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HOW DO HUMANS RESPOND TO SOCIAL AND NON-SOCIAL STIMULI? EVIDENCE FROM NEUROTYPICAL INDIVIDUALS AND INDIVIDUALS WITH AUTISM SPECTRUM DISORDER

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General Introduction

According to the Greek philosopher Aristotle “Man is by nature a social animal”. After 2350 years, we know that this statement is partially true. Although experimental evidence has reported a preference for social stimuli and social interactions in human beings (Farroni et al., 2002; Haxby et al., 2002; Vuilleumier, 2005; Krach et al., 2010; Chevallier et al., 2012;), this conclusion does not apply to every individuals and contexts.

From a psychological and neuroscience literature point of view, the concept of sociality is really complex to define. For this purpose, two approaches have been resulted very effective in capturing the multifaceted nature of this construct. According to the social motivation theory (Chevallier et al., 2012), sociality is the psychological and biological expression of a human predisposition to interact with other conspecifics (i.e., social motivation). Specifically, social motivation emerges by biasing the individual to readily orient attention to social stimuli (i.e., social orienting), to seek value and pleasure in social interactions (i.e., social reward), and to use strategies to maintain social relationships throughout the time (i.e., social maintaining). Biologically, these predispositions rely on biological mechanisms involving the activation of brain areas, such as the amygdala, the orbitofrontal cortex and the striatum, and specific classes of neuropeptides (see Chevallier et al., 2012). Likewise, sociality relies also on cognitive functions that are at the basis of social interaction. This is the theoretical foundation of social cognition, an interdisciplinary field focusing on the role of cognitive processes in modulating social behaviours (Frith & Frith, 2012). Understanding other thoughts, intentions or beliefs represent indeed a fundamental prerequisite for effectively interacting with others. Despite their differences, both these two approaches can be adopted interchangeably to define the complexity of the concepts of sociality and social behaviour. Furthermore, they have contributed to understanding the mechanisms underlying atypical social behaviours as observed in some clinical conditions.

Among the clinical conditions characterized by atypicality in social behaviours and social cognition (e.g., schizophrenia, personality disorders etc.), Autism Spectrum Disorder (ASD) is the most prototypical example. ASD constitutes a multi-faceted and pervasive neurodevelopmental syndrome characterized by both social and non-social difficulties. Social difficulties include problems with social and emotional reciprocity, social skills, verbal and non-verbal communication (APA, 2013). Several theories have tried to understand the nature of the social difficulties observed in ASD. According to the mind-blindness theory, they depend on the inability to attribute mental states to themselves and other individuals (Baron-Cohen, 1997). Contrarily, the social motivation theory of autism stressed the idea that social motivation deficits are at the basis of social problems in ASD (Chevallier et al., 2012). These problems concern the three dimensions determining the typical predisposition to interact with others (i.e., social reward, social maintaining and social orienting).

The preference for the "social world" was demonstrated to emerge at early steps of cognitive processing. In particular, attentional studies demonstrated that stimuli with a social valence are prioritized and capture more attention than non-social stimuli since the first stages of human development (Farroni et al., 2002; Vernetti et al., 2018). For instance, replicated evidence showed an increased sensitivity to human gaze signals in human beings (Driver et al., 1999; Frischen et al., 2007; Ricciardelli et al., 2013). Conversely, several studies have shown that ASD individuals do not exhibit the same level of attentional capture for these stimuli as typically developed (TD) individuals, by instead exhibiting a preference for non-social objects (Sasson et al., 2008; Guillon et al., 2014; Sasson & Touchstone, 2014; Crawford et al., 2016; Gale et al., 2019; Mo et al., 2019;). According to corollary evidence of the social motivation theory, this effect might be explained, respectively, by a decreased value of social stimuli and increased value of non-social stimuli (Watson et al., 2015; Bottini, 2018;). In addition, the

