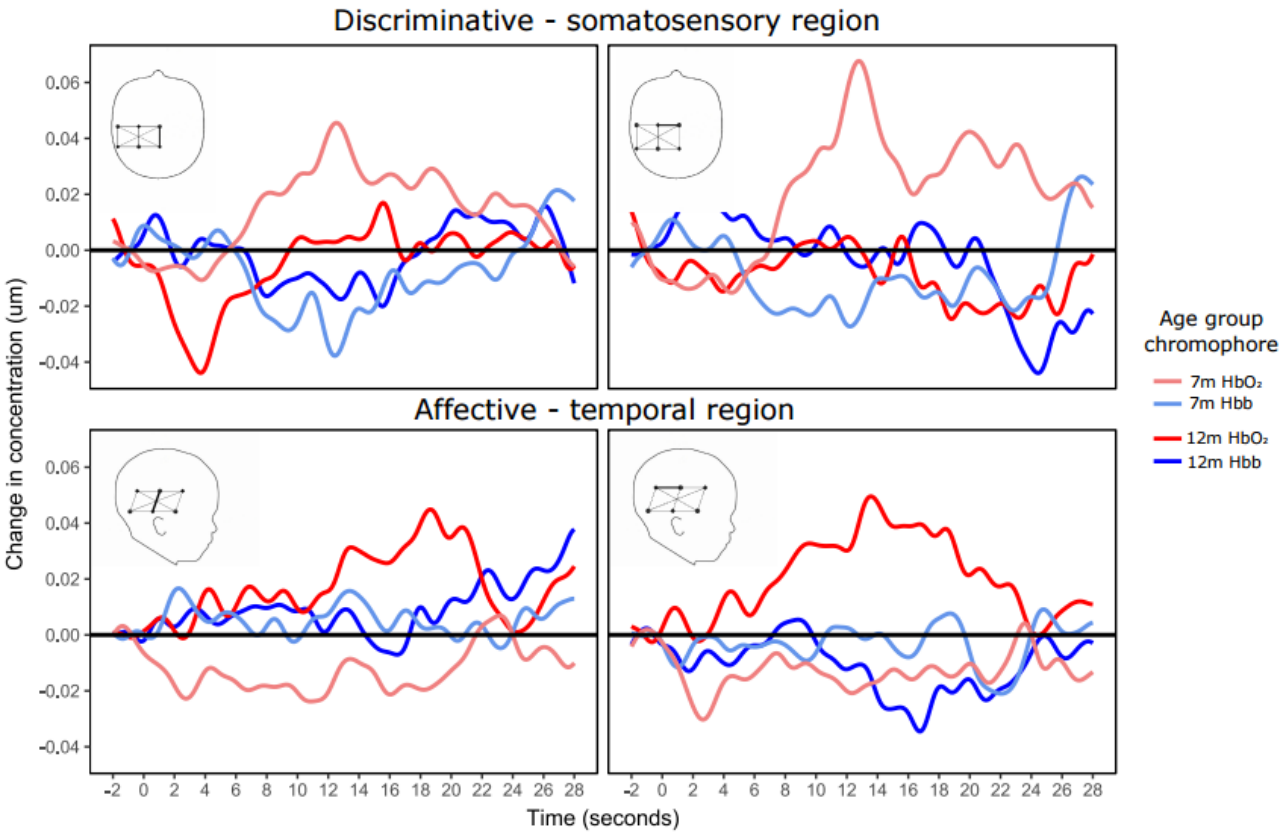


Figure 7. Hemodynamic response function for 7 and 12-month-olds in response to affective and discriminative stimuli. Top panel refers to hemodynamic response function recorded from channels 1 and 2 (placed over the somatosensory region) for discriminative touch; bottom panel refers to hemodynamic response function recorded from channels 14 and 15 (placed over the pSTS region) for affective touch.

Discussion

The current study examined the developmental trajectory of brain responses to affective and discriminative touch, by following longitudinally infants from 7 to 12 months of age. Brain's hemodynamic activity was analyzed in response to two distinct stimuli applied to the infant's forearm: a discriminative stimulus consisting of a wood block that would target Aβ fibers, and an affective stimulus consisting of slow brush strokes targeting CT fibers. Results showed that 7 months of age infants processed both types of stimuli in the somatosensory cortex. However, at 12 months of age infants showed a shift by recruiting a posterior region of the temporal lobe (i.e., pSTS - often associated with the processing of social relevant stimuli) in response to processing affective touch. Moreover, no such activation was found for the 7-month-olds. Another interesting finding was that 7-month-olds presented greater activation to discriminative stimulus in the somatosensory region when compared to the 12-month-olds.

The activation of the ipsilateral temporal region to affective touch in 12-month-old infant's replicates findings with adult samples that have identified pSTS as one of the brain regions consistently activated following slow stroking of the arm (Bennett et al., 2014; Bjornsdotter et al., 2014; Gordon et al., 2013; Kaiser et al., 2016; Voos, Pelphrey, & Kaiser, 2013). According with the affective-motivational role of the CT fibers (Morrison et al., 2010) the posterior temporal region is more responsive to hairy skin versus to glabrous skin (Gordon et al 2013, Bjornsdotter, 2014) and to slower than faster strokes (Voos et al 2013). In infants, the few studies looking at brain activity to affective touch showed similar results (Kida & Shinohara, 2013b; Miguel et al. 2017a). Infants at younger ages (3, 6 and 7-month-old infants) do not yet present brain activation following affective touch, whereas 10-month-old infants do (Kida & Shinohara, 2013b; Miguel et al. 2017a). These studies differ in the region of interest. Kida and Shinohara looked at anterior prefrontal cortex, whereas Miguel et al. looked at pSTS. However, both regions are key-nodes of the social brain, reported to be involved in the processing of affective touch in adults and including the insula, mPFC, the ACC, and the pSTS (Bennett et al., 2014; Bjornsdotter et al., 2014; Gordon et al., 2013; Olausson et al., 2002) Together, the findings suggest that the neural mechanism underlying the processing of affective touch in social regions of the brain emerges by the end of the second semester of life. This finding is consistent with the development of other socially relevant behaviors starting also between 9 and 12 months of age, such as joint attention, social referencing, attachment and implicit mental state attribution (Happe & Frith, 2014; Johnson et al., 2005).

Both age cohorts presented an increased hemodynamic response in optodes placed over the contralateral somatosensory cortex for the two stimuli, confirming that the somatosensory network is recruited to process information sent from both Aβ and CT fibers (Morrison, 2016). Hemodynamic responses of the contralateral somatosensory region to tactile stimuli can be recorded as early as 28 weeks gestation (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006; Verriotis et al., 2016), suggesting that somatosensory networks are already functional prenatally. In fact, at birth, neural dendritic development, synaptogenesis and myelination in the somatosensory cortex are already in place (de Graaf-Peters & Hadders-Algra, 2006; Nevalainen, Lauronen, & Pihko, 2014; Zecevic & Rakic, 1991). In terms of affective touch 5 years of age children present activations in contralateral S1 and S2 in response to slow-stroking of the forearm (Bjornsdotter et al., 2014), and that these activations are similar in adolescents and adults (Gordon et al., 2013; Kaiser et al., 2016; Morrison, 2016).

Interestingly, we found a developmental trajectory for the process of the two types of stimuli: whereas 7-month-olds presented a greater activation for channels placed over the somatosensory region for discriminative touch, 12-month-olds presented an increased hemodynamic activity for the channels placed over the temporal region for affective touch. Discriminative touch is transduced by low-threshold mechanoreceptors that transduce information rapidly, and allow us to immediately identify stimuli in the environment which can be interpreted as primary system, important for survival purposes (McGlone, Wessberg, & Olausson, 2014). It is possible that at 7 months of age, when infants are more dependent on their mothers, they are more prone to identify tactile stimuli in the environment and, consequently, present greater activation in primary sensory region for this stimulus compared to older infants. From 7 to 12 months of age infants face enormous developmental acquisitions in various domains, including motor and emotional (Valla, Birkeland, Hofoss, & Slinning, 2017). It is during this period that infants start to move independently and a group of important social capacities emerge, namely joint attention (Mundy et al., 2007), social referencing (Lin & Green, 2009) and attachment (Minagawa-Kawai et al., 2009). Giving the social-affective specificity of CT afferents (Morrison et al., 2010) it would not be surprising if there was a shift from the neural resources of processing discriminative touch in sensory region to processing affective touch by recruiting the pSTS. The pSTS region matures later than the somatosensory-cortex (Lenroot & Giedd, 2006) and has been shown to be susceptible to individual differences in various domains, including affective touch processing (Bennett et al., 2014; Bjornsdotter et al., 2014; Davidovic, Jonsson, Olausson, & Bjornsdotter, 2016; Voos et al., 2013). The STS presents distinct anatomical and functional features, that support a developmental shift in the processing of affective touch. Not only the STS is the only anatomical structure that is asymmetric at birth, with the right STS being more deep than the left (Glasel et al., 2011), but the temporal lobe undergoes an increasingly rapid maturation in the first years of life (Bonte et al., 2013; Tanaka, Matsui, Uematsu, Noguchi, & Miyawaki, 2012), becoming gradually more specialized and focal (Bonte et al., 2013), what suggests that its function is greatly predisposed by individual differences.

