UNIVERSITY OF TRENTO
Department of Psychology and Cognitive Sciences
Doctoral Course in Cognitive Sciences – XXXIII cycle

Ph.D. Dissertation

Neural mechanisms underlying socioemotional behavior in typical and atypical populations

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Academic Year 2020/2021

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LIST OF ACRONYMS

AASM	American Academy of Sleep Medicine
ACC	Anterior Cingulate Cortex
ADOS	Autism Diagnostic Observation Schedule
AQ	Autism spectrum Quotient
ASD	Autism Spectrum Disorder
AVP	Arginine-Vasopressine
BDI	Beck Depression Inventory
BOLD	Blood Oxygenation Level-Dependent
CR	Conditioned Response
CS	Conditioned Stimulus
CSneu	Conditioned Stimulus with neutral valence
CSpos	Conditioned Stimulus with positive valence
EEG	Electroencephalography
EMG	Electromyogram
EOG	Electrooculogram
ERP	Event-Related Potential
fMRI	functional Magnetic Resonance Imaging
FU	Functional Uncertainty period
LMM	Linear Mixed Model
LPP	Late Positive Potential
lTPJ	left Temporal Parietal Junction
MEG	Magnetoencephalography
N1	Stage 1 of NREM sleep
N2	Stage 2 of NREM sleep
N3	Stage 3 of NREM sleep
NREM	Non-Rapid Eye Movement
NT	Neurotypical
OT	Oxytocin
OXTR	Oxytocin Receptor Gene

PANAS	Positive and Negative Affect Schedule
PET	Positron Emission Tomography
PSD	Power Spectral Density
PSG	Polysomnography
PSQI	Pittsburgh Sleep Qualiy Index
REM	Rapid Eye Movement
ROI	Region Of Interest
SCL-90	Symptom Checklist
SO	Slow Oscillation
STAI	State-Trait Anxiety Inventory
SW	Slow Waves
SWA	Slow Wave Activity
TD	Typical Development
TST	Total Sleep Time
US	Unconditioned Stimulus
WASO	Wake After Sleep Onset

PREFACE

The project of this doctoral thesis was initially conceived in a clear way. Unfortunately, plans were not going as expected, primarily due to the COVID-19 pandemic crisis.

The initial idea was to investigate a specific brain structure, the hypothalamus, in socioemotional behavior. This idea comes from an intuition based on evidence about the involvement of oxytocin – a hypothalamic neuropeptide – in the improvement of socioemotional behavior. In fact, during the last years, several experiments were conducted corroborating the idea that exogenous intranasal oxytocin significantly affects performance in socioemotional tasks. Furthermore, the hypothalamus shows several alterations in its morphology and functionality in Autism Spectrum Disorder (ASD) population, which is characterized by several socioemotional impairments. This is the rationale beyond the review reported in Chapter 1.

Results of this review (Chapter 1) urged the need to investigate the role of the hypothalamus in atypical socioemotional behavior. In particular, the need to find a proper paradigm which can elicit a hypothalamic response related to social stimuli. Hence, we intended to plan a functional Magnetic Resonance Imaging (fMRI) experiment in which we would test a novel paradigm to clarify the hypothalamic involvement in socioemotional behavior. However, the pandemic COVID-19 crisis did not allow us to run the experiment mentioned above due to practical motivations. In order to provide a related contribution, we performed another review, in which we put a specific focus on Pavlovian conditioning as a method to investigate socioemotional behavior using neuroimaging (Chapter 2).

In Chapter 3, we ran an electroencephalography (EEG) experiment. On the one hand, EEG is not an ideal solution to investigate hypothalamic activation; on the other hand, an EEG experiment may potentially be a suitable alternative to test the effectiveness of a novel paradigm. Our focus was (a) on the use of purely social unconditioned stimuli (i.e., video of real actors and actresses that simulated a one-to-one interaction) and (b) on the use of positive-valence stimuli. In this way, we tried to understand the acquisition of the positive-valence value of previous neutral socioemotional stimuli.

Finally, in order to provide a further contribution related to neural mechanisms in ASD, I included in this dissertation a polysomnographic study investigating sleep characteristics in a population with specific socioemotional impairments compared to a typical development population.

In conclusion, albeit the present dissertation does not reflect our initial intentions, I hope that it contributes to deepening our understanding of neural mechanisms underlying socioemotional behavior in typical and atypical (i.e., ASD) populations.

ABSTRACT

This doctoral thesis outlines the review and experimental studies conducted during my Ph.D. that aimed to clarify the neurocognitive processes underlying socioemotional behavior in neurotypical and Autism Spectrum Disorders (ASD) individuals, a clinical population with impairments in the socioemotional core. The thesis is divided into four chapters.

Chapter 1 is concerning the involvement of the hypothalamus in socioemotional behavior. Indeed, despite the large number of studies on the relationship between hypothalamic neuropeptides and social behavior in ASD, only a few studies investigated the association between the hypothalamus and socioemotional response in ASD. Results from this review highlighted anatomical hypothalamic atrophy and functional hypothalamic hypoactivation during face processing and social interaction tasks.

The above results from the review highlighted the need to have an appropriate paradigm to investigate hypothalamic involvement in socioemotional behavior. For this reason, in Chapter 2, I performed a systematic review of the neuroimaging studies that used a classical conditioning paradigm to study socioemotional behavior. Results raised the presence of a gap in the literature: indeed, it has been shown that (1) no study used a purely social unconditioned stimulus; (2) the literature mainly focused on conditioning to aversive stimuli, whereas no study focused on conditioning to positive stimuli.

Building on this evidence, an EEG study, described in Chapter 3, aimed to investigate whether classical conditioning also underlies the acquisition of socioemotional preference using a novel conditioning paradigm employing more ecological positive and neutral social stimuli. Results show that even with a short period of classical conditioning an increase in valence and attractiveness of positive conditioned stimuli, which was previously neutral may be performed. Then, explorative analysis of the event-related potentials (i.e., the Late Positive Potential, LPP) highlights differences about the LPP elicited by the positive conditioned stimuli concerning neutral conditioned stimuli.

Finally, as a side project, Chapter 4 illustrates an investigation that aimed to explore differences in sleep between ASD and neurotypical populations and describe their relationship with the impaired socioemotional characteristics.

CHAPTER 1

Hypothalamic involvement in Socioemotional Behavior[1]

1.1. Introduction

The hypothalamus is the smallest and most specialized region of the human brain, positioned in the diencephalon. It plays a crucial role in different autonomous behaviors, such as physiological arousal, feeding behavior, sleep-wake cycle (Canteras et al., 2018; Saper et al., 2000), and in emotional processing (Kober et al., 2008; Phan et al., 2002) and social behavior (see Torres et al., 2018 for a recent review). While hypothalamic involvement in autonomic behaviors is well known, investigation about its role in emotions and social functioning is less clear.

Toward this, evidence indicates a strong relationship between two hypothalamic peptides, the oxytocin (OT) and arginine-vasopressin (AVP), and socioemotional behavior (Hammock et al., 2012; Meyer-Lindenberg et al., 2011; Torres et al., 2018). For example, animal studies revealed that OT is generally observed to facilitate approach behavior by decreasing avoidance of proximity and reducing defensive behavior, especially in males (Carter et al., 2008). In humans, the effect of intranasal OT administration indicates a reduction of social stress and anxiety facilitating positive approach and social interaction and affiliative behavior (Heinrichs & Domes, 2008; Heinrichs et al., 2009; Quintana et al., 2015; Harari-Dahan & Bernstein, 2014; see Appendix A).

In particular, there has recently been a great deal of interest in studying their role in regulating affiliative and social responses in Autism Spectrum Disorder (ASD) (Quattrocki & Friston, 2014). ASD is a neurodevelopmental disorder characterized by core symptoms in the domain of socioemotional behavior, including impairments in social

[1] Part of this chapter's content has been published as: Caria, A., Ciringione, L., & De Falco, S. (2020). Morphofunctional Alterations of the Hypothalamus and Social Behavior in Autism Spectrum Disorders. *Brain Sciences, 10*(7), 435.

communication, restricted and repetitive behavior, which affected the development of appropriate social skills and the maintenance of social relationships (American Psychological Association, 2013). ASD population shows an alteration in the OT synthesis and release, which seems crucial in the typical impairments observed during social and communication tasks (Quattrocki & Finston, 2014; Rajamani et al., 2018; Tost et al., 2010). Moreover, functional Magnetic Resonance Images (fMRI) studies targeted aspects of social cognition selectively impaired in ASD, just as face perception (Dalton et al., 2005), emotional processing (Harms et al., 2010), or social motivation (Dichter et al., 2012).

There is long-standing evidence of severe socioemotional impairment after hypothalamic lesions, particularly the ventromedial nuclei (Giustina & Braunstein, 2016). For example, both animal (e.g., Wheatley, 1944) and human (e.g., Reeves & Plum, 1969) studies detected behavioral manifestations of rage after ventromedial hypothalamic lesions. Moreover, studies conducted by Herman and Panksepp (1981) in animals (i.e., guinea pigs) highlight separation-induced distress vocalization elicited by electrical stimulation of the medial hypothalamus. In humans, stereotactic stimulation showed altered sexual behavior triggered by accidental focal lesions of rostromedial basal forebrain structures, including the septo-hypothalamic area (Gorman & Cummings, 1992). Also, hypothalamic stimulation can induce pleasurable experiences and prosocial behavior in humans (Bishop et al., 1963; Barbosa et al., 2017). For instance, several investigations highlighted a reduced aggressive behavior and increased social interactions after deep brain stimulation of the posteromedial hypothalamus (Barbosa et al., 2017).

Despite the well-known key role of the hypothalamus in the production of the OT and AVP (Swanson & Sawchenko, 1983), the severe socioemotional dysfunction caused by hypothalamic lesions, and the apparent association between hypothalamic neuropeptides and socioemotional response in ASD and neurotypical (NT) population, hypothalamic involvement remains elusive in most of the neuroimaging investigations exploring the neural correlates of normal and abnormal human socioemotional behavior (Harms et al., 2010; Kana et al., 2014; Dalton et al., 2005; Dichter et al., 2012; Chevallier et al., 2012; Assaf et al., 2013). In particular, very few studies analyzed the implication of the hypothalamus in the social impairment of individuals with ASD.

This chapter aims to provide a synthesis of neuroimaging evidence reporting morphofunctional alterations of the hypothalamus in ASD by examining data from individuals with ASD and NT. There will be first described MR-based anatomical studies reporting abnormal morphology of the hypothalamic region, followed by a description of the few existing task-based and resting-state functional MRI studies reporting hypothalamic alterations in individuals with ASD and healthy carriers of genetic risk variants in OT receptors. Then, functional and anatomical findings will be discussed, attempting to interpret the possible role of the hypothalamus and its functional exchanges with cortical and subcortical networks in the atypical socio-emotional response of ASD individuals. Finally, there will be proposed fundamental open questions to elucidate the morphological and functional hypothalamic anomalies and their impact on social cognition and behavior in ASD.

1.2. Method

Pubmed and Scopus were used as databases to conduct the literature search. Articles were selected following three steps: (1) a first analysis of the journal articles published until April 2020 using the Boolean operators "autism" AND "hypothalamus" AND "social." Results revealed 236 items from Scopus and 22 items from Pubmed. Then, (2) we narrowed the results by adding the term "MRI," and 42 items remained in Scopus and 1 in Pubmed. As a final step, (3) only journal articles reporting original research studies were selected. Remained items were then accurately inspected to identify functional and anatomical studies related to the ASD population.

1.3. Results

1.3.1. Structural MRI studies

One of the first studies investigating the structural alteration of the hypothalamus in the ASD population was conducted by Kurth and colleagues (2011), which assessed structural MRI with brain morphometry in children and adolescents with ASD. The authors highlighted a significant decrease of gray matter volume in the hypothalamic region, independently of age, IQ, or gender (Kurth et al., 2011). A decreased volume in

the bilateral hypothalamus in the ASD population was also found by Shou and colleagues (2017), positively correlated with plasma AVP concentration (Shou et al., 2017). Another study found hypothalamic atrophy in adults with ASD, investigated by two different methods: (1) ROI-based voxel-based morphometry, which revealed a reduced gray matter density of the hypothalamus and increased cerebrospinal fluid density in the third ventricle; and (2) an automatic method applied to a larger cohort to estimate the ventricular volume of the third ventricle. This analysis demonstrated an increase of the third ventricle volume independent of the lateral ventricles – used as a covariate – and thus excluded global brain volume increase.

1.3.2. Functional MRI studies

The impairment of emotional face processing in ASD is reported in several behavioral and neuroimaging studies (see Harms et al., 2010 for a review), suggesting the presence of atypical functioning of several subcortical regions related to impaired social cognition. Specifically, hypothalamic hypoactivation during emotional face processing was detected. A similar activation pattern was detected more recently in a meta-analysis conducted by Aoki and colleagues (2015), which focuses on neuroimaging studies. Here, the 13 fMRI studies conducted in an ASD population examined confirmed the hypothalamic hypoactivation during emotional-face processing and, in addition, activation of the parahippocampal gyrus and the amygdala was detected.

The hypothalamic dysfunction was also highlighted by Chaminade and colleagues (2015), where the brain response of ASD and NT participants was acquired during the "stone-paper-scissor" game, an interactive videogame used as a socioemotional task. During the game, the players faced three different agents: a human being, a humanoid robot endowed with artificial intelligence attempting to win the game based on previous games' results, and a computer that randomly generated the three possible responses. Neuroimaging results reported a decreased activation of the bilateral paraventricular nucleus of the hypothalamus when ASD participants faced against the human compared to the artificial agent, with respect to NT participants. Also, functional connectivity analysis of the left hypothalamus revealed a significant negative correlation between the activation of the left hypothalamus and the left temporal-parietal junction (lTPJ) – a

region associated with anthropomorphization – when NT participants played against the robot and when ASD participants played against the human. This negative correlation might reflect an inhibitory activity exerted by the lTPJ on hypothalamic nuclei, resulting in reduced social motivation and a reward for human interactions in ASD. Moreover, the performance of the ASD participants was negatively correlated with the severity of the autistic symptoms (Baron-Cohen et al., 2001).

Furthermore, this hypothalamic hypoactivation during facial expression perception was also observed in adult carriers of risk OXTR gene mutation for autism (Tost et al., 2010).

1.4. Discussion

This review was conceived starting from the well-known role of the hypothalamus in the production of OT and AVP neuropeptides and the evidence between these hypothalamic neuropeptides and socioemotional behavior in both ASD and NT populations. We aimed to inspect the current neuroimaging literature in humans, searching for evidence about hypothalamic anatomical and functional alterations related to socioemotional impairments in ASD.

Generally, the current studies about structural and functional MRI report consistent – although limited – morphological and functional alterations of the hypothalamus. Specifically, two main findings emerge: (1) anatomical hypothalamic atrophy and (2) functional hypothalamic hypoactivation during face processing and social interaction.

1.4.1. Hypothalamic morphological alterations

Anatomical hypothalamic alterations were mainly related to a smaller and reduced gray matter density volume in ASD individuals (Wolfe et al., 2015). This alteration seems to differ between males and females, following similar gender-related differences observed in other brain regions, for example, the amygdala or the interhemispheric connectivity, along with other differences in hormone-related personal traits, cognition, and behavior (Hines et al., 2010).

These morphological alterations of the hypothalamus are in line with evidence about morphological changes in ASD in other multiple brain regions (Nickl-Jockshat et

al., 2012; Duerden et al., 2012), especially in the "social brain network" (DeRamus et al., 2015; McAlonan et al., 2005; Cauda et al., 2014; Sato et al., 2017). However, the detection of this atrophy does not give specific information about the brain mechanisms leading to it because voxel-based morphometry analysis may be affected by the variation of multiple properties of gray matter. For example, postmortem analysis in the ASD brain highlighted various anatomical anomalies related to neuronal density and size, dendritic spine density, glia, and cerebral vasculature (Varghese et al., 2017). In particular, lower neuronal density has been measured in human brain regions involved in social behavior such as the fusiform gyrus and amygdala (Schumann et al., 2006; Van Kooten et al., 2008; Wegiel et al., 2014), as well as in specific layers of the anterior cingulate cortex (Simms et al., 2009), possibly reflecting specific hypoactivation of these same regions in ASD.

ASD also shows reduced plasma concentration of OT (Zhang et al., 2016), linked to social impairment (Parker et al., 2017). However, it is not sufficient to state a central level alteration: in fact, the possible correlation between plasma and OT concentrations in the central nervous system seems particularly dependent on the assessing methods employed (Lefevre et al., 2017). Thus, there are currently no demonstrations of the specific impact of hypothalamic atrophy on OT transmission to brain circuits in humans.

1.4.2. Hypothalamic functional alterations

Functional alteration of the hypothalamus in ASD was found in several fMRI studies, which reported hypoactivation mainly related to face processing tasks and during interactive play with humans. Notably, it is impossible to directly interpret the neuronal processes underlying this hypoactivation because a decreased BOLD response is not necessarily connected with a reduced OT and AVP release.

