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C-tactile fibers mediate Affective Touch:
from childhood to individual differences to neural correlates

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Introduction

In the past 3 years, throughout my doctoral project, I had the chance to carry out a series of researches ranging from a behavioral to neuroimaging techniques.

The main issue that has interested me since the very first steps of my journey, was the tactile system and in particular a specific function of this system that is the affective touch. The affective touch is a construct that, in the last years, has gained much interest from the international scientific community. This is because the correlates of this construct appear to be linked to different domains of our lives, to the body of course, but also to the human mind, thus both on a physical and on a physiological level. Basically, as the reader will understand moving forward trhough the current thesis, the affective touch is nothing but a simple and powerful behavioral output, it is a feeling of pleasure perceived by stimulating the skin at a specific frequency. The feeling of pleasure is given by a specific group of fibers - C fibers - which have peculiar characteristics such as slow conduction. Up to a few years ago, these fibers were mainly studied for their role on conduction of pain perception. Actually, the step forward that has interested the researchers, is that this class of unmyelinated fibers, if stimulated to a determined frequency, produces a sensation of pleasure that is associated to the human caress. Thus, the fact that stimulation of these tactile receptors evokes a feeling of shared and measurable pleasantness has opened a wide new perspective. My thesis work lays right within this beautiful paradigm and my goal is to study this phenomenon through three experiments. In order to address the contents of the current work more clearly, I decided to divide this manuscript into two main sections. The first, is an introductive and reviewing part in which I will describe the basics that will be useful to the reader to understand the affective touch, the C tactile fibers and the literature directly linked to consecutive experiments.

A second section is dedicated to the experiments that I conducted in my doctoral project. I decided to report the experiments exactly as they will be submitted to the scientific community to allow the reader to know the various stages of researches. So, the reader will find three distinct studies that, however, follow a temporal progression that reflects both the way they have been carried out and the logical sequence of the rationale underpinning my doctoral project.

The first study aimed to verify something very important for me, that is: is the affective tactile system mature also in children as shown in adults? More specifically, if I stimulate a child with the same frequency with which an adult perceives affective touch, will a child perceive that stimulation as pleasant? In other words, is the sensation of affective touch already present in children and from what age? So, the first study wanted to verify whether the stimulations of C-fibers in children had pleasantness as a behavioral output. In the first experiment, I committed myself to demonstrating it.

As for the second study, I tried to apply affective touch in another neuroscientific perspective that has to do with individual differences. In particular, a growing body of literature on affective touch has shown how affective touch perception can be altered in people with psychopathological characteristics such as eating disorders or even in autism. In other words, what is clear is that people with psychiatric and neuropsychological diseases have different responses to affective touch. Now the aim of the second study was precisely to verify whether a particular group of people, i.e. those with a particular pattern of attachment, could respond to the affective touch in a different way. The reasons why I chose the attachment are essentially two. On one hand, because attachment is a psychological pattern linked to cure received, such as human caress that recalls on mind the perception of the affective touch. On the other hand, because the few studies in question have shown that there is a strong correlation between the attachment pattern and the affective touch, but no one had ever implemented it using the only true measure of adult attachment. So, an important aspect of the second study is that we administered the Adult Attachment Interview, which is the gold standard for defining the state of mind with respect to attachment in adults. Thus, we wanted to verify whether individuals with a specific attachment pattern, such as the Disorganized one that is the pattern that has been linked to higher maternal neglect, perceive the affective touch in the same way as individuals with attachment pattern characterized by less difficulties in relationships such as the Organized pattern.

Finally, as a physiological development of this second experiment, we wanted to verify if the interesting results obtained in the previous study, could also have implications at the neural level. We wondered if it was possible to verify if subjects previously classified as Disorganized, and therefore with a behavioral alteration of affective touch perception, could also have specific functional characteristics at the cortical level. So, in the last experiment we conducted a functional magnetic resonance imaging study administering the procedure of affective touch in subjects classified as Disorganized and Organized with respect to their attachment pattern, involving a series of comparative analyses of both the resting-state and the functional activation in response to affective touch stimulation.

It is clear that the three experiments have engaged me in these three years and that while I am writing this thesis the last part of the fMRI study is still ongoing because we would like to confirm the results on a large sample for a wider understanding. Currently these three experiments seem to have clarified that the structure of affective touch is already present in childhood, that the affective touch is perceived differently depending on the type of attachment and that even the cortical circuits that process the response and processing of affective touch in these subjects seem altered.

Section I

Chapter 1. Touch and CT System

In humans, touch is the first sensory system to develop (Bremner & Spence, 2017; McGrath, 2004). The earliest sensations we experienced are tactile. Already at 12 weeks of gestation, the cutaneous receptors and the somatosensory functions are matured (Humphrey, 1964) and the fetus is able to make movements when lips are touched (Hooker, 1952); dissimilarly, other sensory modalities, such as hearing and vision, develop later. The early need of tactile functions in fetal growth, implies that the initial tactile experiences are of crucial importance in the development and the maturation of an organism. This issue has been demonstrated in several developmental pathways, from biological growth (Bremner & Spence, 2017) to psychological maturity (Ardiel & Rankin, 2010), to social skills achievements (Cascio et al., 2018).

The sense of touch is processed by mechanosensory neurons that are embedded in the skin and that transmit signals from the periphery to the central nervous system. In essence, the sensation of touch occurs when a specialized afferent mechanoreceptor in the skin is activated by a contact stimulus. This can be as little as a gentle breeze over the arms, to the high force exerted from trapping a finger in the door. A single mechanoreceptive afferent can encode many aspects of the stimulus (e.g. force, speed, direction and roughness), and when activated together with other mechano and somatosensory afferents, specific percepts are generated (e.g. wetness and oiliness; see Bentley 1900).

Most of the research on the human somatosensory touch system has been devoted to myelinated (Aβ) low threshold mechanoreceptive (LTMR) afferents. This system consists of large diameter fibers with rapid conduction velocities (approximately 50m s^{-1}) optimized for signaling immediate detection of and discriminative information about a touch stimulus. Aβ afferents are present throughout the skin, i.e. both in hairy and in glabrous skin, with the highest innervation density being found in the digit tips and the perioral regions, allowing for high resolution during explorative tactile behavior. This is in contrast to the hairy skin, where the density of myelinated mechanoreceptive afferents is much lower. These fibers are thought to provide information about tactile discrimination and tactile sensitivity, where the sensitivity relates to whether something can be felt or not and discrimination relates to spatial tactile acuity (e.g. differentiating between two points—you could feel a fly that landed on your back but you would not know how many legs it had!). The whole skin is sensitive to a tactile event; for example, the upper half of the body is generally more sensitive than the lower half, where the lips, cheeks and nose are maximally sensitive to pressure (Weinstein, 1968).

Not all types of touch are the same, and specific tactile afferents convey different properties of touch such as discriminative, thermal, painful, pruritic (itch), or affective information to the central nervous system. These input channels can be further classified as sub-serving sensory functions, such as spatial and temporal discrimination, and the provision of essential information for controlling and guiding exploratory manual behaviours, or affective functions that include the provision of the subjective experience of affective or emotional pleasurable touch. As seen above, signaling in fast-conducting myelinated peripheral nerve fibers (Aβ afferents) is important for the discriminative properties of tactile sensations. On the other hand, another class of tactile fibers, namely C-tactile (CT) afferents seems to be important for the rewarding, emotional properties of touch. As a full description of the properties of the tactile system overcome the aims of this dissertation, I will focus on a selective class of tactile fiber, named CT.

It is worth noting that Aβ and CT fibers underpin different properties. As stated above, Aβ fibers encode sensory-discriminative aspects of touch with high rapidity and acuity, with pathways projecting ultimately to primary and secondary sensory cortical areas (see Figure 1 in p. 31).

Instead, CT fibers may ‘‘pick out’’ a range of tactile stimuli likely, for the purposes of further hedonic, rewarding processing in affect-related brain areas such as the insula. Importantly, these two systems are not separate, despite being at least partly dissociable; it is likely that sensory-discriminative and motivational-affective pathways for touch interact. CT afferents may operate as selectors, activated in parallel with Aβ afferents and their cooperation may provide a complete elaboration of a tactile percept. Still, both from a physiological and functional perspective, the CT system is characterized by very peculiar features that I shall describe in the following paragraphs.

1.1. The principal features of CT fibers

The existence of a slow tactile system (C Low Threshold Mechanosensitive Receptors; CLTMR) was first presented almost 80 years ago in animals. In 1939, the Swedish physiologist Zotterman proposed that light touch activates not only large afferents but also small unmyelinated afferents (Zotterman, 1939). Recording from thin strands of the cat saphenous nerve, he noticed that touching the skin on the lower leg produced impulses of three different sizes, designated A beta (β), A delta (δ), and C in accordance with the Erlanger−Gasser scheme (Erlanger and Gasser, 1924). Zotterman emphasized a unique and striking response feature of the low threshold C mechanoreceptive afferents, that is, a prominent and long-lasting after-discharge which was not seen in large diameter tactile afferents. On the basis of this finding, he suggested that unmyelinated tactile afferents might account for the sensation of tickle: “The itching after-sensation to light touch”- Zotterman said- “is most probably due to fibers conducting at C rates” (Zotterman, 1939). An important step was taken about 20 years later when Douglas and Ritchie (1957) demonstrated a number of fundamental properties of the slow tactile system. Using a cat saphenous nerve preparation with intact connection to the skin, Douglas and Ritchie (1957, 1962) monitored the compound C fiber volley produced by repetitive electrical stimuli. They showed beyond doubt, that the slow tactile afferents conducted impulses at a speed of about 1 m s^{-1} indicating unmyelinated axons. In addition, their study demonstrated that these fibers are abundant in nerves innervating hairy skin of the cat.

Single unit analysis of CLTMR was pioneered by Iggo and coworkers, who presented detailed descriptions of response properties to innocuous touch, for example, high sensitivity to skin deformation, large response to hair movements, intermediate adaptation, and pronounced post-activation fatigue effect of the sense organ, which may last up to 30 min (Iggo, 1960; Iggo and Kornhuber, 1977). In 1971, an important publication from Perl's group (Bessou et al., 1971) emphasized a difference between CLTMR and Aβ tactile afferents with regard to their dynamic response properties. They wrote that as the velocity of a glass rod "stroked across the receptive field ... is progressively decreased, the frequency (of the discharge) ... first increases and then declines". In myelinated tactile afferents, on the other hand, impulse rate increases monotonously with velocity of touch movement.

In the last three decades, the investigation of physiological properties of slow-conducting fibers was shifted to human models, highlighting specific neurophysiological, neural and behavioral properties. The CT fibers has specific properties in terms of impulse rate, distribution, density, receptive field, conduction velocity, impulse frequency and fatigue effect.

Impulse Rate: From the literature (Cole et al., 2006; Vallbo et al., 1999), it has been seen that CT afferents respond to very low indentation forces in the range 0.3–2.5 mM and with high-frequency responses (50–100 impulses s^{-1}) to innocuous stimuli, such as gentle stroking with a soft brush. This impulse rate is close to the maximum reported for other C afferents (Kumazawa and Perl, 1977). Despite a very large heterogeneity in CT responses, CTs are nonetheless a electrophysiologically constrained population of cutaneous afferents, the abiding properties of which are well established.

Distribution: The distribution of the slow tactile system has been first verified in the skin of face, forearm, and leg. More specifically, afferent impulses in unmyelinated CT fibers have been recorded in the small supra- and infraorbital nerves innervating facial skin, in lateral and dorsal ante-brachial cutaneous nerves innervating the hairy skin of the forearm and hand dorsum, and in the lateral cutaneous femoral and peroneal nerves innervating the thigh, lower leg, and the foot (Johansson et al., 1988; Nordin, 1990; Vallbo et al., 1993, 1999; Edin, 2001; Wessberg et al., 2003; Löken et al., 2007, 2009). On the other hand, nerves innervating the skin of the trunk have not been exploited so far. Although these findings strongly suggest that CT innervation of human skin is ubiquitous, a distinct exception is indicated by the fact that CT has never been encountered in recordings from the glabrous skin of the hand in spite of extensive analyses of tactile afferents in this skin area. Moreover, the difference between hairy and glabrous skin in man is consistent with findings in cats, rodents, and nonhuman primates where the slow tactile system, that is, CLTMR afferents have never been found in nerves supplying foot pads or monkey glabrous skin.

Density: Information about density of CT afferents comes from microneurography studies. A monkey study indicates a proximo-distal gradient with fewer CLTMR in the distal parts of the extremities (Kumazawa and Perl, 1977). A similar gradient is suggested in a human study focused on distal hairy skin (Löken et al., 2007). Only a few CT afferents were found on hand dorsum and in lower leg in recordings from the radial and peroneal nerves. In general, present data suggest that CTs are abundant in the hairy skin of the human body, scarcer in the distal parts of the extremities and seem to be lacking altogether in the glabrous skin.

Receptive field: Receptive field of CTs mechanoreceptive afferents, defined as the skin area where adequate stimuli are effective to produce afferent impulses, vary considerably in size and complexity. It may be a single spot, about 0.25 mm^2 in size or it may include up to nine hotspots distributed over an area of 35 mm^2; mean field size was 7 mm^2 (s.d. 8 mm^2). Fields are roughly oval in shape with no preferred orientation. No dependence on location along the forearm emerged. This field analysis indicates that the stem fiber of a CT afferent commonly branches to terminate with a varying number of clusters of sensory terminals irregularly distributed within a relatively small area, rather than providing a continuous mesh of responsive terminals as suggested by many previous studies based on handheld field exploration (Olausson et al., 2016).

Conduction velocity: Moving to another feature of the CT fibers, namely the conduction velocity, it is known that it is characterized by a long latency from stimulus to impulse response occurring much later the onset of stimulus due to a 30–50 times difference in propagation velocity. Conduction velocity of CT afferents is about 1 m s^{-1} (0.6–1.2 m s^{-1}) as assessed from the unit's response to mechanical stimuli. Neither significant correlation has been found between conduction velocity of individual afferents and location of receptive field along the extremity, nor with other functional properties of CT units (McGlone et al., 2007).

Impulse frequency: In order to investigate the impulse frequencies, the study of Iggo (1960) showed that stroking with a soft brush across CT receptive fields evokes peak impulse rates between 50 and 100 s^{-1} in a majority of the afferents. Although these rates are not very impressive compared to firing of Aβ afferents, they are, in fact, relatively speaking very high considering that maximal rate of C mechanoreceptive afferents as found in animal experiments is 100 impulses s^{-1} (Iggo, 1960).

Fatigue effect. One of the most distinctive features of CT fibers is the fatigue effect: a specific response feature of CT-units is that sensory endings of CTs exhibit a pronounced postactive depression. This characteristic shows a marked decrease of the response after a single stimulus. When a series of successive indentations are delivered, the response usually decreases with the first 2–4 stimuli to settle around a submaximal level which is dependent on interstimulus interval. Postactivation fatigue may be very long lasting. The response after a resting period of 300 s is substantially larger in terms of impulse rate, number of impulses, as well as duration of discharge than that after 60 s. There are indications that full recovery may take several minutes. However, systematic analyses regarding development of fatigue and time course of recovery remain to be pursued in man (Iggo, 1960; Iggo & Kornhuber, 1977).

Before moving to the behavioral features of the CT system, is of importance to briefly describe the spinal and cortical processing of CT fibers. Data on the spinal pathways enrolled in the CT processing, came from human studies after surgical sectioning of the anterolateral spinothalamic tract for treatment of chronic intractable pain. The earliest observation that cutting this tract impacts on aspects of CT signaling was made by a German neurologist and neurosurgeon, Otfrid Foerster (Foerster et al., 1932):

'Except for the pain and temperature sensations, also other sensory qualities were spoiled after the anterolateral transection. First of all, the feelings of tickle and itch were included, but so were all other feelings of pleasure and displeasure as well'. (p. 43, translated from the original German).

This lack of ''pleasure'' after transection of the spinothalamic tract provides at least circumstantial evidence that CTs ascend in the same tract as C-nociceptors. Lahuerta et al. (1994) made similar observations in a cohort of anterolateral cordotomized patients, reporting that they do not experience cutaneous erotic sensation when receiving low-intensity tactile stimulation. These clinical observations support the existence of a spinothlamic pathway for signaling CT-mediated pleasant properties of touch. Through the caudal part of the posterolateral-ventral and the lateral central nuclei of the thalamus, the sensorial percept reaches primary and higher cortical areas where it is elaborated and decoded (Dum et al., 2009). In healthy humans, a number of studies have found different cortical areas and signatures that relate to pleasant touch, via stroking stimuli that preferentially activate CT afferents. For the sake of reading, I will fully address the issue of the neural correlate of the Affective Touch in the Chapter 3, of my dissertation.

1.2 Behavioral output of CT fibers: affective touch and methodological issues

The CT system has been associated to a pleasant, positive hedonic sensation since it has been systematically studied in humans for the first time. Following the studies by Olausson and colleagues (2002, 2008; see previous section), the relation between CT fibers and pleasantness has been further explored by Löken and colleagues (2009); using a microneurography technique for recording single afferent activity in awake humans and a robotic device to deliver moving tactile stimuli, authors stimulated CT units in the hairy skin of the subjects' forearm with a soft brush moving at different speeds. The relationship between brush stroking velocity and units firing rate was distinctly different between CT and myelinated afferents: CT fibers showed an inverted U-shaped relationship between brushing velocity and mean firing rate, with highest responses at 1, 3 and 10 cm s^{-1}. In contrast, mean firing increased monotonically with brushing velocity in all myelinated afferents. When asked to rate on a visual-analog scale (VAS), the hedonic quality of the brush stroking, subjects rated 1, 3 and 10 cm s^{-1} as being the most pleasant velocities, with a peak of pleasantness around 3 cm s^{-1}. Authors found a significant linear correlation between mean firing rates and mean ratings of pleasantness for CT but not for myelinated units. These results are the first demonstration of a relationship between positive hedonic sensation and coding at level of peripheral afferent nerve, suggesting that CT fibers contribute critically to pleasant touch. This perspective has been further documented by several imaging studies demonstrating the crucial function of the posterior insula in the process of the and recognition of pleasant touch (for a full description of the studies, see Chapter 3)

These evidences sustained the hypothesis that the activation of the CT system is strongly correlated to a pleasant, hedonic sensation that we experience in everyday life when interacting with parents, siblings and peers. This pleasant, affective touch also modulate the activation of the posterior insula, an area that is known for being involved in processing visceral inputs and in emotion regulation. Implications for the discovery of a segregated system that is specifically devoted to signaling and processing affective, emotional and social information will be the focus of the following sections.