To the best of our knowledge this is the first study looking at the developmental trajectory of brain's response activity to affective and discriminative touch. However, there are several challenges and methodological constraints important to note. A major challenge when studying awake infants is the attrition rate. Although we were able to have an attrition rate of 22% in the 7 month-olds which is lower than what is reported in the literature, at 12 month-olds we had an

increased attrition rate (Lloyd-Fox et al., 2016) resulting in smaller sample. To deal with non-compliant infants, future studies should include more than one fNIRS session and larger sample sizes (Lloyd-Fox et al., 2016). Another important aspect concerns the type of baseline stimuli. Since there cannot be a true baseline (no stimuli) for a touch paradigm in infants, we chose to have a silent movie (Fairhurst, Loken, & Grossmann, 2014). This stimulus was chosen to capture infant´s attention and increase the quiet period during data collection, but we do not know the degree of interference of such a task with the hemodynamic signal. Therefore, future studies should test the use visual and auditory stimuli, that are potentially more appealing and control its impact on the hemodynamic response. Another important limitation is that we cannot exclusively target CT afferents, since Aβ fibers are present in both glabrous and hairy skin. CT afferents have been typically examined by manipulating the velocity of the stimuli or the site of stimulation (arm versus hand), but this would be hard to implement in infants without introducing more noise in the process of signal acquisition. This was the reason for opting for the use of a stimulus that would target mainly the discriminative component of touch (i.e., wood block). Finally, the limited number of channels of our system limits the number of cortical regions examined (e.g., hemispheric laterality activations)

Since Harlow first observations (Harlow & Zimmermann, 1959) that the newborn rhesus monkey deprived from a monkey mother preferred tactile comfort over nutrition, the importance of physical contact to proper social and emotional development have been extensively documented. Innumerous studies have documented that in contrast with a more low-level, sensory-perceptual processing of touch, affective touch is also processed in high-order areas of the brain related with the process of social-emotional information, namely the insula, pSTS, ACC and pre-frontal regions. This study contributed to a better understanding of the developmental trajectory of affective touch in the infant brain, as well as informing about discriminative touch processing. In the future, it would be interesting to include a broader age-range, namely newborns, and follow them longitudinally, at important developmental milestones.

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Funding: This study was supported by the Portuguese Science Foundation through an individual doctoral grant to Helga Miguel (SFRH/BD/86694/2012). The work was conducted at Psychology

Research Center (UID/PSI/01662/2013), University of Minho, and supported by the Portuguese Science Foundation and the Portuguese Ministry of Science, Technology and Higher Education through national funds (PSI/01662) and co-financed by FEDER through COMPETE2020 under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-007653).

Conflict of interest: The authors declare they have no conflict of interest.

Chapter 4. Affective responsivity to tactile stimuli impacts the emergence of brain response to affective touch during infancy

Affective responsivity to tactile stimuli impacts the emergence of brain response to affective touch during infancy

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Author contributions: HM conceived the study, participated in its design, collected data, performed data processing and analysis, and drafted the manuscript. OG and AS conceived the study, participated in the study design and helped draft the manuscript. All authors read and approved the final manuscript.

Abstract

Background: Affective touch activates a brain network responsible for processing social-emotional stimuli in infants, children and adults, with a core node in the posterior superior temporal sulcus (pSTS). pSTS is known to be a region highly susceptible to individual variability, namely in terms of tactile stimuli processing. However, little is known on how the brain processes tactile stimuli of different aversive patterns in infancy. **Aim:** The aim of this study was to research pSTS activations in response to tactile stimuli with different affective pattern. **Methods:** A sample of 12 months of age infants (n=25) were given affective and discriminative stimuli to the forearm for 10 seconds followed by 20 seconds of a rest period while they were looking at a mute movie. Brain activation was recorded in the pSTS for measures of oxy-hemoglobin (HbO_2) and deoxy-hemoglobin (Hbb). Behavioral responses to tactile stimuli were measured using the Infant-Toddler Sensory Profile. **Results:** A significant hemodynamic response increase to affective touch was observed in the pSTS for infants with decreased aversive responses to tactile stimuli **Conclusion:** The findings suggest that the emergence of brain activity in the pSTS at 12-month-old for affective touch is modulated by individual differences in affective reaction towards touch.

Keywords: sensory over-responsiveness; affective touch; brain activity; infancy

Introduction

Touch is the primary source of soothing and comfort offered by the mother to her newborn. Nurturing touch is present at very early stages of development (Jean, Stack, & Fogel, 2009) and is related with several markers of well-being in term and preterm infants (Charpak & Ruiz, 2016; Conde-Agudelo & Diaz-Rossello, 2016; Feldman, Eidelman, Sirota, & Weller, 2002; Feldman, Weller, Sirota, & Eidelman, 2002). Animal research suggests that maternal physical care behavior (e.g., licking and grooming) are important for the development of the central nervous system, having a life-long impact on the off-spring's social-emotional development (Harlow & Suomi, 1970; Meaney & Szyf, 2005; Weaver et al., 2004). Touch seems to serve not only an important role in the maturation of the brain throughout development, but it is critical to the foundation of social bonding and emotional communication (Hertenstein, Verkamp, Kerestes, & Holmes, 2006)

A specific category of tactile fibers that respond to gentle, caress-like slow skin-stroking, CT fibers, has been hypothesized to play an important role in socially relevant touch, including the touch present in affiliative behaviors, such as light stroking from the mother to her child, a hug between friends or an intimate caress in a couple (McGlone, Vallbo, Olausson, Loken, & Wessberg, 2007; McGlone, Wessberg, & Olausson, 2014; Morrison, Loken, & Olausson, 2010). These fibers are instrumental for encoding the valence of a stimulus (Loken, Wessberg, Morrison, McGlone, & Olausson, 2009) but have a weak localization resolution (Olausson et al., 2002). In addition, CT afferents are tuned to temperature and their firing more at skin temperature correlates with perceived pleasantness of a tactile stimuli (Perini, Olausson, & Morrison, 2015).

At a brain-level, the stimulation of these fibers elicits activation of the social-brain network, including the posterior insula, posterior superior temporal sulcus (pSTS), medial prefrontal cortex (mPFC) and dorsal anterior cingulate cortex (dACC) (Bjornsdotter, Gordon, Pelphrey, Olausson, & Kaiser, 2014; Gordon et al., 2013; Kaiser et al., 2015; Olausson et al., 2002; Voos, Pelphrey, & Kaiser, 2013), There is evidence that this network is are already in place at around 5 years of age (Bjornsdotter et al., 2014). However, less is known about the emergence of this network in infancy, with only a few studies suggesting that brain response to affective tactile stimuli emerges between the age of 10 and 12 months of age (Kida & Shinoara, 2013b, Miguel, Lisboa, Gonçalves & Sampaio, 2017a; Miguel, Gonçalves, Cruz & Sampaio, 2017b). In Chapters 2 and 3 of this dissertation we present evidence that the brain response the

affective touch in the STS region is present in 12-month-olds (Miguel et al. 2017b) but no not in 7-month-olds (Miguel et al. 2017a) suggesting that is between this period that this network emerges.

Interestingly, in children and adults, the response to slow skin touch in the pSTS seems to be modulated by individual differences. Brain activity in pSTS has been found to correlate with age and gender (Gordon et al., 2013), and autistic traits (Bennett, Bolling, Anderson, Pelphrey, & Kaiser, 2014; Voos et al., 2013),. The temporal brain region seems to be not only sensitive to pleasant tactile stimuli, but also to aversive tactile stimuli, in both healthy individuals and clinical samples (Green et al., 2015). Increase of brain activation in this region to aversive tactile stimuli in individuals with Autistic Spectrum Disorder (ASD) is heightened by an over responsivity to tactile stimuli (Green et al., 2015). It is long acknowledge that individuals with ASD present aversive reactions to sensory stimuli (Ben-Sasson et al., 2009; Rogers & Ozonoff, 2005), showing increased defensive responses and lower pleasantness ratings to tactile stimuli (Tomchek & Dunn, 2007). These defensive responses to tactile stimuli (also referred to sensory defensiveness or sensory over-responsivity – SOR) have been documented in the population with ASD at a behavioral level, but more recently at a brain level as well. SOR to tactile stimuli is related to hyperactivity in brain regions involved in primary sensory processing (Green et al., 2015) but also affective-emotional regions such as the posterior cingulate cortex and the insula (Cascio et al., 2012). Moreover, activity in emotional processing regions, namely the insula, amygdala and temporal regions, are reported to be correlated with parent-reported SOR symptoms (Green et al., 2015) and social impairment (Cascio et al., 2012).

SOR lies under the clinical umbrella of sensory modulation disorder (Miller, Anzalone, Lane, Cermak, & Osten, 2007). SOR is characterized by exaggerated, intense and/or prolonged responses to certain sensory stimuli that same-age peers find innocuous (Dunn, 1997; Miller et al., 2007), reflecting an imbalance between noticing a novel or threatening stimuli (sensitization) and adapting to familiar stimuli (habituation) (Dunn, 1997). It is estimated that the prevalence of SOR is around between 2.5% - 6.5 % in typically developing children (Goldsmith, Van Hulle, Arneson, Schreiber, & Gernsbacher, 2006; Schoen, Miller, & Green, 2008; Van Hulle, Lemery-Chalfant, & Goldsmith, 2015), although it co-occurs in many neurodevelopmental disorders, including ASD (Kern et al., 2007), (Kern et al., 2007; Leekam, Nieto, Libby, Wing, & Gould, 2007), fragile X syndrome (Baranek et al., 2002) or attention deficit hyperactivity disorder (Yochman, Parush, & Ornoy, 2004). Very little is known about the etiology of SOR, but recent

findings on a population-based sample of typically developing twins (Goldsmith et al., 2006; Schoen et al., 2008; Van Hulle et al., 2015), suggest that risk factors as gestational age, birthweight and temperament contribute to the stability of SOR tactile symptoms over time.

Given previous findings that the brain response to affective stimuli within the pSTS emerges between 7 and 12 month of age (Miguel et al., 2017b), and the variability of the pSTS activations in response to affective touch (Bjornsdotter et al., 2014; Davidovic, Jonsson, Olausson, & Bjornsdotter, 2016; Kaiser et al., 2016; Voos et al., 2013) we hypothesized the processing of affective touch by the pSTS at 12 months of age would be dependent on individual differences in processing tactile stimuli with different affective patterns.