The hypothalamic hypoactivation during face processing is often associated with diminished activity in the amygdala, both in ASD (Bookheimer et al., 2008; Hadjkhani et al., 2007) and in carriers of the OXTR rs53576A allele (Tost et al., 2010; Aoki et al., 2015); the opposite findings were also found, but supposedly ascribable to a longer gaze fixation time and higher anxiety level of the ASD participants (Dalton et al., 2005; 2007). Hypothalamic nuclei may be controlled by the amygdala directly and indirectly: directly, through the amygdaloidal pathway and the stria terminalis, and indirectly by the bed

nucleus of the stria terminalis which mediated stimulation of the hypothalamic-pituitary-adrenal axis. Autonomic fear responses are linked to the projection of the central amygdala to the hypothalamus and brainstem (LeDoux, 2000). Moreover, stimulation of amygdaloid oxytocin receptors is then assumed to be associated with aversive response to socially relevant stimuli (Knobloch et al., 2012; Janak & Tye, 2015; Viviani et al., 2011), which would be increased in case of diminished amygdala activation. Accordingly, increased hypothalamic activity and amygdala deactivation appear to mediate the initiation and consolidation of social relationships in healthy individuals. Such a reverse pattern of the hypothalamus and amygdala has been associated with several social behaviors such as other people's trust and trustworthiness (Krueger et al., 2007) and mother-infant and pair bonding (Bartel & Zeki, 2004; Strathearn et al., 2009; Acevedo et al., 2012; Mercado & Hibel, 2017), as well as visual processing of personally known faces including same-sex sibling and best friend with respect to unknown faces (Wolfe et al., 2018).

Prosocial behavior may be enhanced by hypothalamic activity through the modulation of two complementary responses: (1) the enhancement of the salience of social stimuli in information processing and (2) the reduction of fear and avoidance behavior, both mechanisms being strictly dependent on amygdala activity (Shamay-Tsoory & Abu-Akel, 2016; Wittfoth-Schardt et al., 2012).

Notably, AVP and OT have an opposite modulatory effect on fear and anxiety, especially in the process of fear memory consolidation: in fact, OT acts facilitating prosocial interactions by parasympathetic responses and extinction of conditioned avoidance responses. These opposite regulatory responses result from activating the inhibitory network within the medial part of the amygdala and consecutive integration of different afferences to the central amygdala into a modulatory output to the hypothalamus and brainstem for appropriate anxiety and fear responses (Huber et al., 2005). In addition, the socioemotional response may be influenced by the hypothalamus through a complex network that comprehends basal forebrain areas such as the periamygdaloid region and the septal nuclei and other brainstem nuclei through the medial forebrain bundle, which mediated top-down modulation of both somatic and visceral activity by the forebrain and the limbic system, as well as bottom-up influences of higher brain activity by internal organs and bodily interoceptive signals.

In summary, despite the number of previous studies reporting hypothalamic activation co-occurrent to other emotional, motivational, and social brain centers (Shamay-Tsoory & Abu-Akel, 2016; Wild et al., 2003; Hirosaka et al., 2008; Herman et al., 1997; Price, 2003), the evidence about hypothalamic functional connectivity both in ASD and N individuals are scarce. That may partly depend on the variable association between hypothalamic spiking activity and oxytocin release, which is not clear how they interact during typical and atypical socio-emotional behavior. On the other hand, the alterations in hypothalamic functional connectivity detected on healthy carriers of genetic mutations at risk for ASD emphasize more significant functional and structural connectivity between the hypothalamus and the amygdala during facial processing tasks. However, the nature of this interaction remains unknown. In addition, an opposite activation was detected between the hypothalamus and the dorsal anterior cingulate and paracingulate cortex, respectively a decrease and an increase in activity (Tost et al., 2010).

Direct projections of the anterior cingulate cortex (ACC) have been demonstrated in humans and animals (Ongur et al., 1998; Johansen-Berg et al., 2008). Increased activity in the paracingulate cortex and septal area, including the hypothalamus, has been associated with unconditional trust in other people (Krueger et al., 2007). Furthermore, the same scholars have found and proposed that the entire medial prefrontal cortex, including the ACC, can encode the abstract representation of social experiences, guiding social behavior based on an error prediction (Apps et al. 2016; 2017). Consequently, ACC connections with emotion-related and reward-related brain regions such as the orbitofrontal cortex, ventral and dorsal striatum, amygdala, insula, and hypothalamus would support the generation of active inferences of affective, interoceptive values, and reward of socio-emotional responses (Barrett et al., 2017; Ondobaka et al., 2017), as well as the minimization of the prediction error between expected and actual behavioral outcome, the latter compromised in ASD (Quattrocki & Friston, 2014; Balsters et al., 2017).

1.5. Conclusions

This review highlighted a relationship between hypothalamic morphological and functional alterations and their involvement in socioemotional behavior in a population with Autism Spectrum Disorder. Further studies are strongly needed to clarify the

complex functional exchanges of the hypothalamic nuclei with cortical and subcortical networks during the execution of socio-emotional tasks. Also, several limitations need to be highlighted, mainly related to the experimental methodology and Magnetic Resonance signal acquisition techniques. Indeed, it is necessary to design specific protocols that permit the detection of hypothalamic activity during realistic socioemotional scenarios, with rigorous control of the experimental variables, both for ASD and neurotypical population, and MRI acquisition schemes adopted in most of the studies already mentioned were not specifically tailored for the hypothalamus. This is particularly challenging because neuroimaging of the small hypothalamic nuclei needs a very high spatial resolution to delineate the functional divisions, preventing potential partial volume effects, compensation for signal-dropouts occurring in ventromedial subcortical regions, and correction for distortions generate by nearby structures. Nevertheless, the progress in ultra-high-field MRI techniques might support the elucidation of the anatomical and functional properties of small regions such as hypothalamic nuclei.

Finally, a deeper understanding of hypothalamic morphology and functionality is essential not only for the comprehension of socioemotional behavior but also for the direct implication of its neuropeptides in synaptic activity and plasticity (Rajamani et al., 2018) and neurogenesis (Bakos et al., 2016), that may shed light in the comprehension of the ASD pathophysiology.

CHAPTER 2

Neural Mechanisms Underlying Classical Conditioning In Human Social Behavior: A Systematic Review

2.1. Introduction

Classical or Pavlovian conditioning is one of the first and most popular paradigms in experimental psychology, exploring mechanisms involved in learning and motivational processes. Beyond experimental settings, its use is quickly extended to clinical settings and, despite its ancient history, it still represents a valid treatment in cognitive-behavioral therapy.

A typical classical conditioning paradigm involves learning an association between a previously neutral stimulus (the conditioned stimulus, CS) and a positive or negative valence stimulus (the unconditioned stimulus, US). In positive – or appetitive – conditioning, the neutral stimulus acquires a new positive valence through its association with a reward. Moreover, in negative – or aversive – conditioning, the neutral stimulus elicits a range of defensive responses, even when the US is no longer presented (Davis & Whalen, 2001; LeDoux, 2000). The CS acquires aversive or appetitive properties and elicits a response (conditioned response, CR) that is often similar to the response individuals exhibit to the US (Braveman, 1979). Pairings can be offset through sufficient CS-alone and US-alone trials that degrade the information value of the CSs (extinction; Rescorla, 1966)

The critical factor in the formation of the association, according to contemporary theories, is the predictive relationship between CS and the US (Wagner & Rescorla, 1972). Furthermore, another central aspect of classical conditioning, but not enough to generate it, is the close temporal proximity in the presentation of the CS and subsequent US (Pavlov, 1927). The CS will appear predictive of the US event; then, they will be associated (Hamm & Vaitl, 1996).

One form of classical conditioning that may better describe associative learning in a social context is evaluative conditioning. Evaluative conditioning, introduced by Martin and Levey (1978), is defined as a learning process involved in likes and dislikes and the

most used form of conditioning in social psychology. Different from classical conditioning, in evaluative conditioning the formerly neutral CS does not acquire a predictive value but merely attains the affective qualities of the liked or disliked US (Walther et al., 2011). Also, the US does not elicit a biological response or a physiological reflex (De Houwer, 2011), and the conditioning process usually happens using a second-order CS as the US, usually explained by the formation of an association between the cognitive representation of the CS and the US (Walther et al., 2011). Moreover, evaluative conditioning seems resistant to extinction (Baeyens et al., 1988; 2005; Gawronski et al., 2015), even if some type of evaluative conditioning studies do not show this peculiarity (Bouton, 2004; Delamater, 2004). This can happen because of the inhibitory learning perspective of classical conditioning: in this case, the learning acquired through the CS-US pairing is supposed not to be erased, but some new learning that counteracts the acquired response expression can cause the unexpected extinction (Nishiyama, 2020).

Aversive conditioning is often studied using physical threats (such as electric shock) as the primary US, and their effect has a definite evolutionary meaning (Miskovic & Keil, 2012). Similarly, positive conditioning is often investigated using stimuli with a vital biological component (such as food or sex; see Martin-Soelch et al., 2007). This is crucial when examining primary threat defense or approach systems, but nowadays, the events we experience are different and with a vital social component. Despite its significance, a small number of scientific approaches to truly social USs are very few (Ahrens et al., 2015; Blechert et al., 2015; Hermann et al., 2002; Lissek et al., 2008; Pejic et al., 2013; Wieser et al., 2014).

2.1.1. Neural mechanisms underlying classical conditioning

Classical conditioning, especially in its negative – or aversive – form, is mediated by the amygdala and the amygdaloid complex (Phelps & LeDoux, 2005). It might also elicit differential neural responses depending on the various amygdala's connections with cortical and subcortical areas. In fact, different neural systems are involved in the detection, recognition, and memory of conditioned and unconditioned signals (Schupp et al., 2006).

Functional neuroimaging findings suggest that a neural network, including the

amygdala, the orbitofrontal cortex, the anterior cingulate cortex, and the *nucleus accumbens* underlies classical conditioning and behavior (Everitt et al., 2000; Schoenbaum et al., 2003). The characteristics of CS and US, both physical and emotional, are coded by different neural systems, and their representations are stored in different brain regions.

The amygdala is involved in emotional significance to events, independent from negative or positive valence and attentional processes. In animal studies, its role is established (Everitt et al., 2003: Hatfield et a., 1996: Schoenbaum et al., 1999), but in human studies, the results of neuroimaging results are less consistent and remain to be clarified (Cox et al., 2005; Gottfried et al., 2002).

The orbitofrontal cortex seems to be involved in encoding outcome expectancies because of its connections with the amygdala's basolateral nuclei (Carmichael & Price, 1995; McDonald, 1998). Neuroimaging studies in humans have found orbitofrontal activation in response to conditioned stimuli with positive and negative valence, with a specific activation in the anterior part for the positive valence and the lateral part for the negative valence (Gottfried et al., 2002).

The anterior cingulate is usually implicates in discriminative processes (Botvinick et al., 2004; Carter et al., 1998) and learning (Parkinson et al., 2000). Even if its involvement in discriminative processes is evident in animal studies, neuroimaging studies in humans are not so visible. In fact, its involvement may be the consequence of second-order conditioning, not as a primary reinforcement (Gottfried et al., 2002).

The *nucleus accumbens* is a crucial structure involved in processing rewarding stimuli, and it has received much attention in the study of conditioning, especially appetitive conditioning. Its activation has been reported in response to primary and secondary CS during appetitive conditioning (Cox et al., 2005; Gottfried et al., 2002; Kirsch et al., 2003).

Classical conditioning also has important clinical implications: it represents the primary basis of contemporary etiological accounts of disorders with impairments in the social domain, such as social anxiety (Duits et al., 2015; Lissek et al., 2005, 2010, 2014) and depression (Kuhn et al., 2014; Nissen et al., 2010). Investigating mechanisms underlying classical conditioning for social behavior in a population with social impairments can lead to a better comprehension of the phenomenon of social conditioning

per se.

This systematic review aims to provide an overview of the research on classical conditioning's neural mechanisms for social stimuli in humans from neuroimaging studies. Specifically, we aim to highlight the importance of the US's characteristics in conditioning paradigms for the social domain; furthermore, we hope to stimulate interest in these processes as a line of research in psychopathology's neurobiology for a clinical outcome.

2.2. Methods

To conduct this review, we followed the PRISMA statement (Liberati et al., 2009; Moher et al., 2009), an evidence-based protocol developed to help authors improve the reporting of systematic reviews and meta-analyses.

PsycINFO, Scopus, and Pubmed databases were used to browse for articles on classical conditioning for social stimuli. The selection of the articles was made by the boolean operators: "classical conditioning" OR "pavlovian conditioning" AND "social behavior". Items selected were published up to March 2020. In PsycINFO (AB "classical conditioning" OR AB "pavlovian conditioning" AND AB "social behavior"), limitations about All Journal, Abstract, human and English language were selected, for 747 results. In Scopus, Boolean operators must be in title, abstract, and keywords for 78 results. In Pubmed, 177 articles were found. As a first step, 47 duplicate items were excluded. Then, irrelevant literature was excluded after reviewing the title and the abstract following inclusion and exclusion criteria. The inclusion criteria were: the use of neuroimaging methods (EEG, fMRI, PET), items are experimental studies or reviews about the classical conditioning paradigm in social behavior study. Exclusion criteria were: items that refer to pharmacological and molecular aspects or not written in English; items referred to sex, alcohol, and animal experiments: 911 records were excluded. At this point, records selected for the full-text screening were 34. After the full-text screening, 21 items were included following inclusion and exclusion criteria. 6 Additional records were identified during the full-text screening using the snowball technique.

2.3. Results

After the papers' systematic revision, 19 studies have been included in this systematic review (see PRISMA flowchart, Figure 1.1). These are all studies that used a classical conditioning paradigm with social CS, such as faces. The most crucial distinction seems to be the US's nature: 13 studies used the physical US, such as aversive noise or electric shock; 4 studies used the social US; 2 used physical and social US (see Table 1.1).

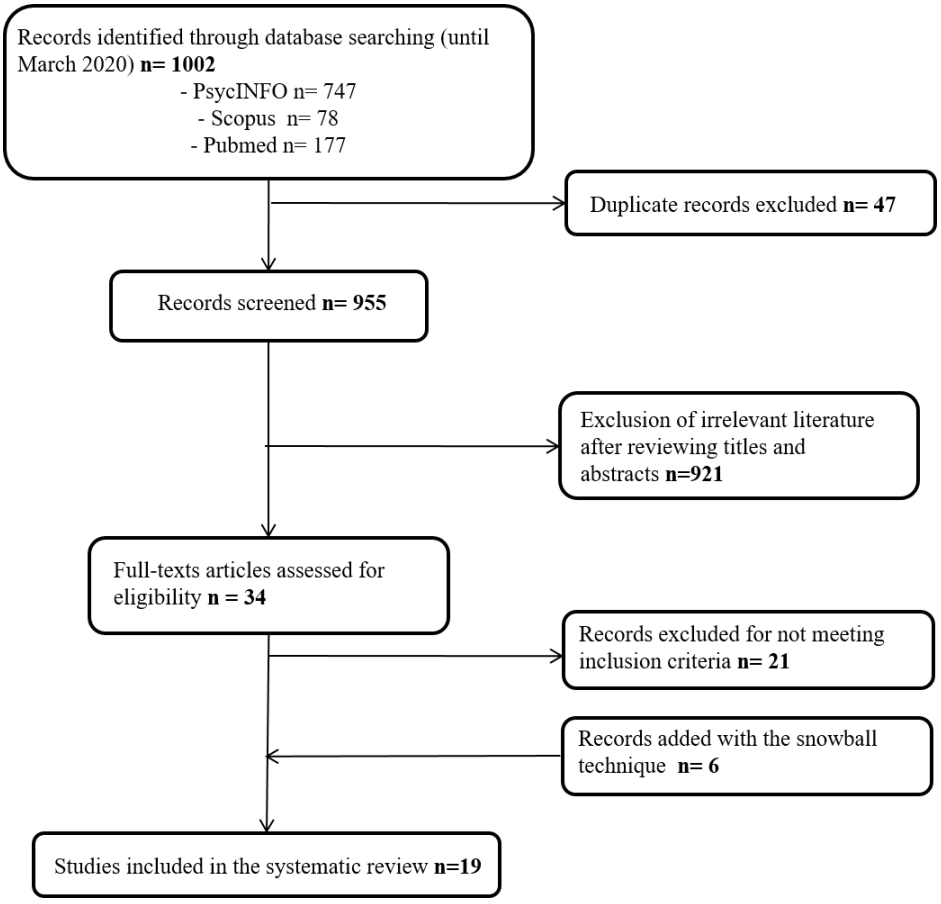

Figure 1.1. Flow diagram of literature search and study selection.

In what follows, I introduce results separated for studies using neuroimaging and studies using EEG.

The majority of the studies used neuroimaging techniques such as EEG (Camfield et al., 2016; Ferreira de Sà et al., 2019; Flor et al., 2002; Kotchoubey & Pavlov, 2019;

Levita et al., 2015; Pastor et al., 2015; Pizzagalli et al., 2003; Rehbein et al., 2018; Wiggert et al., 2017) and fMRI (Birbaumer et al., 1998; Davis et al., 2010; Hooker et al., 2006; Koban et al., 2019; Morris et al., 2001; Pejic et al., 2013; Schneider et al., 1999; Veit et al., 2002). Two more studies used the MEG (Dolan et al., 2006; Steinberg et al., 2012). Here, EEG and fMRI studies' results will be briefly described because of the US's social nature in the paradigm.

The high temporal resolution of the EEG can help detect the temporal dynamics of social associative learning, from the early stages of the stimulus processing to the late component, more related to social cognition. Also, the high spatial resolution of the fMRI allows investigating the activation of subcortical areas.

2.3.1. EEG studies

Camfield and colleagues (2016) used a classical conditioning paradigm to investigate the classical conditioning paradigm's effect in the modulation of early sensory processing in the human brain, especially in a population with depressive symptoms. A paradigm with social US (aversive or pleasant imagery) was used to experiment with healthy and clinical (depressed) populations. To test the early sensory processing, the N170 event-related potential was analyzed, strongly associated with facial processing elicited in the posterior superior temporal sulcus (Itier & Taylor, 2004). In the first experiment, changes to N170 amplitude were investigated using both visual (aversive or pleasant imagery) and auditory (aversive noise burst) stimuli as the US and neutral faces as CSpos. N170 amplitude was recorded in healthy and depressed participants in the second experiment, using aversive and pleasant imagery as UCS and neutral faces as CSpos. This study's primary findings were that aversive unconditioned stimuli could modulate the early sensory processing of faces. Specifically, the N170 amplitude at P7 was increased for the CSpos/aversive condition compared to CSneu in the conditioning block versus baseline. Surprisingly, no differences between depressed and healthy participants were found.