Empathizing-Systemizing theory provides a complementary explanation of the reasons underlying this pattern (Baron-Cohen, 2009; Greenberg et al., 2018). According to this theory, the reduced interest to social stimuli in ASD would be the expression of the difficulty to attune with others, whereas restricted interests or behaviours for certain objects (e.g., mechanical or electronic objects) or activities would be explained by an increased tendency to systemize information (i.e., ability to infer repetitive patterns and variables in a system by deriving the underlying rules). This theory can be also extended to TD individuals, since it claims that the 'empathizing-systemizing' continuum might be the expression of an 'extreme female brain' and an 'extreme male brain' continuum, where females would be physiologically and cognitively more prone to social interaction and empathy and, conversely, males more prone to systemize (Baron-Cohen, 2009). In this sense, ASD would represent an exaggeration of the gender differences observed in the TD population (i.e., Extreme Male Brain theory; Baron-Cohen, 2002).

In general, this reduced orienting to social stimuli is likely to be one of the reasons precluding social interaction and the access to other mental states and emotions in ASD individuals. Indeed, early attention to relevant stimuli (social stimuli) was described as the first step of stimulus cognitive and physiological processing leading to emotional and social responses (see Scherer, 2009). Apart from the clinical relevance of these studies, this evidence may contribute to opening new questions on the relevance of social stimuli. While these studies have concluded a preference for social stimuli in TD respect to ASD individuals, they did not investigate if this attentional priority, observed in TD individuals, also emerges when social stimuli compete with non-social stimuli with a significant incentive value (e.g., monetary stimuli). In fact, most of these studies presented non-social stimuli that are intrinsically neutral for TD individuals. In other words, to the best of our knowledge, no previous evidence has investigated the saliency of social stimuli by comparing them with highly salient non-social stimuli.

Another issue of previous research concerns the poor evidence on the role of the physiological and visceral systems in the processing of social vs non-social stimuli. After the discovery of the mirror neurons system (Gallese et al., 1996) and the somatic marker hypothesis (Damasio et al., 1991; Damasio, 2008), the classic Cartesian dualism was officially overcome by fostering a new approach looking at an interdependent integration of cognitive and physiological functions. Both empirical evidence (Oosterwijk, 2012; Barrett, 2017; Azzalini, 2019; Fridman et al., 2019;) and computational models (Scherer, 2009) stressed the importance of considering physiological processes as an active part of stimulus processing and response, since the physiological system is strongly and bidirectionally interconnected with higher cognitive systems.

Aims of the dissertation

In light of the considerations expressed afore ahead, the main aims of the present dissertation can be summarized as follows:

i. Investigating whether social stimuli are prioritized even when they attentively compete with other relevant non-social stimuli. The aim of Chapter 1 is to understand the saliency that TD individuals attribute to social stimuli, by exploring whether monetary incentives (i.e., strong motivational drive in the Western society) can modulate social attention (i.e., attentional orienting induced by another agent's gaze direction). To this purpose, a behavioural experiment was designed. The experiment consisted of a gaze cueing task performed before and after an implicit learning task in which participants could win a monetary reward or not.

ii. Investigating whether and how individuals with ASD differently respond to social vs non-social stimuli compared to TD individuals. In Chapter 2, a systematic review of the literature has been conducted to understand the state-of-the-art of research comparing attention to social vs non-social stimuli in ASD and TD individuals. Due to the modest number of research investigating the physiological correlates of social vs non-social stimuli processing, Chapter 3 is addressed to compare ASD and TD individuals' physiological responses to pain observed in other humans (social agent) and robots (non-social agent). In detail, Skin Conductance Responses were measured by referring to two different processes: pain anticipation (i.e., anticipating the consequences of a painful stimulation on another agent) and pain perception (i.e., responding to an actual painful stimulation on another agent). A traditional statistical approach was combined to a more advanced Machine Learning approach to deal with the complexity of the issue.

iii. Investigating whether the differences between TD and ASD individuals in social vs non-social stimuli processing are the expression of a familiar phenotype. Accordingly, Chapter 4 investigated whether the different attentional patterns, documented in Chapter 2 systematic review, are also observed in the parents of these two populations. A Dot-Probe behavioral task was designed to answer this research question.

iv. Investigating whether it is possible to modify the salience of social stimuli in ASD individuals through an Attention Bias Modification Treatment (ABMT) methodology. Chapter 5 is also targeted at understanding the degree of which attention to social stimuli is permeable to external modifications. A dedicated implicit learning and reward-based AMBT has been structured and administered to a sample of ASD children. The study has been conducted on children participants due to the evidence reporting a high brain plasticity during childhood (Kolb & Gibb, 2011).