Methods

Participants

Participants were 25 12-month-old infants (mean age 387.15 ± 9.33 days, range 372 – 406). Twenty additional infants were tested but excluded due to fussiness (n=4), not having the minimum number of trials to be included (n=7), motion artifact and/or noisy data (n=7) and experimental error (n=2). From the initial sample, 9 infants missed the follow up visit. A total of fifteen infants have good data at 7 and 12 months. Our attrition rate was 45%, similar to other NIRS studies in infancy (Lloyd-Fox, Szeplaki-Kollod, Yin, & Csibra, 2015). Infant demographics from are shown in Table 7. The study protocol was approved by the local Ethics Committee, and the mothers signed informed consent prior to data collection.

Table 6. Sample demographics.

Characterization of the sample	Mean ± SD
Age at birth (weeks)	39.167 ± 1.167 (37- 41)
Age at study (days)	387.15 ± 9.33 (372 - 406)
Weight at birth (g)	3245.96 ± 457.27 (2420 -4390)
Height at birth(cm)	48.58 ±1.51 (44 - 52.9)
Apgar 1	9.33 ± .96 (6 -10)
Apgar10	9.96 ± .20 (9-10)

Total N =25 (11 females)

Stimuli

Stimuli consisted of a 7cm wide watercolor brush and 2 x 2 cm squared-shape piece of wood. These stimuli were chosen to represent the affective (brush) and discriminative (wood block) dimensions of touch (Bennett et al., 2014; Kida & Shinohara, 2013). Affective stimuli included slow strokes (8cm/s) moving the watercolor brush in the bare forearm of the infant, in a proximal- distal direction (Triscoli, Olausson, Sailer, Ignell, & Croy, 2013). This velocity is known to target CT fibers (Loken et al., 2009). Discriminative touch consisted of applying the wood-block in the bare forearm of the infant, also in a in a proximal-distal direction, for the same period of time. Each run (10 seconds) comprised between 21 and 24 stimuli applied.

There were two blocks for each experimental condition (affective, discriminative), each block consisting of 8 trials each (Bennett et al., 2014). One trial consisted of 10 seconds of stimulation followed by a period of 20 seconds of rest. Stimuli were pseudorandomized, so that there were no consecutive blocks of the same stimuli. The baseline stimuli (rest) was a silent movie (Fairhurst, Loken, & Grossmann, 2014) that played continuously throughout the session, and simultaneously with the task. The schematic representation of the paradigm is displayed in **Figure 8.**



Figure 8. Experimental design. Each block consisted of a tactile stimulus delivered for 10 seconds, followed by 20 seconds of rest, repeated 8 times. There was a total of 2 blocks per condition (2 affective + 2 discriminative).

Measures

NIRS recording

Infants were tested using the UCL – fNIRS topography system (Everdell et al. 2005), using 2 continuous wavelengths of source light at 780 and 850 nm, sampled every 100 ms (10 Hz). The system consisted 9 channels, placed over right temporal region (**See Figure 9**). The NIRS probe was customized for this experiment using an elastic cap (Easy Cap), with reference to the 10-5 system (Jurcak, Tsuzuki, & Dan, 2007). Inter-optode distance was 22 mm. Measurements of head circumference and nasion-inion were taken to align the headgear with the 10-5 system before the experiment started. The cap was placed in the top of Cz, with channel 11 (correspondent to TP8) placed above the peri-auricular point.

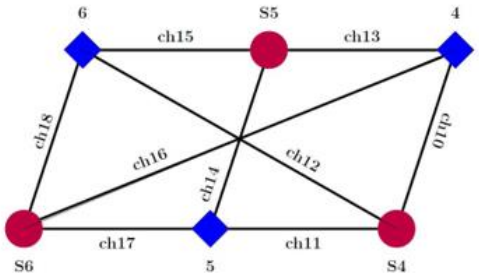




Figure 9. Display of the fNIRS probe in a 12-month-old infant. Hemodynamic activity was recorded from a total of 9 channels placed over the STS. Red circles represent sources, and blue squares (schema of the array) and yellow circles (picture of the array) represent detectors.

Infant/ Toddler Sensory Profile

The Infant/ Toddler Sensory Profile is a parent questionnaire that assesses how sensory processing in various domains affects the child´s daily function, in children from birth to 36 months (Dunn, 2002). It consists of 48 judgment-based caregiver questions relative to sensory systems, including auditory, visual, tactile, vestibular and oral; and sensory patterns, including seeking, avoiding, sensitivity and registration. Each item is scored on a 5 point Likert Scale (1= "Almost Never", 2= "Occasionally", 3= "Half of the time", 4= "Frequently", 5= "Almost Always"). Scores one standard deviation or more from the mean are expressed as More than Others or Less than Others, respectively. Scores two standard deviations or more from the mean are expressed as Much More Than Others or Much Less than Others, respectively. In thus study, only the touch section of Infant-Toddler Sensory Profile was only on the Touch Section. The mean raw scores on Touch Section for the 12-month-old infants scored under *Just like the Majority of the others* (M = 47.48±7.75). To obtain a measure of aversive behaviors towards tactile stimuli/ SOR/ tactile defensiveness, we summed all of *Avoiding* and *Sensitivity* items from the Touch Section. This sum was used before since sensitivity and avoidance are highly correlated (Ben-Sasson et al., 2008; Miguel et al., 2017c).

Procedure

Sessions were scheduled according with the mother availability and infant sleeping cycle, preferably after the infant took a nap, was fed and was in a quiet alert state. After the mother completed the consent form, the experimenter did the demographic questionnaire. During this time, the infant played, and got familiarized with the setting and with the experimenter. The infant was sat in the mother lap and a second experimenter played with the infant to direct his/her attention away, while head measurements were taken and the cap was being placed. The baby was then seated in a baby seat (Jelly Mom baby chair) to avoid physical contact with the mother, and the silent movie started being displayed immediately (Czech cartoon Krtecek as in Fairhurst et al. 2014).

The mother and infant sat in front of a computer screen, with the infant at approximately 70 cm from the screen. The experimenter sat in the right back hand side of the infant and parent, administering the stimuli and re-directing the infant's attention to the screen when needed. The parents were instructed to avoid any kind of interaction with the infant, and to only interfere when the he/she became fussy. The experimenter also avoided interaction with the

infant during the experiment. When needed, the experimenter introduced breaks to keep the infant involved in the session. The experiment finished when the infant completed all the 4 blocks (16 minutes) or when he/she became fussy. All the sessions were videotaped for offline coding. The experiment took place in a dimmed-light room to avoid light-interference.

Data processing and analysis

The video from each session was coded offline, by an observer who was blind to the inclusion criteria. Participants were only included if they completed at least 3 good quality trials (Lloyd-Fox, Wu, Richards, Elwell, & Johnson, 2015). Inclusion criteria included: (1) the infant did not move the arm in any direction while the stimulus was being administered; (2) the infant was not looking at the experimenter or the mother while the stimulus was being administered; (3) the infant did not touch the experimenter or the mother while the stimulus was being delivered. Participants completed an average of 6.68 ± 2.15 affective trials (range 4 -13) and 6.32 ± 2.52 (3- 12) discriminative trials. No statistical difference was found for number of trials completed at (χ^{2}- 31.39, p = 0. 885).

Changes in concentration of oxy-hemoglobin (**HbO_2**) or deoxy-hemoglobin (**Hbb**) measured in micromolar (µmol) were processed using HOMER2 (Huppert, Diamond, Franceschini, & Boas, 2009) a MATLAB (The MathWorks, Inc., Natick, MA, USA) software package. The attenuated light intensities measured by the detecting optodes were converted to optical density units and assessed for movement artifact using Principal Component Analysis (PCA) set at 0.9. (Cooper et al., 2012). We choose to use PCA because we only included trials in which the infant was not moving the arm, and is preferable to reject trials than correct them as other approaches do, as for example wavelet motion correction. Data were low- pass filtered at .5 (Lloyd-Fox, Szeplaki-Kollod, et al., 2015) and used to calculate the change in concentration of the hemoglobin chromophore according with the modified Beer-Lambert Law (Delpy et al., 1988) assuming a pathlenght factor of 5.13 (Duncan et al., 1995). Traces were segmented into 30 second epochs, starting 2 seconds prior to each stimulus. Baseline corresponded to the mean time from -2 to 0, as in previous fNIRS studies (Ravicz, Perdue, Westerlund, Vanderwert, & Nelson, 2015). This preliminary analysis allowed to determine that the long-channels (diagonal channels 12 and 16 in **Figure 9**) resulted in noisy data, and were excluded from further analysis.

Statistical analysis was performed using SAS (Statistical Analysis Software) 9.4v. Both a significant increase in **HbO_2** or a decrease in **Hbb** are accepted as indicators of hemodynamic activity, but according with the preliminary analysis, the majority of concentration changes were seen for HbO_2, and we choose to use only this chromophore as indicator of hemodynamic activity as in previous NIRS studies (Lloyd-Fox et al., 2016). For each channel, the maximum change in **HbO_2** (increase in chromophore concentration) in response to each experimental condition (affective and discriminative) was assessed relative to baseline using a mixed-effect regression model (the detailed description of the analysis is reported in Chapter 3). Following this initial analysis, a mixed model was computed for the channels that showed an increase in hemodynamic activity and SOR as a factor. Since SOR was computed from the Touch Section, there are no normative values that determine whether an infant presents "More Behaviors than Others" or "Less Behaviors than others", as there are for the Touch Section (Dunn, 2002). Therefore, infants were divided into 2 groups using a median split: high SOR scores and low SOR scores.

Results

Effect of condition.

As reported in Chapter 3, the contrast affective > discriminative resulted in significant increases of hemodynamic activity in 3 channels (channels 10, 14, and 15) placed over the temporal region. No significant results were found for the contrast discriminative > affective. Therefore, only affective touch was included in the following model.

Effect of SOR pattern in brain response to CT-touch.