Wiggert and colleagues' (2017) study was the first that used a purely social CS and US. They used four pictures of neutral faces of actors as CSs, followed by videos of the same actors with negative vs. neutral sentences as USs. They investigated the

modulation of mid-to long-latency event-related potentials (ERPs) and alpha and theta oscillations. A mid-latency P280 was found as a specific conditioned response in posterior sites, linking with selective attention and short-term memory during the stimuli' processing. This P280 ERP is also linked with theta oscillations, reflecting memory processes' involvement through a late positive potential (LPP). The LPP is an electrophysiological index involved in emotional processing (Liu et al., 2012). Its enhancement may reflect a cognitive evaluation and categorization of the affective stimuli or the encoding in memory (Olofsson et al., 2008).

The LPP was also detected in a study conducted by Kotchoubey and Pavlov (2019), where classical conditioning was combined with the passive oddball. They used both physical US (painful shock) and social US (names) using two different tasks: the aversive conditioning task, which used painful shock paired with different sounds, and the name conditioning task, where the name of participant, familiar names, and standard names was used as social stimuli. In the acquisition phase, a harmonic CS+ tone was paired with the name of the participant, and a CS- tone was randomly paired with three other familiar names. Standard has presented without any relation to other stimuli involved the participant's name, familiar names for the participant, and standard names used as the social US. The subjects' names denote a potentially high significant stimulus, but it can not be precisely defined in terms of valence. This type of conditioning was compared with the classic aversive conditioning paradigm to assess ERPs and time-frequency analysis. LPP amplitude results larger in both tasks, reflecting the cognitive evaluation and categorization of the stimuli. Despite this, a larger N1 and P3a to CS+ rather than CS- was detected only in the aversive conditioning task, but not in the name conditioning task.

2.3.2. fMRI studies

Hooker and colleagues (2006) were the first to use a classical conditioning paradigm with the social US to investigate the amygdala response to emotional association learning in humans. Participants performed two behavioral tasks in a 4T fMRI: the association-learning task and the expression-only task. The association-learning task is a reversal-learning task where a woman would react with a happy vs.

neutral (or fearful vs. neutral) to a cued object, creating an emotional association with it. After some trials, this association reversed, so the cued object change its associative emotional value. Fear (and happy) association learning were investigated in separate fMRI runs, allowing the comparison of object–emotion and object–neutral association learning. In the expression-only task, participants saw the same woman's neutral face and determined whether it would become fearful versus neutral or happy versus neutral. After the prediction, the woman displayed a facial expression without any objects to form an association. The face stimuli were the same in the two tasks and consisted of three different expressions (fearful, happy, and neutral) from one woman. Greater activation of the right amygdala was found in the association-learning task concerning the expression-only task. This finding supports the amygdala's activation related to emotional content and not in neutral association learning generally. Behavioral data also support this specificity because participants show the faster prediction of emotional reactions concerning neutral reactions to the objects.

Some years later, Davis and colleagues (2010) did a 3T fMRI experiment to investigate the differences across the human amygdaloid complex during social conditioning, hypothesizing differential habituation rates for regions. Here, one individual face always predicted adverse social outcomes (i.e., insults), another always predicted positive social outcomes (i.e., compliments), whereas the third always predicted neutral social outcomes. Participants reported liking or disliking the faces in accordance with their learned social values. They found that the amygdala's overall activation shows a habituation tendency after a short conditioning phase (Alvarez et al. 2008; Büchel et al. 1999; Morris et al. 2001; Phelps et al. 2001). Specifically, the dorsal and medial ventral regions showed increased signals to faces predicting negative and positive outcomes. Furthermore, in the amygdala's lateral ventral region, they observed a linear representation of valance such that negative > positive > neutral. These results accord with the learned valence of faces, with the greatest sensitivity to faces predicting negative social outcomes (Kim et al. 2003; Repa et al. 2001).

Pejic and colleagues (2013) have also investigated the role of the amygdala during social conditioning. Their experiment focused on the relationship between social anxiety and conditionability, hypothesizing a great conditioned response in neural activation in individuals with high social anxiety. To do that, they did a 2-days fMRI conditioning

protocol where measured BOLD response, ratings, and electrodermal activity. It results in a significant differentiation between CSpos and CSneu in the left amygdala and the left hippocampus. Furthermore, this activation is negatively associated with social anxiety scores. Moreover, during the extinction recall, a differentiation between CSpos and CSneu was also found in the ventromedial prefrontal cortex activity, which is implicated in the inhibition of the amygdala response to fear expression. This finding is also in line with the previous study (Gottfried and Dolan, 2004; Phelps et al., 2004).

Table 1.1. Studies selected for the systematic review.

Original Paper	Participants n (f)	Age: Years (SD/Range)	Method	US-Type	US-Valence	Main Findings
Birbaumer et al., 1998	7(0) SP 5(0) HC	26.3(5.4) SP 25.2(4.8) HC	fMRI	Physical (Odor)	Negative	Increased amygdala activation in SP in response to potentially fear-relevant stimuli
Camfield et al., 2016	Exp 1 24(12) HC Exp 2 26(17) HC 18(13) Patients	Exp 1 21.07(3.38) Exp 2 25.97(9.42) HC 23.26(4.01) Patients	EEG	Physical (Sound) and Social (Pictures)	Negative and Positive	Enhanced N170 in the condition of neutral faces paired with low valence imagery or acoustic startle in comparison to condition with unpaired faces; Increased N170 in the left hemisphere from pre- to post-conditioning for CSpos to CSneu.
Davis et al., 2010	42(21) HC	24.3(3.96)	fMRI	Social (Sentences)	Negative and Positive	Differences in the activation in the regional response of the amygdaloid complex
Dolan et al., 2006	10(10) HC	24.5(20-28)	MEG	Physical (Noise)	Negative	Early modulation of visual-evoked responsed to a conditioned faces that precedes the typical face response.
Ferreira de Sá et al., 2019	24(12) HC	24.1(4.8)	EEG	Physical (Electric Shock)	Negative	ERPs of motivated attention (EPN, LPP, SPN) appear to be stable markers of social cue-oriented fear.
Flor et al., 2002	12(0) HC 12(0) PP	28.70(7.32) HC 33.67(5.36) PP	EEG	Physical (Odor)	Negative	Deficit in association formation in PP

Hooker et al., 2006	12(7) HC	25(19-36)	fMRI	Social (Faces)	Negative and Positive	Greater right amygdala activity in object–emotion associations learning compared to emotional expression without any learning requirement.
Koban et al., 2019	36(20) HC	27.1(18-50)	fMRI	Physical (Heat)	Negative	Both social information and learning influenced expectation on pain by different brain networks.
Levita et al., 2015	21(11) adolescents 23(11) adults	13.14(1.06) adolescents 20.43(3.04) adults	EEG	Physical (Sound)	Negative	Increased N170 amplitude in both groups, for both the active and the passive warning stimuli.
Morris et al., 2001	6(2) HC	29.3(ND)	fMRI	Physical (Noise)	Negative	Parallel changes of neural activity involved in segregated amygdala subregions and unimodal sensory cortices
Pastor et al., 2015	34(26) HC	24.4(5.1)	EEG	Physical (Electric Stimulation)	Negative	Enhanced LPP toward paired relative to unpaired stimuli after as compared to before learning not showed in autonomous responses.
Pavlov & Kotchoubey, 2019	Exp 1 19(12) HC Exp2 17(11) HC	Exp1 24.63(2.29) Exp2 24.88 (2.28)	EEG	Physical (Tactile Stimulus) And Social (Names)	Negative and Positive	Increased learning-induced P3a in aversive conditioning, and increased LPP in both experiments.
Pejic et al., 2013	41(19) HC	23.49(3.07)	fMRI	Social (Videos)	Negative	Positive correlation of social anxiety score and conditioning responses on valence and fear rating; significant CSpos/CSneu differentiation in the left amygdala and the left hippocampus.
Pizzagalli et al., 2003	50(24) HC	19.02(1.07)	EEG	Physical (Noise)	Negative	Involvement of amygdala, OFC, ventromedial PFC and insula in aversive conditioning.
Rehbein et al., 2018	36(9) HC	24.4(5.1)	EEG	Physical (Shock)	Negative	Influence of LPP, N250r-like components and EPN-like components in conditioned responses.

Schneider et al., 1999	12(0) SP 12(0) HC	30.8(5.7) SP 27.6(4.6) HC	fMRI	Physical (Odor)	Negative	Signal decrease in the amygdala and hippocampus for CS paired with negative odor in HC; opposed activation in patients with SP.
Steinberg et al., 2012	24(12) HC	25.5(22-34)	MEG	Physical (Odor)	Negative	Enhanced neural activity in PFC in lateral and orbital regions for CSpos compared to CSneu.
Veit et al., 2002	4(0) PP 4(0) SP 4(0) HC	ND(21-41)	fMRI	Physical (Tactile Stimulus)	Negative	Brief amygdala activation in PP; increased activity to the faces in the amygdala and orbitofrontal cortex in SP.
Wiggert et al., 2017	59(40) HC	25.12(3.36)	EEG	Social (Videos)	Negative	Larger P280 and LPP for CSpos rather than CSneu; differences in theta oscillations for CSpos and CSneu.

Legend: SP: social phobia; HC: healthy controls; PP: psychopaths; fMRI: functional magnetic resonance image; EEG: electroencephalography; MEG: magnetoencephalography; CS: conditioned stimulus; ERP: event-related potential; EPN: early posterior negativity; LPP: late positive potential; SPN: stimulus-preceding negativity.

2.4. Discussion

The present review aimed to summarize studies about neural mechanisms underlying classical conditioning for social stimuli in humans. In doing so, we searched the literature on three databases, using keywords as *classical conditioning*, *pavlovian conditioning*, and *social behavior*, in order to select relevant articles about the above-mentioned topics.

Our systematic review results included 19 studies, primarily distinguished for the nature of the US. More in detail, the majority of studies concerned the physical US, such as an electrical shock (e.g., Ferreira de Sá et al., 2019) or aversive noise (e.g., Pizzagalli et al., 2003), while few studies used the social US, such as pictures of people (e.g., Hooker et al., 2006). Hence, the first contribution of this review is that it highlights the paucity of studies using the social US. Indeed, the use of physical USs (e.g., electrical shock) may elicit a stronger response in arousal (consistent with its evolutionary functioning), but the outcomes could not be clearly applied in the social domain (Simons et al., 2017). Thus, using the social US could be more appropriate; hence, our systematic review highlights the need for more studies using the social US.

The second contribution of this systematic review is the valence of negative conditioning (i.e., conditioning paradigms where the US has a negative emotional valence). Indeed, we found that most of the studies have used negative conditioning, much more than the positive one. More in detail, 15 studies have used negative US, whereas 4 studies have used both negative and positive US (see Table 1.1).

The fact that most of the studies on classical conditioning are mainly focused on negative stimuli may be a signal of the underestimation of positive stimuli in classical condition research. This finding may be related to the easiness of eliciting negative conditioning instead of a positive one. However, the importance of studies using positive social stimuli should not be underestimated, given that they may reveal new insights on socio-emotional and affiliative behaviors (e.g., De Houwer et al., 2001). Hence, this review call for more studies using positive stimuli.

2.5. Conclusions

More research is needed to shed light on underlying human conditioning mechanisms better. Our systematic review showed that two ways to enhance literature in

this field are (a) to increase the number of studies using social US and (b) to increase the number of studies using positive valences instead of negative valences only. In order to tackle both points, in the subsequent chapter, I introduce an ERPs study on positive conditioning of human socioemotional behavior.

CHAPTER 3

An ERPs Study On Positive Conditioning Of Human Socioemotional Behavior

3.1. Introduction

Social cognition can be defined as "a scientific approach to studying social processes that emphasizes cognitive mechanisms" (Amodio, 2019, p. 23-24). From the dual-process models (Smith & Decoster, 2000), research on social cognition has been developed together with cognitive science and research, which emphasized the role of cognitive processes in understanding social behavior, particularly memory processing, attention, and learning mechanisms. One of these mechanisms, the classical or Pavlovian conditioning, is one of the most used paradigms in experimental psychology to investigate learning processes, particularly associative learning (see Chapter 2).

Nowadays, it is crucial to consider and evaluate human beings' social nature and how our threats have a social nature instead of a physical one. One of the associations that we do is relative to social evaluation from and to others, which sometimes regulates our approach to or avoidance behavior. So, it is essential to study also the mechanisms that regulate associative learning made by social stimuli. The previous chapter of this thesis highlighted this gap. It was especially highlighted how the few studies on social conditioning had the US with a physical nature, such as an electric shock or an aversive noise. There is no experimental paradigm that uses purely social US with positive emotional valence to our knowledge. This may be explained by the difficulties in findings social stimuli with high arousal without a solid biological component (for example, food or sex) and exquisitely social nature. In contrast, it is much easier to find stimuli for aversive conditioning (think of how an insult is more effective than a compliment, leaving traces of our memory and generating an avoidance behavior).

From a neural perspective, the perception of a stimulus with an emotional value generates a related potential event called late positive potential (LPP; Schupp et al., 2000). This potential is involved in the implicit processing of emotional stimuli, and it is generated around 700-1500 msec in the central and posterior areas of the brain. Therefore, it appears to be linked to later processing with a greater allocation of resources in the

stimulus processing; it has been found in several studies that have investigated trustworthiness (Manssuer et al., 2015; Yang 2011). These studies highlighted a modulation of the LPP amplitude in response to aversive stimuli (Bacigalupo et al., 2018; Wiggert et al., 2017).

Therefore, the presence or absence of this potential is linked to a strong emotional connotation of the stimulus, as it is absent for neutral stimuli. However, some clinical conditions may reveal abnormalities in the generation of conditioning and the perception of the valence of external stimuli. For example, individuals with social anxiety had a robust potentiation of the startle blink reflex for the CS with negative valence to CS with neutral and positive valence (Lissek et al., 2008). This is consistent with the persistent and robust hypervigilance, typical in anxious individuals (American Psychological Association, 2013), that made them responsive to potential dangers in situations with the ambiguity of threat presence (Kastner-Dorn et al., 2018). Also, the presence of depressive symptoms may interfere with the classical conditioning procedure. Individuals with a high level of depressive symptoms are usually less sensitive to positive valence of stimuli (American Psychological Association, 2013), as resulted by EEG studies that investigated an abnormality of N170 relative to emotional face-processing (Levita et al., 2015) in individuals with depressed symptoms (Camfield et al., 2016).

The current study aims to provide a novel paradigm to test positive social learning by a classical conditioning paradigm. The aim was to test whether a short period of classical conditioning (i.e., two days) can regulate the subjective evaluation of socially relevant stimuli. Specifically, I hypothesized that the CSpos score at T2 (post-conditioning) is higher than CSpos at T1 (pre-conditioning) in valence (H1), arousal (H2), and attractiveness (H3). Moreover, in an explorative way, I investigate whether specific changes in the neural signature occur during the acquisition of social preference. Specifically, I investigate whether the Late Positive Potential elicited by CSpos and CSneu are significantly different.

3.2. Methods

3.2.1. Participants

For this study, 42 participants (mean age 23.36, s.d. 4.6; 21 females) were

recruited at the University of Trento. They filled informed consent according to the Declaration of Helsinki and received 25 euros for participation. The local Ethics Committee approved the study. All participants were right-handed, Italian mother-tongue, and had a normal or corrected-to-normal vision. No participant reported a previous or current neurological or psychiatric disorder.

3.2.2. Classical conditioning paradigm

For the video recording, showed during the conditioning phase, professional Italian actors and actresses were asked to be as neutral as possible. Indeed, they all wore a black t-shirt during the recording, they were asked not to have beards, mustaches, earrings, eyeglasses, visible makeup, and hair tied up. Performances were recorded in front of the camera, and photos of neutral expression were acquired from the videos. Every video started with a few seconds of neutral faces. Actors and actresses were asked to gradually change their expression into positive or neutral, according to the emotional valence of the sentence they were about to pronounce. Furthermore, voice prosody was coherent with the emotional valence of the sentence (see Figure 3.1. for a typical conditioning phase).

Figure 3.1. A typical conditioning phase.

Four actors and three actresses were recorded, and everyone was recorded for the pronunciation of 20 positive and 20 neutral sentences. Then, one actor was excluded

because of a little presence of beards. Another one was excluded because of his emotional prosody; also, to have the same number of male and female videos, one actress was excluded. Finally, videos and photos of two actors and two actresses were used as stimuli.

For the final choice of the sentences, we did a preliminary survey. In this survey, every voice recorded was rated for valence and arousal. All judgments were made on a 5-point scale ranging from 1 (*neutral*) to 5 (*very positive*) for the valence and from 1 (*not aroused*) to 5 (*very aroused*). Both male and female actors pronounced all sentences.

In order to select the most appropriate sentences, a preliminary survey has been run. In more detail, thirty participants (15 females) rated the valence and the arousal of every sentence, and they have selected eight neutral sentences with neutral valence and fewer arousal ratings. Moreover, eight positive sentences with major valence and arousal ratings were selected (see Table 3.1. for the final selections of the sentences).

Table 3.1. English translation of the final sentences selected for the conditioning phase. Positive sentences: Mean valence = 3.59 ± 0.19 Mean Arousal = 3.34 ± 0.11. Neutral sentences: Mean valence = 1.27 / 5 ± 0.09 Mean Arousal = 1.22 / 5 ± 0.08.