The growing number of studies involving affective touch and its relationship with the CT system highlighted the necessity to develop controlled and valid paradigms to explore this new dimension of touch. Even in recent years very approximate stimulus control has been accepted for the study of emotional touch, with hand application of soft cosmetic or artist's brushes being commonly used as a prototypically pleasant stimulus (Cascio et al., 2008; Olausson et al., 2002, 2008). This is acceptable in the sense that a pleasant stimulus, such as a soft cosmetic brush, remains pleasant almost regardless of how it is moved across the skin, even if it is not delivered with the optimal stimulus parameters. Nevertheless, it was necessary to set precise parameters and create standard, endorsed and reproducible paradigms allowing for a scientific approach for the exploration of affective touch.

A primary issue with any psychophysics is how to adequately control the parameters of stimulation. One of the early attempts to provide improved stimulus control was via a brushing stimulator that allowed different materials to be moved across the skin with controlled velocity (Essick et al., 1999). The development of this robotic device was a primary step in CT-related work, not only to provide hitherto unavailable stimulus control, but also to control for experimenter-induced effects. For example, the physical attractiveness of the experimenter can influence the responses he/she obtains from participants (Donley and Allen, 1977; Hartnett et al., 1976). To overcome these limits, Essick and colleagues (2010) implemented an automatic device, termed the 'Rotary Tactile Stimulator' (RTS). The RTS allows stimuli to be brushed onto, across, and then off the skin with control of brushing direction, speed, and force of indentation into the skin, and with continual readings of the forces and torques occurring during delivery. The main psychophysical study that has used the RTS was relatively complex, assessing pleasantness responses to multiple fabric materials, at multiple body sites, for both sexes (Essick et al., 2010); they demonstrated the curvilinear nature of the pleasantness response with stimulus speed. What Essick and colleagues have left unexplored is whether the use of RTS could actually control for the potential influence of the *humanity* of the experimenters or not. A more recent study from Triscoli and colleagues (2013) compared pleasantness ratings in response to caress-like brush strokes on the hairy skin of the forearm either produced by the RTS or by hand by an experimenter with three different velocities (0.3, 3, and 30 cm s^{-1}). Results showed that pleasantness ratings were very similar in both conditions. This was found across stimulus velocities and regardless of whether the subjects were informed about the source of the on-going stroke or not. As robot and human touch are highly comparable in terms of perceived pleasantness, handheld stimulation may be used in studies on AT, allowing for a more ecologic and affordable to examine this dimension of touch.

Another methodological issue concerns the specific activation of CT fibers. According to the physiological properties of CT afferents, many studies (e.g. Olausson et al., 2002, 2008; Löken et al., 2009; Morrison et al., 2011a, 2011b) have used different velocities to stimulate this population of fibers; specifically, velocities between 1 and 10 cm s^{-1} are considered optimal to selectively activate CT afferents (Löken et al., 2009). Other studies used the site of stimulation as control for the selective activation of these fibers. In fact, CT afferents are not present in the glabrous but only on the hairy skin of mammals (Johansson et al., 1988; Nordin, 1990; Vallbo et al., 1993, 1999); behavioral studies have shown that CT optimal stimulation on the forearm are rated as being more pleasant than when delivered on the palm (Essick et al., 2010; Triscoli et al., 2013). Similar findings are reported in a fMRI study by Perini and colleagues (2015); authors delivered brush stroking on the participants' palm and forearm at five different velocities (0.3, 1, 3, 10, 30 cm s^{-1}); following stimulation in each trial, participants actively chose whether the caress they would receive in the next trial would be the same speed or different. Since preferred stroking speed should be sought with greater frequency than non-preferred speeds, this paradigm provided a measure of such preferences in the form of active choices. Results showed a preference for stimulations delivered at 1, 3 and 10 cm s^{-1} on the forearm and only at 3 cm s^{-1} when delivered on the palm. Referring to different control methods, Ackerley and colleagues (2014) assessed tactile pleasantness using five velocities (0.3, 1, 3, 10, 30 cm s^{-1}), over five skin sites: forehead, arm, palm, thigh and shin. The assessment of tactile pleasantness over the skin resulted in a preference for the middle velocities (1 - 10 cm s^{-1}); this preference was found across all the skin sites, apart from the palm, where no decrease in pleasantness for the faster stroking velocities was seen.

Before moving to the next chapter, it is important to clarify a terminological issue. Certainly, the reader is now more than convinced that the tactile stimulation of a hairy body part at a rate of 1 - 10 cm s^{-1}, produces a pleasant sensation, similar to a human caress; and maybe, the reader will be tempted to associate the pleasantness of a caress with the affective aspect of touch. This possible scenario has been evoked by several authors, who coined the term **"Affective Touch",** just to labelled the behavioral and perceptual output of the CT-fibers stimulation at 1 - 10 cm s^{-1}. For this reason, I will refer to Affective Touch (rather than CT-fibers stimulation, CT optimal stroking velocity or CT targeted stimulation), throughout the rest of my dissertation.

Chapter 2. Experiencing affective touch

In the second chapter, I will address two mains aspects related to affective touch: the development and the individual differences. As mentioned in the introduction, in the first paragraph, I will examine the literature on affective touch in the lifespan that is directly linked to my first study. Subsequently in the second paragraph, I will describe how the individual differences and the social relationships, may affect directly and/or un-directly the perception of the Affective Touch.

2.1. Affective touch in the lifespan

Touch serving as a "sensory scaffold on which we come to perceive our own bodies and our sense of self (Bremner and Spence, 2017)". In the first few months of postnatal life, touch is a key "active ingredient" in the development of secure attachment (Duhn, 2010) and the formation of family bonds (Gordon et al., 2010). In the last years, researches on touch have pointed out the essential role of CT fibers in conveying emotional and rewarding features of touch, proposing these afferents as a strong candidate for the biological substrate of affective touch. Recent studies showed that the CT system responds to a pleasant, affective touch in an adult-like manner in infants at 7 (Miguel et al., 2017) and 2 months (Jönsson et al., 2017) and at 11-36 days (Tuulari et al., 2017) after birth, suggesting that AT processing already exists in childhood and evokes specific neural (Björnsdotter et al., 2014; Kida & Shinohara, 2013; May et al., 2014) and autonomic responses (Fairhurst, Löken, & Grossmann, 2014).

A growing number of studies examined affective touch at different stages of life, aiming to provide new evidence on how the neural and behavioral responses to pleasant touch emerge and develop throughout our lifetime. For example, Björnsdotter and colleagues (2014) used functional magnetic resonance imaging (fMRI) to study brain responses to soft brush stroking of both glabrous (palm) and hairy (forearm) skin in healthy children (5–13 years), adolescents

(14–17 years), and adults (25–35 years). Results showed a significant activation in the primary and secondary somatosensory cortices, the insular cortex and right posterior superior temporal sulcus, in all groups of age, suggesting that brain mechanisms associated with both sensory-discriminative ad affective-motivational aspects of touch are established in school-aged children. A similar study by May and colleagues (2014) examined behavioral and neural processing as a function of age during stimulation of A-beta (Aβ) and CT afferents using a soft brush stroke task. 16 adolescents (ages15–17), 22 young adults (ages20–28), and 20 mature adults (ages 29–55) were stroked whether on their forearm or palm at 2 cm s^{-1}, during fMRI. Results showed that adolescents displayed greater bilateral posterior insula activation than young and mature adults across all conditions. Despite this, no behavioral differences were found between groups when asking to participants to rate pleasantness in response to forearm and palm stimulations. Behavioral differences as a function of age were found by Sehlstedt and colleagues (2016) in a study examining affective touch responses in a sample of healthy subjects from 13 to 82 years of age. Keeping the intensity of touch controlled by using the RTS, stimulations were delivered on the participants' left forearm at six different velocities (0.1, 0.3, 1, 3, 10, e 30 cm s^{-1}) in a pseudo-randomized order asking to rate subjective pleasantness on a VAS. Results showed that pleasantness ratings for all velocities grew as a function of age and, specifically, the intermediate speeds (1, 3 and 10 cm s^{-1}) were those considered as the most pleasant. Conversely, intensity perception was negatively correlated to age. Authors suggest that the perception of tactile intensity and the perception of hedonic properties of touch follow dissociated developmental pathways: in fact, despite touch is perceived as less intense as age grows, its hedonic values enhances as a function of age. In a recent study (Croy et al., 2017), the behavioral response to affective touch was measured also in a sample of children from 5 to 12 years old, showing higher pleasantness ratings for CT-optimal stroking velocities already at this age. Interestingly, the preference for CT-optimal speeds is positively correlated with age, suggesting that affective touch is a dynamic facet that changes over time.

Taken together, these results show that the brain differently processes affective touch and non-affective touch since early stages of life. Human newborns are extremely dependent on their caregivers and early formation of an attachment is critical for survival. Infant brain possesses a specialized system which enables them to distinguish affective from non-affective tactile cues already few weeks after birth (Tuulari et al., 2017; Jonsson et al., 2017). This, highlights the importance of affective touch early in life and could add important implications for the care of newborn babies under both normal and more special circumstances such as preterm care and care in cases of mothers suffering post-partum depression where interaction with the newborn is sometimes compromised (Feldman and Eidelman, 2007). Moreover, this kind of touch is associated to a pleasant, rewarding sensation from childhood to old age (Sehlstedt et al., 2016; Croy et al., 2017). Affective touch has been linked to functional roles in the social touch perspective, including affiliative behavior and communication (Morrison et al., 2010; McGlone et al., 2014). The important social roles of the affective aspect of touch can be regarded from the perspective of social neuroscience and will be the core of the following section.

The first experimental study of my Phd experience, has been totally devoted to the investigation over the presence/absence of an effective response to tactile stimulation already in young and preadolescent children.

2.2. The social touch perspective and individual differences in experiencing Affective Touch

Research in social neuroscience tends to focus on visual and auditory channels as routes for social information. However, because the skin is the site of events and processes crucial to the way we think and feel about, and interact with the other one, touch can mediate social perceptions in various ways (Morrison et al., 2010). Anyway, the fact that tactile stimulation may evoke pleasure is mentioned in the early papers on cutaneous psychophysics. Müller (1838) listed *Kitzel* (meaning tickle/titillation) and *Wollust* (meaning lust/pleasure) among the cutaneous, sensory qualities. His brief comment on the subject was that feelings of *Kitzel* and the closely associated *Wollust* could be evoked from all parts of the body. Von Frey (1926) was more explicit. He noted that *Kitzel* was a fickle sensation, which could not be captured unless the stimulus was moving and that this sensory quality required stimulation characteristics, which were similar to those of the tactile sensibility.

Hedonically positive touch in human social interactions is ubiquitous despite cultural differences in its regulation, with roles ranging from the casual to the sexual. Sexual and parent–infant interactions are undeniably vital arenas of social touch. For example, the erotic dimension of human touch affects everyday interactions even among people who are not sexually involved, by introducing a culturally influenced ''erotic barrier'' which precludes certain types of casual touch (Heslin and Alper, 1983; Olausson et al., 2016). Touch also influences developmental pathways: maternal licking of rat pups can influence the behavior of the adult rat (Menard et al., 2004), and monkey infants deprived of tactile contact with a mother or mother surrogate become stressed and even ill-nourished (e.g., Harlow, 1958). Here, however, we focus on primarily nonsexual, positively hedonic forms of interaction between adult humans, while acknowledging that these may have sources in and links with sexual and maternal touch behavior.

The most salient nonsexual, positively hedonic forms of social touch can be tentatively divided into categories. ''Simple'' touch involves brief, intentional contact to a relatively restricted location on the body surface of the receiver during a social interaction; the person who pats the hand of the little old lady on the bus or gently touches the waiter's elbow while making a request is engaging in ''simple'' touch. ''Protracted'' touch involves longer and often mutual skin-to-skin contact between individuals, and usually includes a component of pressure, for example embracing, holding hands, and cuddling. Finally, ''dynamic'' touch involves continuous movement over the skin from one point to another, and can often be repetitious, as in stroking, rubbing, and caressing. What is the role of ''pleasantness''—the positive hedonic facet—in these categories of human social touch? First, pleasant touch may serve as a foundation for affiliative behavior. For example, holding a loved one's hand can reduce the anxiety posed by an impending threat (Coan et al., 2006) and stroking an infant can not only give rise to positive emotions in the baby, but can also modulate negative ones, compared to other forms of touch (Pelaez-Nogueras et al., 1996). Second, it may provide a mechanism for the formation and maintenance of social bonds. For example, in romantic partnerships, relationship satisfaction, previous experience of familial affection, and trust were positively correlated with self-reports of mutual grooming (Nelson and Geher, 2007). The same study showed that individuals who scored higher on anxiety subscales of an attachment questionnaire also reported more frequent grooming behavior, suggesting that an anxious attachment style may be accompanied by behavior likely to lead to more secure bonds. Third, it is a nonverbal means for the communication of emotions (Morrison et al., 2010) that it can be used to convey thoughts and feelings, to regulate them in others, or both. Tactile communication need not always involve mutual touching, but the giver's touch may affect participants' emotions and consequent signals without answering touches (Hertenstein et al., 2006).

In light of what has been said, touch is a fundamental channel for interactions and emotions. Specifically, CT fibers and the affective touch for their properties seem to play a primary role in signaling emotional and hedonic information through caress like touch, mediating the relationship between touch and the intra – and interpersonal life. For example, recent animal studies have posited that the mammalian CT system has evolved to signal the rewarding value of physical contact in nurturing and social interactions. In humans, affective touch has important functions in social interactions and beneficial implications in the modulation of pain (Krahé, Drabek, Paloyelis, & Fotopoulou, 2016; McGlone, Wessberg, & Olausson, 2014; von Mohr, Kirsch, & Fotopoulou, 2017); moreover, it has been suggested that CT afferent stimulation mediates the release of oxytocin during affiliative tactile interactions (Walker, Trotter, Swaney, Marshall, & McGlone, 2017).

Furthermore, the relation between these social aspects and affective touch, seems to recall the research of Harlow (1958, 1959) on the rhesus monkeys and Bowlby's theory (1969, 1982) on the human attachment. In his famous studies, Harlow demonstrated that infant rhesus monkeys would rather cling to a surrogate wire mother covered in warm cloth, than to one that provided milk but made up only of wires. Indeed, Harlow also observed that in case of a sudden frightening stimulus the cloth model was again preferred to the wire one, with the monkeys sought immediate physical contact with the cloth model after which their fear decreased. Finally, from these findings, Harlow suggested that the absence of comforting touch led to psychological stress in the monkeys. Probably, these studies provided the seminal evidence of the influential role of bodily contact in the development of the infant monkey's attachment.

On the other hand, in the attachment theory, Bowlby suggested that children come into the world biologically pre-programmed to form attachments with others, because this will help them to survive. According to Bowlby's theory (1969, 1982), the attachment behaviors are instinctive and are activated by any conditions that seem to threaten the achievement of proximity, such as separation, insecurity, and fear. In respect to the purpose of our work, what seems of interest is that after the nineties', several authors used the sense of touch to further explore the theory of attachment. For example, Reite (1990) suggested that in human, touch is fundamental because it allows the formation of an affective relationship with the caregiver which in turn forms a "secure" base that facilitates the development of learning, emotions regulation as well as social interactions. On the basis of similar premises, Anisfeld et al. (1990) found strong evidence that in infants at 13 months of age, increased physical contact would promote more secure attachment. In another study on touch and attachment, Weiss et al. (2000) explored aspects of maternal touch and its relation to a low-birth-weight infant's security of attachment at 1 year of age. Results of this observational study showed that at 1 year, nurturing touch was associated with more secure attachment; authors also found that children whose mothers felt more secure about their own childhood experiences of touch were more likely to develop secure attachments. More recently, Krahé and colleagues (2016) have used affective touch to study the influence of the attachment styles in the perception of physical pain. Specifically, the authors investigated whether different properties of touch may modulate subjective and neural responses to pain in respect to individual attachment style. Interestingly, results showed that pleasant touch reduces the perception of pain in individuals with higher attachment anxiety and conversely it increases pain in individuals with higher attachment avoidance. Finally, in a more recent study always on pleasantness perception of affective touch and attachment (Krahé et al., 2018), authors found that insecure and anxiety attachment was associated with reduced pleasantness discrimination between affective vs. non-affective, neutral touch.

Taken together the results suggest that there is a strong link between social dimensions and touch. In addition to specific aspects of development, the intrinsic bonding between affective touch and psychological dimension may imply an alteration of the former in case of psychological vulnerabilities. These circumstances have been investigated in several studies, among which the majority focused on autism traits. Probably, the first research that explored such a relationship, was that of Voos and collaborators (2013), who found that autistic traits of healthy participants, were associated with diminished neural response to affective touch. These findings have been successively confirmed by Kaiser (2016) who found that, in respect to a healthy control group, children and adolescents with Autism Spectrum Disorder, exhibited reduced activity in response to Affective Touch stimuli on the forearm CT- versus non-Affective Touch stimuli on the palm, in a network of brain regions typically involved in social–emotional information processing. Furthermore, the link between affective touch and psychopathology has been investigated also from the perspective of psychiatric disorders. For example, Crucianelli (2016), demonstrated that patients affected by Anorexia Nervosa perceived affective touch less pleasant than healthy controls. In a descriptive study, Croy et al. (2016a) tested the modulation of affective touch in a large sample of outpatients' psychotherapy affected by a broad range of mental disorders (mood and affective disorders, disorders of personality, post-traumatic stress disorder and anxiety disorders). The authors found that patients rated touch generally less pleasant than controls but interestingly this effect was stronger in patients with disorders of personality. Interestingly to note, the autistic spectrum, anorexia nervosa and personality disorders share impaired skills in the social domain.

There is growing circumstantial and neurobiological evidence that touch is more than a sensory input for discrimination of what is on the skin, or control of movement, and that the rewarding value of physical contact in nurturing and social interactions reflects the presence of an evolutionary mechanism—mediated via CT/CLTMs—that promotes physical contact in specific contexts. From the proposed perspective, touch may be viewed as a biologically necessary form of stimulation, not just a sentimental and romantic human indulgence (Casler, 1965; Korner and Grobstein, 1966; Thayer, 1986) and its alteration may be associated to atypical patterns of development characterized by social and behavioral abnormalities.

Having said that, the second study of my dissertation deals with the possibility that diverse attachment patterns (and social experiences), may affect the perception of the Affective Touch.

Chapter 3. The neural correlates of affective touch

In the following and last chapter of the first part of this dissertation, I will expose the empirical literature on neural correlates and brain mechanism involved in processing information driven by the CT system and affective touch perception. The review of the researches published until now has guided and inspired the third study of the current thesis. Specifically, I will address the role of the principal areas of a complex brain network involved in the processing of affective touch and the abnormality expression in psychopathology.