The mixed linear model for the hemodynamic activity with SOR as a factor, revealed a significant interaction for channel 10, $F(1, 120) = 4.90$, $p = 0.029$. Infants with less aversive behaviors toward tactile stimuli presented a higher hemodynamic response than children with more aversive behaviors (M = 0.032, SE = 0.015 and M = -0.014, SE= 0.015, respectively). No interactions were found for channels 14, $F(1, 120) = 0.07$, $p = 0.788$, or 15, $F(1, 20) = 0.96$, $p = 0.328$. See **Figure 10.**

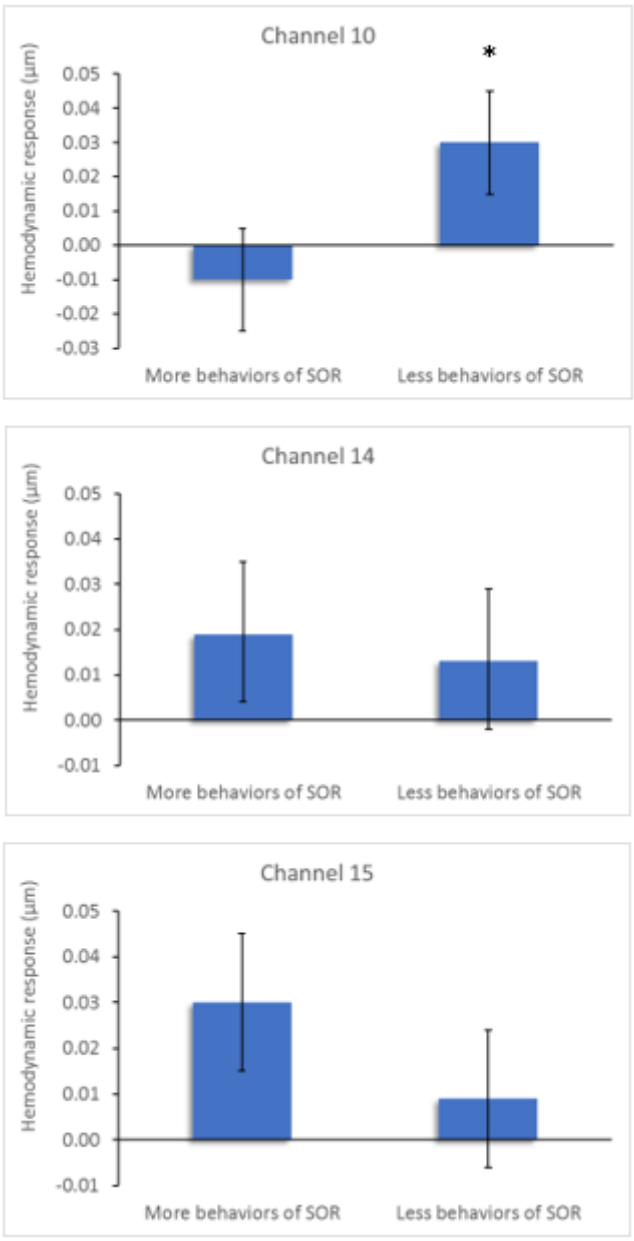


Figure 10.Hemodynamic response function by SOR behavior. Hemodynamic response to affective touch in channels placed over the temporal region in infants with more and less behaviors of SOR (sensory over-responsiveness). *Statistically significant difference with $p < 0.05$.

Discussion

In this paper, we examined if the brain response to affective touch in the pSTS region was associated with infant's behavioral differences to tactile sensory stimuli. Specifically, we used fNIRS to measure brain activity in the pSTS region to different types of tactile stimuli in a sample of infants at 12 months of age. Overall, our results confirm previous findings observed in adults (Bjornsdotter et al., 2014; Gordon et al., 2013; Kaiser et al., 2016; Voos et al., 2013), children

(Kaiser et al., 2015) and infants (Miguel et al. 2017b) showing that the pSTS, is involved in processing CT- targeted touch in infancy. More important, we found that the emergence of brain activity to affective touch within the pSTS at 12 months of age was related with individual differences regarding affective processing of tactile stimuli. Infants with a lower SOR (i.e., less aversive reaction) at 12 months of age presented a higher hemodynamic response to affective touch. Previous studies found that the pSTS activation to affective touch is affected by individual variability, as for example age and gender (Bjornsdotter et al., 2014), perceived pleasantness (Davidovic et al., 2016), or autistic traits (Bennett et al., 2014; Voos et al., 2013). However, to the best of our knowledge this is the study reporting this effect in such early stages of development. The right STS seems to be particularly susceptible to inter- individual variability, probably due to specific structural and functional characteristics of this region. In fact, at an anatomical level, asymmetries between hemispheres in the STS region can be seen as early as 26 weeks gestation, with the right STS being more deeper than the left (Dubois et al., 2010; Glasel et al., 2011). This rightward bias of the right STS (one of the few regions that is asymmetric since birth) suggests an anatomical specificity, that may explain its involvement in several high-order functions, including language and theory of mind, as well as its abnormal function in some neurodevelopmental disorders (Glasel et al., 2011). At a functional level, it is known that regions sub-serving sensory motor functions mature earlier in development, whereas associative high-order regions, including the temporal lobe, mature later (Lenroot & Giedd, 2006). The temporal lobe undergoes an increasingly rapid maturation in the first years of life (Bonte et al., 2013; Tanaka, Matsui, Uematsu, Noguchi, & Miyawaki, 2012) reaching a peak for gray-matter between the age of 9 and 11. During this process, the STS region becomes gradually more specialized and focal (Bonte et al., 2013), suggesting an increased sensitivity to individual differences. Therefore, it is not surprising our finding of pSTS activity differences associated with distinct affective processing of tactile stimuli.

SOR to tactile stimuli is known to be present in 2.5% - 6-5% of the general population (Goldsmith et al., 2006; Schoen et al., 2008). Overall, sensory symptoms remain stable over the first years of life (Ben-Sasson, Carter, & Briggs-Gowan, 2010), although there are inter-individual variations, with some children decreasing in symptoms, and others with latter onset (Van Hulle et al., 2015). For clinical populations, namely ASD, the trajectory is more consistent, with children presenting more stable symptoms across time, which are reported as one of the most challenging concerns by parents (Rogers & Ozonoff, 2005). Moreover, retrospective studies show

that infants avoidance behaviors to tactile stimuli are predictive of social impairments related with ASD in toddlerhood (Baranek, 1999; Mammen et al., 2015). Altogether, these findings suggest that sensory processing could be a valid tool when trying to understand more about ASD, since atypical sensory symptoms emerge before the onset of language, which is when the ASD diagnosis is currently made (APA, 2013)..

Although this study is the first to examine behavioral differences in the development of brain mechanisms associated with affective touch in infancy, it is important to note some limitations. The difficulty in standardizing cap placement because of head size and shape is a limitation inherent to fNIRS. Though we used 10-5 landmarks, future studies should incorporate digital localization to normalize channel placement in a standard space (Aasted et al., 2015). This would allow further inferences regarding the activity of each specific channel. The use of a questionnaire to measure of SOR may introduce subjectivity bias. Future studies should complement questionnaires with direct observation of infant response to tactile stimuli. Measuring brain activity in infants using fNIRS is challenging and the attrition rate results in small number of infants included in the analysis. Future studies should rely on larger samples in order to potentiate variability in brain and behavioral measures. Additionally, it would be also interesting to include measures capturing mothers' behavior and attitudes toward touch, as well as instances of touching interactions in mother-infant dyads (Brauer, Xiao, Poulain, Friederici, & Schirmer, 2016). In conclusion, this study supports the affective-motivational dimension of CT afferents (McGlone et al., 2007; McGlone et al., 2014; Morrison et al., 2010), and provides evidence that this system is not only present early in development, but is also associated with different profiles of affective touch processing.

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Funding: This study was supported by the Portuguese Science Foundation through an individual doctoral grant to Helga Miguel (SFRH/BD/86694/2012). The work was conducted at Psychology Research Center (UID/PSI/01662/2013), University of Minho, and supported by the Portuguese Science Foundation and the Portuguese Ministry of Science, Technology and Higher Education through national funds (PSI/01662) and co-financed by FEDER through COMPETE2020 under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-007653).

Conflict of interest: The authors declare they have no conflict of interest.

Chapter 5. Touch processing and social behavior in ASD

A version of this Chapter is published in the Journal of Autism and Developmental Disorders

Touch processing and social behavior in ASD

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Abstract

Abnormal patterns of touch processing have been linked to core symptoms in ASD. **Purpose:** This study examined the relation between tactile processing patterns and social problems in 44 children and adolescents with ASD, aged 6-14 (M=8.39±2.35). **Methods and Results:** Multiple linear regression indicated significant associations between touch processing and social problems. No such relationships were found for social problems and autism severity. Within touch processing, patterns of hyper-responsiveness and hypo-responsiveness best predicted social problems, whereas sensory-seeking did not. **Conclusion:** These results support that atypical touch processing in individuals with ASD might be contributing to the social problems they present. Moreover, it supports the need to explore more in depth the contribution of sensory features to the ASD phenotype.

Keywords: ASD; sensory processing; touch processing; social behavior

Introduction

Autism spectrum disorders (ASD) are clinically characterized by a qualitative impairment in social cognition, social interaction and communication abilities, with restricted and repetitive topics of interest. Deficits in multisensory integration and cross-modal binding, impaired responses to tactile, visual and auditory stimuli have also been a long recognized feature of ASD (Baker, Lane, Angley, & Young, 2008; Brandwein et al., 2015; Marco, Hinkley, Hill, & Nagarajan, 2011) and are possibly related to other core features of the disorder, including the development of aberrant behavior and later prognosis (Baranek, Foster, & Berkson, 1997). As a result, just recently, abnormal patterns of sensory-perceptual processing were recognized as a characteristic of the ASD phenotype and therefore added to the DSM-5 as part of one of the diagnostic criterion (APA, 2013).