Neutral sentences	**Positive sentences**
"You have reached the square"	"I am happy for you to be here"
"You opened the door"	"You are brilliant"
"You brush your teeth with a toothbrush"	"I have a gift for you"
"You unpacked your suitcase"	"You have really brilliant ideas"
"You did your shopping at the supermarket"	"I know I can trust you"
"Sometimes you watch the TV"	"You are really smart"
"You wore the jacket"	"You did a great job"
"You crossed the street"	"I know I can count on you"

3.2.3. Experimental Procedure

All the participants underwent the study on two different subsequent days at the same hour.

On the first day, participants filled questionnaires to assess positive and negative affect, state and trait anxiety, and depressive symptoms. Then, participants were exposed to the pre-conditioning habituation phase (habituation task) using OpenSesame software 3.1 (https://osdoc.cogsci.nl; Psychology Software Tools, Pittsburgh, PA) on a 27-inch monitor (Philips 300 x 300). They saw six faces and six objects at the center of the screen for 1500 msec with 500 msec of jitter between one image and another. Faces were 6: four images of real actors and two images from the Chicago Face Database (Ma et al., 2015), all with a neutral expression. Objects were all gathered from the International Affective Picture System database (Lang et al., 2007), selected by their neutral valence and arousal. Between one image and the following one, a fixation point appeared. Participants were asked to press the bar space when a face with blue eyes appeared to keep their attention to the task. For each participant, 240 trials were randomly run (15 times x 4 irrelevant faces and 6 objects; 45 times x 2 CSpos and CSneu faces). After that, participants were asked to rate every actor's face for the dimensions of valence, arousal, and attractiveness using an online questionnaire.

Then, participants were exposed to the conditioning phase (acquisition task): Two of the actors (1 female) already seen in the habituation task appeared in videos, and they pronounced sentences with positive or neutral valence from a list (see table 3.1. for the sentences). For each participant, the characteristics of the conditioning phase were as follows: (a) one actor and one actress were associated with positive sentences and with neutral sentences, respectively; (b) every actor/actress pronounced all the 8 sentences of respected valence; (c) in total, each participant watched 80 videos (8 times x 2 videos with neutral faces, as baseline; 4 times x 8 videos with positive sentences; 4 times x 8 videos with neutral sentences).

On a subsequent day, participants were exposed again to the conditioning phase (acquisition task) and then to the post-conditioning extinction phase (extinction task). The extinction task was the same as the habituation task regarding the stimuli' number and timing. After the extinction phase, participants were asked to rate again the faces already

seen after the habituation phase for the same three dimensions (valence, arousal, and attractiveness).

The experimental session took place in a room with semi-darkness constant luminance guaranteed by a lamp positioned one meter away behind the participant.

EEG signal was recorded in all three phases but considered in the analysis only for the habituation phase and the extinction phase.

3.2.4. Measures

Questionnaires

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) is a 21-item self-report questionnaire. It was developed to assess depressive symptoms and their severity over the previous two weeks. Items were evaluated through a 4-Likert-type scale, ranging from 0 to 3. The score range of 0 – 13 indicates absent to minimal depression symptoms, 14 – 19 indicates mild to moderate depression symptoms, 20 – 28 indicates moderate to prominent depression symptoms, and 29 – 63 indicates severe depression symptoms. The reliability of the BDI-II was satisfactory (α = *.88).*

The State-Trait Anxiety Inventory – Form Y (STAI-Y; Spielberger et al., 1983) was designed to measure anxiety and its different acute *versus* chronic aspects. It consists of two subscales, Y1 (20 items) and Y2 (20 items), which measure state and trait anxiety. State anxiety is a transient condition of tension experience and apprehension; instead, trait anxiety is a stable tendency of the individual to experience anxiety symptoms. Items were evaluated through a 4-Likert-type scale, ranging from 1 to 4. The reliability of the STAI-Y was satisfactory (α = *.91 for the Y1 subscale;* α = *.93 for the Y2 subscale*).

The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) consists of two 10-item mood scales measuring positive affect and negative affect. Items were evaluated through a 5-Likert-type scale, ranging from 1 to 5. The reliability of the PANAS was satisfactory (α = *.84 for the positive affect scale;* α = *.89 for the negative affect scale*)

Pre- and Post-Conditioning response

Pre- and Post-Conditioning response was evaluated using Qualtrics online questionnaires (www.qualtrics.com), where the faces of actors and actresses were

displayed and asked to be evaluated for Valence, Arousal, and Attractiveness.

Valence was evaluated through a single question that reads "*How pleasant or unpleasant do you find this person?* [Quanto piacevole o spiacevole trovi questa persona?]", and was rated by participants through a slider that ranged from -7 (*Very unpleasant* [Molto spiacevole]) to +7 (*Very pleasant* [Molto piacevole]).

Arousal was evaluated through a single question that reads "*How calm or emotion does this person get you?* [Quanta calma o emozione/attivazione ti suscita questa persona?]", and was rated by participants using a slider that ranged from 0 (*Very calm* [Molta calma]) to 9 (*Very arousing* [Molta emozione]).

Attractiveness was evaluated through a single question that reads "*How much does this person attract you?* [Quanto ti attrae questa persona?]" and was rated by participants using a slider that ranged from 0 (*Not at all* [Per niente]) to 9 (*Very much* [Moltissimo]).

EEG Recording and Preprocessing

EEG was recorded from the scalp with a 32-channel cap. During the recording, the left mastoid was used as a reference and AFz electrode as the ground. Electrode impedance was maintained below 10 KΩ.

Pre-processing was done using EEGlab and ERPlab toolboxes (http://www.sccn.ucsd.edu/eeglab/). Raw data were down-sampled to 250Hz, then the channel location was checked, and every dataset was digitally filtered with a basic FIR bandpass filter of 0.1-40 Hz. Then, the EEG data were re-referenced, computing the average reference of all the electrodes. Filtered data were epoched from 200 ms before stimulus onset and 1500 ms after stimulus presentation. In order to remove blinks, muscular and line noise artifacts, an Independent Component Analysis was applied. After all, data epochs were automatically rejected selecting a threshold of 150microvolts; finally, a manual visual inspection of the epochs was done, and an ERP file was created.

3.2.5. Data analysis

Questionnaires (PANAS, STAI-Y, BDI-II)

After reversing reverse-items, we computed a composite score for each construct (depression in BDI-II, state anxiety in STAI-Y1, trait anxiety in STAI-Y2, positive affect,

and negative affect in PANAS) through summing the corresponding items. Then, we calculated reliability (reported in the measure's section), descriptive statistics, and zero-order correlations.

Pre- and post-conditioning response

For each positive conditioned stimulus, we calculated descriptive statistics of Valence, Arousal, and Attractiveness. Then, we ran three one-way ANOVA in which we used time as the dependent variable and valence/arousal/attractiveness as the outcome.

EEG and ERPs

The EEG analysis was relative to the potentials elicited by CSpos versus CSneu during the extinction phase with respect to the habituation phase.

For the ERPs analysis, bins have been used to remove, for every trial, the habituation phase from the extinction phase – as a baseline correction: Every item was associated with a specific bin, distinguishing CSpos and CSneu. At this point, the mean amplitude for CSpos and CSneu has been calculated. Then, electrode clusters were used for the calculation of the LPP: Paired samples t-tests were displayed. The LPP calculation was computed the mean amplitude 700–1500 ms on central and posterior electrodes (C3, Cz, C4, CP5, CP6, P7, P3, Pz, P4, P8; Wiggert et al., 2017).

3.3 Results

3.3.1. Descriptive statistics

Zero-order correlations and descriptive statistics for each study variable are reported in Table 3.2.

Regarding constructs measured through questionnaires (depression, state anxiety, trait anxiety, positive affect, and negative affect), correlations were consistent regarding size and direction. For example, state and trait anxiety correlated significantly and positively; depression was significantly and positively correlated with positive affect, while significantly and negatively correlated with negative affect; positive affect was significantly and negatively correlated with trait anxiety.

Regarding valence, arousal, and attractiveness, the only significant correlation

was that between attractiveness and valence.

Regarding the relationships among constructs measured with questionnaires and CSpos, correlations ranged from r = -.11 (arousal with state anxiety) to r = .30 (arousal with depression).

Table 3.2. Means, standard deviations, and correlations with confidence intervals.

Variable	*M*	*SD*	1	2	3	4	5	6	7
1. State Anxiety	34.03	8.91							
2. Trait Anxiety	43.55	10.84	.64** [.40, .80]						
3. Positive Affect	31.34	5.89	-.14 [-.44, .19]	-.52** [-.72, -.25]					
4. Negative Affect	17.82	6.38	.49** [.21, .70]	.73** [.53, .85]	-.24 [-.52, .09]				
5. Depression	9.47	8.12	.56** [.29, .75]	.83** [.69, .91]	-.47** [-.68, -.17]	.64** [.40, .80]			
6. CSpos Valence	-0.66	3.02	.10 [-.23, .41]	.06 [-.27, .37]	.15 [-.18, .45]	.18 [-.15, .47]	-.04 [-.35, .28]		
7. CSpos Arousal	4.38	1.59	-.11 [-.41, .22]	.22 [-.10, .51]	-.24 [-.52, .09]	.21 [-.11, .50]	.30 [-.02, .57]	-.23 [-.51, .09]	
8. Cspos Attractiveness	2.36	2.37	-.05 [-.36, .28]	-.03 [-.34, .30]	.04 [-.28, .36]	.19 [-.14, .48]	-.03 [-.34, .30]	.54** [.27, .74]	.18 [-.15, .47]

Note. M and *SD* are used to represent mean and standard deviation, respectively. Values in square brackets indicate the 95% confidence interval for each correlation. The confidence interval is a plausible range of population correlations that could have caused the sample correlation (Cumming, 2014). * indicates $p < .05$. ** indicates $p < .01$.

3.3.2. Pre-post conditioning subjective responses

Descriptive statistics conditioned to time, helpful in running ANOVA were reported in Table 3.3., 3.5., 3.7., while results from ANOVA were reported in Table 3.4., 3.6., 3.8.

As it can be seen, ANOVA revealed that there were no mean-level differences in arousal scores between the evaluation at T1 and T2 [$F(1, 74) = 0.56$, $p = .456$; partial $\eta^2 = .01$]. Thus, H2 is not supported by data.

Instead, ANOVAs for valence and attractiveness revealed significant within-level differences. In particular, valence scores were significantly higher at T2 ($M_{T1} = -0.66$, $M_{T2} = 1.94$) as attested by ANOVA result [$F(1, 74) = 16.89$, $p < .001$; partial $\eta^2 = .19$], thus supporting H1. Then, attractiveness scores were significantly higher at T2 ($M_{T1} = 2.36$, $M_{T2} = 4.09$) as attested by ANOVA result [$F(1, 74) = 9.91$, $p = .002$; partial $\eta^2 = .12$], thus supporting H3.

Figure 2.2. provided box plot for each of the above-reported mean-level comparisons.[2]

[2] In order to probe potential gender differences for dependent variables, we ran a series of one-way ANOVA. As it can be seen in Table B1 in Appendix B, no gender effect has been found.

Valence, Arousal, and Attractiveness

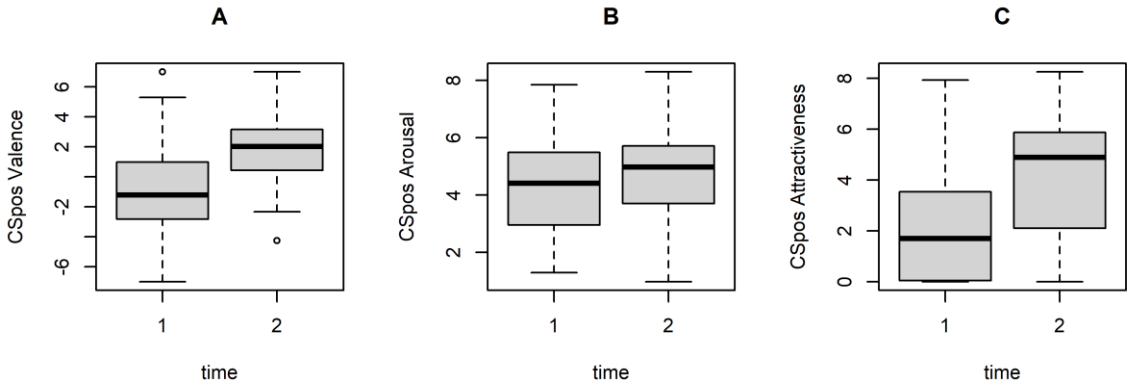

Figure 3.2. Boxplot of valence, arousal, and attractiveness ratings for CSpos, before (time 1) and after (time 2) conditioning phase.

Valence

Table 3.3. Descriptive statistics for CSpos valence as a function of time.

time	*M*	*SD*
1	-0.66	3.02
2	1.94	2.47

Note. M and *SD* represent mean and standard deviation, respectively.

Table 3.4. Fixed-Effects ANOVA results using CSpos valence as the criterion

Predictor	Sum of Squares	*df*	Mean Square	*F*	*p*	$_{partial}\eta^2$	$_{partial}\eta^2$ 90% CI [LL, UL]
(Intercept)	16.74	1	16.74	2.20	.142		
time	128.61	1	128.61	16.89	.000	.19	[.07, .31]
Error	563.52	74	7.62				

Note. LL and UL represent the lower-limit and upper-limit of the partial η^2 confidence interval, respectively.

Arousal

Table 3.5. Descriptive statistics for CSpos arousal as a function of time.

time	*M*	*SD*
1	4.38	1.59
2	4.67	1.72

Note. M and *SD* represent mean and standard deviation, respectively.

Table 3.6. Fixed-Effects ANOVA results using Cpos arousal as the criterion.

Predictor	Sum of Squares	*df*	Mean Square	*F*	*p*	$_{\text{partial}}\,\eta^2$	$_{\text{partial}}\,\eta^2$ 90% CI [LL, UL]
(Intercept)	729.40	1	729.40	264.32	.000		
time	1.55	1	1.55	0.56	.456	.01	[.00, .07]
Error	204.20	74	2.76				

Note. LL and UL represent the lower-limit and upper-limit of the partial η^2 confidence interval, respectively.

Attractiveness

Table 3.7. Descriptive statistics for CSpos attractiveness as a function of time.

time	*M*	*SD*
1	2.36	2.37
2	4.09	2.42

Note. M and *SD* represent mean and standard deviation, respectively.

Table 3.8. Fixed-Effects ANOVA results using CSpos attractiveness as the criterion.

Predictor	Sum of Squares	*df*	Mean Square	*F*	*p*	partial η^2	partial η^2 90% CI [LL, UL]
(Intercept)	212.03	1	212.03	37.01	.000		
time	56.75	1	56.75	9.91	.002	.12	[.03, .24]
Error	423.94	74	5.73				

Note. LL and UL represent the lower-limit and upper-limit of the partial η^2 confidence interval, respectively.

3.3.3. ERPs analysis

By comparing CSpos versus CSneu during extinction with respect to habituation, we measured a significant decrease of LPP amplitude between 700-1500 msec for CSpos as compared to CSneu.

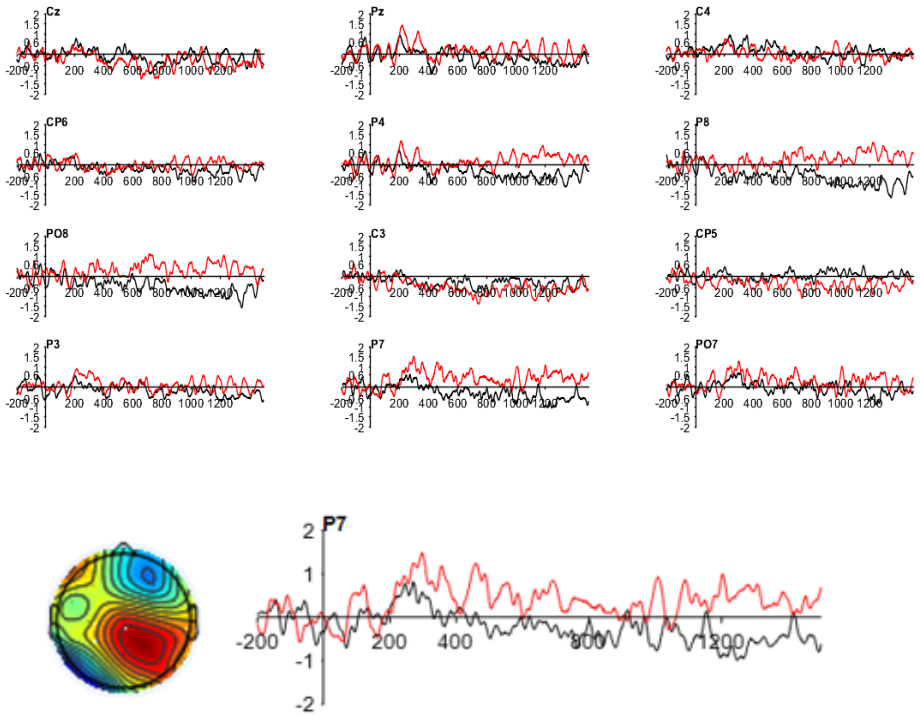

Figure 3.3. Grandaverage of LPPacross central and posterior channels (CSpos in black and CSneu in red).

Differences between CSpos and CSneu across channels

In Table 3.9. a series of *t*-test for analyzing differences between signals elicited by CSpos and CSneu by central and posterior channels were reported. As it can be seen, only one paired *t*-test was significant, namely the difference between CSpos and CSneu in P7 posterior channel, for which the test revealed that CSneu_P7 scores were lower than CSpos_P7 (t = -2.027, df = 41, p = .049; Cohen's d = .31).

Table 3.9. A series of t-test on differences between CSpos and CSneu across channels.