CTs system neural projections have been studied for the first time on a patient who suffered permanent specific loss of large-diameter myelinated afferents, including Aβ fiber (Olausson et al., 2002). By studying her brain responses to gentle touch stimulations, researchers found out that the somatosensory cortices were not activated. Instead the insula was found activated like in healthy controls: consistent activations were found in the posterior Ig2 (granular) region of the insular cortex in the hemisphere contralateral to the stimulated limb. Similar results came from another study from the same group (Olausson et al., 2008) who observed the same pattern of insular activation in another patient lacking large-diameter myelinated afferents. Interesting, for both patients, who were unable to detect any touch stimuli applied on their skin surface, a soft stroking on the skin was reported as a faint pressure that was clearly pleasant, while failing to provide a percept of intensity. Complementary studies came from Morrison and colleagues (2011a, 2011b) that further explored the relation between CT fibers and insular cortices. Authors found that in healthy adults within this region a slow stimulation, optimal to activate CTs (3 cm/s), elicits a larger brain response than a faster stimulation (30 cm/s) (Morrison et al., 2011a). Moreover, a study conducted on patients with selective loss of CT afferents (HSAN type V) without affecting Aβ afferents showed that they perceive slow arm stroking but rate it as less pleasant than matched controls. This abnormal hedonic perception is accompanied with a lack of insular cortex activation following CT-optimal stroking velocity (3 cm/s), showing no differences with non-optimal stroking velocity (30 cm/s) (Morrison et al., 2011b). Taken together, these results agree on the role that the insular cortex plays as the primary neural target of the CT fibers.

The insula is associated with an astonishing array of functions, ranging from basic processing of sensory and visceral information (Augustine, 1985) to complex processing of emotion and self-awareness (Craig, 2009). Insular cortex is a region of great interest in relation to affective mechanisms and is considered as a gateway from sensory systems to the emotional systems of the frontal lobe (Augustine, 1996; Craig, 2008). It responds to a wide number of visceral and noxious stimuli (Segerdahl et al., 2015) and is anatomically connected to the somatosensory cortices (Dum et al., 2009; Cerliani et al., 2012). At the same time, it is important to consider the insula as a part of a wider brain network that co-works in processing this kind of stimuli. According to Craig's model (2009), the insula plays an important role in the awareness of the physiological condition of the body. From this perspective, the posterior insula is the basis for the sense of the physiological condition of the entire body. These conditions are then re-represented in the mid-insula and again in the anterior insular cortices (on the left or right side or both, depending on the source of the activity). The mid-insula integrates these homeostatic re-representations with activity that is associated with emotionally salient environmental stimuli of many sensory modalities, probably by way of input from higher-order sensory regions, the temporal pole and the amygdala. Thus, this posterior-to--anterior progression provides a substrate for the sequential integration of homeostatic conditions with the sensory environment and with motivational, hedonic and social conditions represented in other parts of the brain, and this substrate is constructed on the foundation provided by the feelings from the body (Craig, 2009).

Other cortical areas seem to be involved in the processing of affective touch, although they probably receive less input from the CTs pathway compared to posterior insula. In fact, primary and secondary somatosensory cortices activation have been observed during affective stimulations. It is important to remember that these two systems are not separate, despite being at least partly dissociable; it is likely that sensory-discriminative and motivational-affective pathways for touch interact (McGlone et al., 2014). CT afferents may operate as selectors, activated in parallel with Aβ afferents and their cooperation may provide a complete elaboration of a tactile percept. For example, secondary somatosensory cortex (S2) is associated with intensity perception and salience of stimuli (Case et al., 2017); although it is not associated with perception of touch pleasantness, a recent meta-analysis showed that S2 is likely activated by both affective and discriminative aspects of touch. Probably, S2 is tied only indirectly to processing of tactile pleasantness (Morrison, 2016a). Moreover, posterior insula and sensory cortices are activated by tactile stimulations delivered on palms (where CTs are absent) and arms (where CTs are abundant); however, preferred arm stroking engaged only the posterior insula whereas preferred palm stroking involved parietal, primary and secondary somatosensory areas as well. This finding corroborates the hypothesis that different skin types involve different, yet related, processing on the cortical level (Perini et al., 2015).

Beyond somatosensory cortices, particular importance has the "social brain", which refers to the neuronal networks enabling our interactions with the social world: for example, our interest in others, our sensitivity to their emotions and thoughts, and our ability to interact with them (Brauer et al., 2016). Furthermore, affective touch is considered to be the scaffolding through which the social brain is shaped (Crucianelli & Filippetti, 2018). There are different areas and functions that interact in this network. For instance, the network involved in processing CT afferents seems to interact with reward and decision-making networks; in fact, several studies linked Orbitofrontal Cortex (OFC) to affective touch processing (Francis et al., 1999; Disbrow et al., 2000; Rolls et al., 2003; McCabe et al., 2008; McGlone et al., 2014) which is a fundamental area involved in sensibility to reward and in problem solving. Different areas of the OFC are activated by gentle touch or painful stimuli and pleasantness derived from CT stimulations appears to be related to the activation of the medial/mid-orbitofrontal cortex (Rolls, 2016). Thus, the mid-anterior OFC, an area that encodes subjective pleasure (Kringelbach and Rolls, 2004), is activated by CT-optimal stimulations, while Aβ mediated touch does not produce such activation (McGlone et al., 2012). Affective touch elicits the activation of medial Prefrontal Cortex (mPFC) as well. This region is associated with mentalizing abilities, social-cognitive processes such as self-referential (Gusnard et al., 2001) and other-inferential (Mitchell et al., 2005) tasks. Therefore, this result may be the consequence of a self-reflection on one's own feelings induced by affective touch, or alternatively it may represent the personal reflection on the brusher's mental state (Voos et al., 2013).

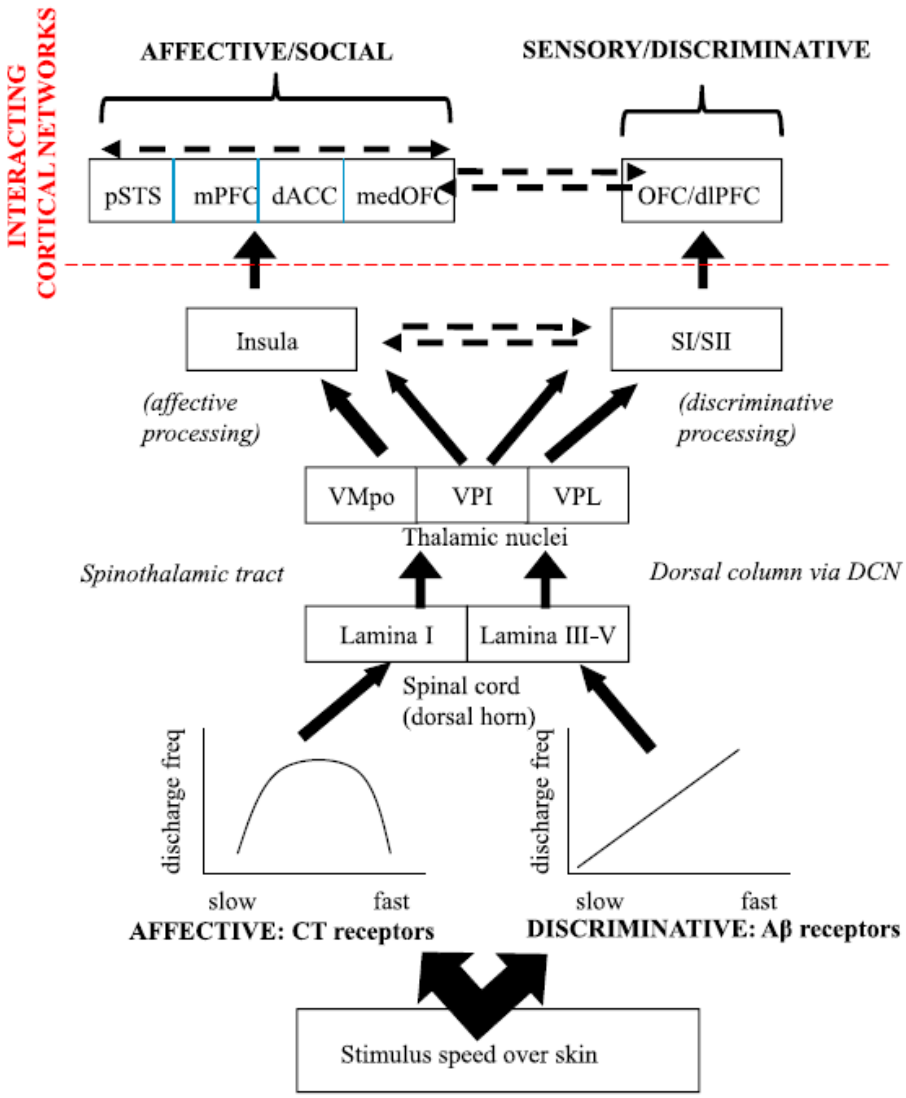
Another evidence is that during an affective tactile stimulation an increased functional connectivity between the mPFC/dorsoanterior cingulate cortex (dACC), the insula and amygdala can be seen (Gordon et al., 2013). The amygdala is greatly involved with social processing, emotion, reward learning and assessment of hedonic value of stimuli; its activation in association with affective touch may be a signal of social relevance (Sander et al., 2003). The activation seen between amygdala, mPFC/dACC and insula may represent a circuit devoted to coding the social relevance and social reward of affective tactile stimulations (Gordon et al., 2013). Little is known about how the amygdala may process touch; however, it is known that there are touch-sensitive neurons in the primate amygdala which may contribute to extract positive or negative valence of tactile stimuli similarly to other neurons in this area (Mosher et al., 2016).

Moreover, a meta-analysis reported that parietal opercular regions (PO) are more likely to be activated by affective touch, but this activation – unlike insular cortex - appears to not be selective since parietal operculum seems to be activated by both affective and discriminative touch. Parietal opercular somatosensory areas may be minor cortical targets of the CT-spinothalamic pathway since this area is adjacent and interconnected with the posterior insula. One possibility is that PO regions are able to process certain aspects of affective touch which are integrated with more selective information from insula through cortico-cortical connections (Morrison, 2016a).

From the study by Vrticka and Vuilleumier (2012) has been seen that temporal lobes are essential for social cognition and for a healthy development of attachment. The posterior superior temporal sulcus responds strongly to a wide range of social stimuli in various sensory domains; its involvement in the neural processing of affective touch is confirmed by fMRI studies (Voos et al., 2013) and this result has been replicated with the use of fNIRS (Bennett et al., 2013). Interestingly, posterior Superior Temporal Sulcus (pSTS) responses correlated significantly only with participants' subjective pleasantness of affective touch.

To sum up, besides insular cortex, CTs seem to have minor connections with other brain areas such as the OFC, PO and STS suggesting the presence of a wide network involved in processing affective touch and tactile information driven by the CT system (see figure 1).

Figure 1. Schematic model of affective and sensory-discriminative pathways for dynamic touch in hairy skin.



Another researches have focused on whether this network may show abnormalities related to psychopathology. For example, a study conducted by Davidovic and colleagues (2018) proved the presence of abnormalities in cortical processing of affective touch in patients suffering from anorexia nervosa (AN). Interestingly, they did not found any differences between subjects with AN and healthy controls regarding neural response to AT in the insular cortex. However, the AN group showed significantly less activity in areas including caudate nucleus and lateral occipital cortex (LOC). LOC is not involved in the tactile domain, but it has a role in the processing of human body's images and in self-representation; thus, this abnormal activity may be due to their disturbed body image perception. On the other hand, Bischoff-Grethe and colleagues (2018) found that women remitted from AN had a lower brain response relative to controls during anticipation of touch, but a greater response when experiencing touch in the right ventral mid-insula.

Another finding comes from a research on adults with autistic traits. Voos and colleagues (2013) showed that in healthy individuals CT-optimal stimulations produce an activation of the medial prefrontal cortex, insula, amygdala, superior temporal sulcus and orbitofrontal cortex while in adults with more autistic traits such stimulations produce less activation in the latter two areas (Voos et al., 2013). Similarly, results from another study (Cascio et al., 2012) showed that gentle stroking of the forearm's skin (5 cm/s), conducted with 3 different textures (a plastic mesh material, a soft cosmetic brush and a burlap fabric) produces different patterns of activation in healthy subjects and in adults with autism spectrum disorders. The former group showed significant increases in BOLD response to all three textures relative to the latter group's responses. Interestingly, subjects with autism exhibited greater BOLD response compared to healthy subjects in areas such as the posterior cingulate cortex and the insula when the stimulation was delivered with the most unpleasant texture. These results show that autism is associated with brain's over-reactivity to unpleasant and under-reactivity to pleasant textures, which may stand for autism's typical tactile defensiveness. Moreover, it was found out that children and adolescents with autism (with ages ranging from 6 to 20 years) appear to have an atypical social brain hypoactivation since they showed a hypo- reactivity - following CT optimal touch versus CT suboptimal stimulation - in a network of brain regions which is involved in social–emotional information processing. The network included: the bilateral insula and insular operculum, the right posterior superior temporal sulcus, bilateral temporoparietal junction extending into the inferior parietal lobule, right fusiform gyrus, right amygdala, and bilateral ventrolateral prefrontal cortex including the inferior frontal and precentral gyri (Kaiser et al., 2016).

Section II

As seen in the previous chapters, the affective touch and the C tactile fibers are crucial in different dimensions of our biological and social lives. Despite the growing interest displayed by the scientific community towards this new and thriving research field, many interesting aspects have been left unexplored. Section II will address and discuss the results coming from three empirical studies I have conducted throughout my doctoral project. These researches focused on three specific issues concerning different declinations of affective touch: development, individual differences and neural correlates. As briefly reported in the introduction, I decided to report the three studies as they have been submitted to the scientific community, leaving a final discussion as an overall exposition of the strengths and limits of my works. In the first study, I will explore and discuss how the perception of discriminative and affective features of touch change as a function of age from childhood to early adolescence; In order to do so, I recruited a sample of 160 subjects across different schools of Rome. In the second study, I will show and discuss how the affective touch perception changes in relation to different attachment patterns in a sample of healthy adults. For the evaluation of adult attachment, it was decided to use the Adult Attachment Interview. Despite it requires a long work both in the administration and in the transcription of the interview, the Adult Attachment Interview is the gold standard for the evaluation of the state of mind with respect to the attachment. It is easy to imagine that the recruitment procedure was prolonged and demanding in order to achieve a sample of over 60 subjects, where three days of work were required to correctly code the state of mind for each subject. Considering results from this study, I chose to implement a new research to investigate whether the behavioral differences observed between groups, would have been reflected also in differences on the cortical activations of the participants of the two groups. More specifically, we reproduced the affective touch stimulation procedure during an fMRI protocol to assess the presence of structural and functional differences in subjects with different attachment patterns. Until now this study is yet to be completed because data recollection started during my third and last year of doctoral project and the entire procedure is taking some time. Despite this, I will present the preliminary results of this work.

Study I: Tactile sensitivity, tactile acuity and affective touch: from childhood to early adolescence

3.1 Introduction

The sense of touch is thought to be the first sense to develop and, perhaps, it continues to be the most emotionally central throughout our lives. However, even though the maturation of the tactile perception has been well characterized among adults, very little is known about how tactile functions develop in childhood. If on one hand it has been demonstrated that tactile abilities decline with age, on the other, the literature is not consistent on the essential question of whether tactile functions improve, decline, or remain unchanged with age early in life (Bleyenheuft et al., 2006; Güçlü & Oztek, 2007; Stevens & Choo, 1996).

The lack of data on the maturation of touch in childhood seems unexpected if we think to the fundamental roles that the touch plays in the early stage of human development. For example, it has been showed that in premature neonates deprived of normal sensory stimulation, substitute stimulation facilitates growth and development (Ardiel & Rankin, 2010). Similarly, the administration of 10 minutes of additional handling per day produced a significant reduction in regurgitation (Hopper & Pinneau, 1957). In older children**,** Casler (1965) reported that institutionalized infants receiving an additional 1000 minutes of extra tactile stimulation administered impersonally for 10 weeks, had higher scores on developmental assessments. The aforementioned studies, together with other similar reports, suggest that the physical and cognitive deficits observed in deprived children could have been the effect of the lack of sensory deprivation (namely mechanosensory stimulation) rather than merely the maternal care withdrawal. Touch is also important for the development of affective and social interactions. In a recent review on this topic, Cascio et al. (2018) revised an impressive number of studies, both in animals and in humans, demonstrating the crucial role of touch in social and affective development. Among studies on humans, several authors adopt a definition of affective and social touch that is based on stroking speed (Della Longa et al., 2017; Miguel et al., 2017; Pirazzoli et al., 2018; Tuulari et al., 2017). It has been proposed that a specific class of tactile fibers, known as C-Tactile (CT) afferents (Löken et al., 2009; McGlone & Spence, 2010), respond optimally when the skin is stroked at a speed of about 1–10 cm/s (Morrison et al., 2011a; Sailer & Ackerley, 2017). These fibers are found in the hairy, but not in the glabrous skin and they are linked with the perception of pleasant touch similar to a caress. Several authors proposed the term Affective Touch to label the pleasant tactile perception evoked by the stimulation of the CT-system (Gordon et al., 2013; McGlone et al., 2014; Perini et al., 2015).

Coming back to the initial reflection, it seems that the literature on the development of the basic functions of discriminative touch in normal childhood is lacking. Moreover, there have been relatively few studies of tactile sensitivity and acuity on hairy skin that is the preferential site for Affective Touch stimulation. As a matter of fact, studies on tactile sensitivity and tactile acuity in the lifespan, focused on the glabrous skin (Peters & Goldreich, 2013; Stevens & Patterson, 1995) and, with the exception of the study of Mancini and colleagues (2014) on adults, no data are available on tactile sensitivity and acuity in the hairy skin of children and early adolescents.

Under these circumstances, the first aim of this study is to explore the tactile sensitivity and the tactile acuity, two dimension of basic somato-sensation, of hairy skin from early childhood to early adolescence; we hypothesized that both tactile functions could be modified by age growth. A second aim of this study is to analyze whether tactile sensitivity and acuity are linked to affective touch. Recent evidence points to orthogonal somatosensory subsystems for basic discriminative functions of touch and affective touch in adult (McGlone et al., 2014), so we hypothesized that, also in childhood and early adolescence, the two tactile systems should not be connected. Lastly, a third aim is to analyze whether or not the perception of affective touch changes from early childhood to early adolescence.