Sensory processing abnormalities have been described as the most challenging concerns of parents of children with ASD (Rogers & Ozonoff, 2005). Within the sensory domains, impaired responses to tactile stimulation is one of the most reported (Hilton et al., 2010; Lane, Young, Baker, & Angley, 2010) with ASD children presenting atypical sensory responses to textures, preoccupations with sensory features of objects, and problems habituating to prior sensory experiences. In addition, children with ASD show significantly more defensive reactions and lower pleasantness ratings to tactile stimuli than typically developing children (Tomchek & Dunn, 2007). These symptoms combined have been reported in 85% to 95% of children with ASD (Kientz & Dunn, 1997; Puts, Wodka, Tommerdahl, Mostofsky, & Edden, 2014; Rogers & Ozonoff, 2005; Tomchek & Dunn, 2007). This atypical touch processing has also been examined in psychophysical studies and findings suggest that children with ASD show increased pain sensitivity, increased sensitivity in C – tactile innervated areas (Riquelme, Hatem, & Montoya, 2016), and also more defensive reaction and lower pleasant ratings that typically developing children (Cascio, Lorenzi, & Baranek, 2016). Neuroimaging and electrophysiological studies have also confirmed abnormal touch processing in this population. Results show that children and adolescents with ASD demonstrate diminished brain responses for pleasant stimuli in brain regions involved in social-emotional information processing (Kaiser et al., 2016), while presenting specific patterns of neural activity to touch that relate with behaviors of hypo- and hyper-responsiveness (Cascio, Gu, Schauder, Key, & Yoder, 2015; Green et al., 2015).

Although this relation between sensation and behavior goes back to (Kanner, 1943) and his first description of autistic symptoms that included differences in sensitivity to external

sensory stimuli, there is still a lack of evidence about the contribution of sensory processing to the core symptoms presented by individuals with ASD. In 1997, Dunn proposed a model to classify patterns of dysfunction in sensory processing in typically developing children. Classifications were defined according to behavioral responses to stimuli and neurological thresholds and included: low registration – the degree to which a child misses sensory input; sensation seeking – the degree to which a child obtains sensory input; sensory sensitivity – the degree to which a child detects sensory input; and sensation avoiding – the degree to which a child is bothered by sensory input (Dunn & Brown, 1997). Baranek and colleagues (2006) observed similar sensory patterns in a sample of children with ASD but applied different classification terminology: hyper-responsiveness - when children present a low threshold for stimuli in the environment that most people find inoffensive; hypo-responsiveness – when the child fails to register sensory input; and sensory seeking – when the child seeks more sensory stimulation than the majority of people (Baranek, David, Poe, Stone, & Watson, 2006). Both models agree that that sensory patterns are not mutually exclusive and that a child might present behaviors from 2 or more of these patterns.

There are two main approaches used to study the relation between sensory processing and behavior in ASD. The first is by grouping the individuals in subgroups according to the response to sensory stimuli (visual, auditory, vestibular, tactile, gustatory and olfactory modalities), individually or collapsed. Within this approach, the literature suggests that atypical responses to tactile, taste/smell and multisensory stimuli are related with a greater lack of social responsiveness (Hilton et al., 2010) and maladaptive behavior (Lane et al., 2010) in children with high function autism. Furthermore, Lane and colleagues also found that movement sensitivity and auditory filtering contribute to maladaptive behavior (Lane et al., 2010). One specific behavior that has been examined in relation to sensory symptoms in ASD is repetitive behavior (Chen, Rodgers, & McConachie, 2009), and the findings suggest that sensory features, namely, tactile and visual/auditory sensitivity are related with it.

The second approach is to look at the patterns of responsiveness. According with this approach, repetitive behaviors have been related with patterns of hyper responsiveness (Boyd et al., 2010), but also under responsiveness (or hypo responsiveness) (Wigham, Rodgers, South, McConachie, & Freeston, 2015), which is consistent with the fact that two or more sensory patterns can co-occur in the same individual (Brown & Dunn, 2010). Other core-symptom of ASD, namely ritualist behavior, has been related with the sensory seeking (Boyd et al., 2010),

and the patterns of hypo responsiveness and sensory seeking are more likely to occur in non-verbal children (Patten, Ausderau, Watson, & Baranek, 2013). Although this approach is useful to better understand the relation between sensory abnormalities in ASD behavior and function, it does not provide information about the contribution that each sensory domain has in behavioral problems presented by this population. To do this we need to join both approaches by looking at a single sensory modality, and examine the sensory patterns on it. To our knowledge only one study looked at the individual contribution of tactile processing to core symptoms in ASD. (Foss-Feig, Heacock, & Cascio, 2012) examined this relation in a group of children from 5 to 8 years old using parent report and direct observation, and found that behaviors of hypo-responsiveness and sensory seeking for the tactile modality had a strong correlation with increased social and communication impairment.

While the literature suggests a link between tactile processing and social behavior in ASD, the tactile modality has received less attention than other sensory modalities in the study of ASD (Wiggins, Robins, Bakeman, & Adamson, 2009). Still, touch is of extreme importance for human social bonding and affect communication (Gallace & Spence, 2010; Morrison, Loken, & Olausson, 2010) being the primary channel of communication in the first year of life. Besides its contribution to primary reflexes (Muir, 2002) , and fine and gross motor skills (Weiss, Wilson, & Morrison, 2004) touch plays an important role in the development of bonding and secure attachment (Weiss, Wilson, Hertenstein, & Campos, 2000) which lays the foundation for healthy behaviors later in development. Moreover, touch reduces infants response to stress(Jean & Stack, 2009; Stack & Muir, 1990) and promotes emotion regulation in infants (Hertenstein & Campos, 2001; Weiss et al., 2000). Research with animal models have shown that deprivation of early maternal licking and grooming behaviors have a negative impact in the offspring stress response and behavior, and that this pattern is present even in adulthood (Champagne, 2008; Menard, Champagne, & Meaney, 2004).In fact, touch is the main form of interpersonal communication in many animal species (Hertenstein, Verkamp, Kerestes, & Holmes, 2006b) and evolutionarily it precedes verbal communication (Dunbar, 1998), what suggests that touch might play an important role in social behavior and communication in humans as well.

Considering the importance of touch in early development, and its relation with social and communicative behavior later in life, it is not surprising that there might be a relation between the tactile behavior in individuals with ASD and the social problems they present. Very few studies have looked at this specific relation, and to our knowledge no other study have looked

at this relation in children and adolescents. Therefore, the primary aim of this study is to understand if touch processing predicts social problems in a sample of children and adolescents with ASD. The secondary aim is to determine which sensory patterns within the tactile modality – hypo-responsiveness, hyper-responsiveness or sensory seeking, best explain the problems presented by the children and adolescents.

Methods

Participants

Participants were 44 children and adolescents with ages between six and fourteen (M =8.39±2.35) with the diagnosis of ASD, of an ongoing project from the Galician Foundation of Genomic Medicine– Santiago de Compostela, Spain, on the relationship between phenotype and genotype of ASD. These participants were part of a cohort of youth diagnosed with autism (N = 135, 6-18 years) that did not have data on our measure of sensory processing but where data were available for social problems and autism severity. Therefore, descriptive data on both social problems and autism severity were provided separately for both our sample and the full cohort in order to assure that the participants used in this study did not differ consistently from the youth enrolled in the project. See **Table 7** and **Table 8** for sample demographics.

Participants were referred through institutions that provide support to families who have children diagnosed with ASD. All the participants have been previously being diagnosed by an experienced psychiatrist and all 135 participants met criteria for ASD.

Table 7. Sample characteristics for the sub-sample.

	Frequency	
	Number	%
Age classification		
Total 6- to 11-years-old	39	88%
Gender male	32	82%
Total 12- to 14-years-old	5	11.4%
Gender male	3	60%
Overall gender: Male	35	79.5%
SCQ Classification (n=44)		
> 15 (clinical)	28	63%

N =44

Table 8. Sample characteristics for the total sample.

	Frequency	
	Number	%
Age classification		
Total 6- to 11-years-old	92	68%
Gender male	73	79%
Total 12- to 18-years-old	43	32%
Gender male	31	72%
SCQ Classification (n=126)		
< 15 (normal)	47	35%
> 15 (clinical)	79	59%

N = 135

Measures

Child Behavior Checklist (CBCL)

CBCL is part of Achenbach System of Empirically Based Assessment (ASEBA) developed by Thomas M. Achenbach (M. & L.A., 2001) and measures emotional and behavioral problems in school age children from 6 to 18 years of age Spanish standards were used (Unitat

d´Epidemiologia i Diagnòstic en Psicopatologia del Desenvolupament, 2013). The CBCL contains two empirically-derived broadband scales - *Internalizing Domain* and *Externalizing Domain*, and eight syndromes scales - *Anxious/Depressed*, *Withdrawn/ Depressed*, *Somatic Complaints*, *Social Problems*, *Thought Problems*, *Attention Problems*, *Rule Breaking* and *Aggressive Behavior*. Total Problems scale quantifies the overall impairment.

It consists of 113 items scored on a three-point Likert Scale (0=" Not true"; 1= "Somewhat or Sometimes True"; 2= "Very true or often true"). Raw scores for each scale are converted to *T-scores* (M = 50, SD = 10) for age and gender, within the 6-11 and 12-18 age range. A *T-* score ≥ 64 on broadband scales, and ≥ 67 on syndrome scale is considered *clinically significant.*

Social Communication Questionnaire (SCQ)

Social Communication Questionnaire (SCQ) is a parent report that measures communication skills and social functioning in children who have autism or autism spectrum disorders (Rutter, Bailey & Lord, 2003). SCQ was designed as a screening questionnaire, and it is based on the Autism Diagnostic Interview (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and DSM-4 (APA, 1994).