Paired Samples T-Test

			statistic	df	p	Mean difference	SE difference	Cohen's d
CSpos_Cz	CSneu_Cz	Student's t	1.187	41.0	0.242	0.4610	0.388	0.1832
CSpos_Pz	CSneu_Pz	Student's t	-0.204	41.0	0.839	-0.0880	0.431	-0.0315
CSpos_C4	CSneu_C4	Student's t	0.895	41.0	0.376	0.2709	0.303	0.1380
CSpos_CP6	CSneu_CP6	Student's t	-0.538	41.0	0.594	-0.1316	0.245	-0.0830
CSpos_P4	CSneu_P4	Student's t	-0.467	41.0	0.643	-0.1895	0.406	-0.0720
CSpos_P8	CSneu_P8	Student's t	-1.595	41.0	0.118	-0.6125	0.384	-0.2462
CSpos_C3	CSneu_C3	Student's t	1.283	41.0	0.207	0.3306	0.258	0.1980
CSpos_CP5	CSneu_CP5	Student's t	1.846	41.0	0.072	0.3782	0.205	0.2849
CSpos_P3	CSneu_P3	Student's t	-0.249	41.0	0.804	-0.0968	0.388	-0.0385
CSpos_P7	CSneu_P7	Student's t	-2.027	41.0	0.049	-0.7205	0.355	-0.3128

3.4. Discussion

Social cognition relies on efficient learning and memory systems to generate representations of the person we meet in our daily social life, integrating our social experiences (Eagly & Chaiken, 1993). This is the first study to investigate positive social conditioning with purely social CSs and USs after a short period of conditioning, to the best of our knowledge. Indeed, differently from most previous studies, this paradigm, to our knowledge, is the first to use dynamic, social, and realistic stimuli during the conditioning phase. Thus, this paradigm has the potential to fill the gap in the literature about classical conditioning in the study of socioemotional behavior by providing a specific focus on the social stimuli with a positive valence.

The analysis of pre- and post-conditioning subjective response of CSpos in the dimensions of valence, arousal, and attractiveness shows that while arousal is stable

across time, both valence and attractiveness significantly increased after a short period of conditioning. This increase is probably due to the effect of conditioning. This result is consistent with our expectations, supporting the validity of our paradigm. The arousal's stability despite the period of conditioning may be expected because of the difficulties in finding positive purely social US stimuli with high arousal.

However, these behavioral results are associated with neural results. In fact, according to previous studies (Bacigalupo et al., 2018; Wiggert et al., 2017), we expected greater differences in LPP between CSpos and CSneu. Consistently, in this context, we found a significant effect ($t_{(41)} = -2.027$, $p = .049$) along with a small/medium effect size (Cohen's $d = -0.31$). An integration between EEG and fMRI could help better explain the localization of the LPP in central and posterior sites. Also, an improvement of this paradigm with a behavioral task in the pre-and post-conditioning phase may improve the conditioning's power and distinguish the implicit from the explicit aspects of conditioning.

Our findings indicate that modification of social stimuli perception is attainable after a short period of positive conditioning. Moreover, an increased positivity of previously neutral faces is associated with a decreased LPP amplitude. This result might indicate acquired social preference for CSpos stimulus more than CSneu as previous studies reported a crucial role of the LPP during learning of trust (Manssuer et al., 2015).

This seems to be the first study about the influence of classical conditioning in inducing specific modifications of neural signals underlying evaluation changes of social stimuli, from neutral to positive, suggesting a potential mechanism regulating affiliative behavior.

The current study faces some limitations that should be noticed for future experiments. First, during the task, the participant should not do anything but see the faces and the videos. A future study may introduce a more engaging task in order to facilitate its efficacy. Moreover, a greater number of recording channels may help better detect the conditioning's neural signature. Also, a longer duration of the study – not two times, but repeating the conditioned phases more and doing the post-conditioning phase after more exposition to videos, may give precious information to the conditioning's learning effect.

CHAPTER 4

Sleep Characteristics In ASD Populations: A Polysomnographic Study

"Sleep is the price we pay for plasticity."
(Tononi & Cirelli, 2014, p. 12)

4.1. Sleep and learning

About 45-86% of individuals with Autism Spectrum Disorder (ASD) manifests sleep difficulties such as reduced sleep time and sleep fragmentation (Hermann, 2016). Reduced sleep time and sleep fragmentation may cause a disturbance in sleep-dependent memory consolidation (Diekelmann & Born, 2010).

Many studies corroborate the role of sleep in learning since 1924 when Jenkins and Dallenbach observed a difference in memory recall after a period of sleep with respect to a non-sleep period (Jenkins & Dallenbach, 1924). This phenomenon was called "the sleep effect". Since that moment, an increased amount of studies confirmed sleep in memory consolidation and learning processes. For example, the most famous is Diekelmann & Born (2010), about the process by which memory storage of procedural and declarative information becomes stronger and more efficient (Diekelmann & Born, 2010; Stickgold, 2005).

Several models have explained this particular role of sleep on cognitive abilities from a theoretical perspective, but one of the stronger ones is called the *synaptic homeostasis hypothesis* (Tononi & Cirelli, 2003, 2006). According to this model, the information that we elaborate on during the day – and the wakefulness – causes a progressive synaptic strengthening, with a learning effect. This phenomenon causes an increase in energy demands, reducing the selectivity of neuronal responses, and saturates the ability to learn other information (Tononi & Cirelli, 2014). The result of this process is a progressive impairment of cognitive functioning. According to this theory, the most critical function of sleep is to restore synaptic homeostasis. Sleep, by its slow-wave activity (0.5-4 Hz), reduces the synaptic strength, restoring neuronal selectivity and the

ability to acquire and learn new information.

In order to further the knowledge about several neuroimaging findings, Rasch and Born (2013) developed *the active system consolidation* model, which results informative about the involvement of sleep in learning processes and, in particular, in memory consolidation, stabilization, and integration (Rasch & Born, 2013). According to this model, during wakefulness, the information is encoded initially parallel in neocortical networks and the hippocampus (Diekelmann & Born, 2010). During sleep, particularly during slow-wave sleep (N3), the new memories are repeatedly re-processed and reorganized in the neocortex, creating persistent memory traces that become independent from the hippocampus through the re-distribution and the consolidation in neocortical networks (Born & Wilhelm, 2012). This process is also allowed by the activity of particular waves called *sleep spindles*. Sleep spindles are short oscillatory bursts of 11-16Hz originating in the reticular thalamus and occurring during non-rapid eye movement sleep (NREM), specifically during N2 and N3 sleep (De Gennaro & Ferrara, 2003). These two NREM sleep stages have been associated with learning processes, memory consolidation, and intellectual abilities (Mednick et al., 2013; Nishida & Walker, 2007; Fogel & Smith, 2011).

However, the two models are not exclusive to each other but were conciliated in a more comprehensive model (Genzel et al., 2014). Here, the role of sleep spindles and synaptic downscaling is highlighted in terms of shaping information in the neocortex by sharp-wave ripples during the N1 and N2 stages of sleep, followed by slow oscillation in the neocortex. These waves are responsible for the replay of the memory trace. Then, sleep spindles induce local plasticity in selected neuronal circuits previously reactivated during the first period of N1 and N2 stage of NREM sleep (Genzel et al., 2014). Then, promoting consolidation through the transfer of memory traces from a short-term store in the hippocampus to long-term cortical representations (Lewis & Durrant, 2011). After that, the synaptic downscaling reduces the strength of the synapsis in the neural circuits. Consequently, the weak connections disappear, but the previously potentiated circuits remain strong, and it is reflected in the restoration of learning ability and consolidation of information in memory.

4.2. Sleep and Autism Spectrum Disorder

Commonly, the ASD population reports sleep disturbances (Baker et al., 2019; Cohen et al., 2014), both in children and adults (Richdale & Schreck, 2009). The main findings have underlined a reduction of sleep efficiency accompanied by an increase in sleep latency (Baker et al., 2013; Polimeni et al., 2005).

These disturbances may be secondary to co-occurring psychiatric comorbidities, like anxiety, mood disorders, and Attention Deficit Hyperactivity Disorder, which are very common in ASD (Rosen et al., 2018; Vannucchi et al., 2014). Thus, it is common to use medications like benzodiazepines or antidepressants, which primary contraindication is the alteration of sleep architectures (Henry et al., 2006). It is also difficult to define if the sleep disturbance is secondary to these treatments, or it is relative to the ASD spectrum itself.

In ASD, sleep has been studied with objective and subjective measures, including actigraphy, polysomnography and video-somnography, questionnaires, and sleep diaries. These measurements revealed that ASD individuals experience more sleep disorders than the average population, to the extent that sleep problems have been thought to be part of the autism phenotype (Limoges et al., 2005).

Sleep problems in ASD have been found to correlate with several variables as age, IQ, comorbid psychiatric symptoms, and autism severity (Mayes & Calhoun, 2009), but, on the other hand, evidence of sleep stages quantity abnormalities are inconsistent. Studies found reductions in NREM sleep and no in REM sleep quantity. In contrast, other researches showed the opposite trend (Limoges et al., 2005; Godbout et al., 2000). However, autistic individuals seem to be characterized by a fragmented sleep period and altered sleep spindles characteristics (Bruni et al., 2007; Lambert et al., 2013).

In children with low-functioning ASD, the gravity of symptoms such as repetitive behaviors and social difficulties (Park et al., 2012; Tudor et al., 2012), as well as self–injury and aggressive behavior (Goldman et al., 2011; Henderson et al., 2011) is intensified by an insufficient time of sleep and sleep quality.

A recent systematic review and meta-analysis regarding sleep problems in adults with ASD show a significant impairment of subjective parameters of sleep quality, such as lower sleep efficiency, longer sleep onset latency, and wake after sleep onset in ASD group with respect to TD group (Morgan et al., 2020). The strength of this work is relative

to the use of both subjective (questionnaires, such as Pittsburgh Sleep Quality Index) and objective (polysomnography and actigraphy recording) parameters (Morgan et al., 2020). These results highlight the presence of sleep disturbances during the all life-span in the ASD population (also see Bangerter et al., 2020).

Most of the studies on sleep and ASD have been focused on children, but sleep disturbance refers to all life span. For this reason, we decided to put our focus on a group of young adults with high-functioning ASD.

On these bases, this study aims to elucidate how sleep characteristics can help explain ASD symptomatology. In particular, we expect that ASD participants may have an atypical sleep pattern with respect to TD participants, explicated by a differential amount of sleep stages and an altered distribution across the night, including the calculation of sleep stability and continuity. Moreover, we looked at sleep microstructure, such as sleep spindles, slow waves, and EEG activity across the night period.

4.3. Materials and methods

4.3.1. Participants

Thirty-two participants were recruited in the current study. Six of them were then excluded from the analysis due to noisy sleep recording. Of the remaining participants, 13 were in the ASD group (23.9±7.19 years, 1 female) and 13 in the TD group (23.9±2.43 years, 2 F).

ASD participants were recruited among the population of patients of the Observation and Functional Diagnosis Lab (ODFLab) at the University of Trento. All ASD participants received a high-functioning ASD diagnosis by expert clinicians. The exclusion criterion was the use of medication that may alter sleep architecture (e.g., benzodiazepines), often used by patients with ASD.

TD participants were recruited through advertisements posted on university bulletin boards and social networks. Inclusion criteria were the following:

(a) absence of any relevant psychiatric condition, as attested by The Symptom Checklist (SCL-90-R; Derogatis, 1977; Italian adaptation by Sarno et al., 2011);

(b) lack of autistic symptoms, as attested by the Autism-Spectrum Quotient (AQ; Baron-Cohen et al., 2001; Italian adaptation by Ruta et al., 2012);

(c) a good self-reported sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI; Buysse 1989; Italian adaptation by Curcio et al., 2013).

Participants gave written informed consent to participate in the experiment. The study was approved by the University of Trento ethical committee. All participants provided written consent before participation in this study. ASD participants received 100 euros for their participation, while TD participants received 40 euros.

4.3.2. Experimental procedure

Sleep recordings were performed in one night at participants' home. The polysomnographic montage began at 9.00 p.m. to allow participants to go to bed immediately after.

All participants were asked to push one button on the SOMNOmed device to trigger the exact moment they went to bed. Furthermore, there were recommended to wake up naturally the following morning.

The following morning, participants either went to the lab for returning the device or waited for the researcher to do that.

4.3.3. Polysomnographic recording

Polysomnographic (PSG) recordings during the nighttime were conducted using a portable device (SOMNOscreenTM plus Neuro+, SOMNOmedics GmbH) (SOMNOscreenTM plus Neuro+, SOMNOmedics GmbH) at participants' home. The PSG included 6 active electroencephalographies (EEG) electrodes (F3, F4, C3, C4, P3, P4) referenced to contralateral mastoids, 2 electrooculograms (EOG) electrodes placed below the left and above the right canthi, and 2 electromyograms (EMG) electrodes placed over the left and right musculus mentalis. According to the American Academy of Sleep Medicine (AASM) guidelines (Iber et al., 2007), all signals sampled at 256 Hz. The EEG and EOG signals were filtered between 0.3 and 35 Hz, whereas the EMG signal was filtered between 10 and 100 Hz. A 50-Hz notch filter was applied to all channels. Sleep scoring (WAKE, N1, N2, SWS, and REM) was visually performed on 30-sec EEG epochs from C3 in line with AASM criteria (2005). Whenever the signal of C3 was too noisy, C4 was used.

4.3.4. Data Analyses

Spindles Analysis

During NREM sleep, sleep spindles were automatically detected using a recently developed algorithm (Lacourse et al., 2019) implemented by Wonambi 6.12 (https://wonambi-python.github.io/). This method – named "A7" – detects spindles using a combination of 4 parameters related to sigma power (see Lacourse et al., 2019 for details about the algorithm). Based on the peak frequency, we divided sleep spindles based on slow and fast spindles (10–13 Hz and 13–16 Hz, respectively, see Merikanto et al., 2019). We computed the number, density (number of spindles per 60-second epoch), duration (s), amplitude (root-mean-square of the signal, µV) of the frontal (F, averaging F3 and F4 data), central (C, averaging C3 and C4 data), and parietal (P, averaging P3 and P4 data), spindles. We also derived spindles intensity as duration (s) multiplied by amplitude (µV). Epochs containing technical artifacts or extremely high muscle activity were detected and excluded from the analysis.

Power Spectral Density

Power Spectral Density (μV^2/Hz) was computed on N2 and N3 epochs on each channel. Fast Fourier transform was applied to 4-sec bin with 2-sec overlap using a Hann window. We extracted information about Slow Oscillations (SO; 0-5-1 Hz), Delta (1-54 Hz), Theta (4.0–8.0 Hz), and Alpha (8-11 Hz) activity.

Slow Wave Activity

Slow waves (SW; 0.3–4.0 Hz; >75 µV) were detected using the AASM/Massimini 2004 algorithm available on Wonambi 1.62 (https://wonambi-python.github.io/). The signal was filtered with a passband of 0.3-4 Hz, and then the algorithm detects slow waves based on several parameters, including a) a negative peak of less than −40 µV; b) a peak-to-peak amplitude greater than 75 µV; c) duration of negative and positive deflection of >250 ms and <1000 ms, respectively. Amplitude (µV), slope (µV/s), and duration (s) of the SW, as well as the density (number of SW per minute) per computed separately for each channel (F, C, P) during N2 and N3.

Sleep continuity, stability, and organization

Parameters related to sleep continuity (awakenings frequency and duration) sleep stability (state transitions and arousals frequency), and sleep organization (sleep cycle number and mean duration; see for exact definitions) were calculated following Conte and colleagues (2012) guidelines. In details, we computed:

a) sleep continuity: total frequency of awakenings per hour of AST; frequency of brief (< 4 epochs) and long (≥ 4 epochs) awakenings per hour of AST; frequency of awakenings from N1, N2, N3, REM sleep per minute of that stage;

b) sleep stability: frequency of arousals per hour of AST (here arousals are defined as all transitions to shallower NREM sleep stages and from REM sleep to N1); frequency of arousals from N2, N3, REM sleep per minute of that stage; frequency of state transitions (defined as all transitions from one state to another) per hour of TST; frequency of "functional uncertainty periods" (FU periods; defined as periods in which a minimum of 3 state transitions follow one another with no longer than 1.5 min intervals) per hour of TST; percentage of total time spent in FU (TFU) over TST;

c) sleep organization: number of complete sleep cycles, defined as sequences of NREM and REM sleep (each lasting at least 10 min) not interrupted by periods of wake longer than 2 min (as in [23]); total time spent in cycles (TCT) over TST.

Statistical Analyses

Demographics and sleep variables were compared between the two groups using the Mann-Whitney U test. As a measure of effect size, the rank biserial correlation was reported.

To assess the proportion of time spent in different stages, we used a mixed ANOVA with Group as between factor and Stage (N1, N2, N3, REM) as within-subject.

To assess potential differences in spindles characteristics in the two groups, we employed linear mixed models (LMM), which take into account factors whose levels are randomly extracted from a population (i.e., participants), yielding to more generalizable results (Baayen et al., 2008). For spindles density, amplitude, duration, and intensity, we built a model using *Participant* as crossed random effects and *Group* (ASD, TD), *Type* of

Spindle (Slow, Fast), *Stage* (N2, N3), and *Channel* (F, C. P) as fixed effect. For the post-hoc comparisons, we used the Bonferroni test.

Differences in spectral power density were assessed using LMM with *participant*s as crossed random effects and *Group* (ASD, TD), *Stage* (N2, N3), and *Channel* (F, C. P) as a fixed effect. The same LMM was used to analyzed SW characteristics (density, amplitude, slope, duration).

Lastly, we explored potential associations (using Spearman' Rho) between individuals' trait characteristics and sleep parameters in the two groups.

All analyses were run in 1.6.1. (The Jamovi project, 2020), with the level of significance set at $p < 0.05$.