3.2 Material and Methods

3.2.1 Participants

186 children were recruited from primary schools in the area of Rome. The exclusion criteria were sensory impairments, neurological disorders, difficulties with developmental, behavioral, and cognitive processes. The absence of any cognitive or psychological impairment was ensured by the school database (based on performance on psychological and cognitive tests), as provided by the teachers. Also, given the existence of a relationship between touch and eating disorders (see Spitoni et al., 2015; Crucianelli et al., 2016), we decided to exclude participants with an extreme age-corrected BMI Zscore (Inokuchi et al., 2011). Following the exclusion criteria, the final sample was of 160 right-handed participants ranging in age from 6 to 14 years. Child's hand preference following a name writing request, defined the child's handedness for this study. A study by Corey, Hurley, and Foundas (2001) used writing hand identification to compare left versus right hemisphere dominance. Writing hand correlated significantly with scores on handedness determination measures (Corey et al., 2001). All participants were in good health, as reported by their parents. All parents provided written informed consent prior to the study. The sample was divided into 9 age groups. Table 1. shows the demographic and anthropometric values of the sample.

Table 1. Demographics and anthropometrics values in the age groups.

	6 (N=12) F=8 M=4	**7 (N=27) F=16 M=11**	**8 (N=20) F=9 M=11**	**9 (N=19) F=10 M=9**	**10 (N=19) F=10 M=9**	**11 (N=19) F=7 M=12**	**12 (N=19) F=9 M=10**	**13 (N=19) F=13 M=6**	**14 (N=6) F=5 M=1**
Weight (kilos)	23,25	27,03	31,05	35,73	35,42	40,7	46,1	51	49,33
Mean (SD)	(3,7)	(4,2)	(6,7)	(7,5)	(4)	(7,5)	(15,4)	(9,7)	(8,38)
Height (cm)	120	125	132	141	143	145	153	161	165
Mean (SD)	(0,05)	(0,07)	(0,1)	(0,02)	(0,04	(0,06)	(0,08)	(0,06)	(0,08)

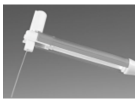
Note: SD = standard deviation.

The research was approved by the ethics committee of the Department of Psychology, Sapienza University of Rome and conforms to the World Medical Association Declaration of Helsinki of 1975, as revised in 2008.

3.2.2 Procedure and protocol

Each participant was tested individually in a quiet room provided by the school. As the child was picked up from his class, the examiner presented the principal aims of the research as a game to play together. The children were free to withdraw from the study at any time without any consequences. The experimental session took approximately 30 minutes and comprised 3 tactile measures: Von Frey's Monofilaments for the assessment of tactile sensitivity, the 2 Point Discrimination test (2PD) for the assessment of tactile acuity and Affective Touch (AT) stimulation procedure. Before starting the experiment, the participants were familiarized with the stimuli. First, they experienced Von Frey's stimulation 10 times (4.0-g weighted filament) and conclusively they went through 8 tactile comparisons for the 2PD, then they were asked to undergo 10 AT trials. At the end of the familiarization session, an informal interview confirmed that the participants could distinguish between the presence and absence of a stimulus on the skin (tactile sensitivity), between the presence of 1 or 2 tactile taps on the forearm (tactile acuity) and between pleasant and unpleasant sensations (AT). All participants were stimulated on the right forearm. Table 2 reassembles the main features of the protocol.

Table 2. Main features of the protocol.

Measure	**Sensory function**	**Question**	**Answer**
Von Frey 	Sensitivity	Am I touching you?	Verbal
2Point Discrimination 	Acuity	Do you fell one or two taps?	Verbal
Affective Touch 	Touch Pleasantness	Can you sign on this line how this touch feels?	VAS

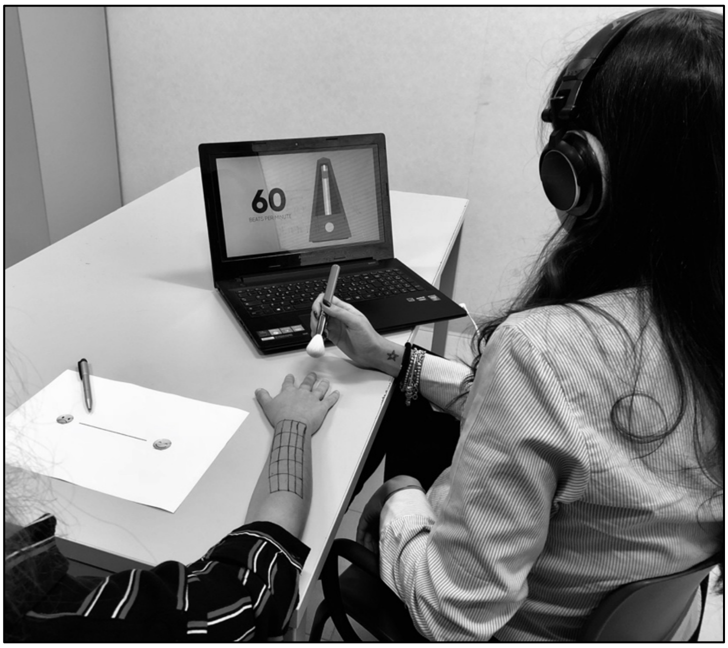
3.2.3 Measures

Tactile Sensitivity. The *Von Frey* monofilaments test is a classical measure of sensitivity to tactile pressure that is used for diagnostic and research purposes (North Coast Medical, Inc., Morgan Hill, CA, USA). In this test, the tip of a fiber with a specific weight (from 0.008 to 300 g) is pressed against the skin at right angles. The force of application increases as the researcher advances the probe until the fiber bends. In this study, the participants were instructed to sit still with their eyes closed during the procedure and focus on the tactile sensation. The procedure was repeated using various weights of fibers, forming an ascending and descending staircase. At each level of the staircase, 10 actual stimulations and 5 catch trials (a total of 15 stimulations) were presented. In each trial, the experimenter asked the participants whether they felt the stimulus on the forearm, or not. The individual threshold was established at the level when the subjects reported 6 out of 10 stimuli correctly. The outcome measure was the Subjective Sensitivity Threshold (SST) and it was expressed in grams. Higher SST reflects lower tactile sensitivity.

Tactile Acuity. *Two-point discrimination* thresholds were estimated using an adjustable esthesiometer (Med Core, St. Louis, MO, USA) with 2 separate tips. Participants were instructed to sit still with their eyes closed during the procedure and to discriminate between single and double taps. In this procedure, double or single taps were administered randomly. Only double taps were used to calculate the acuity threshold. The separation between the 2 starting taps was 1 and 5 cm in the ascending and descending modes, respectively. The separation was then decreased by 0.5 cm after each correct response. When an error was made, the separation rose by 0.5 cm. The participants' threshold was derived from the minimum distance that was perceived between the 2 points 5 times consecutively. The outcome measure was the Subjective Acuity Threshold (SAT) and it was expressed in centimeters. Higher SAT reflects lower tactile acuity.

Affective Touch. Tactile stimulation of the right dominant dorsal forearm (i.e., stroking) was delivered manually with a soft goat's hair brush (1 cm wide, 3 cm long). Manual stimulation has been successfully used in previous studies (for example Etzi et al., 2018; Liljencrantz et al., 2017; Löken et al., 2011) since evidence demonstrated that the CT optimized skin stroking delivered by hand or robot is analogous (Triscoli et al., 2013). In order to guarantee the highest control of the stimulation, the experimenter wore earphones and was skilled to use acoustic signals to stimulate at the precise velocity and in the correct temporal sequence. Earphones were triggered by a remote computerized metronome, previously programmed to provide the exact velocities. To guide the experimenters during the stimulation, a grid was drawn on the hairy skin of the long axis of the participants' dominant forearm; to minimize CT habituation, four different areas delimitated by the grid of the forearm were stroked in a proximal to distal direction. Participants were stimulated at 2 velocities – Affective Stimulation (CT optimal; 3 cm/s) and Neutral Stimulation (non-CT optimal; 30 cm/s) for a total of 30 trials. Ten Affective and 20 Neutral Stimulations were delivered to each subject in a pseudorandomized order. The participants were instructed to sit still with their eyes closed during the procedure and to focus on the tactile sensation. The participants were asked to rate their subjective perception of pleasantness for each stroke on a 100 millimeters long visual analog scale (VAS), with unpleasant (sad face) and pleasant (smiley face) as endpoints, ranging from 0 to 100. Before starting, the children were asked to indicate on various points on the VAS (e.g., ‘totally unpleasant,’ ‘pretty unpleasant,’ ‘average,’ ‘pretty pleasant,’ ‘totally pleasant’) to evaluate their comprehension of the instructions. To prevent fatigue, the trials was divided into 2 halves that were separated by a break. The outcome measures were: 1) the subjective pleasantness perceived following the Affective Stimulation (CT optimal stroking velocity); 2) the subjective pleasantness perceived following the Neutral Stimulation (non-CT optimal stroking velocity). In order to simplify the reading of the results, the term “CT optimal stimulation” was relabeled Affective Stimulation and the term “non-CT optimal stimulations” was relabeled Neutral Stimulations. Figure 1 shows the experimental set-up.

Figure 1. Experimental set-up.



3.2.4 Statistical Analysis

In order to describe the normative distributions of tactile sensitivity and tactile acuity in the nine groups of age, descriptive statistics were run on SST and SAT.

Before running the analyses, participants' subjective tactile thresholds have been transformed because the two variables were non-normally distributed as indicated by the Kolmogorov-Smirnov (KS) test (SST $p < 0.001$; SAT $p < 0.001$). Log-transformation (base 10) greatly improved normality, with KS tests revealing no significant violations of normality (SST $p = 0.091$; SAT $p = 0.07$). Age was always treated as a continuous variable. Accordingly, to test the correlation between age and tactile sensitivity and tactile acuity of hairy skin, two tailed Pearson r correlations, were run between age (from 6 to 14 years) and SST and SAT. Moreover, before running the analyses on the Affective Touch, we computed the Affective Touch Index (AT Index) for each participant. As proposed by Croy et al. (2017), the AT Index provides the individual preference for Affective (CT optimal) and Neutral (non-CT optimal) Stimulations and it is defined as the individual difference in pleasantness rating between the Affective and Neutral Stimulations, weighted by the overall pleasantness of the touch. Positive values for the AT Index indicate a preference for the Affective over Neutral Stimulations.

As expected from previous studies (see for example Croy et al., 2017), pleasantness ratings for the Affective Stimulation and AT Index were non-normally distributed as indicated by the KS test (Affective Stimulation $p < 0.001$; AT Index $p < 0.001$). As far as the AT Index contains negative values, the log transformation was not allowed, therefore non-parametric tests have been employed for all the analyses involving pleasantness ratings for the Affective and Neutral Stimulations, and AT Index. Wilcoxon signed-rank test was used to compare the perceived pleasantness following the Affective and Neutral Stimulations.

To analyze the relationship between individual differences in pleasantness ratings for affective touch (Affective vs Neutral Stimulations) and tactile sensitivity and tactile acuity, Spearman Rho correlation was performed between AT Index and SST and SAT.

To investigate the relationship between individual differences in pleasantness ratings for affective touch (Affective vs Neutral Stimulations) and age, Spearman Rho, correlation analysis was performed between AT Index and age.

Finally, to explore possible sex differences in our sample, we run a series of *t*-tests between males and females on SST, SAT, pleasantness ratings for affective touch (Affective vs Neutral Stimulations) and AT Index.

3.3 Results

The normative values of tactile sensitivity and tactile acuity of hairy skin in early and late childhood has shown in table 3.

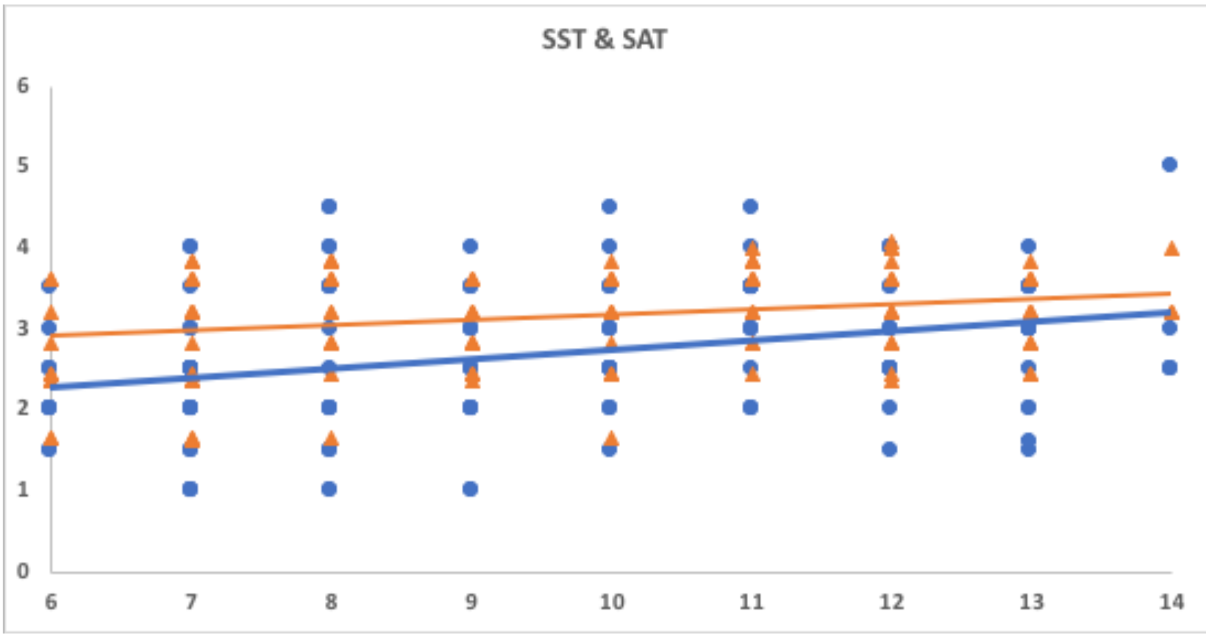
Table 3. Normatives of tactile sensitivity and tactile acuity in the nine groups of age.

	Sensitivity (SST) - Von Frey (grams)			**Acuity (SAT) – 2Point Discrimination (cm)**		
Age	Minimum	Maximus	Mean (SD)	Minimum	Maximus	Mean (SD)
6	1,65	4,08	3,33 (0,81)	1,5	3,5	2,5 (0,63)
7	1,65	4,08	3,26 (0,65)	1	4	2,37 (0,76)
8	1,65	3,84	3,45 (0,54)	1	5	2,85 (1,19)
9	1,65	3,84	3,12 (0,59)	1	4	2,55 (0,81)
10	1,65	3,84	3,26 (0,58)	1,5	4,5	2,81 (0,74)
11	2,36	4,08	3,35 (0,44)	1	4,5	2,92 (0,97)
12	2,36	4,61	3,24 (0,5)	1,5	4,5	2,89 (0,67)
13	2,44	3,84	3,67 (0,39)	1,5	5	3,56 (0,67)
14	3,22	4,61	3,98 (0,15)	2	5	3,71 (1,06)

Note: SD = standard deviation.

Regarding correlation between age and tactile sensitivity and tactile acuity, Pearson r analyses showed a positive correlation (r = 0,512; $p < 0.000$) between age and SST. Coherently, the analyses of correlation between SAT and age showed a positive Pearson correlation index (r = 0,175; p = 0.013). These findings suggest a progressive reduction of sensitivity ad acuity as age grows (see Figure 2).

Figure 2. Scatterplot between SST, SAT and age.



Note: ▲ = SST – Von Frey; ● = SAT – Two Point.

To analyze the relationship between individual differences in pleasantness ratings for affective touch (Affective vs Neutral Stimulations), and tactile sensitivity and tactile acuity, a Spearman Rho correlation was also performed between AT Index and SST and SAT. As shown in table 4, AT Index was not correlated with tactile acuity and tactile sensitivity.

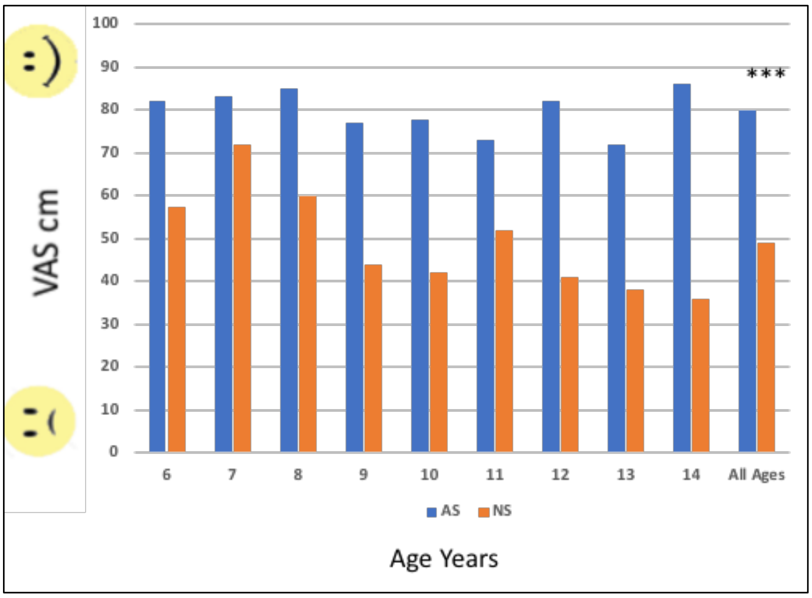
Table 4. Correlations between AT Index, tactile acuity and tactile sensitivity.

	Sensitivity (SST)	Acuity (SAT)	AT Index
Sensitivity (SST)	1,000	-	-
Acuity (SAT)	**0,350****	1,000	-
AT Index	0,129	0,073	1,000

Note: significant coefficients are in bold. ** = $p < 0.01$.

Regarding affective touch pleasantness, Wilcoxon signed-rank test yielded a significant effect of stroking velocity on pleasantness ratings with Affective Stimulation (3 cm/s) being rated significantly more pleasant than Neutral Stimulation (30 cm/s) (Z = -8,98, p < 0,000 positive ranks). Figure below (Figure 2) shows the mean values of pleasantness ratings for the Affective and Neutral Stimulations in the nine groups of age.