The items are based on three areas of functioning: reciprocal social interaction, communication, and restricted, repetitive and stereotyped patterns of behavior. It is available in two forms – Lifetime and Current, and both versions contain 40 questions presented in a yes or no format. The Lifetime form focuses on the child´s entire developmental history, and the Current form looks at the child´s behavior over the most recent 3-month period. A Total Score above 15 on each is considered clinically significant. For statistical purposes, we used the measure as continuous.

Sensory Profile 2 (SP2)

The Sensory Profile 2 is a family of assessments that evaluate sensory processing in children (Dunn, 2014). The child form helps identify the effect of sensory processing on functional participation in children aged 3 -14. It consists of a set of judgment-based caregiver questions relative to sensory systems (auditory, visual, touch, movement, body position and oral), behavior (behavior, conduct, social-emotional and attentional), and sensory pattern scores

(seeking, avoiding, sensitivity and registration). It contains 86 items scored on a 5 point Likert Scale (1= “Almost Never”, 2= “Occasionally”, 3= “Half of the time”, 4= “Frequently”, 5= “Almost Always”). Scores one standard deviation or more from the mean are expressed as More than Others or Less than Others, respectively. Scores two standard deviations or more from the mean are expressed as Much More Than Others or Much Less than Others, respectively. Touch processing, which is the primary focus of this study, consists of 9 items across the different sensory pattern scores. Questions include for example “Shows need to touch on objects, surfaces or textures” (sensory seeking), “Shows an emotional or aggressive response when someone touches him/her”, (sensory avoiding), “Shows anxiety when needs to be close to others (standing on a line) “(sensitivity) or “Seems not to notice when his hands or face is dirty” (registration).

Procedure

The study protocol was granted ethical approval from the Galician Clinical Research Ethics Committee (2012/ 098). Parents gave informed consent before children were enrolled in the study. As part of the ongoing study on genetics, children did a visit to Fundación Pública Galega de Medicina Xenómica/ Santiago de Compostela Hospital. During the visit, CBCL, SCQ and SP2 were administered to the parents. When missing, data were detected in any of the measures, parents were contacted in order to have the maximum number of complete cases. Only complete cases were used for the analysis described below.

Statistical Analysis

Statistical analyses were performed using the statistical package IBM SPSS Statistics 21 for Windows (SPSS Inc., Chicago, USA). Descriptive statistics were first computed for both the sample used in this study (N = 44) and the original cohort (N = 135) on available concurrent scales for CBCL and the severity of autism (i.e., SCQ). This first analysis ensured the generalizability of our sample to youth enrolled in the cohort. The examination of generalizability was followed by inspection of the distributions of touch processing in our sample and its relations with social problems after adjusting for autism severity. More specifically, we used multiple linear regression analysis with touch processing and autism severity scores as our predictor variables

and social problems as our outcome of interest. This model was replicated using aggregated tactile item scores to reflect sensory processing patterns – sensory seeking, hypo - responsiveness (registration/bystander), and hyper-responsiveness (the sum of avoiding and sensitivity items). This sum was used before since sensitivity and avoiding are highly correlated (Ben-Sasson et al., 2008). Associations were defined as being statistically significant when β-weights reached $p \leq 0.05$.

Results

Participants included in the present study (N =44) and the overall project (N=135) were similar in their scores for CBCL and SCQ. Detailed descriptives for these measures and SP2 are presented below and followed by the regression results. In addition, for the CBCL and SP2, only the subscale Social Problems and Touch Processing, respectively, were used for analyses. However, all subscales from the 2 measures are described.

CBCL

Mean *t*-scores of CBCL for the subset of the sample (N = 44) on the subscale Social Problems were above clinical cut-off (M = 67.77±14.43). The total sample (*N*=135) scores were borderline (M = 66.48±13.84). Scales Withdrawn/ Depressed (M = 67.35±16.22), Thought Problems (M = 69.8±17.37) and Attention Problems (M = 68.15±9.93) scored also above the clinical cut-off for the subset of the sample. Anxious-Depressed (M = 53.91±10.82), Somatic complaints (M = 53.04±8.8), Rule Breaking (M = 54.35± 9.69), Aggressive Behavior (M = 58.27± 11.78), Internalizing (M = 59.46±12.34), Externalizing (M = 57.31±10.33) and Total Problems (M = 63.50±11.11) scored below the clinical cut-off.

SCQ – Current form

Mean raw scores for SCQ – current form was 18.54±6.55 for the subset of the sample (N = 44), with 63% of children (N =28) scoring above the clinical cut-off. For the total sample (N = 126), 59% of the children (N =79) scored above the cut-off.

SP2

Mean raw scores on Touch Section scored under *More than Others* (M = 25.79±10.7). Sensory Sections Auditory (M = 23.59±8.80), Visual (M = 12.58±5.17), Movement (M = 17.53±7.46), Body Position (M = 13.76±8.27) and Oral (M = 23.22± 10.55) scored under *Just Like the Majority of the Others*. Regarding the Behavioral Scores, Conduct scored *Just Like the Majority of the Others* (M = 22.29±8.72), whereas Social Emotional (M = 41.18±12.58) scored *More than Others*, and Attentional (M = 30.37±10.90) scored *Much More than Others*. Concerning the Quadrants, children scored *Just Like the Majority of Others* for Seeking/ Seeker (M = 45.37±15.18), and scored *More than Others* for Avoiding/ Avoider (M =54.65±16.08), Sensitivity/Sensor (M = 50.03±16.84) and Registration/ Bystander (M = 49.11±21.02).

Regressions analysis

A multiple linear regression was calculated to predict Social Problems based on Autism Severity and Touch Processing for the subset of the sample (N =44). A significant regression equation was found (F (2,44) = 7.65, p < 0.01), with an R^2 of 0.22. Social Problems increased 0.83 for each increase unit of touch processing. Only Touch Processing was a significant predictor of Social Problems (see **Table 9**).

A significant regression equation was found for hypo-responsiveness (F (2,44) = 10.02, p< 0.01) with an R^2 of 0.34, and a borderline regression equation for hyper-responsiveness (F (2,44) = 2.69, p = 0.08), with an R^2 of 0.12. No significant effect was found for tactile seeking (F (2,44) = 1.50, p = 0.09), with an R^2 of 0.07).

Table 9. Multiple linear regression models for CBCL Social Problems.

	Adjusted R^2	B	SE B	*B*	*p*
Model 1	0.22				
SCQ		-0.39	0.32	-0.18	0.23
Touch Processing		0.83	0.21	0.43	0.00
Model 2	0.34				
SCQ		-0.31	0.3	-1.45	0.30
Tactile -hypo		2.15	0.48	0.61	0.00
Model 3	0.12				
SCQ		-1.42	0.347	-0.66	0.68
Tactile-hyper		1.25	0.55	0.36	0.03
Model 4	0.07				
SCQ		0.03	0.34	0.02	0.91
Tactile-seeking		0.95	0.56	0.27	0.10

Discussion

This study examined the relation between tactile processing patterns and social problems in children and adolescents with ASD. Our results support the hypothesis that atypical touch processing is related with increased social problems in ASD. The associations between atypical touch processing and social problems were also more pronounced among children with hypo and hyper-responsiveness profiles. These findings can have clear implications when translated to situations of daily life. It has been demonstrated that the inability to orient to sensory stimuli, in social and non-social conditions, can have an impact in broader social-communicative outcomes in children with ASD (Baranek et al., 2013). Sensory processing also appears to be an important contributor and even the foundation for the development of more complex skills, as initiation and response to joint attention. The pattern of hypo-responsiveness to sensory stimuli in ASD, including tactile, may lead to failure in responding to the environmental cues and missing learning opportunities, which are the foundation of more complex processes, such as social interaction.

The finding that children and adolescents with ASD present abnormal sensory touch processing has been extensively reported in the literature (Hilton et al., 2010; Lane et al., 2010).

Studies show clear differences between youth with ASD and typical developing children on atypical sensory responses to textures (i.e., more defensive reactions) and lower pleasantness ratings to tactile stimuli (Cascio et al., 2016; Cascio et al., 2012) These patterns also seem to hold independently of the measure used to characterize touch processing as suggested by studies using parent reports, direct observation, electrophysiological measures, and neuroimaging measures (Baranek et al., 2006; Dunn, Gomes, & Gravel, 2008; Kaiser et al., 2015; Kientz & Dunn, 1997; Tomchek & Dunn, 2007). In our study, we used a parent report to measure sensory processing (i.e., SP2), and found that our sample with ASD scored above the typical behavior cut point for the tactile sub-scale (i.e. 21). A score above this cut point indicates that the child present atypical tactile behaviors "more than others".

Youth with ASD often present CBCL scores above the clinical cut-off for Social Problems syndrome (Havdahl, von Tetzchner, Huerta, Lord, & Bishop, 2016; Mazefsky, Anderson, Conner, & Minshew, 2011), Thought Problems and Attention problems (Havdahl et al., 2016; Mazefsky et al., 2011). We were also able to confirm these patterns and reinforce the notion that social problems are characteristic of children and adolescents with ASD. The findings were also aligned with our expectations. We were particularly interested in a measure of social behavior in ASD, and the choice of using Social Problems subscale from CBCL had to do with the fact that this tool has been shown to be sensitive to differences in the various subscales between children and adolescents with ASD and typically developing children (Hartini, Sunartini, Herini, & Takada, 2016; Ooi, Rescorla, Ang, Woo, & Fung, 2011).