4.4. Results

4.4.1. Demographics and sleep macrostructure

The descriptive statistics of the sample are shown in Table 4.1.

Table 4.1 Demographics, psychological measures, and sleep parameters of the sample.

	ASD	TD	U_{24}	*p*	ES
Age (years)	23.9±7.2	23.90±2.4	55.5	.141	0.34
Gender (F/M)	1/12	2/11	-	-	-
Polysomnographic parameters					
Time in Bed	443±68.7	463±47.6	72.0	.545	0.15
Total Sleep Time (min)	376±51	409±60.5	50.5	.086	0.40
Sleep Latency (min)	11.8±7.5	17.5±26.3	84.0	.949	0.02
WASO (min)	55.8±49.1	36.4±25.5	66.0	.356	0.22
Sleep Efficiency (%)	85.5±8.6	88.2±8.4	64.0	.311	0.24
N1 (min)	22.3±9.93	24.3±12.2	76.5	.700	0.10
N2 (min)	196.2±44.4	244.0±44.0	32.0	.006	0.62
N3 (min)	72.5±28.1	62.8±20.0	65.0	.305	0.24
REM (min)	84.8±33.4	78.1±20.6	82.0	.918	0.03
N1 (%)	5.84±2.27	6.01±3.25	79.0	.801	0.07
N2 (%)	52.6±11.1	59.4±4.46	52.0	.101	0.39
N3 (%)	19.3±7.3	15.5±4.78	57.0	.169	0.31
REM (%)	22.3±7.1	19.1±3.74	59.0	.204	0.30
REM latency	142.0±78.2	131.0±51.1	82.5	.939	0.02
Switch Index	0.24±0.07	0.26±0.07	75.0	.650	0.11
Sleep Fragmentation Index	0.12±0.04	0.12±0.04	59.0	.840	0.05

Notes. Data are presented as mean±standard deviations. WASO: Wake After Sleep Onset.

There are not any demographic differences between the two groups. Regarding sleep architecture, we observed a reduced amount of time spent in N2 in the ASD group, and a lower total sleep time in this group. Also, even if it did not reach statistical significance, sleep efficiency was lower in the ASD group.

Analyzing the distribution of sleep stage in the two groups we observed an expected Stage main effect, and a Stage × Group interaction ($F_{(3, 72)} = 3.04$, $p = .034$, partial $\eta^2 = .112$, see figure 4.1), with Holm post-hoc showing a reduction in the

proportion of N2 in the ASD compared to TD (p = .047).

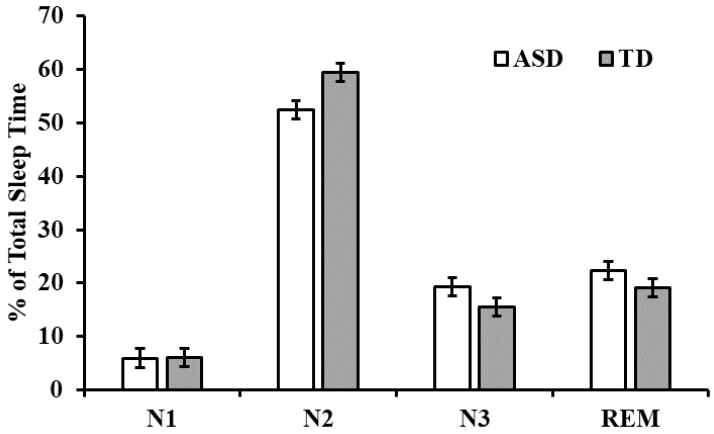

Figure 4.1. Proportion of sleep stages in the two groups.

Power spectral density are also displayed in Figure 4.2 (for N2 stage) and in Figure 4.3 (for N3 stage), considering frontal, central and parietal sites.

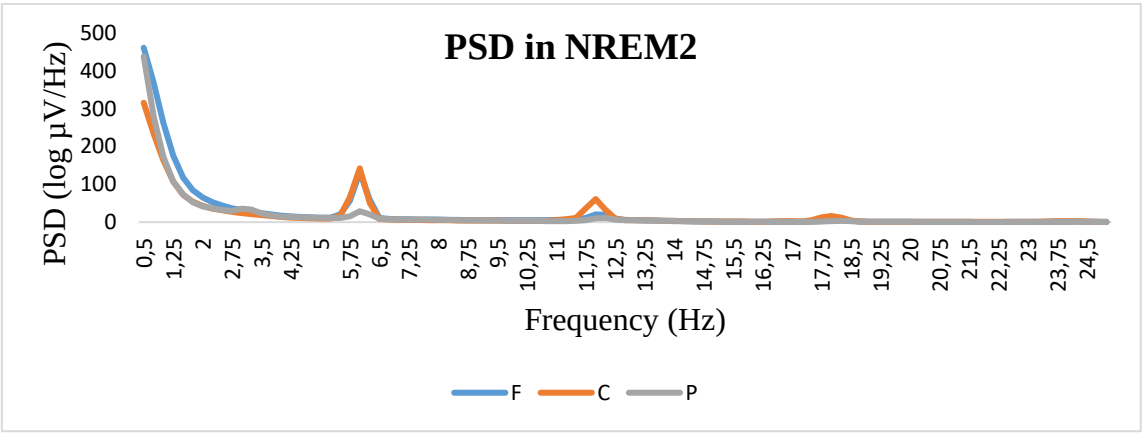

Figure 4.2. Power spectral density across channels in N2.

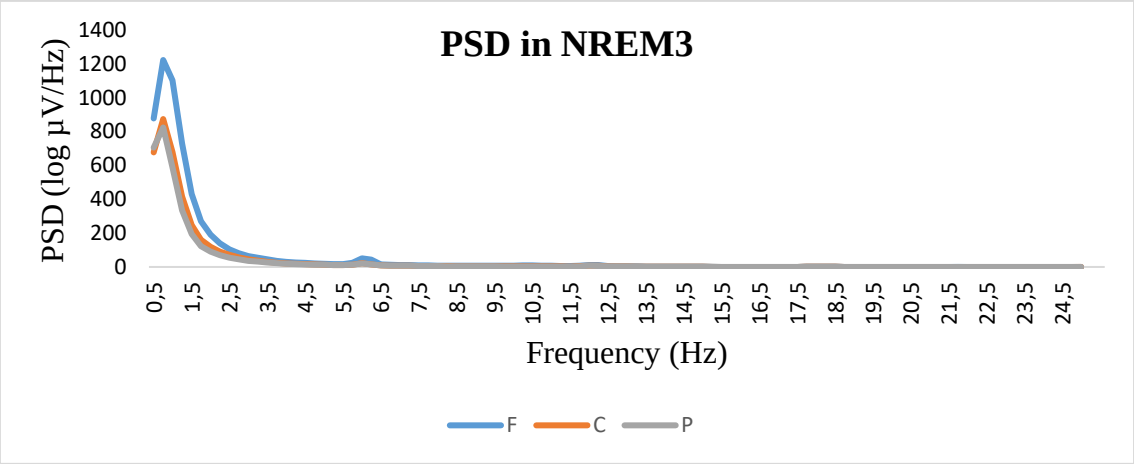

Figure 4.3. Power spectral density across channels in N3.

4.4.2. Spindles activity

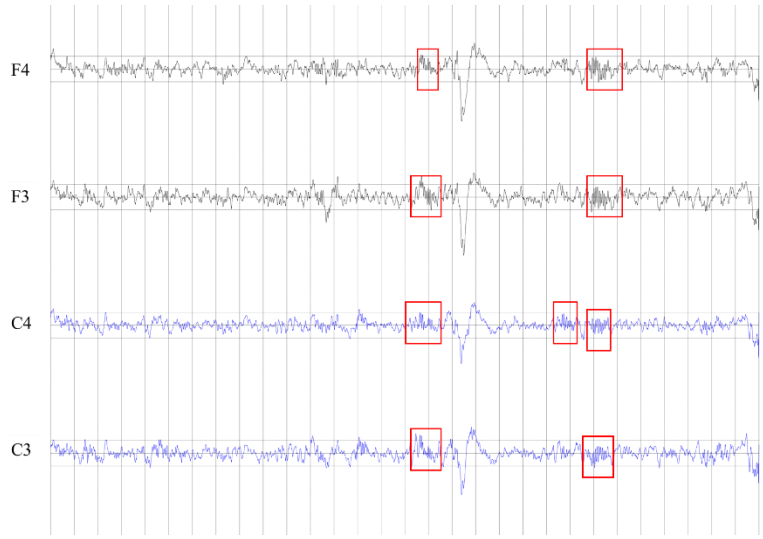

Figure 4.4. Example of sleep spindles waveshapes (in red) in a 10-s epoch

Density

The LMM on spindle density showed a significant Stage effect ($F_{(1, 252.4)} = 164.6$, $p < .001$), with lower density in N3 sleep, a Type × Channel interaction ($F_{(2, 252.4)} = 18.7$, $p < .001$), with a reduction of slow spindles density from frontal channel to central ($p = .036$) and parietal ($p = .002$) channels. On the contrary, fast spindles increase their density

from frontal channel to central (p = .002) and parietal (p < .001) channels. Compared to fast spindles, slow spindles were more predominant in frontal channels (p < .001), but no differences were observed for central (p > .99) and parietal (p = .295) channels. We also observed a Group × Spindles interaction ($F_{(1,\ 252.4)}$ = 6.13, p = .014), with the only significant comparison being a reduced density for fast compared to slow spindles in the TD group (p = .013), and a Group × Type × Stage interaction ($F_{(1,\ 252.4)}$ = 4.52, p = .034), with TD showing a nominal higher density for slow spindles in N2 compared to ASD (p = .204).

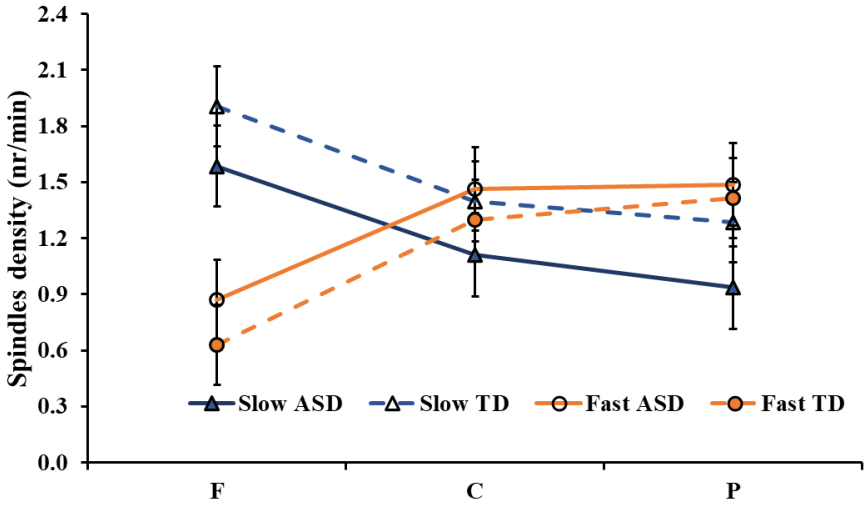

Figure 4.5. Slow and fast spindles density for ASD and TD across the channels.

Duration

The LMM on spindle duration showed a significant Type main effect ($F_{(1,\ 251.9)}$ = 6.6, p = .011), with a longer duration for fast spindles, and a significant Stage main effect ($F_{(1,\ 251.9)}$ = 308.1, p < .001), with a longer duration in N2. We also observed a significant Type × Channel interaction ($F_{(2,\ 251.9)}$ = 6.1, p = .002), with a longer duration for fast spindles compared to slow at the parietal level (p = .010), and a Group × Stage interaction ($F_{(1,\ 251.9)}$ = 6.8, p = .010, Figure 4.6), with a decreased duration in N3 for both group (p's < .001).

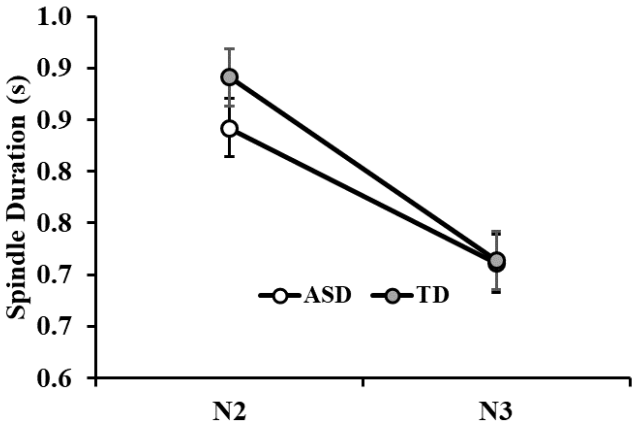

Figure 4.6. Spindles duration of ASD and TD in N2 and N3 sleep.

Amplitude

The LMM on spindles amplitude showed only a significant Channel main effect ($F_{(2, 252.3)} = 57.7$, $p < .001$, Figure 4.7), with a linear decrease in amplitude from frontal (F) to central (C) and parietal (P) channels (all p's <.001).

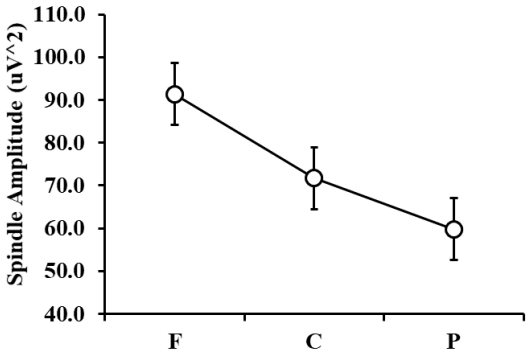

Figure 4.7. Spindles amplitude across the channels.

Intensity

The LMM on spindle intensity showed a significant Stage main effect ($F_{(1, 252)} = 31.5$, $p < .001$), with higher intensity during N2, and a significant Channel main effect ($F_{(2, 252.2)} = 47.5$, $p < .001$), with a linear decrease in intensity from frontal to central and parietal channels (all p's $< .001$). No group differences were observed (all p's $> .311$).

Peak Frequency

The LMM on spindles peak frequency showed a Type main effect ($F_{(1, 252.5)}$ = 2390.2, $p < .001$), a significant Stage main effect ($F_{(1, 252.5)} = 4.9$, $p = .027$), with a higher spindles frequency during N2, and a significant Channel main effect ($F_{(2, 254.9)} = 12.3$, $p < .001$), with a linear increase in peak frequency from frontal to central ($p < .001$) and parietal channels ($p < .001$). We also observed a significant Type × Channel interaction ($F_{(2, 252.5)} = 8.4$, $p < .001$), with a linear increase in slow spindles frequency from frontal to parietal channels (all p's < .001), whereas no channel differences were observed for fast spindles (all p's > 854). The ASD group showed a higher frequency peak than TD, although the comparison did not reach statistical significance ($F_{(1, 23.9)} = 3.1$, $p = .089$). Nevertheless, we observed a significant Group × Type interaction ($F_{(1, 252.5)} = 3.4$, $p < .001$, Figure 4.8), with the ASD showing a higher frequency peak for fast spindles ($p < .001$) compared to the TD group, whereas no significant difference was detected for slow spindles ($p = .061$).

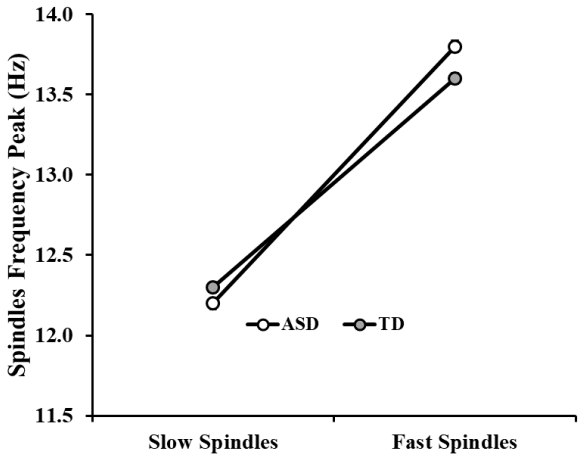

Figure 4.8. Spindles Frequency peak for slow and fast spindles in the two groups.

4.4.3. Spectral Activity

The analysis on SO showed an expected Channel main effect ($F_{(2, 115.1)} = 14.1$, $p < .001$), with a linear spectral decrease from frontal to central ($p < .001$) and parietal ($p < .001$) sites, a main effect of Stage ($F_{(1, 114.3)} = 114.3$, $p < .001$), with higher SO activity in N3 compared to N2. We also observed a Group × Stage interaction ($F_{(1, 114.3)} = 5.9$, $p =$

.016, Figure 4.9), with a nominally higher SO activity of the ASD group on N2 compared to the TD group (p = .129).

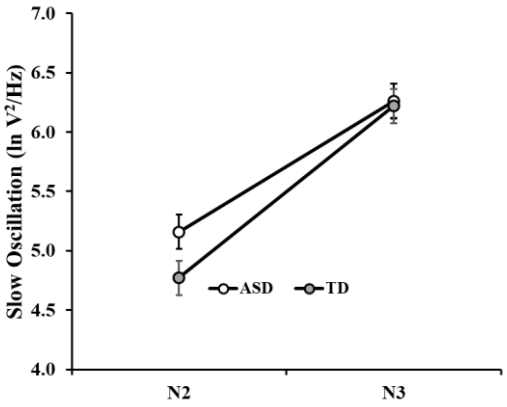

Figure 4.9. Slow Oscillation (0.5-1 Hz) activity in N2 and N3 for the two groups.