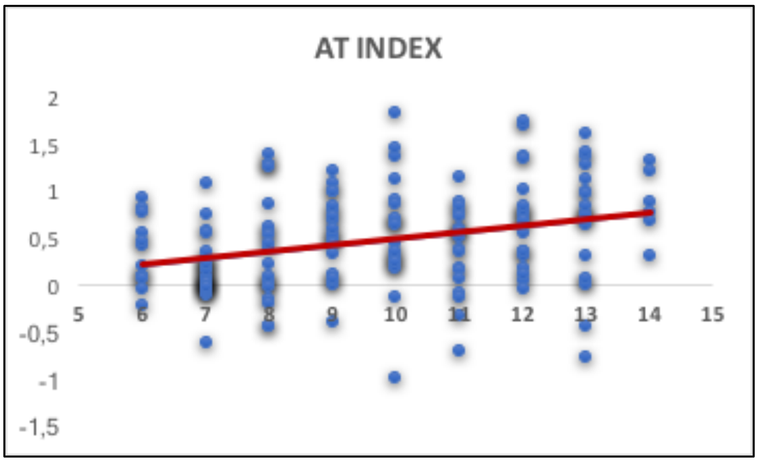
Figure 3. Mean values of pleasantness ratings for the Affective and Neutral Stimulations.



Note: *** = p < .000; AS = Affective Stimulation; NS = Neutral Stimulation.

Referring to the relation between age and individual differences in pleasantness ratings for affective touch (Affective vs Neutral Stimulations,) Figure 3 shows the scatterplot between AT Index and age. Spearman Rho correlation analysis showed a strong positive correlation between individual preferences for Affective Stimulation and age ($r_s = 0,34$; $p < 0,000$). These evidences seem to imply an increase of pleasantness ratings as age rises.

Figure 4. Scatterplot between AT Index and age.



Referring to sex analyses, *t*-test comparisons reported no significant differences for the considered dependent variables (see table 5)

Table 5. Sex differences (means and standard deviation) in the tactile variables of the study.

	Male (N = 73)	Female (N = 87)	$t_{(157)}$	*p*
SST	3,32 (0,94)	3,09 (0,96)	- 1,83	.60
SAT	2,75 (0,76)	2,67 (0,76)	- 0,52	.07
Affective Stimulation	79,04 (17,2)	79,98 (13,5)	0,39	.70
Neutral Stimulation	51,78 (24,7)	51,77 (23,0)	- 0,00	.99
AT Index	0,51 (0,67)	0,45 (0,52)	- 0,62	.53

3.4 Discussion

This study examined somato-sensation and affective touch in the hairy skin of children from childhood to early adolescence. As expected, we have found that somato-sensation, namely acuity and sensitivity, decreased as a function of age. Regarding affective touch, we missed to find a correlation with somato-sensation, but interestingly we found that in general children preferred the Affective Stimulation in respect to Neutral Stimulation; also, we found that the AT Index increased with age.

Our first result comes from the analysis on our sample's tactile acuity and sensitivity. Literature on the development of the basic functions of touch in normal childhood is lacking. Specifically, no data were available on tactile sensitivity and acuity in the hairy skin of children and early adolescents until now. In our study for the first time these two components of somato-sensation have been investigated in hairy skin of children and we found that both tactile acuity and sensitivity decrease as a function of age. Referring to studies across glabrous skin sites, it has been demonstrated a general decrease as a function of age that involves different facets of tactile acuity (Stevens & Patterson, 1995; Stevens & Choo, 1996) and tactile sensitivity (Thornbury & Mistretta, 1981). Our results showed that tactile sensitivity and acuity decrease starts from early age also in hairy skin. Data are consistent with the hypothesis that all age-related losses of sensitivity and acuity reflect a common mechanism, namely, the progressive thinning of the primary receptor mosaic described by the histologists (Bolton et al., 1966; Gescheider et al., 1994). Bolton et al. (1966) reported parallel decline between two-point threshold and density of Meissner corpuscles in the finger and toe. The same decline of receptor density purported to explain acuity, has also been suggested by Gescheider et al. (1994) as the reason for age-related decline of absolute sensitivity to vibration of various frequencies. Despite further studies are needed, in the present study we showed that sensitivity and acuity of hairy skin follows a similar decrease as a function of age as observed in the glabrous skin, suggesting a similar mechanism of gradual decline in innervation density.

The second aim of study was to analyze whether tactile sensitivity and acuity are linked to affective touch. Our finding suggests a behavioral separation implying that the discriminative touch and affective touch are no directly linked with each other. Different studies in adult humans have shown that the C and Aß systems are distinct with regard to their neuroanatomical and functional features (Björnsdotter et al., 2010; McGlone et al., 2014). Our data suggests functional segregation of the behavioral outcomes that are aimed at underpinning selective functions of these two systems. Whereas the Aß system appears to be involved in sensory-discriminative touch from birth (Johansson & Westling, 1987), the affective touch hypothesis (McGlone et al., 2014) implies that the CT system and AT are critical in providing or supporting emotional, hormonal, and behavioral responses to skin-to-skin contact with conspecifics, processing the motivational and hedonic aspects of touch. Furthermore, this functional distinction between systems is already present in childhood, thus reflecting an efficient fulfillment of their purpose since early stages of life.

The last aim of our study was to examine the relation between affective touch and age. Our analysis indicates that the AT Index increases with age showing that older children prefer the Affective Stimulation rather than Neutral Stimulation. A general rise in preference for Affective Stimulation as age increases is consistent with the findings of Croy and colleagues (2017). We confirmed this finding in a larger sample. Moreover, our results also showed that children of all ages rated the Affective versus Neutral Stimulation as more pleasant. Previous studies have reported that individuals of all ages rate affective with respect to neutral stimulation as more pleasant (Sehlstedt et al., 2016; Croy et al., 2017). Our findings confirmed this pattern. These evidences and our data leads us to conclude that although affective touch processing is already present at birth (Jönsson et al., 2018; Miguel et al., 2017; Tuulari et al., 2017), and it might have a contribute to the development. In fact, C-tactile fiber stimulation is linked with pleasantness (Löken et al., 2009; Ackerley et al., 2014) and reduces heart rate in infants (Fairhurst et al., 2014). Gentle stroking also has beneficial health effects in preterm babies (Kramer et al., 1975; Pepino and Mezzacappa, 2015; Field et al., 2010) and another study showed also that parents stroke their babies using slow velocities, optimal for targeting C tactile fibers (Croy et al., 2016b). This suggests that infants are familiar with AT stimulations and that C-tactile targeted touch could shape a child's preference for affective or neutral stimulation. On the other hand, C-tactile-targeted touch has also been linked to social behavior deficits (Cascio et al., 2008; Voos et al., 2013; Croy et al., 2016a; Kaiser et al., 2016). Therefore, it is possible that C-tactile perception constitutes a stable trait since infant and that is related to social and relational behavior, suggesting that individuals with a higher preference for affective stimulation are more responsive to social interactions. Clearly, such data are inherently noisy due to individual differences and further studies are needed to determine the environmental contribution to affective touch processing.

This study has several limits. Among them, the first is the range of ages included in the sample; in our study, in fact, we collected data of children from 6 to 14 years, leaving unexplored the performances of pre-school children. Regarding tactile acuity and sensitivity, it would be interesting to explore whether the age-related decline of somato-sensation in the hairy skin recorded in children from 6 years of age starts from earlier stages of life or it is a specific pattern occurring from the school age. Similarly, despite few studies have shown an implicit preference for CT-Optimal stimulations in infants already within the first year of life (Jonsson et al., 2018; Miguel et al., 2017; Tuulari et al., 2017), it would be interesting to assess the affective touch, in children younger than 5 years.

A second limit is that, despite we assume that pleasantness ratings for Affective Stimulations would be related to a greater firing rate of CT fibers in children as observed in adults (Löken et al., 2009), we couldn't use any microneurography. In fact, it is known that this technique is invasive and painful and it would have been not suitable for children.

Study II: Altered perception of affective touch in disorganized attachment

4.1 Introduction

The initial tactile experiences are of crucial importance in the development and the maturation of an organism in several developmental pathways, from biological growth (Bremner & Spence, 2017) to psychological maturity (Ardiel & Rankin, 2010), to social skills achievements (Cascio et al., 2018). The first primary stimulation that children experience is the interaction with caregiver. In the attachment theory, Bowlby (1969) suggested that children come into the world biologically pre-programmed to form attachments with others, because this will help them to survive. In respect to the purpose of our work, what seems of interest is that after the nineties', several authors used the sense of touch to further explore the theory of Attachment. For example, Reite (1990) suggested that in human, touch is fundamental because it allows the formation of an affective relationship with the caregiver which in turn forms a "secure" base that facilitates the development of learning, emotions regulation as well as social interactions (for a more detailed discussion of this issue, refer to the introductory chapters of this document).

Referring to this topic, why should a system that conveys hedonic feeling of touch be of some utility in the development of an organism? Clearly there is not a solely answer to this question. When reviewing the principal feature of the CT-system, McGlone (2014) identified a fundamental function of the pleasant touch: the CT fibers are tuned by caress like stimuli providing a peripheral mechanism for signaling pleasant skin-to-skin contact in humans which in turn promotes the interpersonal touch and affiliative behavior. This psychobiological perspective seems to support the aforementioned studies of Bowlby (1969, 1982), who suggested that the attachment system is activated when, after a separation from the caregiver, the child seeks proximity to the parent/caregiver in the form of physical contact which consent him to feel secure and safe.

Furthermore, different studies (Crucianelli, 2016; Croy et al., 2016a) seems to suggest that the interpersonal and social functions decoded by affective touch system, may be traceable also in adults who experience difficulties in the ways to relate to others in the affectivity domain, and in the impulse control (for a more detailed discussion of this issue, refer to the introductory chapters of this document). Interestingly, these two difficulties characterize a specific attachment pattern, namely the disorganized-unresolved. According to the attachment literature, the disorganized-unresolved pattern triggers dissociated traumatic memories related to fearful or neglecting experiences of attachments (Meares, 2012) and includes contradictory and dramatic expectations related to caregivers (Hesse et al., 2003; Liotti, 2004; Lyons-Ruth & Jacobvitz, 1999). This pattern has been associated to emotion dysregulation extreme behavioral reactions in stressful situations (Main et al., 2002) and frequently, to self-harming conducts; due to its features, it is overrepresented in clinical samples characterized by phenomena of dissociation (e.g. Post-Traumatic Stress Disorder) and impulse and emotional dysregulation (e.g. borderline personality disorder) (Bakermans-Kranenburg and Van IJzendoorn, 2009).

Given these circumstances, it is likely that affective difficulties and impulse discontrol observed in adults with disorganized attachment (i.e. self-cutting behaviors in patients with borderline personality disorder), may be reflected in an altered perception of affective touch.

Considering these evidences, we formulated a specific research hypothesis that deals with the relationship between the attachment and affective touch patterns. Specifically, we wanted to verify whether the perception of affective touch is altered in individuals with different attachment patterns. We predict that the perception of affective stimulation would be less pleasant in disorganized with respect to organized individuals. To do so, we also assessed the presence of possible bias in perception of basic tactile functions (i.e. tactile acuity and sensitivity and thermal sensitivity) and possible differences in psychological and psychopathological manifestations: we don't expect to find group differences in our sample.

4.2 Methods

4.2.1 Participants

64 healthy subjects were recruited from the general population by word of mouth and the use of flyers distributed in a commercial area of downtown (e.g., bookshops, cafeterias, and public library). After exclusion of one subjects (a women) due to low level of Italian as native language, the experimental group was composed of 63 participants (31 females and 32 males). Exclusionary criteria, assessed during a pre-screening semi-structured interview, were: diagnosis of neurological disease, substance abuse/dependence and pregnancy or childbirth within the last 12 months. All participants were Caucasian.

4.2.2 Procedure

The protocol was approved by the local Ethics Committee and conformed to The Code of Ethics of the World Medical Association (Declaration of Helsinki), as printed in the British Medical Journal (July 18, 1964). All participants provided written informed consent. First, participants were evaluated for possible inclusion in the study by means of an informal interview aiming to get a thorough acquaintance. Then, participants were invited to arrange an appointment with the researcher for the experimental meeting and all of them were evaluated in a single session lasting about 75 minutes. The protocol consisted in three steps: the Adult Attachment Interview (AAI), an experimental tactile procedure and the drawing up of psychological and psychopathological scales. The AAI has been always conducted firstly, whereas the remaining assessment were balanced between participants; thus, 50% of participants received the experimental tactile procedure before the psychological scales, and the remaining 50% took these latter before the tactile session.

4.2.3 Measures

Adult Attachment Interview. The Adult Attachment Interview (AAI; George et al., 1996) is a semi-structured, clinical interview designed to assess an individual's current state of mind with respect to past caregiver–child attachment-related experiences (Hesse, 2008). Interpretations of the adult attachment categories do not rely on the assumption that they represent veridical accounts of early childhood experience; rather, transcripts of the interviews are coded by trained raters according to how coherently people recall their past experiences. The individual's strategy during the AAI (e.g., derogating or minimizing of attachment vs. valuing and rendering a balanced, coherent narrative despite positivity or negativity of actual experience) is supposed to reflect the quality or security of one's current state of mind with respect to attachment (Hesse, 2008). Typically, one out of three possible main classifications is assigned to the most prominent state of mind throughout the interview as a whole: secure/autonomous (F), insecure-dismissing (Ds), or insecure-preoccupied (E), of which secure/autonomous is considered the most beneficial. Furthermore, when present, discussions of experiences of loss, abuse, or other potential trauma are scored for disorientation in reasoning or discourse and, when sufficiently marked, may lead to a primary classification of a disorganized/unresolved (Ud) state of mind. In such a case, a secondary (organized) classification of secure/autonomous, insecure/dismissing, or insecure/preoccupied is assigned for the remaining narrative. Interviews in which a singular organized state of mind cannot be identified (e.g., because marked indications of several states of mind are present) are coded as cannot classify (CC; Reijman et al., 2017). The AAIs were transcribed verbatim, and identifying information was removed prior to coding. To assess individual differences in attachment, transcripts were coded by a certified AAI coder, who had achieved greater than 80% agreement with on the official reliability test.

Psychological scales. Personality Inventory for DSM-5. The personality Inventory for DSM-5 (PID-5) is a 220-item self-report measure of the DSM-5 alternative personality disorder model traits (Krueger et al., 2012). The PID-5 measures 25 personality traits that can be organized into five overarching domains (i.e., negative affect vs. emotional stability, detachment vs. extraversion, psychoticism vs. lucidity, antagonism vs. agreeableness, and disinhibition vs. conscientiousness). Each trait is assessed by 4 to 14 items and evidence from non-clinical samples indicated that the PID-5 latent trait domain structures were concordant with Five Factor Model traits (Thomas et al., 2013) and demonstrated good convergence with well-established personality trait measures (Anderson et al., 2013; Ashton, Lee, de Vries, Hendrickse, & Born, 2012; Fossati, Krueger, Markon, Borroni, & Maffei, 2013; Wright et al., 2012).

Symptom Checklist-90-R. The Symptom Checklist-90-R (SCL-90-R; Derogatis, 1994) is a self-report questionnaire composed of 90 items exploring the frequency of several psychological symptoms in the last week. Respondents are asked to answer on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The nine clinical subscales are Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Phobic Anxiety, Psychoticism, Paranoid Ideation, and Hostility. The global indices include the Global Severity Index (GSI), the Positive Symptom Distress Index (PSDI), and the Positive Symptom Index (PSI). Overall, the SCL-90-R subscales have demonstrated excellent internal consistency (.77 to .90) and test–retest reliability (.78 to .90) (Payne, 1985).

Tactile Experimental procedure

Before administering the experimental procedure, all participants were tested with measures of tactile sensitivity and tactile acuity. These measures allowed the experimenters to exclude any possible damage in the tactile perception that could indeed affect the subsequent experiment.

Von Frey Monofilaments & Two-Point discrimination test (Please, see descriptions of these tests in the paragraph 3.2.3 of the previous study).

Thermal sensitivity. Caloric sensitivity was tested using a TSA II device (MEDOC Inc., Ramat Ishai, Israel). Baseline temperature was always set to 32℃ and then successively heated with a ramp rate of 1℃ per second. A warming cylinder with 1,5 cm of diameter was placed on the dorsal side of the right forearm and participants were instructed to indicate verbally as soon as the heat became intolerable. To prevent tissue damage, maximum duration of the heat exposure was set at 40sec. The assessment was administered five times and the average of the measurements was used in the analysis.

Affective Touch Experimental procedure

(Please, see descriptions of these procedure in the paragraph 3.2.3 of the previous study).

In order to simplify the reading of the results, the term "CT optimal stimulation" was relabeled Affective Stimulation and the term "non-CT optimal stimulations" was relabeled Neutral Stimulations.

4.2.4 Statistical Analyses

Data processing was performed using SPSS (IBM). Partial eta-squared (ηp^2) and Cohen's d were calculated to quantify the effect sizes of all comparisons. On the bases of the AAI, the entire sample has been split into two groups, namely Organized Attachment (OA; N = 46) and Disorganized Attachment (DA; N = 17).

To evaluate group differences in the demographics and clinical variables of the study, two sample *t*-tests were computed on age, education, SCL-90-R, PID, Von Frey (SST) 2PD (SAT) and Thermal Sensitivity. Chi-square comparison was conducted to test for pre-existing differences in sex distribution.

MANOVA. To examine the differences in Affective touch between Organized Attachment (OA) and Disorganized Attachment (DA), a Multivariate Analyses of Variance (MANOVA) with 'group' (OA vs DA) as between-subject factor, and Affective Touch (Affective Stimulation, Neutral Stimulation) as the dependent variables, was run.

***t*-TEST.** To analyze groups difference in AT-index, a conclusive independent samples t-test was run between OA and DA.

4.3 Results

Given the absence of sex distribution differences between the two groups ($\chi2 = 1.37$; $p = 0.18$), gender was not included as a covariate in the statistical analyses. The demographic and clinical information of OA and DA participants are reported in Table 1.

Table 1. Pre-existing group differences (means and standard deviations) in the demographic, clinical variables of the study.

	OA (N=46)	DA (N=17)	Student *t*	Cohen's *d*
Age (years)	29,02 (8,01)	31,59 (11,08)	-1,01,	- 0,266
Education (years)	16,3 (7,71)	15,9 (7,5)		
PID – Negative Affect	1,08 (0,54)	1,2 (0,61)	-0,7,	- 0,208
PID – Detachment	0,69 (0,41)	0,7 (0,62)	-0,08,	- 0,019
PID – Antagonism	0,61 (0,47)	0,7 (0,48)	-0,68,	- 0,189
PID – Disinhibition	0,78 (0,47)	0,9 (0,54)	-0,86,	- 0,237
PID – Psychoticism	0,7 (0,56)	0,9 (0,65)	-1,21,	- 0,330
SCL90 (global score)	0,66 (0,52)	0,9 (0,59)	-1,53,	- 0,432
Von Frey (SST)	3,01 (0,63)	3,09 (0,62)	-0,44,	- 0,128
2PD (SAT)	4,09 (1,68)	3,73 (0,97)	0,83,	0,262
TS	44,62 (1,64)	44,8 (1,46)	-0,39,	- 0,116

Note: OA = Organized Attachment; DA = Disorganized Attachment; PID=; SCL90; 2PD = Two Point Discrimination; TS = Thermal Sensitivity.