Our results, overall, provide supporting evidence for the contribution of the touch processing domain to the social problems presented by youth with the disorder. These findings are partially in agreement with Foss-Feig, Heacock, & Cascio (2012), who also found that patterns of hypo-responsiveness to the tactile modality were related with social impairment in a sample of 5-8 years-old children diagnosed with ASD. This is also consistent with other literature that has identified hypo-responsiveness as being the most sensitive indicator to differences between children with ASD, and typically developing children (Baranek et al., 2006; Ben-Sasson et al., 2009). Contrary to these studies, we did not find a relation between tactile seeking behavior and social problems. To our knowledge no other study looked specifically to the hyper-responsiveness pattern in the tactile domain and the relation with social problems in children ASD however it is well accepted that hyper-responsiveness in children with ASD is related with maladaptive behavior (Baker et al., 2008), negative emotions, anxiety and depressive symptoms

(Ben-Sasson et al., 2008), or other core symptoms of ASD (e.g., repetitive behaviors) (Boyd et al., 2010). The study from Baranek illustrates this by showing that infants (9 to 12 months of age) later diagnosed with autism, had a pattern of behaviors that differentiated the ASD group from typically developing children. Behaviors included social touch aversions which can be included under the hyper-responsiveness pattern (Baranek, 1999).

The methodological differences between previous studies and ours (e.g., measures, age of the participants) might explain some of the discrepancies found. Foss-Feig and colleagues used a different parent report and used direct observation to measure tactile responses. These methods can provide a more objective estimate of tactile response however might limit the ecological validity and depiction of a typical response to tactile as responses in an experimental setup that might not reflect everyday responses to touch. The differences between the measures included in the protocol might also explain the lack of an association between ASD and sensory-seeking behaviors. Sensory-seeking behaviors in our study was captured by items such as "touches people and objects to the point of annoying others" or "touches people and objects more than same-aged children". In Foss-Feig study sensory-seeking was measured by a single item "does not respond to pain", and by the Tactile Defensiveness and Discrimination Test using seeking reactions to tactile stimuli (e.g., excessive engagement with/and, very strong positive affective response to the stimuli) which makes comparisons difficult to establish. Our measure included multiple items to characterize sensory-seeking behaviors, and they used a combined measure of direct observation and a single item of a questionnaire. The differences in study samples (i.e., participants) are also likely to contribute to the differences in the findings. Foss-Feig´s study examined 5-8 years-old children whereas our sample age ranged from 6 to 14 years. The age differences between these two samples are very relevant and might explain the lower prevalence of sensory symptoms in our sample. Studies have shown that sensory symptoms decrease with age (Baranek et al., 2006) and that that associations seen in young children might not hold at older ages.

This study contributes to the understanding of how sensory processing relates to behavior in a sample of children with ASD, however it is important to note a few limitations while providing insights for improvement in future studies. The study sample enrolled in our study was relatively small even though participants were part of a larger cohort. We were still able to uncover some of the expected characteristics of children with ASD (e.g., hypo-responsiveness profiles) while finding important associations between touch processing and social problems. Our

study is one of the few studies that has examined the relation between social problems and tactile processing in children with ASD and can provide valuable insights for studies that will follow. It is particularly important that future studies use larger samples to examine whether it is possible to discriminate the sensory threshold by which a child would have social problems. A bigger sample size would allow the use of more sophisticated data statistical analysis as receiver operating characteristic (ROC) curves to determine this relation. In our study, we also used a parent report to rate the sensory behaviors and behavioral problems. This approach has value however there is the potential for bias and subjectivity. We could have used more objective measures to capture this information however that would come at a cost of ecological validity and therefore, we chose to use parent reports. In addition, we also used a screening measure (SCQ) as an indicator of autism severity. Interestingly, we found that only 63% of our sample scored above the clinical cutoff (i.e., score of 15) (Rutter, Bailey, & Lord, 2003). This measure lacks sensitivity to discriminate the severity of autism however we did supplemental analyses and found that if we were to use a cut-off of 11 as suggested in the literature (Corsello et al., 2007; Eaves, Wingert, Ho, & Mickelson, 2006; Snow & Lecavalier, 2008) 89% of our sample would be classified as having ASD. These discrepancies illustrate the challenges with cutoffs developed for this measure and therefore we chose to use scores that would be independent of the threshold while maximizing our statistical power and adjusting our models for the confounding effect of autism severity. Another important limitation to note was the fact that SCQ did not correlate with social problems. This can possibly be explained by the "Current Form", which refers to the most recent 3 months of the child´s life. It can be the case that parents focused on the best (i.e., lifetime) of the child´s function, and as result, attributed higher scores (greater percentage of "no behavior"). This might have limited our ability to uncover these associations, as over-reporting in this scenario would contribute to the attenuation of the relation between SCQ and social problems. Future studies that include both subjective (e.g., parent and/or teacher reports) and objective (e.g., observation) measures should be able to quantify the impact of such bias when determining these associations. This methodological improvement would allow for a better understanding of ASD behavior patterns and their relation to tactile processing. In conclusion, this study contributes to a better understanding about ASD phenotype and provides evidence about sensory symptoms in this population. The study also adds to the scarce of literature on the implications of atypical touch processing for every-day behaviors. The study can inform and help develop sensory-based interventions for this population.

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Funding: The study was supported by Fundación María José Jove. H. Miguel is supported by an individual doctoral grant from Portugal Science Foundation SFRH/BD/86694/2012R. Martínez-Regueiro is supported by a public fellowship from ISCIII/ FI14-00510/ cofunded by FEDER. C. Gutiérrez López-Dóriga is supported by a Grant of Young Employment Promotion Ref. PEJ-2014-P-01190 from Ministry of Economic Affairs.

Conflict of interest: The authors declare they have no conflict of interest.

Chapter 6. General discussion and conclusion

The sense of touch is of paramount importance for child development and is thought to precede important processes underlying the development of socio-emotional competencies (e.g., language, emotional expressions) (Dunbar, 1998; Hertenstein, Verkamp, Kerestes, & Holmes, 2006). The relative importance of touch for has been demonstrated in studies of disorders that lack social-emotional reciprocity, namely ASD, where atypical touch processing has been associated with core symptoms of the disorder (Foss-Feig, Heacock, & Cascio, 2012). Likewise, during infancy, touch has also demonstrated to have an important role in the establishment of secure attachment (Weiss, Wilson, Hertenstein, & Campos, 2000; Weiss, Wilson, & Morrison, 2004) and emotion regulation (Hertenstein & Campos, 2001). Overall, studies on touch suggest that it may have an important contribution towards children social-emotional development; however very little is known about the underlying neural mechanisms.

Some studies have proposed that a specific group of tactile fibers (CT afferents) are likely to mediate this affective-motivational component of touch (McGlone, Vallbo, Olausson, Loken, & Wessberg, 2007; McGlone, Wessberg, & Olausson, 2014; Morrison, Loken, & Olausson, 2010) but the role of these fibers, particularly during the first year of life is still uncertain. This rationale set the stage for the current dissertation work: the first 3 chapters describe a series of studies that explored the brain mechanisms underlying touch processing during the second semester of postnatal life (i.e.,7 through 12 months) while in the chapter 5 we explored the association between social development competencies and touch in a clinical sample of children with abnormal sensorial processing – Autism Spectrum Disorder (ASD). The key findings obtained from each of these studies are described in the sections below.

In **Chapter 1** the sense of touch was introduced in the context of infant development, and examined with regards to two main domains, the sensory-discriminative and the affective-motivational, with a focus on the second. The evidence suggests that CT fibers might be a strong candidate to mediate touch used in affiliative behaviors and social interaction, since early stages of development (McGlone et al., 2007; McGlone et al., 2014; Morrison et al., 2010). However, very few research has been conducted to test this hypothesis in infancy. In addition, individuals who lack social-communicative competencies, namely individuals with ASD, seem to process affective touch differently than typically developing individuals (Kaiser et al., 2016), emphasizing

the putative role of this system in social behavior. Despite this, the contribution of touch processing to core-behaviors presented by this population remains to be answered. Altogether, the literature is scarce in the developmental trajectory of the affective-motivational dimension of touch, including the brain mechanisms behind it. However, there is strong evidence that this system might present during the first year of life. This hypothesis was addressed in Chapters 2, 3 and 4 of this dissertation. The contribution of touch processing to a core-behavior of ASD - social behavior, was explored in Chapter 5.

In **Chapter 2** we examined brain responses for affective and discriminative touch in 7-month-old infants using fNIRS. Brain's hemodynamic activity was analyzed in response to two distinct stimuli applied to the infant's forearm: a discriminative stimulus consisting of a wood block that would target Aβ fibers, and an affective stimulus consisting of slow brush strokes targeting CT fibers. Two regions of interest were targeted: somatosensory cortex and temporal region, specifically the pSTS. The results showed that 7-month-old infants process both affective and discriminative components of touch in the somatosensory cortex, but that the right temporal region is not yet recruited at this age to process affective touch. The recruitment of primary sensory regions as the somatosensory cortex to process stimuli provided by Aβ (Bartocci, Bergqvist, Lagercrantz, & Anand, 2006; Nevalainen, Lauronen, & Pihko, 2014; Verriotis et al., 2016) and (non-exclusive) CT (Bjornsdotter, Gordon, Pelphrey, Olausson, & Kaiser, 2014) receptors is consistent with other studies in infancy and childhood. The lack of activation in the temporal region following CT stimulation, suggests that brain activation to affective touch follows a specific developmental trajectory. Apparently, at 7 months of age, our results suggest that infants do not yet use higher-associative regions, namely the pSTS, to process affective touch, as children, adolescents and adults (Bennett, Bolling, Anderson, Pelphrey, & Kaiser, 2014; Bjornsdotter et al., 2014; Gordon et al., 2013).

Together, the activation of somatosensory region and lack of activation of the temporal region seem to be a unique pattern in this age cohort, as other studies also failed to find brain activity in social-emotional regions to affective touch in 3 and 6 month-old infants (Kida & Shinohara, 2013). To our knowledge, this was the first study that used fNIRS to measure touch processing by contrasting Aβ to CT targeted touch in infancy, examining two distinct regions of interest. This contributed to the validation of fNIRS to measure basic sensory processing in infancy, and helped to determine the distinct activation of the two classes of fibers in early development.