Similar results were observed for Delta activity. The analysis showed an expected Channel main effect ($F_{(2,\ 115.6)}$ = 40.7, p < .001), with a linear spectral decrease from frontal to central (p < .001) and parietal (p < .001) sites, a main effect of Stage ($F_{(1,\ 114.9)}$ = 427.1, p < .001), with higher Delta activity in N3 compared to N2. We also observed a Group × Stage interaction ($F_{(1,\ 114.9)}$ = 5.3, p = .023), but the nominal difference observed for SO disappeared (p = .486).

Also, Theta activity showed a Channel main effect ($F_{(2,\ 114.7)}$ = 20.4, p < .001), with a linear spectral decrease from frontal to central (p < .001) and parietal (p < .001) sites, a main effect of Stage ($F_{(1,\ 114.1)}$ = 34.6, p < .001), with higher Theta activity in N3 compared to N2. We also observed a Group × Stage interaction ($F_{(1,\ 114.1)}$ = 5.6, p = .020, Figure 4.10), with a significant increase in Theta activity from N2 to N3 in TD (p < .001) but not in the ASD group (p = .078). We also observed a significant Group × Channel interaction ($F_{(1,\ 114.7)}$ = 5.2, p = .007), with higher Theta activity in frontal channels compared to central and parietal in ASD (all p's < .001) but not in TD (all p's > .072).

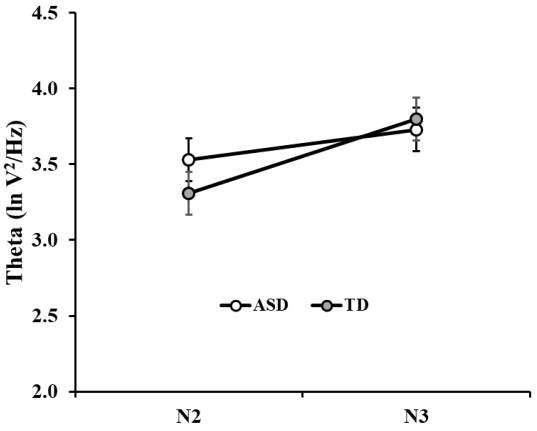

Figure 4.10. Theta (4-8 Hz) activity in N2 and N3 for the two groups.

The analysis on Alpha showed an expected Channel main effect ($F_{(2, 116.1)} = 34.4$, $p < .001$), with a linear spectral decrease from frontal to central and parietal (all p's < .001) sites, and a significant interaction Stage × Channel ($F_{(2, 115.8)} = 6.5$, $p = .002$), with a steeper decrease from frontal to central sites in N3 compared to N2. We also observed a trend for a Group × Stage interaction ($F_{(2, 115.8)} = 6.5$, $p = .051$), but no significant comparison emerged from pos-hoc analysis (all p's > .863).

The analysis on Sigma (11-17 Hz) showed a Channel main effect ($F_{(2, 116.0)} = 22.8$, $p < .001$), with a linear spectral decrease from frontal to central and parietal (all p's < .001) sites, a Stage main effect ($F_{(1, 115.7)} = 97.0$, $p < .001$), with higher Sigma activity in N2 compared to N3. We also observed a significant interaction Group × Channel ($F_{(2, 116.0)} = 7.7$, $p < .001$, Figure 4.11), with a significant decrease from frontal to central and parietal sites (all p's < .001) in the ASD group, whereas no significant differences were observed for the TD group (all p's > .481).

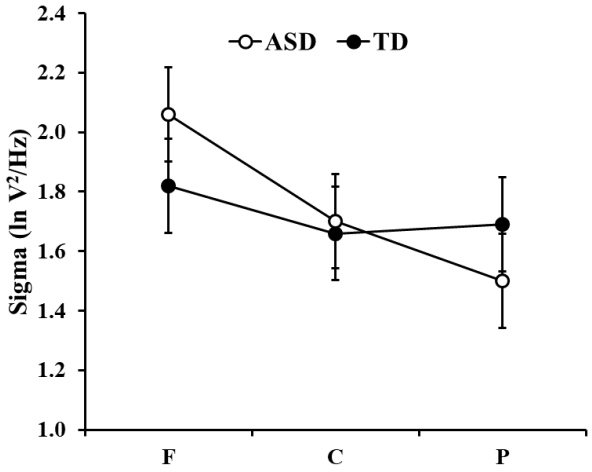

Figure 4.11. Sigma (11-17 Hz) activity across channels for the two groups.

Lastly, the analysis on Low-Beta activity (17-25 Hz) showed a significant Channel main effect ($F_{(2,\ 115.1)} = 14.9$, $p < .001$), with a linear spectral decrease from frontal to central and parietal (all p's < .001) sites, a Stage main effect ($F_{(1,\ 114.5)} = 88.8$, $p < .001$), with higher low beta activity in N2 compared to N3. We also observed a significant interaction Group × Channel ($F_{(2,\ 115.1)} = 4.0$, $p = .022$), with the ASD group showing higher activity in frontal compared to central ($p = .001$) and parietal ($p < .001$) sites, whereas the TD did no show any significant difference (all p's > .999).

4.4.4. Slow waves activity

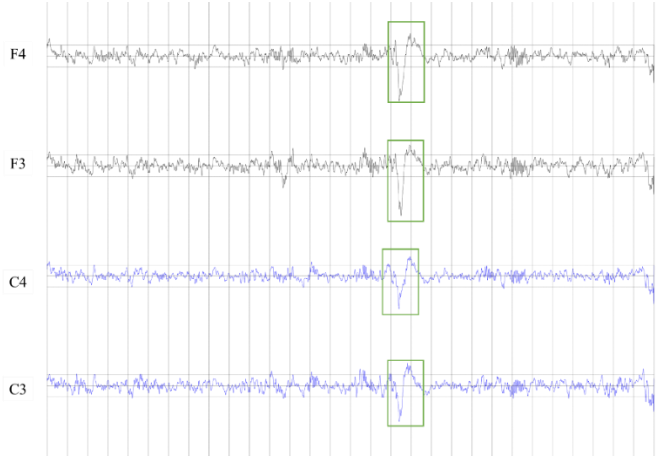

Figure 4.12. Example of slow waves (in green) in a 10-sec epoch

The analysis on SW duration showed only a Stage main effect ($F_{(1, 115)} = 85.0$, $p <$ .001), with a longer duration in N3 compared to N2 spectral. The LMM on amplitude showed a Channel main effect ($F_{(2, 115)} = 5.9$, $p < .001$), with a decrease in amplitude from frontal to parietal sites ($p = .003$), and a significant Group × Channel interaction ($F_{(2, 115)} = 2.3$, $p = .043$, Figure 4.13), with ASD showing a greater amplitude in frontal compared to parietal sites ($p = .001$), whereas this difference was not observed in the TD group ($p > .999$). The ASD group also showed a nominally higher amplitude in the frontal site compared to the TD group ($p = .178$). The Slope showed a significant Stage main effect ($F_{(1, 115)} = 4.7$, $p = .041$), with a faster slope in N2 compared to N3, a significant Channel main effect ($F_{(2, 115)} = 5.8$, $p = .004$), with a linear decrease in slope velocity from frontal to parietal sites ($p = .003$), and a significant Group main effect ($F_{(1, 23)} = 4.7$, $p = .041$), with a faster slope in the ASD compared to the TD group. Although the interaction Group × Channel did not reach the level of significance ($F_{(2, 115)} = 2.8$, $p = .067$), the trend was similar to what was observed for SW amplitude (Figure 4.13).

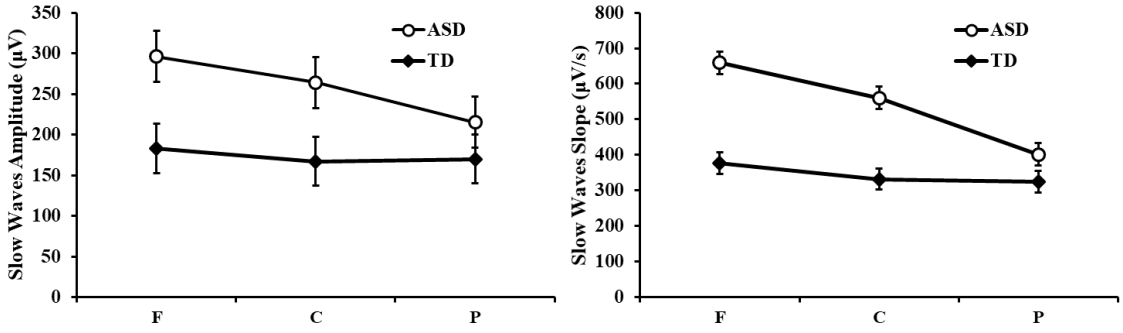

Figure 4.13. Slow waves amplitude (left) and slope (right) across channels for the two groups.

4.4.5. Sleep continuity and stability

Sleep continuity

There was no Group difference in for total awakening frequency (ASD = 2.89±1.4, TD = 3.19±0.90, $U = 66.0$, $p = .362$, ES = 0.22), brief awakening frequency (ASD = 2.12±1.9, TD = 2.65±0.90, $U = 62.0$, $p = .264$, ES = 0.27), and long awakening frequency (ASD = 0.63±0.4, TD = 0.39±0.28, $U = 57.5$, $p = .174$, ES = .32). There was a non-significant difference between awakening duration in ASD (3.62±4.78 min) and in TD

(1.94±2.68 min, $U = 50.0$, $p = .081$), however the medium effect size (ES = 0.41) suggests that awakening time in ASD group was higher than in TD group. Also, the frequency of awakenings in different sleep stages was not significantly different between the groups (all p's > .139).

We also checked the number of transitions in REM from wake, which was not significantly different in the two groups (ASD = 4.00±3.8, TD = 3.92±3.0, $U = 75.0$, $p = .640$, ES = 0.11),

Sleep stability

There was no Group difference in the total frequency of arousals (ASD = 4.11±1.3, TD = 3.99±2.03, $U = 69.0$, $p = .448$, ES = 0.18), state transitions (ASD = 14.6±4.7, TD = 15.7±4.04, $U = 71.5$, $p = .521$, ES = 0.15), and frequency of arousal in different sleep stages (all p's > .336).

4.4.6. Explorative correlation between ADOS score and sleep parameters

Spearman correlation showed only a negative association between ADOS score and spindles peak frequency ($r = -.70$, $p = .026$, Figure 4.14). All the other associations were not significant (all r's < |.448|, all p's > .190).

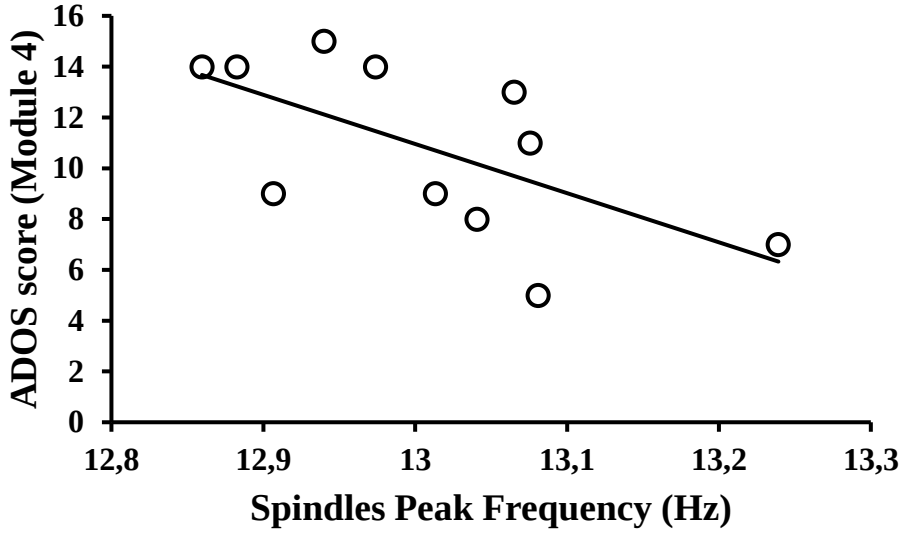

Figure 4.14. Association between ADOS score and spindles peak frequency in the ASD group.

4.5. Discussions

The present study aimed to examine differences in sleep characteristics of young adults with high functioning ASD, a specific population with impairments in social domain and learning, with respect to young adults with typical development. Sleep disturbances are the most prevalent comorbidities of ASD, and they occur in all the life-span. Until now, studies have failed to report a clear sleep pattern in the ASD population. To do that, we implemented a polysomnographic study to investigate both macro-and micro-structures of sleep after a strict selection of participants – because of the typical tendency of ASD adults to assume medications that may alter sleep architecture.

As expected, and in line with previous studies (Godbout et al., 2000; Limoges et al., 2005), the ASD group showed general differences in sleep parameters compared to the TD group. In particular, the ASD group show a reduced proportion of N2 compared to the TD group, but, in contrast with Limoges et al. (2005), our data showed a nominally higher proportion of N3 in ASD. We do not report a higher number of awakenings in ASD individuals (Morgan et al., 2020) on sleep continuity analysis. However, there was a tendency to increased waking durations compared to TD participants.

The quantity of time spent in sleep is reduced in ASD patients, as it is visible from the decrease of total sleep time and the increase of awaking durations. However, they seem to compensate for their lower sleep time, with an increase of deep sleep, reflected by a reduced N2 duration and an increased proportion of N3.

The spectral analysis also supports this assumption, showing topographic differences in spectral power distribution between the two groups. The ASD group showed the usual trend about the power decreasing of Slow Oscillation, Delta, and Alpha activities from frontal to central and parietal derivations (Ferrara & De Gennaro, 2011). However, different from the TD group, Theta, Sigma, and Low-Beta activities have the maximum power in frontal channels.

A decrease of Slow Waves Activity amplitude, from frontal to parietal channels, is also shown in the ASD group but not in the TD group, with a higher frontal amplitude. This finding contrasts with Lehoux and colleagues' (2019) data in children (from 6 to 13 years old) with high-functioning ASD, which show the opposite pattern of topographical differences. However, participants' age is relative to a period during which Slow Wave Activity goes extensive maturational changes (Buchmann et al., 2011).

Concerning the analysis of sleep spindles, participants in the ASD group seem to show an alteration in spindles activity compared to individuals with typical development, particularly on the topography of the slow and fast spindles distributions. Unfortunately, we can not compare this result to other scientific evidence because there is no discrimination between slow and fast sleep spindles. However, studies in ASD adults reported a reducted spindle density on central sites, where fast spindles are usually detected (Limoges et al., 2013, 2005). This altered oscillatory activity may result from the atypical connectivity of thalamocortical circuits already noticed in ASD (Chen et al., 2016), which may also explain their general sleep difficulties reported. From a neural perspective, individuals with ASD also report atypical connectivity of thalamocortical circuits (Chen et al., 2016). According to our results, this may be in line with elaborating a considerable amount of information during sleep, which we can expect based on ASD etiology. However, this assumption needs to be investigated using specific cognitive tasks pre- and post-sleep period.

Another peculiarity of the ASD group is the analysis of the spindle frequency peak. Unlike TD, ASD had a lower frequency peak for slow spindles and a higher peak for the fast spindles, underlying a more significant variation in the spindles frequency range. The higher frontal Slow Wave Activity reported in ASD could cause a reduced slow spindles frequency peak. SWA probably affects slow sleep spindles, mainly located in frontal sites and, consequently, lower frequencies.

Our spindle analysis reveals a possible alteration in the thalamocortical system subserving spindle production, evident as differences in sleep spindle characteristics between ASD and TD participants. However, the spindle production system seems not to be deficient in adults with young functioning autism because the overall spindle density did not significantly differ between the two groups.

Since several reported results showed only nominal differences between the two groups, our findings need to be taken with caution. A reason for the missing statistical significance could be related to the small sample size. Another limitation may be the lack of a behavioral task, as a memory of vigilance tasks, to explain these differences' cognitive manifestation and their link with memory systems. However, it is essential to highlight that the polysomnographic recording has been conducted at participants' home, increasing our study's ecological validity. However, one night of recording is not often

sufficient to completely assess participants' sleep patterns. Participants should adapt to instruments and become more comfortable, to resemble a usual night. Consequently, future studies must record at least two nights of sleep or using a sham instrument for habituation.

Moreover, we computed sleep perceived quality only in the TD group and not in the ASD group. The subjective perception of one own sleep quality could not necessarily co-vary with objective sleep characteristics (Buysse et al., 1991; Werner et al., 2016). Thus it is always preferable to analyze both measurements.

Also, we assessed the eventual presence of psychiatric disorders in the selection phase of TD participants. However, we failed to investigate the presence of comorbidities in the ASD group, which influence sleep characteristics.

Future studies should take multiple directions: first, adding some cognitive tasks in order to understand better the role of sleep parameters linked to memory and learning mechanisms; second, knowing that it is hard to find adult ASD individuals that do not use medication, a larger sample would be more informative; finally, it could be useful to also investigate changes in sleep parameters in populations with several sleep pathologies, which are common in ASD population, but not investigated.

CONCLUSIONS

The present thesis investigated the neural mechanisms underlying socioemotional behavior in typical and atypical (i.e., ASD) populations.

The first narrative review (Chapter 1) highlighted the importance of investigating small subcortical structures such as the hypothalamus in their anatomical and functional characteristics for a deeper understanding of socioemotional behavior in populations with socioemotional impairments, such as ASD. In particular, the recent progress in the ultra-high-field of neuroimaging allows to focus on these small structures, often neglected because of their small size, position in the forebrain, and the structures and bones in the nearby area. For this reason, it needs to have a particular sequence to use during the signal acquisition, or it needs to be investigated by powerful machines such as 7 or 9.4 Tesla.

Subsequently, the second systematic review aimed to investigate how classical conditioning can be a tool to understand the acquisition of emotional valence in social stimuli. In particular, it has been found that few studies addressed the focus on social and positive-valence stimuli, preferring physical and negative-valence ones. This gap in the literature was highlighted, and then the EEG study in Chapter 3 tried to fill it.