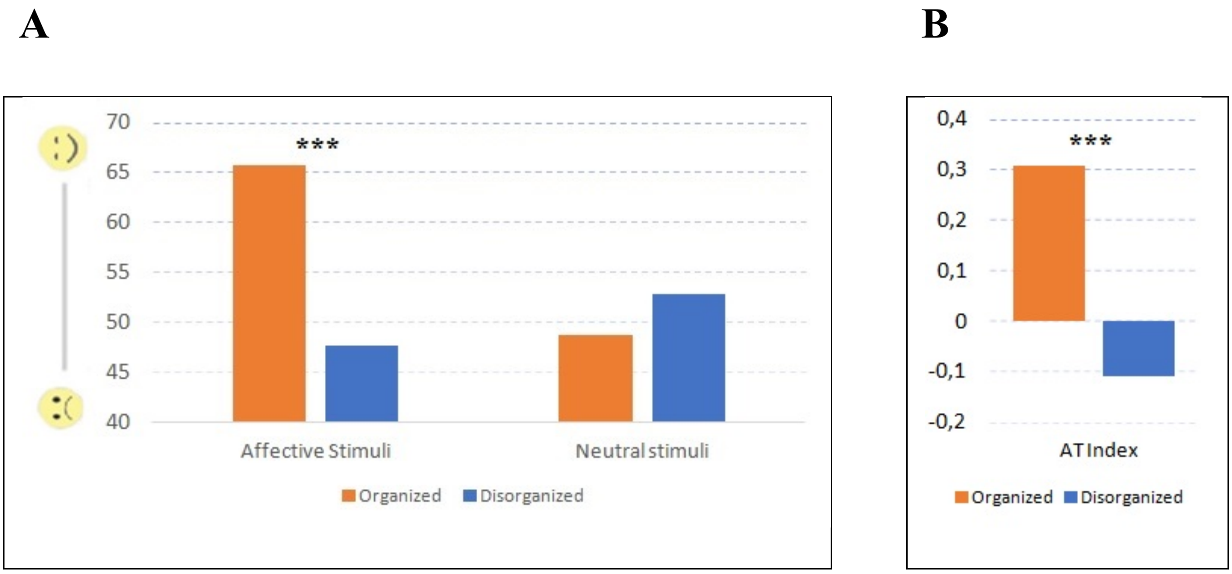
As expected, when OA participants were compared with DA no significant difference emerged in self-report (PID-5 and SCL90) and in basic somatosensory measures (Von Frey, 2PD and Thermal Sensitivity).

MANOVA

The MANOVA with Affective Touch ratings (Affective Stimulation, Neutral Stimulation) as dependent variables and Attachment pattern (OA – DA) as between subjects factor, showed that DA exhibited a significant different evaluation of the stimulations outcomes (Pillai's trace= 0.9; $F_{(3, 626)}$ = 19,98; p = .000; Partial eta-squared = 0.087 and observed power = 1) with respect to OA. The between groups comparisons showed that DA participants reported a significant lower level of touch pleasantness for Affective Stimulation (Figure 2A), whereas no difference was found in the evaluation of Neutral Stimulation.

The final t test on AT Index, showed that OA evaluated the Affective Stimulation as more pleasant with respect to Neutral Stimulation (t = 1.98; $p < .05$). (Figure 2B).

Figure 2. A) Groups comparisons on Affective and Neutral stimulations; B) Groups comparison, on AT Index.



Note: *** = $p < .05$.

4.4 Discussion

The aim of the present study was to investigate whether the perception of affective touch would be reduced in disorganized compared to organized participants. The results confirmed our first prediction showing that individuals with disorganized attachment pattern perceived affective touch as less pleasant compared to organized participants.

It has long been established that individuals with psychological and psychopathological impairments, such as patients with autistic spectrum (Voos et al., 2013; Kaiser et al., 2016), patients with anorexia nervosa (Crucianelli et al., 2016) and patients with personality disorder (Croy et al., 2016a), rated affective touch generally less pleasant than controls. In our study, we demonstrated that also individuals with disorganized attachment compare to individuals with organized attachment showed perceived Affective Touch as less pleasant. This latter finding seems to suggest that the interpersonal and social functions decoded by affective touch system, may be traceable also in adults who experience difficulties in the ways to relate to others in the affectivity domain, and, specifically, referring to attachment history. We can hypothesize that individuals who have developed a disorganized attachment are less sensitive to affective tactile stimulation. Disorganized pattern is associated both to internalizing (e.g., suicidality and borderline psychopathology) and externalizing disorders (e.g., antisocial personality disorder). Notably, these disorders are characterized by difficulties in emotions regulation and interpersonal relationships (Bakermans-Kranenburg & Van IJzendoorn, 2009). Moreover, maternal borderline personality disorder, characterized by intense and unstable relationships and impulsive, self-damaging behavior, including suicidality (Hobson, Patrick, Crandell, García-Pérez, & Lee, 2005), and maternal depressive symptoms (Martins & Gaffan, 2000; see also Toth, Rogosh, Manly, & Cicchetti, 2006) have also been associated with elevated rates of disorganized pattern in infants. It is possible that individuals with disorganized attachment who have experienced, and then developed, difficulties in the relational and affective aspects, may show a specific impairment in processing affective tactile information. Indeed, in our sample disorganized and organized participants did not show differences in tactile acuity and sensitivity and in thermal sensitivity suggesting that attachment could be linked only to affective aspect of touch. In fact, the skin is the site of events and processes crucial to the way we think about, feel about, and interact with one another and touch can mediate social perceptions in various ways (Morrison et al., 2010). The cutaneous senses are crucial mediators of social interactions, contributing not only to sensation but to emotions. This aspect of tactile sensation, i.e. affective touch, is at the heart of the social skills domain, allowing positive hedonic experience ranging from the reassurance of a pat on the back to the rills of a sensual caress (Morrison et al., 2010). In the developmental age, the dyadic experience with caregiver is the place where infant primarily interacts with other. For example, stroking an infant can not only give rise to positive emotions in the baby, but can also modulate negative ones, compared to other forms of touch (Pelàez-Nogueras et al. 1996). Our result could highlight the potential role of dyadic relationship, i.e. attachment, in shaping the responsiveness to affective aspect of tactile interaction.

This study has several limits. First, even if the unequal distribution of participants in the two groups (i.e. organized and disorganized) reflects normative data, the different size in the two groups may have biased the results. It is desirable that future studies would use larger samples to allow the examination of potentially relevant sex differences, as well as within-group differences. Second, the disorganized attachment classification includes individuals with unresolved traumas or losses (U; unresolved) but also those that cannot be classified because of the presence of marked indications of several states of mind (CC; cannot-classify). Furthermore, future studies should explore other attachment patterns, such as secure and unsecure, which were not explored in the current study.

Study III: Brain mechanism for processing affective touch in disorganized attachment: preliminary results

5.1 Introduction

The emotional aspect of touch has been called "Affective Touch" (AT), a category term capturing tactile processing with a hedonic or motivational component. It has been proposed as a relatively distinct category of touch, with qualitative and anatomical correlates distinguishable from the more well-mapped pathways of "discriminative touch" (Olausson et al., 2010; McGlone et al., 2014; Morrison et al., 2010). In this perspective, affective touch preferentially drives affective, motivational or hedonic tactile stimuli, especially in contexts in which touch can carry affective significance such as social interactions or mother-infant bonding (Morrison, 2016b). The activation of CT fibers, thought to convey affective valence of touch, via soft brush stroking on hairy skin activates the classical somatosensory areas (i.e. S1 and S2) as well as the posterior contralateral insular cortex. Insular cortex is a region considered as a gateway from sensory systems to the emotional system of the frontal lobe and is of great interest in relation to affective stimuli processing. Beyond the insular cortex, other brain regions such as the medial prefrontal cortex, dorsoanterior cingulated cortex, posterior superior temporal sulcus (Gordon et al., 2013) and supramarginal gyrus (Kaiser et al., 2015) are implicated in processing CT-targeted touch.

Despite its central role, the activation of the neural network that processes AT stimuli may be modulated by psychological factors such as individual differences. For instance, Kaiser and colleagues (2015) found differences in the activation of areas recruited by young healthy individuals and patients with autistic spectrum disorders in processing pleasant touch; more recently, Davidovic and colleagues (2018) and Bischoff-Grethe and colleagues (2018) showed that patients with current anorexia nervosa and women remitted from the pathology are characterized by abnormal neural responses to pleasant affective stimulations when compared to healthy controls.

Given the important role of AT in social interactions and that neural processing of pleasant touch seems to be already mature within the first weeks after birth (Jönsson et al., 2018; Miguel et al., 2017; Tuulari et al., 2017), one may hypothesize that AT can play a fundamental part in mediating mother-infant bonding and the creation of a dyadic attachment. AT perception seems to be altered in people with different attachment patterns (Krahé et al., 2016, 2018) but nothing is known about whether these behavioral differences are reflected in abnormal neural responses or not. What is missing in the above mentioned studies is the exploration of the affective touch in the Disorganized attachment dimension. Disorganized attachment is conceived in terms of an unintegrated attachment trauma that is ascribed to the underlying dynamics of a severe form of emotional dysregulation and has been linked to abnormal neural activation in medial temporal regions including the amygdala and the hippocampus in response to attachment memories recollection (Buchheim et al., 2006).

Thus, the aim of our study is to compare brain responses via fMRI to CT optimal (Affective Stimulation) and non-CT optimal (Neutral Stimulation) stroking velocity in a sample of healthy adults classified as having whether an Organized or a Disorganized attachment assessed by the administration of the Adult Attachment Interview, the gold standard for evaluation of adults' state of mind with respect to attachment memories. We hypothesize that individuals with a Disorganized attachment pattern, relative to Organized subjects, would exhibit atypical brain responses to slow, pleasant, CT optimal (Affective Stimulation).

5.2 Methods

Participants

Participants were 20 healthy right-handed individuals (mean age: 31.15 and SD: 10.26; ten women) who had no history of neurological or psychiatric disorders. Our sample was composed of a randomly selected subset of participants of the previous study (see Study II in this thesis); Participants were further divided into two groups according to their attachment pattern as follows: group 1 Organized Attachment (OA; N = 12, 5 Females and 7 Males) and group 2 Disorganized Attachment (DA; N = 8, 5 Females and 3 Males). Exclusionary criteria, assessed during a pre-screening semi-structured interview, were: diagnosis of neurological disease, substance abuse/dependence and pregnancy or childbirth within the last 12 months. All participants were Caucasian and provided written informed consent prior to the experimentation. The protocol was approved by the local Ethics Committee and conformed to The Code of Ethics of the World Medical Association (Declaration of Helsinki), as printed in the British Medical Journal (July 18, 1964).

PreScan behavioral ratings and interview

Prior to the scan, participants were assessed respect to attachment pattern by the Adult Attachment Interview (AAI; George et al., 1996), and psychopathological difficulties by the Symptom Checklist-90-R (SCL-90-R; Derogatis, 1994). Please, see descriptions of these tests in the paragraph 4.2.3 of the previous study.

Since exposure to trauma, such as physical or sexual abuse (as present in Disorganized pattern (Main et al., 2002), may also predispose persons to respond to stress somatically (Stuart & Noyes, 1999) we planned to explore the potential mediator role of the SCL-90-R Somatization scale scores in the relation between Attachment and brain response to Affective Touch.

Experimental Design

The tactile stimuli consisted of manual strokes with a 4-cm wide watercolor brush applied on the hairy skin of the dorsal forearm. The stimuli were applied with strokes at CT optimal

(Affective Stimulation; 3 cm/s) or non-CT optimal (Neutral Stimulation; 30 cm/s) stroking velocity (Löken et al., 2009). In each participant, 15 cm of the forearm were marked to control for the length of stimulated skin, and two trained experimenters administered the stimuli. Continuous brushing (back and forth) was applied to the right forearm according to a block design, characterized by four run of stimulation in addition of two resting state sessions (Figure 1). The 2 experimental conditions (CT optimal, non-CT optimal) alternated, and there were 10 repetitions (5 rep. for CT optimal, 5 rep. for non-CT optimal) of 12-s periods of touch followed by 12 s of rest (no touch). The experimenter instructed participants to close their eyes during the procedure, to remain very still, and to focus on the touch they experienced. In order to simplify the reading of the results, the term "CT optimal stimulation" was relabeled Affective Stimulation (AS) and the term "non-CT optimal stimulations" was relabeled Neutral Stimulation (NS).

Figure 1. Experimental paradigm.

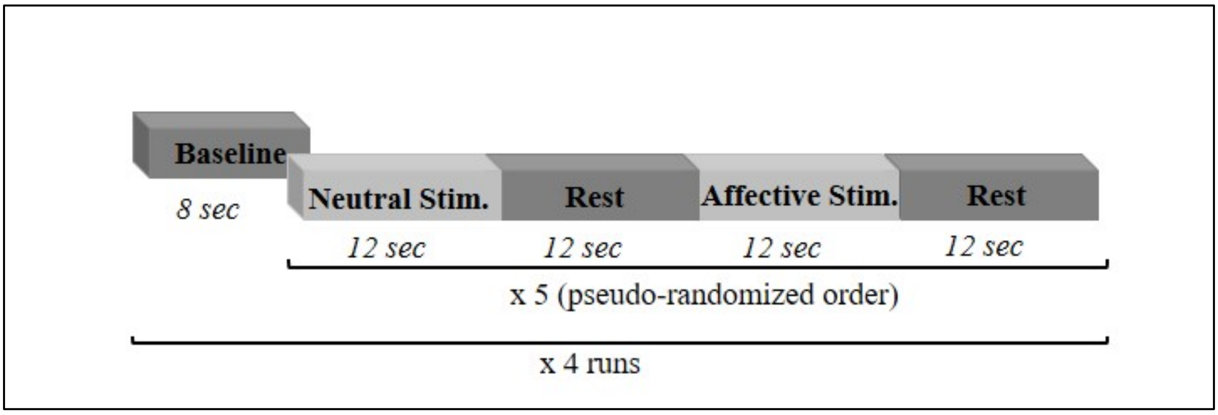


Image Acquisition

Magnetic resonance imaging (MRI) scans were collected using a 3T Philips Achieva scanner (32-channels SENSE head coil). Head movements were minimized with mild restraint and cushioning. Functional T2*-weighted images were collected both for resting state and task-based protocols using a gradient echo EPI sequence to measure the blood-oxygen-level-dependent (BOLD) contrast over the whole brain (parameters: 122 fMR scans, 38 slices, in-plane resolution = 2.5 x 2.5 mm, slice thickness = 4 mm, repetition time (TR) = 2 s, echo time (TE) = 30 ms, flip angle = 77 deg). We also acquired a three-dimensional high-resolution T1-weighted structural image for each subject (parameters: 342 slices, in-plane resolution = 0.5 x 0.5 mm, slice thickness = 0.5 mm, TR = 2 s, TE = 5.75 ms, flip angle = 8 deg).

Image analysis

Image analysis was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The first four volumes of each scan were discarded to allow for T1 equilibration. Differences in the acquisition time of each slice in a MR frame were compensated by sync interpolation, so that all slices were aligned to the middle time point of the frame. Functional data were realigned within and across scans to correct for head movement and co-registered with structural scans. Following movement correction and co-registration, images were warped into the MNI152 template (Mazziotta et al. 1995) using a non-linear stereotaxic normalization procedure (Friston et al. 1996) and resampled into 3-mm isotropic voxels. Images were then spatially smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel.

Functional images were analyzed for each subject separately on a voxel-by-voxel basis according to the general linear model (GLM). Neural activation during the blocks was modeled as a boxcar function spanning the whole duration of the blocks and convolved with a canonical hemodynamic response function, which was chosen to represent the relationship between neuronal activation and blood oxygenation (Friston et al. 1997). Separate regressors were included for each type of tactile stimulation (AS or NS). Inter-block intervals were also modeled in relation to the nature of the previous block (AS-rest or NS-rest). Group analysis was performed on estimated images that resulted from the individual models of each condition (AS or NS) compared with its baseline (AS-rest or NS-rest), treating subject as a random factor. At the group level, we first performed a voxel-wise analysis across the whole brain by means of a full factorial design, including Group (OA and DA) and tactile stimulation (AS or NS) as factors. We computed an F omnibus contrast of all conditions, masked by a t-contrast, which was obtained by contrasting the tactile stimulations (AS and NS) against the baseline. The resulting statistical parametrical maps were thresholded at $p < 0.05$ at the cluster level using Family Wise Error correction (FWE), after forming clusters of adjacent voxels surviving a threshold of $p < 0.001$ uncorrected. For each subject and region, we computed a regional estimate of the amplitude of the hemodynamic response in each experimental condition by entering a spatial average (across all voxels in the region) of the pre-processed time series into the individual general linear models. The regional hemodynamic response was then analyzed with mixed factorial ANOVA, with the same factorial structures of the above-mentioned full factorial design (Group by Tactile Stimulation).

Statistical analysis of resting-state functional connectivity

Images were preprocessed using the SPM12 (Wellcome Department of Cognitive Neurology, London) following the same procedure described above. We performed a connectivity analysis of the fMRI data collected at rest, using a seed-to-seed connectivity approach across regions whose hemodynamic response was found to be modulated by different tactile stimulation, hereafter called seed regions. The time course of each seed region was used as a covariate of interest in a general linear model (GLM) applied at each and every brain voxel. For each model, first-level subject-specific GLMs were used to compute whole-brain regression parameter estimates reflecting the effect of the four seed regions regressors on each voxel. Sources of spurious variance were removed by including extra regressors as nuisance covariates. We included the global signal time course, estimated as the average BOLD signal within the default SPM within-brain mask, plus several other regressors summarizing voxel time courses in regions where the time series data are unlikely to be modulated by neural activity, to reduce noise due to physiological fluctuations, and other sources, such as subject motion. In particular, we included four white matter and four cerebrospinal fluid (CSF) regressors, computed as the first four eigen-variates of a singular value decomposition of the resting-state time courses of all voxels within the white matter and CSF, respectively. We also included six head movement regressors to further reduce motion-induced noise. Individual seed time courses were orthogonalized with respect to nuisance regressors. The GLM also included constant terms to model overall differences across scans. Since the majority of the previous fcMRI studies focused on slow (<0.1 Hz) BOLD fluctuations (Fox and Raichle 2007), images were temporally filtered using a low-pass filter with a cut-off frequency of 0.1 Hz before entering the GLM.