In **Chapter 3**, we examined the developmental trajectory of brain activity to affective touch, by following longitudinally infants from 7 to 12 months of age. The paradigm and regions of interest were the same as described in Chapter 2. Similarly, 7-month-old infants processed both discriminative and affective touch in the somatosensory cortex. However, at 12 months of age, infants showed a shift by activating also a posterior region of the temporal lobe, the pSTS, following affective, but not discriminative touch, as children, adolescents and adults do (Bennett et al., 2014; Bjornsdotter et al., 2014; Gordon et al., 2013). This finding supports the developmental trajectory of brain mechanisms to process CT fibers, which are hypothesized to serve an important role in social behaviors (McGlone et al., 2007; McGlone et al., 2014; Morrison et al., 2010; Olausson et al., 2002). Moreover, the emergence of brain mechanisms to process affective touch is consistent with the development of other socially relevant behaviors starting such as joint attention, social referencing, attachment and implicit mental state attribution (Happé & Frith, 2014; Johnson, 2005), which emerge between 9 and 12 months of age.

Another striking finding from this study was that 7-month-olds presented greater brain activation in the somatosensory region for discriminative touch, while 12-month-olds presented an increased hemodynamic activity in the temporal region for affective touch. Indeed, recent studies have claimed dissociable regions for affective and discriminative aspects of touch in adults (Case et al., 2016; Case et al., 2017; Morrison, 2016), and our results are consistent with this view, namely that affective-motivational and sensory- discriminative co-activate different networks, but share somatosensory co-activations. Our study was the first to report this trajectory over time, registering the shift in the neural resources of processing discriminative touch in sensory region to process affective touch by recruiting the pSTS.

Having determined the developmental trajectory of brain response to affective touch from 7 to 12 months of age, we were further interested in understanding if the brain response in the temporal region was associated with infant's behavioral differences to tactile sensory stimuli at 12 months of age. In the study presented in **Chapter 4** we addressed this question by using fNIRS to measure brain activity in the temporal region to affective and discriminative touch in the same sample of infants at 12 months of age. In addition, we measured negative emotional responses to touch - sensory over responsiveness (SOR), using parent report. We found that the infants who presented the greatest activity in social-emotional regions of the brain (STS) following affective touch stimulation, were the infants who presented less behaviors of SOR towards tactile stimuli.

This study is the first to report variability in pSTS to affective touch, in infancy, similarly to has been described in children and adults (Bjornsdotter et al., 2014; Davidovic, Jonsson, Olausson, & Bjornsdotter, 2016; Voos, Pelphrey, & Kaiser, 2013). Moreover, it supports the right pSTS susceptibility to individual differences (Bonte et al., 2013), that has been linked to abnormal function in some neurodevelopmental disorders, including autism or schizophrenia (Glasel et al., 2011).

More important, the results also suggest that the infants who have the lowest avoidance toward touch experiences, are the ones who present the greatest increase in brain activity when touched with the brush, providing a link between behavioral responses to touch, and the reward value of being touched. This finding is particularly relevant in the context of ASD, where individuals lack social-communication skills (APA, 2013), present behaviors of SOR to tactile stimuli (Baranek, Boyd, Poe, David, & Watson, 2007; Baranek, Foster, & Berkson, 1997; Foss-Feig et al., 2012; Green et al., 2015), and show abnormal brain responses to affective touch (Kaiser et al., 2015).

This set of three studies conducted in infants provide evidence, at a brain level, that the networks that subserve the sensory-discriminative and affective-motivational dimensions of touch of are in place in the second semester of life. Furthermore, our results suggest that these networks follow a developmental trajectory that accompanies other developmental acquisitions, namely at a social-emotional and motor levels. Lastly, our results point to a relation between decreased brain activation of the affective-motivational dimension of touch in a social-emotional region, and negative responses to touch, at a behavioral level. Together, our findings suggest that the CT system contributes to the affective-motivational aspect of touch, supporting the *skin as a social organ* hypothesis (Morrison et al., 2010; Olausson et al., 2002). This former assumption was thus still understudied and therefore we conducted an additional study to test this hypothesis, by exploring, in **Chapter 5,** the relation between tactile processing patterns and social problems was examined in a sample of children and adolescents with ASD. (H et al., 2017). We used parent reports to evaluate Tactile Processing, Social Problems and Autism Severity.

The results from this study support the hypothesis that atypical touch processing is related with core symptoms in ASD (Baranek et al., 1997; Foss-Feig et al., 2012). Specifically, patterns of hyper-responsiveness to tactile stimuli result in increased social problems, as previously reported in the literature (Foss-Feig et al., 2012). Our study confirms that the inability to orient and respond adequately to sensory stimuli, in social and non-social conditions, can have an impact in broader

social-communicative outcomes in children with ASD (Baranek et al., 2013). Moreover, recently it has been found that patterns of SOR to tactile stimuli disrupt the ability to respond effortfully to social relevant stimuli, at a brain level (Green, Hernandez, Bowman, Bookheimer, & Dapretto, 2017). Together, these findings suggest that atypical touch processing plays an important role in social-reciprocity in this population. However, what dimension of touch contributes to these issues, remains to be answered.

In conclusion, the current dissertation work contributed to a better understanding of touch processing at a brain and behavioral levels. At a brain level, we extended on what was known regarding the cortical processing of both sensory-discriminative and affective-motivational components of touch, using fNIRS in infancy. Therefore, in a sample of infants followed longitudinally (7 and 12 months-old), we measured brain activity in a primary sensory region (somatosensory cortex) and a higher-level associative region (pSTS), in response to a discriminative stimulus and an affective stimulus. At a behavioral level, we measured atypical tactile processing in the same sample of infants, but also in a sample of children and adolescents with ASD. Together, the findings from the studies support that touch is important for social-emotional and that the motivational-affective dimension of touch seems to play an important role in these processes.

The use of fNIRS allowed the measurement of cortical brain activity in this age, which would have been limited by the lack of feasible neuroimaging techniques that could be used in infants (Lloyd-Fox, Blasi, & Elwell, 2010). fNIRS has opened the opportunity to study brain activity in response to target stimuli under less controlled environments (Lloyd-Fox, Papademetriou, et al., 2014; Lloyd-Fox, Szeplaki-Kollod, Yin, & Csibra, 2015) that in past would only be possible using techniques as functional magnetic resonance imaging or positron emission tomography, which require the participant to be sedated or asleep. More important, because of its characteristics, fNIRS allows the study of longitudinal changes in brain function (Lloyd-Fox et al., 2016; Minagawa-Kawai, Mori, Naoi, & Kojima, 2007), which is especially relevant in the first years of life, when the brain goes through tremendous structural and functional changes. To our knowledge our study was the first to report changes in the tactile domain.

Limitations and Future Directions

Despite the contributions discussed above, it should be acknowledged that the studies were conducted with small sample sizes (n ranging from 25-35 infants and 44 children with ASD),

and therefore future studies should examine the importance of touch using more diverse samples of infants. Our sample was very homogeneous, with all the infants being Caucasian and from highly educated families. Our findings are still very relevant considering that this is the first work to explore these relations and that our paradigms were conducted in a well-controlled lab setting. Another limitation/challenge worth mentioning is the use of subjective field measures to quantify touch. In our studies, we use a crude measure of touch processing, the Sensory Profile to assess touch processing patterns. This measure can be subject to bias however this type of bias is likely to confound our associations towards the null (i.e., attenuate the associations between sensory processing and brain activation). Despite inherent bias associated with these instruments, we were still able to find important associations. Future studies should explore these associations using more objective measures of touch processing, as direct observation of the child to different types of touch/textures, or within child-mother interaction. A bigger and more diverse sample would have also allowed to test other variables that might influence the processing of affective touch at a brain level, as for example breast-feeding or mother-infant interaction. It has been shown that children whose mothers use more touch in the interaction with them, present more resting brain connectivity in the network involved in the right dorso-medial prefrontal cortex (Brauer, Xiao, Poulain, Friederici, & Schirmer, 2016). Studying touch in the context of prematurity, when infants are deprived of physical contact, would also shed light on the processing of CT afferents, especially because attenuated responses to touch in this population have been related with the quality of touch experiences (Maitre et al., 2017). Finally, although fNIRS have good spatial resolution (Lloyd-Fox et al., 2010) and we infer brain locations by placing the cap according with the 10/5 landmarks (Jurcak, Tsuzuki, & Dan, 2007), and surface map from a fNIRS – fMRI co-registration study in infants (Lloyd-Fox, Richards, et al., 2014), the precise cortical localization is still limited. Future studies should use 3D digitizers to localize precisely the position of the optodes with respect to infant's heads and co-register to an infant template.

The studies compiled in this thesis set an important rationale for the study of affective-motivational system in the context of neurodevelopmental disorders. By understanding how the CT fibers are processed at a brain and behavior level in typically developing children, one can think about using this approach to a more comprehensive view of infants at risk of neurodevelopmental disorders, namely ASD. Moreover, because the CT system is a low-level sensory processing, it could help inform about atypical trajectories in this population earlier than current approaches that rely on higher-level capabilities such as language or social interaction. Some neuroimaging studies

had already started to focus on atypical touch processing in the population with ASD (Cascio et al., 2012; Green, Ben-Sasson, Soto, & Carter, 2012; Green et al., 2015; Kaiser et al., 2016), but more evidence is needed to clarify to what extent is the sensory-discriminative or the motivational-affective dimension, or both, are affected, and how basic-sensory processes affect high-order competencies in this population (Green et al., 2017). This would help clarify the symptoms presented by individuals with ASD, understand if the current interventions are designed to target them, and specially help design new approaches to address those. More important, it could bring together families, clinicians and researchers, and ultimately improve assessments and interventions for people with ASD (Cascio, Woynaroski, Baranek, & Wallace, 2016).

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