The EEG study was based on creating a new ad hoc classical conditioning paradigm, creating videos and pictures with professional actors and actresses to make the task as ecological as possible. EEG allows the investigation of the temporal dynamics of the processes because of its high-temporal resolution technique. While it is beneficial for an event-related potential analysis, it is less informative about the spatial resolution. In order to do that, a future investigation by the fMRI signal is suggested. The use of fMRI allows investigating the involvement of subcortical structures, such as the hypothalamus, in response to our classical conditioning paradigm.

Finally, the last chapter aimed to investigate sleep characteristics in the ASD population. This study highlighted the characteristics of sleep macro- and micro-structures in ASD and a specific analysis of the thalamic sleep spindles (Chapter 4). Although this is one of the few studies investigating sleep characteristics in young adults with ASD (because of the complicated recruiting process), it is essential to note that the

ASD defects in neuronal patterning are presumably more visible in studies in which the brain is engaged in active, demanding task.

In conclusion, the present Ph.D. thesis aimed to raise and address some of the recent gaps currently present in literature dealing with socio-emotional behavior and its underlying neural mechanisms. Much effort should still be made, but this four-study thesis may contribute to the literature in this way.

APPENDICES

APPENDIX A

Oxytocin is a neuropeptide produced and secreted from the paraventricular nucleus and the supraoptic nucleus of the hypothalamus. In humans, intranasal oxytocin administration's effects are related to facilitation in positive social approach and interaction, both in the typical and atypical population (Heinrichs et al., 2008; 2009; Harari-Dahan, O. & Bernstein, 2014; Quintana, 2015). Furthermore, it seems that oxytocin-receptor genes are mainly involved in modulating neural and physiological pathways contributing to social behavior and the etiology of ASD (Cataldo et al., 2018; Carìa et al., 2020).

Oxytocin regulates activation in specific brain areas that involved limbic and paralimbic structures, such as the amygdala, medial prefrontal cortex, and insula in individuals with ASD (Yamasue, 2016). On the other hand, numerous studies evidence a significant influence of single or multiple intranasal exogenous oxytocin doses and their effects on socioemotional behavior (see Table A1 and A2).

From these studies, data are consistent about an enhancing performance in behavioral tasks assessing social abilities after one single dose of intranasal oxytocin, particularly in the ASD population but also in typical (see Table A1). Despite this, the effects of long-term oxytocin administration are not so clear (see Table A2).

Short-term effects of intranasal oxytocin in ASD

In humans, intranasal oxytocin administration's effects are related to facilitation in positive social approach and interaction (Heinrichs et al., 2008; 2009; Harari-Dahan, O & Bernstein, 2014; Quintana, 2015). Even if data are consistent to indicate a positive effect of one single dose of oxytocin on the behavioral tasks that measure social abilities (see Table A1), the effect of long-term oxytocin administration is less clear (see Table A2).

In the last decade, the interest in the effect of a single dose of intranasal oxytocin in social behavior has been grown. Initially, it was used as an intravenous administration (Hollander et al., 2003; 2007) to facilitate the introduction of the oxytocin directly to the

blood flow. In these early studies, the improvement of social cognition in ASD participants was already evident, and the reduction of repetitive behavior.

The subsequent single doses studies preferred the less invasive intranasal formulation. Neuroimaging studies observed an enhancement in the activation of the early visual areas in response to social stimuli (faces) despite non-social ones (Andari et al., 2016). Also, modulation of the amygdala and the hippocampal activation was reported in a social context. At a cortical level, the mid-orbitofrontal cortex activity was enhanced in response to a fair partner and insula in response to an unfair partner (Domes et al., 2013; Andari et al., 2016). The medial prefrontal cortex's involvement in social contexts has also been reported by Watanabe and colleagues (2014), and its activation was stable even after a 6-weeks oxytocin administration (Watanabe et al., 2015).

Furthermore, in a specific task for the recognition of the emotions (the Reading the Mind in The Eyes), Gordon and colleagues (2013) highlighted an increased activity in the striatum, the middle frontal gyrus, the medial prefrontal cortex, the right orbitofrontal cortex, and the left supramarginal gyrus. Despite the non-social judgment, in social judgment, the striatum's activity, *nucleus accumbens*, superior temporal sulcus, and premotor areas seem enhanced by a single dose of intranasal oxytocin (Gordon et al., 2013).

Another social task used to assess the effect of intranasal oxytocin on enhancing social ability is the social ball-tossing game (Aoki et al., 2014). The social ball-tossing game is used as a first-order false belief task to challenge the ability to infer the emotional states without explicit emotional cues like facial expression (Aoki et al., 2014). In a within-subject design, ASD participants who received a single dose of intranasal oxytocin reported an improved socio-emotional inference performance and showed diminished right insula activity.

Andari et al. (2016) used the same task, but they also created a specific Face Matching Task where the participant should match a target face or a target geometric shape presented on the top of the screen with one of the two stimuli on the bottom of the screen. Some of the faces were already shown in the social ball-tossing game previously done. Performing this task during the fMRI measurement, the authors observed that participants treated with intranasal oxytocin showed increased activity in visual areas to

social compared to non-social stimuli.

In the Facial emotion recognition task reported by Domes and colleagues (2014), participants watched photographs of four different individuals displaying six basic facial emotions (Ekman & Friesen, 1976). An emotional, verbal label, half-correct, and half-incorrect, followed facial stimuli. Participants were asked to indicate whether the label was correct or incorrect by pressing a button. During this task, the activity in the right amygdala in response to social stimuli was increased. This task was also used by Di Simplicio and colleagues (2009), which showed slower reaction times to identify fearful faces correctly and reduced misclassification of positive emotions after a single dose of intranasal oxytocin. This effect on the amygdala's activity was consistent with Domes and colleagues (2013).

A study with eye-tracker used a Face Perception task (Andari et al., 2010), defining five regions of interest on the face: the two eyes, nose, mouth region, forehead, and the two cheeks. For each picture, gaze fixation time was computed for each region of interest. This task, performed with the social-ball tossing game, shows an increased gazing time at eyes, linked with enhanced trust in a partner in the social-ball tossing game.

Reading the Mind in the Eyes Test is a task used to infer the mental state from facial sections depicting the eye region (Guastella et al., 2010; Tauber et al., 2011; Gordon et al., 2013). Participants should either label a mental state from pictures of social objects or label the category of non-social objects. It seems that a single dose of intranasal oxytocin increases the performance in this task (Guastella et al., 2010) or increases the activity in some brain areas during social judgment (Gordon et al., 2013).

In the Friends of Foe task, participants watched short movies with actors speak an emotional word (verbal information) with an emotional facial expression and expressive voice prosody (nonverbal information). There were two types of emotionally congruent movies with negative or positive nonverbal and verbal information and two incongruent movies. Participants are instructed to make a "friend or foe" judgment of the actor in each movie. According to the type of information with the most substantial effects on the judgments, the incongruent stimuli' responses were classified into nonverbal information-based judgments and verbal-information based judgments. A single intranasal oxytocin dose seems to improve the nonverbal information-based judgment, increasing the activity

in the ventromedial prefrontal cortex (Watanabe et al., 2014). The same effect is performed with a 6-week intranasal oxytocin treatment (Watanabe et al., 2015).

The study of Lin and colleagues (2014) used a task to detect the selective response to human and non-human affective sounds after a single dose of intranasal oxytocin, monitoring the skin conductance responses and the change in the peripheral blood vessel constriction as an indicator of sympathetic responses. The skin conductance was increased in both neurotypical and ASD groups in response to human sounds. Only one study does not show any effect of the intranasal oxytocin on social skills (Althaus et al., 2015). This is the only study that used evoked brain potentials, comparing the effect of a single dose of intranasal oxytocin to placebo on the brain reactivity to complex social scenes of varying valence. However, it seems that oxytocin enhanced orientation toward affective, social stimuli in a subgroup of participants who reported high distress levels in a tense social situation.

Overall, results suggest that a single dose of intranasal oxytocin increases social cognitive functions such as emotion recognition, social affiliation, and social attention, typically impaired in ASD. However, the possibility to predict the therapeutic potential of one single dose of intranasal oxytocin is minimal.

Long-term effects of intranasal oxytocin in ASD

On the other side, studies about the long-term effect of intranasal oxytocin in ASD are just a few, and results are not clear. Some of the studies of the long-term effect of oxytocin use psychological tasks for social abilities (Anagnostou et al., 2012; Dadds et al., 2014; Guastella et al., 2015; Watanabe et al., 2015; Gordon et al., 2016) or questionnaires (Tachibana et al., 2013; Yatawara et al., 2016; Munesue et al., 2016; Hirosawa et al., 2017; Parker et al., 2017).

As expected, oxytocin seems to be implicated in a preference for social versus non-social stimuli. Gordon and colleagues (2016) have shown better performance in the Biological Motion task to test biological motion. In the Affective Voices task, participants listened, eyes shut, to alternating blocks of angry and happy non-word vocalizations. In addition, Watanabe and colleagues (2015) have investigated the effect of long-term oxytocin on the social judgment by the Friend/Foe judgment task. The results indicated

that the 6-weeks of intranasal oxytocin significantly reduced autism core symptoms specific to social reciprocity (Watanabe et al., 2015). In particular, this research group has already tested the effect of a single dose of oxytocin before, and they could confirm that the current continual administration significantly mitigated behavioral and neural responses during the task. Furthermore, despite its more extended administration, these effect sizes were no larger than seen in the previous single-dose intervention (Watanabe et al., 2014).

Despite these positive results, the number of studies with inconsistent results is significant (Anagnostou et al., 2012; Dadds et al., 2014; Guastella et al., 2015). These results are also critical in evaluating the compound's long-term therapeutic potential (Macdonald & Feifel, 2013).

Table A.1. Studies that used behavioural tasks to test the effects of a single dose of IN-OT.

Paper	Sample(F); Mean Age(SD)	IQ	Behavioural Task	Effects of a single dose of IN-OT
Kanat et al., 2017	29 ASD (0); 38.2 (10.6) 30 TD (0); 32.1 (12.3)	Wortschatztest: ASD 34.3 (5.0); TD 34.2 (3.0)	Dot-probe task	Enhanced attention to social compared to non-social stimuli.
Andari et al., 2016	20 ASD (0); 26.37 (8.45)	93.54 (17.07)	Social ball-tossing game; Face Matching task	Enhanced brain activity in visual areas to social compared to non-social stimuli.
Aoki et al., 2015	40 ASD (0); >20	>80	Friend/Foe Judgment task	Changes in medial prefrontal NAA levels correlated with OT-induced changes in medial prefrontal activity
Althaus et al., 2015	32 ASD (0); 22.69 (4.83) 30 TD (0); 22.60 (3.21)	ASD: 104.97(17.49); TD: 104.38(10.25)	IAPS task	No overall effect of OT administration
Aoki et al., 2014	EXP I: 17 ASD (0); 29.6 (8.0) 14 TD (0); 30.4 (5.6) EXP II: 20 ASD (0); 30.8 (6)	EXP 1: ASD 106.7 (12.0); TD 108.7 (7.6). EXP 2: 108.5 (10.1)	Sally-Ann task modified	Enhanced in accuracy in understanding others' social emotions
Lin et al., 2014	16 ASD (0); 32.56 13 TD (0); 34.69	ASD: 108.83 (11.68); TD: 110.87 (10.21)	Listen passively to human and non-human affective sounds	Increased skin conductance to human sounds in both TD and ASD groups
Watanabe et al., 2014	33 ASD (0); 28.5 (5.9)	106.4 (11.2)	Friend/Foe judgment task	Improvement in nonverbal information-based judgment
Domes et al., 2013	14 ASD (0); 24.0 (6.9) 14 TD (0); 24.3 (5.4)	ASD: 122.4 (24.1); TD: 125.6 (15.4)	Face Discrimination task	Increased activity in the right amygdala in response to social stimuli

Gordon et al., 2013	17 ASD (0); 13.2 (2.7)	Not specified	RMET	Increased activity in some brain areas and in salivary OT concentration during non-social judgment
Tauber et al., 2011	24 ASD (0); 28.5 (18.7-43.6)	51	RMET; Sally-Ann task	Increased trust in others and decreased sadness tendencies with less disruptive behaviours.
Andari et al., 2010	13 ASD (0); 26 (17-39)	92 ± 17.47	Social-ball tossing game; Face perception task	Enhanced feelings of trust in partner; increased gazing time at eyes.
Domes et al., 2010	17 TD (17); 24.2 (2.5)	Not specified	Photographs of individuals with basic facial emotions and neutral facial expression	Enhanced BOLD signals in left amygdala, fusiform gyrus and superior temporal gyrus in response to fearful faces and in the inferior frontal gyrus in response to angry and happy faces
Guastella et al., 2010	16 ASD (0); 14.88 (2.42)	Not specified	RMET	Improvement in task's performance
Di Simplicio et al., 2009	29 TD (0); 22.46 (2.72)	OT: 118.96 (2.89); PLC: 117.42 (2.81)	Face expression recognition task; Cambridge Face Memory task; Emotional Categorization and Memory; Attentional Visual Probe task	Slowed RT to correctly identify fearful faces and reduced misclassification of positive emotions
Domes et al., 2007	13 ASD (0); 25.7 (2.9)	Not specified	Implicit Facial Affect Recognition Task	Reduction of the right amygdala in response to emotional faces

Legend: ASD: Autism Spectrum Disorder; TD: Typical Development; BOLD: Blood Oxygen Level-Dependent; RT: Reaction Times; RMET: Reading the Mind in the Eyes Task; OT: Oxytocin; PLC: Placebo;

Table A.2. Studies that used behavioural tasks to test the effects of multiple doses of IN-OT.

Authors	Sample (Mean Age (SD))	IQ	Behavioural task	Treatment duration	Effect of multiple doses of IN-OT
Kosaka et al., 2012	1 ASD (1); 16	Not specified	Social-ball tossing game	Improvement in social functioning and global improvement	Improvement in social functioning and global improvement
Gordon et al., 2016	20 ASD (3); 13.16 (2.79)	109.80 (18.24)	Biological Motion task; Affective Voices task	2 times (second to 3-78 days of distance since first)	Enhanced brain activity in reward and socioemotional processing systems for social stimuli versus non-social stimuli.
Guastella et al., 2015	50 ASD (0); 13,93 (1.79)	OT: 80.04 (19.18); PLC: 93.14 (21.11)	RMET; DANVA	8 weeks	No significant effect
Watanabe et al., 2015	18 ASD (0); 32.2 (6.75)	OT first: 109.3 (9.1); PLC first: 101.8 (12.6)	Friend/Foe judgment task	6 weeks	Improvement in nonverbal information-based judgment
Dadds et al., 2014	38 ASD (0); 11.27 (2.6)	OT: 90.47 (11.70); PLC: 88.64 (7.98)	Parent-Child interaction training; Facial emotion task	7 months	No significant effect
Anagnostou et al., 2012	19 ASD; 33.20 (13.29)	107 (24)	RMET; DANVA	6 weeks	No significant effect

Legend: ASD: Autism Spectrum Disorders; RMET: Reading the Mind in the Eyes Task; DANVA: Diagnostic Analysis of Non-Verbal Accuracy; OT: Oxytocin; PLC: Placebo.

APPENDIX B

Table B1. ANOVA resuts of gender differences for independent variables

Indipendent variable	*F*	*df*	*p*
val1	0,1070	1, 16	0,7480
val2	0,0160	1, 19	0,9000
val3	0,1560	1, 16	0,6980
val4	0,5520	1, 18	0,4670
arou1	0,2820	1, 16	0,6030
arou2	0,0430	1, 19	0,8380
arou3	1,2700	1, 16	0,2760
arou4	0,0460	1, 18	0,8330
attr1	3,6470	1, 16	0,0743
attr2	0,6210	1, 19	0,4400
attr3	0,8870	1, 16	0,3600
attr4	4,3430	1, 18	0,0517

Note. The above analyses refer to US relative to specific actors

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LIST OF SCIENTIFIC CONTRIBUTIONS

Peer reviewed international journals

Caria, A., **Ciringione, L**., & Falco, S. D. (2020). Morphofunctional Alterations of the Hypothalamus and Social Behavior in Autism Spectrum Disorders. *Brain Sciences*, *10*(7), 435.

Poster presentations

Ciringione, L., Carìa, A. (2020, July 1-4). *The acquisition of social preference: an ERPs study on classical conditioning to positive social stimuli*. 5th International Conference of European Society for Cognitive and Affective Neuroscience, Budapest, Hungary. Conference postponed because of COVID-19.

Ciringione, L., Carìa, A. (2020, January 26-31). *Pavlovian positive conditioning of social stimuli: an ERPs study*. European Workshop of Cognitive Neuropsychology, Brixen, Italy.

Carìa, A., **Ciringione, L**. (2019, June 09-13). *Midbrain involvement in anterior insula-mediated emotion regulation.* Organization for Human Brain Mapping Conference 2019, Rome, Italy, 09-13/06/2019.

Ciringione, L., Cellini, N., Mazzoni, M., Zinke, K., De Falco, S., Venuti, P., Born, J., Caria, A. (2019, June 09-13). *Sleep spindles characteristics in adults with Autism Spectrum Disorder and Typical Development*. Organization for Human Brain Mapping Conference 2019, Rome, Italy, 09-13/06/2019.

Oral presentations

Ciringione, L.. (2020, January 26-31). *Pavlovian positive conditioning of social stimuli: an ERPs study*. European Workshop of Cognitive Neuropsychology, Brixen, Italy.

Ciringione, L. (2019, September 18-20*). Neural correlates of affiliative conditioning: an EEG study* [Correlati neurali del condizionamento affiliativo: uno studio EEG]. XVI Congresso dell'Associazione Italiana di Psicologia - sezione Sperimentale, Milano.