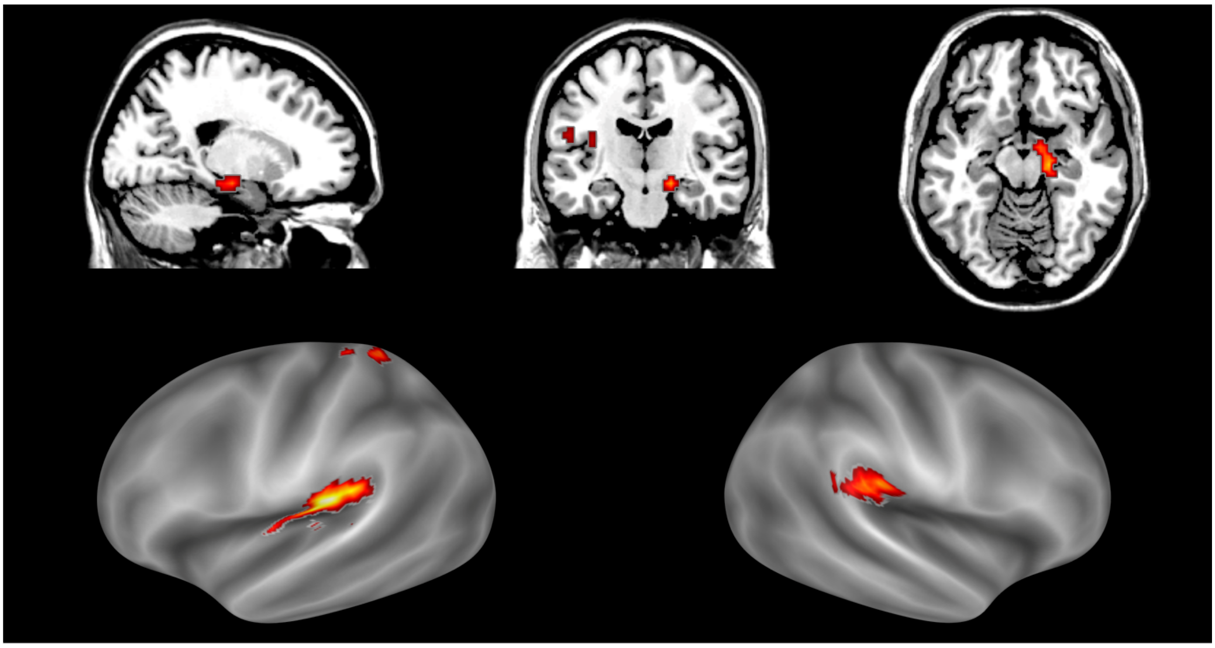
For each subject, we computed a correlation matrix of inter-regional couplings. After transforming correlations coefficients to z-values using the Fisher transform. Relevant seed-to-seed combinations have been defined using one-sample t-tests to assess whether correlation coefficients were significantly higher than zero. Differences between groups (OA vs. DA) for significant seed-to-seed combinations were assessed using two sample t-tests. A Bonferroni adjustment was used to create confidence intervals for all the pairwise comparisons.

5.3 Results

Neural network of Affective and Neutral Stimulations processing

The first step of the analysis provided a general picture of the cerebral regions involved in processing of Affective and Neutral Stimulations. We found a network of areas encompassing the left Posterior Insula (PI), as well as the left Primary Somatosensory Cortex (S1), the right Supramarginal Gyrus (SMG) and right Amygdala (Amy) (Figure 2). To disentangle the effect of Group and Stimulation within this network, we performed a 2 x 2 mixed factorial ANOVA on average regional hemodynamic response. Results of this analysis are reported in the three paragraphs below, according to the effect of Group, Stimulation and their interaction.

Figure 2. Activation of areas involved in processing tactile stimuli



Region	Hemisphere	Label	cluster p(FWE)	peak F	peak p(unc)	k	x	y	z
Posterior Insula	LH	PI	0.000	21.471	0.000	144	-48	-28	19
				19.236	0.000		-39	-25	19
Amygdala	RH	Amy	0.027	13.423	0.000	27	18	-19	-14
				8.793	0.000		12	-7	-14
Supramarginal gyrus	RH	SMG	0.001	12.008	0.000	53	51	-28	25
				6.874	0.000		63	-37	25
Primary Somatosensory Cortex	LH	S1	0.030	9.515	0.000	26	-21	-40	61
				7.976	0.000		-30	-31	64

Note: brain activations to Affective and Neutral Stimulations in Healthy adults. F omnibus contrast of all conditions, masked by a t-contrast, which was obtained by contrasting the tactile stimulations (AS and NS) against the baseline.

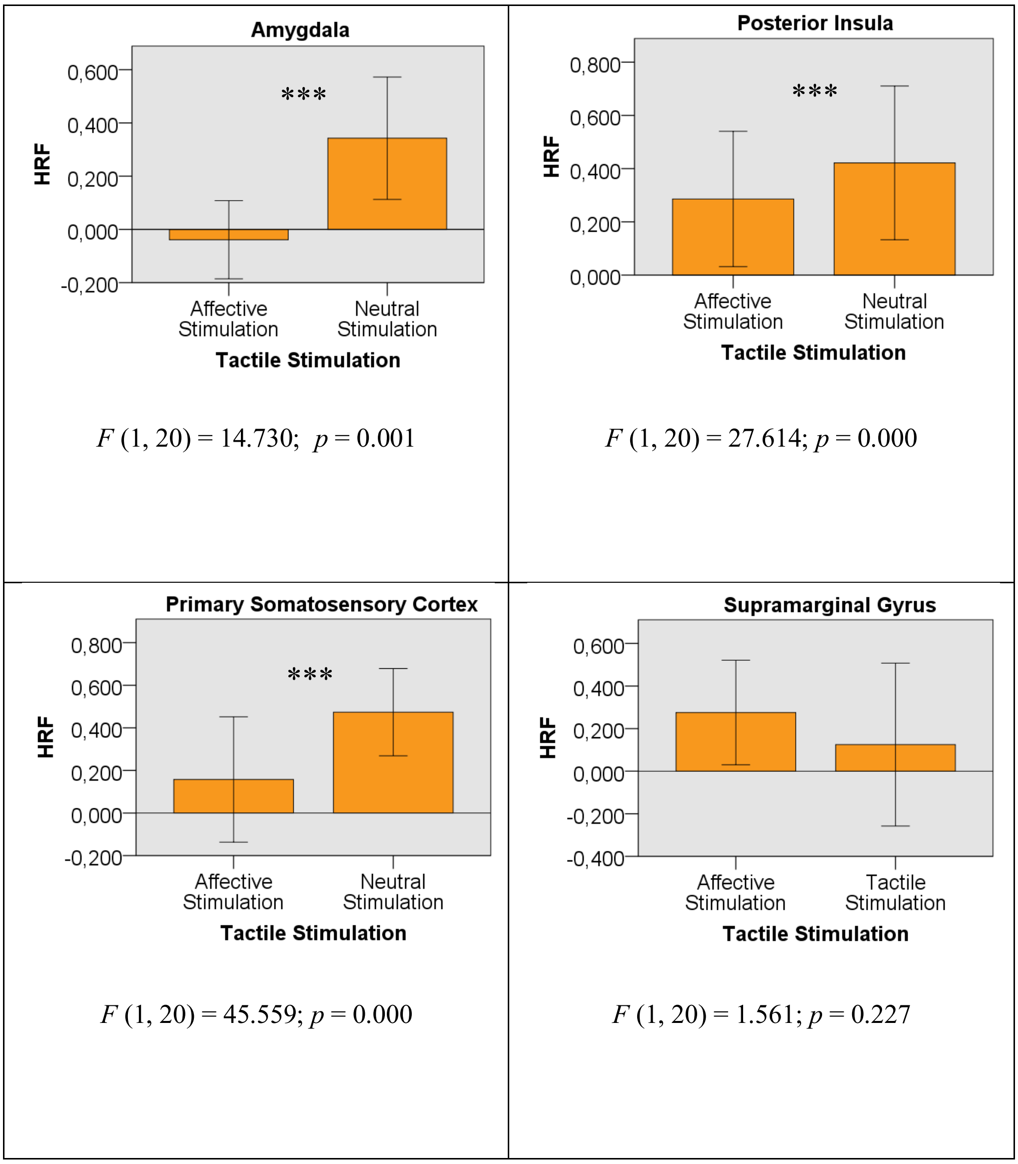
Resting-state functional connectivity

Analysis of resting-state functional connectivity revealed a connection between PI and S1 (*r* = .880, *p* = .000), and between PI and SMG (*r* = .503, *p* = .000).

The main effect of stimulation

We found a main effect of Stimulation in the PI, the S1 and the Amy: these areas were more activated during Neutral Stimulation as compared with Affective Stimulation. Statistics are fully reported below in Figure 3.

Figure 3. Activation of areas involved in processing tactile stimuli.

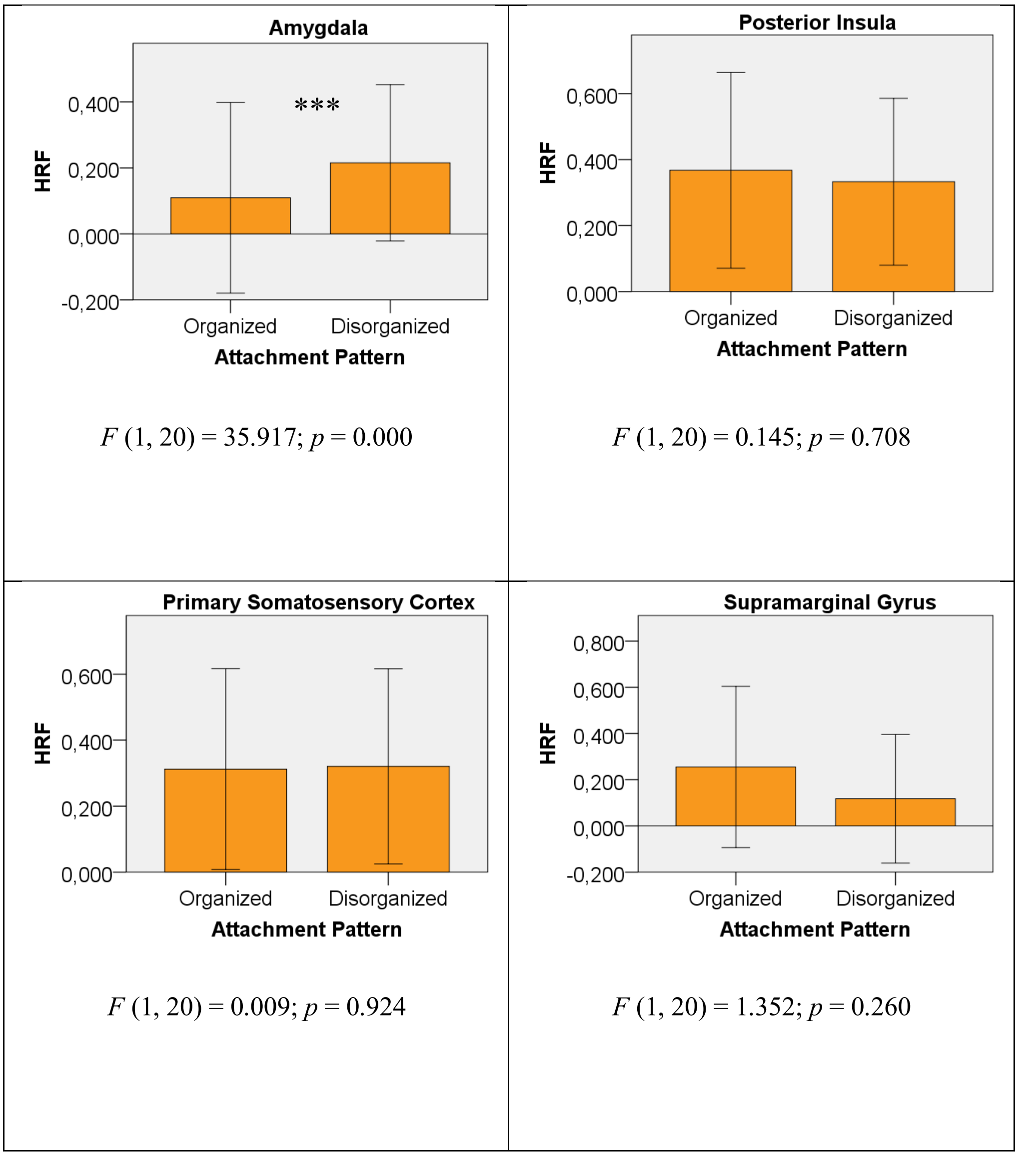


Note: *** = $p < 0.001$.

The main effect of group

We found a main effect of Group in the right Amy, with DA showing stronger activation than OA participants. Statistics are fully reported in Figure 4.

Figure 4. Activation of areas involved in processing tactile stimuli between groups.



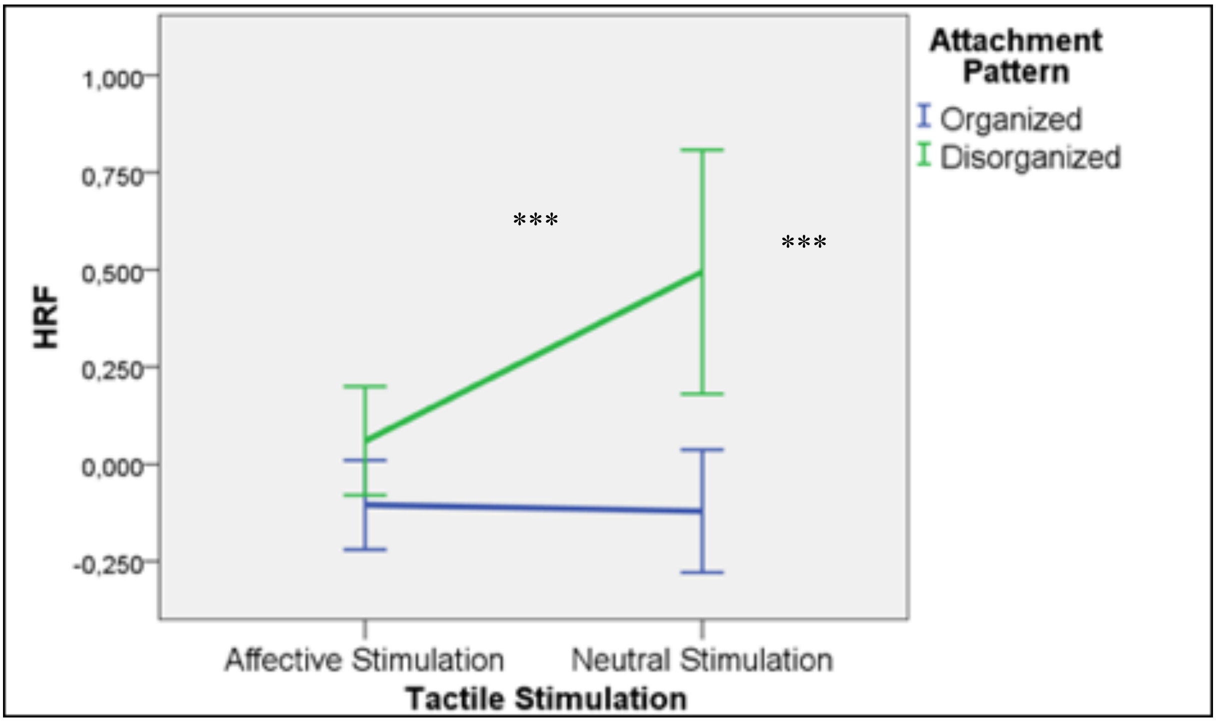
Note: *** = $p < 0.001$.

The interaction between group and stimulation

Interestingly, we found an interaction between Group (OA vs DA) and Tactile Stimulations (Affective vs Neutral Stimulation) F (1, 20) = 17.138, p = 0.001, in the right Amy (Figure 5). Post hoc comparisons showed that Neutral stimulation yielded to higher activation than

Affective one in DA, but not in OA: indeed, DA showed higher HRF levels in response to Neutral stimulation as compared with Affective Stimulation (p = 0.000), whereas Organized participants showed no differences between Affective and Neutral Stimulation (p = 0.814).

Figure 5. Interaction between groups and stimulation in amygdala area.

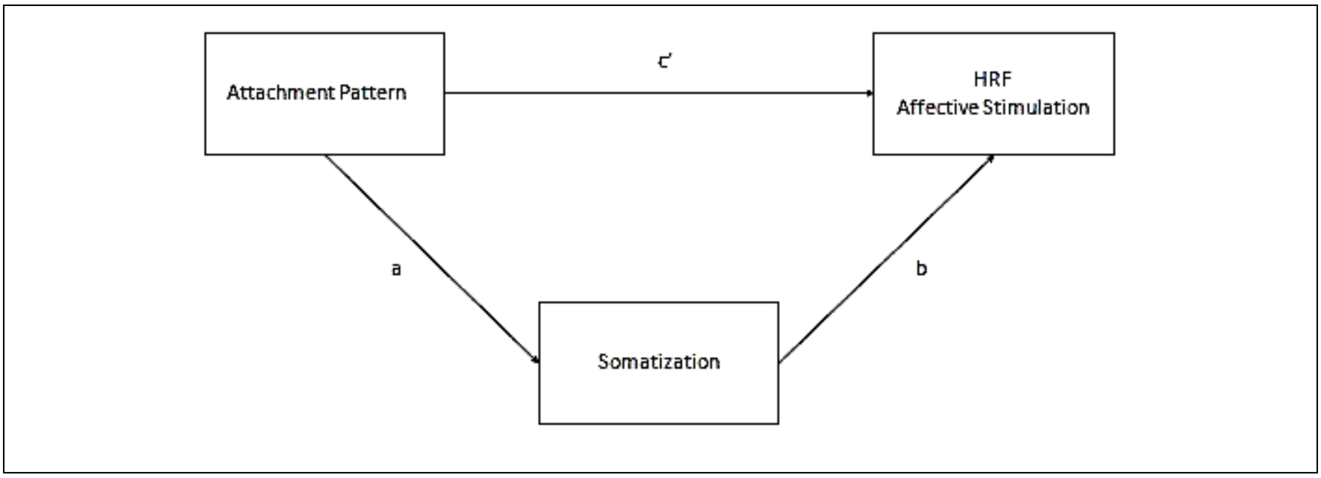


Note: *** = $p < 0.001$.

Mediation results

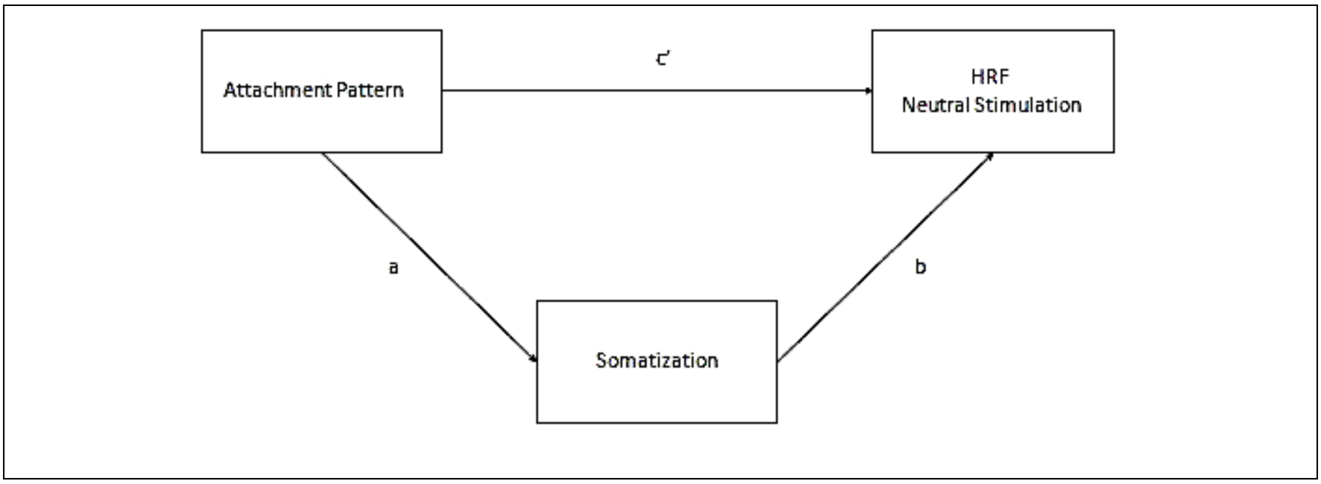
From a simple mediation analysis conducted using ordinary least squares path analyses in PI area, attachment pattern indirectly influenced bold signal at tactile stimulation through its effect on SCL-90-R Somatization scale scores. As can be seen in Figure 6, participants' different attachment pattern influence somatization ratings. Namely, DA individuals expressed higher scores of somatization respect to OA participants. Moreover, somatization ratings predicted the bold signal at both tactile stimulation (Affective - Fig. 6a - vs Neutral Stimulation - Fig. 6b -), where higher somatization scores predict less activated bold signal for both tactile stimulations.

Figure 6a. Mediation analyses between attachment, somatization and hrf affective stimulation signal.



		Consequent						
		M (Somatization)				Y (HRF Affective Stimulation)		
Antecedent		Coeff.	SE	*p*		Coeff.	SE	*p*
X (Attachment Pattern)	a	0.387	0.189	0.05	c'	0.111	0.113	0.34
M (Somatization)		-	-	-	b	-0.355	0.127	0.01
Constant	i_1	0.102	0.280	0.72	i_2	0.358	0.151	0.03
		$R^2 = 0.189$				$R^2 = 0.317$		
		F (1, 18) = 4.208; $p = 0.05$				F (2, 17) = 3.949; $p = 0.04$		

Figure 6b. Mediation analyses between attachment, somatization and hrf neutral stimulation signal.



		Consequent						
		M (Somatization)				Y (HRF Neutral Stimulation)		
Antecedent		Coeff.	SE	*p*		Coeff.	SE	*p*
X (Attachment Pattern)	a	0.387	0.189	0.05	c'	0.080	0.080	0.33
M (Somatization)		-	-	-	b	-0.342	0.090	0.00
Constant	i_1	0.102	0.280	0.72	i_2	0.581	0.108	0.00
		$R^2 = 0.189$				$R^2 = 0.467$		
		F (1, 18) = 4.208; $p = 0.05$				F (2, 17) = 7.417; $p = 0.00$		

5.4 Discussion

We examined brain responses to Affective and Neutral Stimulations in hairy skin of individuals with a disorganized or organized attachment pattern. From the analyses of brain responses, we found a network of regions that is involved in processing these kind of tactile stimuli, including S1, PI, Amy and SMG in all participants. A resting-state functional connectivity analysis also revealed a connection between PI and S1, and between PI and SMG. Through a direct contrast between disorganized and organized attachment pattern, we found that Disorganized have a different activation in response to tactile stimulations in Amy when compared to Organized individuals; interestingly, concerning Amy activation, Disorganized individuals reported a higher level of BOLD signal in response to Neutral vs. Affective Stimulation, whereas in the Organized group we found no differences in the activation between the two stimulations. Finally, a mediation analyses showed that, despite not being directly linked to BOLD signal in PI, attachment pattern has an indirect effect on PI activity mediated by levels of somatization.

Referring to the first results, PI, S1, Amy and SMG seem to play a role in the processing haptic stimuli with hedonic value. PI activation is consistent with previous studies of selective CT stimulation (Olausson et al., 2002; Gordon et al., 2011; Ebisch et al., 2011; Morrison, 2016a). Converging evidence indicates that this region is an early cortical target for an afferent pathway including CTs (Olausson et al., 2002; Craig, 2009). Furthermore, primary somatosensory cortices represent an overlap between pure discriminative sensory network and an affective processing network (Morrison, 2016a). Regarding to the activation of SMG, this area is part of inferior parietal lobule (IPL), which is implicated in attentional processing (Culham and Kanwisher, 2001); In particular, it seems that this region plays an important role in tactile attention (Burton et al., 1999) and has previously been associated to AT processing

(Voos et al., 2013). Also, results from a resting-state functional connectivity analysis confirm a connection between areas that we found, suggesting that may be part of the same network.

When comparing the activation in response to the two tactile conditions, we found that PI, S1 and Amy showed a higher activation during Neutral Stimulation compared to Affective stimulation. Conversely to our results, other studies found a higher activation in insular cortex mainly in response to CT-optimal stimulations. It is important to note that these studies that had investigated areas of affective touch, used to stimulate two different kind of skin, namely glabrous and hairy skin (e.g. Bjornsdotter et al 2014; Gordon et al., 2011) that have different distribution of tactile receptors; in fact, CT-fibres are not present in glabrous, but Aβ fibres are widely present on both hairy and glabrous skin (McGlone et al., 2014). On the contrary, in our study, we used the forearm as a single area for both tactile stimulation (i.e. Neutral and Affective). That means that the difference in activation for affective and neutral stimulation between literature and our study may be due to methodological issue, i.e. the stimulated sites. Furthermore, another possible confounding factor may be the composition of our sample. In fact, individuals classified as Disorganized composed 40% of our sample. Studies on attachment showed that around 15% of the normative population is classified as having a Disorganized state of mind (Van IJzendoorn et al., 1999). Not considering this difference at the first step, may have led to this result. In fact, in the direct contrast between the two different attachment patterns and two different tactile stimulations we found a higher activation in Amy for both stimulations in the Disorganized compared to Organized individuals. Notably, Disorganized reported higher level of BOLD signal in response to Neutral vs Affective Stimulation, whereas in the Organized group we have not found differences in the activation between two stimulations. To state, the amygdala functions are vast, dynamic and complex and include processing of social behaviour, emotion and reward learning (Adolphs, 2010). In general, amygdala codes salience or relevance of a stimulus regardless his negative or positive valence. For this reason, any kind of interpretation must be done with caution. On one hand, it is possible to consider amygdala activation for Neutral Stimulation as a neural correlate of negative emotional arousal as if disorganized individuals interpret the stimulus like a threat. For example, in a recent study (Buchheim et al., 2016) authors examined the neural correlates of attachment dysregulation in a group of Borderline Personality Disorder (BDP) patients compared to controls, showing a higher amygdala activation during the exposure to scenes that depict events associated with attachment activation such us separation, death or threat. BPD is one of the major outcome of adverse attachment experiences such as maltreatment, emotional neglect, sexual and physical abuse (Bandelow et al., 2005; Gunderson et al.,2006; Zanarini et al., 2006; van Dijke et al., 2011; Keinänen et al., 2012; Frías et al., 2016) and it has been associated with increased occurrence of Disorganized attachment representation (Agrawal et al., 2004; Bakermans-Kranenburg and van IJzendoorn, 2009; Buchheim and George, 2011). Interestingly, the amygdala demonstrated activation in individuals with Unresolved attachment representation irrespective to the presence or absence of BPD (Buchheim et al., 2016). On the other hand, it is well known that amygdala neurons respond not only to threatening stimuli, but also to reward valued stimuli (Adolphs, 2010). In this prospective, the higher Amy activation may be due to the rewarding value attributed to physical contact in individuals that lack of this experience in their attachment relations. Another hint comes from the behavioural results discussed in study II of this thesis: we remind that DA rated as less pleasant than OA individuals the affective stimulation. This difference between group seems to be mirrored in the activity of the amygdale, suggesting a potential top-down modulation carried out by this area on the subjective perception of the affective touch. Further studies are needed to explore both these possibilities.

Finally, a mediation analysis showed that attachment pattern is not directly influencing the BOLD level on PI, but instead predicts levels of somatization, which in turn predict the decrease of BOLD signal in the same area. It means that the higher the somatization levels, the lower the activity in PI. Namely, DA individuals expressed higher scores of somatization respect to OA participants. A wide range of literature agrees on the role that insular cortices play in monitoring visceral signals, interoception awareness and emotion regulation (Craig, 2002; Simmons et al., 2013). The empirical evidence related to the accuracy of the perception of internal signals in individuals experiencing somatoform symptoms is mixed: Scholz et al. (2001) demonstrated higher interoceptive awareness in somatoform diseases, whereas other studies have indicated the opposite pattern (Bogaerts et al., 2010; Pollatos et al., 2011). Reduced interoceptive awareness is assumedly associated with difficulties in the consolidation of somatic markers required for guiding individual behavior by signaling stimulus significance to the body as proposed in the somatic marker theory by Damasio (1999). It could be hypothesized that a low level of interoceptive awareness in combination with altered attachment patterns could, via such a mechanism, mediate processes of emotional experience which might explain the different activation in PI.

There are several limitations to our study that need to be taken into account when interpreting our findings. First, main limitation is the small sample size. As declared above, the current study is yet to be completed and our goal is to increase the number of participants of our sample. Second, the unequal distribution of participants in the two groups (i.e. organized and disorganized) may have biased the results. This limit has already been taken in account across the discussion of the results and we aim to conclude the current study including a sample that better reflects the normative distribution of different attachment pattern in the population (Bakermans-Kranenburg & van IJzendoorn, 2009). Third, the Disorganized attachment classification includes individuals with unresolved traumas or losses (Unresolved) but also those that cannot be classified because of the presence of marked indications of several states of mind (Cannot-Classify). Furthermore, future studies could explore other attachment patterns, such as secure and unsecure, which were not explored in the current study.

General Discussion

This thesis aimed to increase the understanding of the functional role of affective touch through the investigation of its properties in childhood, in healthy adult with specific attachment pattern and, finally, in the brain network involved in its processing. The three experiments presented are independent and aimed to answer different questions about the role of affective touch in our lives. However, looking at the results of these experiments, we can find two wide branches that state, on one hand, that the affective touch system is already present in childhood and, on the other hand, that the attachment system can play a role in this somatosensory perception both from a behavioral and neural perspective.

The question that stems from the findings of my researches, and by scientific background, is: how can we interpret these findings? And more specifically, can we draw a line to connect these apparently independent dots? The short answer I would give is: "Yes, there is"; but in order to be clearer, I shall take the longer route for a better explanation of my thinking.

First things first. Coming back to the central focus of this work, affective touch is the behavioral output of specific tactile fibers that is linked to a sense of tenderness like the one that stems from a caress. But, beside its physiological and neuroscientific characteristics, I think that we may be able to define affective touch as a psychobiologic phenomenon that represent a good link between mind and body. The fact that different kinds of touch are bond to the human mind was firstly said by authors of different disciplines in the past. For example, Sigmund Freud, neurophysiologist before psychoanalyst, defined the concept of psychic impulse as: "The psychic agent of the inner stimuli that stems from the body and comes to the psyche as a measure of the operations required to the mind because of its bond with the body" (Freud, 1915). Shifting to a neuroscientific perspective, Damasio (1999) has suggested that the sense of touch arises from nerve activation patterns that correspond to the state elicited by the external world, whereas emotions are nerve activation patterns that correspond to the state of the internal world. If we experience a state of fear, then our brain will record this body state in nerve cell activation patterns obtained from neural and hormonal feedback, and this information may then be used to adapt behavior appropriately. In other words, all the information and emotions we process pass through our body in a necessary way and our body becomes the first and principal mean by which we experience the external and internal world. Thus, body and mind are related and touch is an important sense that mediates this link. From the definitions I reviewed until now, the concept that body and mind are strongly related to each other is not new. Instead, what is astonishing is the recent notion that the concept of the affective touch represents a very peculiar "path" of the tactile perceptions that promoted a step forward in this way. Over the years it has grown evidence that touch, and affective touch naturally, is more than a sensory input of what is on the skin and that the rewarding value of physical contact in nurturing and social interactions reflects the presence of an evolutionary mechanism. How can we not mention the revolutionary Harlow's studies on the Rhesus monkeys, which demonstrated the importance of social touch and care for normal development (Harlow 1958). In addition, one cannot but quote neurophysiological studies on cross-fostering in rats and mice that highlight how maternal deprivation is associated with changes in the behavioral and neuroendocrine responses to stress in the rat pup; interesting to note, stroking neglected pups can reverse almost all of the effects created by maternal deprivation (van Oers et al., 1998).

Coming back to us, it seems obvious to me the importance of touch in development and the first question I asked myself in this thesis was to demonstrate if the affective touch was present in children. Through the first experiment, I showed that already at the age of 6-year, the stimulation of the affective touch is perceived as more pleasant than neutral stimulation and that this preference increases with age. This suggests that children are familiar with hedonic stimulations and that it may be related to relational outcomes and social interactions. On this point, if we look back to late sixties, we can find the theories of Donald Winnicott, another author who theorized the importance of touch in the development of human children, who said "Handling is the way a mother manages the moment to moment physical care of her infant such that the baby gets to know his own body. It necessarily involves the mother and infant going on in a psychosomatic partnership; as if they formed one unit" (Winnicott, 1964). The importance of tactile stimulation has also been demonstrated at the neuroscientific level. For example, it has been showed that in premature neonates deprived of normal sensory stimulation, substitute stimulation facilitates growth and development (Ardiel & Rankin, 2010). Apart from the importance of the affective touch for development, we also know the opposite view. From studies on neglected children, Spitz theorized that a lack of care, a deprivation of maternal care, can lead to what is called anaclitic depression in infants (1946). In addition, this perspective seems to refer directly to John Bowlby's works, in which he established the importance of touch as a confirmation by the caregiver and its influence on the emotional development of the child (Bowlby, 1969). Respect to these theories, it was the very first step that led me to investigate whether and how the experiences of perceived care can play a role in the perception of the affective touch. Indeed, in the second study we demonstrated that individuals with Disorganized attachment patterns show less pleasantness to affective tactile stimuli than Organized individuals. Our current findings suggest that individuals with disorganized attachment who have experienced, and then developed, difficulties in relational and affective aspects, may show a specific alteration in the processing of affective tactile information. In addition, there are the results of the third study presented in this thesis. We demonstrated that individuals with a Disorganized attachment have a neural response to affective and neutral stimuli that differs from the Organized ones'. In particular, we have observed that in the amygdala Disorganized individuals have a greater neural signal response for both stimulations than Organized individuals do. It would be interesting to understand whether this atypical response to affective touch is to refers to a negative or positive value of these stimuli.

This leads us back to the main question on how to give a uniform explanation. If we were to speculate, I would say that, although affective touch has been present since childhood, the quality of relationships, especially primary relationships such as attachment bonds, could influence this system both at a behavioral and neural level. Moreover, if we go a little further, we could say that a non-affective attachment, such as the Disorganized one, could lead to perceive the affective touch not so pleasant. The reader may wonder how something as simple as touch with affective value can influence so much. We have seen in many places how treatments during the first years of growth are of fundamental importance for development. We also know that lack of treatment can lead to negative results. Furthermore, we know that the Disorganized attachment has a link with pathologies with strong relational deficits such as borderline personality disorder (Agrawal et al., 2004; Bakermans-Kranenburg and van IJzendoorn, 2009; Buchheim and George, 2011). These patients, among other things, have a particular relationship with their bodies, often displaying auto-lesive behaviors such as cutting their forearms (the principal body site where the CT fibers are present) probably with the principal aim of "feeling more". One possible explanation has to do precisely with the relationship between the affectionate touch and the parent-child bond (Hatfield, 1994). If a child does not receive an adequate affectionate touch because his or her parents are emotionally neglected, then the child and parents will not form an adequate emotional bond. Lack of bonding will cause unhappiness and lack of trust on the part of the child. As a child grows, this will manifest itself as an inability to relate to other people, which will cause further unhappiness and stress. I believe that this is the keystone of my thinking. That is, loving care during development as well as having an influence on the relational, behavioral and life in general, can also change a tactile perception. Naturally, future studies should confirm the findings from my studies, perhaps expanding the results toward this way. But I like to imagine that my experiments may have had the merit of raising more questions. For example, a question arise in me: is the affective touch an innate predisposition that can shape relationships like attachment? Or are relationships that can somehow influence this tactile system? As we have seen in the course of this thesis, the affective touch is present since early childhood and therefore it seems evident that there would be other factors, such as relationships, that influence its mechanism. We have to say that this second vision is the way to go. With these works, I have shown that there is a link but still much more to be discovered. For example, I ask myself that, if it is true that attachment influences the affective touch, how and precisely when does this happen? Furthermore, we might ask what other factors can interact within this field? For example, could the loss of a loved one cause a person to retire on an emotional level and therefore be related to an altered perception of affective touch? From another perspective, it would also be interesting to understand if affective touch could be used as therapy. Is it possible that the tactile stimulation of these fibers could play a therapeutic role, who knows, for the pathologies of the borderline area?

These all are questions that I find interesting and worth investigating. I hope that with this work I have provided a small further step toward the explanation of this complex, yet so timely, phenomenon and, more importantly, I have given the stimulus to experiment with new approaches and visions.

Conclusion

The reader may have had the opportunity to read, I hope with pleasure, that in these three years I have been engaged in the careful analysis of the affective touch. The results from my experiments have shown that it is worth investigating this construct in the future. From a personal point of view, it seems to me that this set of three experiments is a *trait d'union* between neurosciences, which we all know and fascinate us because of their ability to measure very complex phenomena, and other constructs associated with a more clinical perspective such as attachment. I therefore hope that my doctoral thesis will be a humble contribution to a wider view of clinical and neuroscientific phenomena.

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