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CHAPTER 1

Eyes or money? Investigating the relevance of social and monetary stimuli in a sample of typically developed individuals

Introduction

The relevance of human gaze

Social signals have a strong valence for human beings since they provide crucial information about others' mental states (Baron-Cohen et al., 2001) and adaptive information such as communicating the presence of a possible threat (Byrne and Whiten, 1991). Previous literature has particularly focused on the role played by gaze direction in modulating attentional orienting (e.g., Ricciardelli et al., 2002; 2013; Frishen et al., 2007). Specifically, the relevance of gaze emerges as the tendency of human beings to attend the same stimulus that another individual is attending to (i.e., joint attention; Bruner, 1983). This automatic capacity was demonstrated to emerge from two months of age and to be a precursor of higher level social cognitive skills such as theory of mind (Baron-Cohen, 1994). Joint attention has been also observed in controlled experimental contexts by employing a modification of the traditional Posner's cueing paradigm (Posner & Cohen, 1984), namely the so-called the gaze cueing paradigm (Friesen and Kingstone, 1998; Driver et al., 1999; Ricciardelli et al., 2002).

The gaze cueing paradigm requires participants to detect a target appearing to the left or right of a centrally presented face. Instead of arrow cues, the eyes of face act as a cue that can be oriented to the same location (congruent condition) or to the opposite location with respect to the target's side (incongruent condition). An extendedly replicated effect showed that participants are faster in congruent trials than in incongruent trials, and that this facilitation emerges with early SOA (i.e., Stimulus Onset Asynchrony) (< 300 ms) and tends to disappear with SOAs larger than 1000 ms (Friesen & Kingstone, 1998; Frishen et al., 2007; Hamilton, 2016; Ulloa et al., 2018), although the SOA effect was found to vary as a function of intercultural differences (Takao et al., 2018). This effect is better recognized as the Gaze Cueing Effect (GCE; Frishen et al., 2007 for a review).

It is still a matter of debate whether the GCE is automatic or voluntary. In principle, first studies approaching this issue considered the GCE very similar to the spatial cueing induced by exogenous cues (Friesen & Kingstone, 1998; Driver et al., 1999; Friesen et al., 2004), namely salient stimuli appearing in the periphery and automatically capturing participant attention towards the cued location, although it was task-irrelevant (Posner & Cohen, 1984). On the other hand, other evidence has stressed that the GCE can be modulated by voluntary processes as in the case of contextual cues, or expectations about other's actions (Bayliss et al., 2010; Wykowska et al., 2014; Perez-Osorio et al., 2017; Hayward & Ristic, 2018; Dalmaso et al., 2020 for a recent review).

The relevance of monetary reward

Beyond social stimuli, there are other classes of stimuli which can be strongly salient for human beings. These non-social stimuli do not have particular biological or evolutionary properties, but their relevance is mainly determined by shared social representations (Moscovici, 2000). A prototypical example is money, that has acquired a particular symbolic meaning in the current capitalistic society. Several studies analyzed the impact of monetary reward on human cognitive system. In particular, attentional studies demonstrated a modulatory effect of monetary reward on selective visual attention (Chelazzi et al., 2013).

Evidence from behavioral studies showed that monetary reward significantly improves target detection in spatial attentional tasks by acting as an incentive to the participants' performance (Engelmann et al., 2009; Pessoa and Engelmann, 2010). Interestingly, the modulatory motivation effect, determined by the monetary reward, was found to enhance the validity effect (i.e., faster responses in congruent trials) and to reduce reaction times in incongruent trials (Engelmann et al., 2009). This evidence suggests that the rewarding stimuli may impair cue processing or, alternatively, facilitate the disengagement from an incongruent cue location (Engelmann et al., 2009). In addition, Bourgeois et al. (2017) suggested that highly rewarding stimuli may mitigate the facilitation typically induced by visual cues in visual search tasks.

On the basis of the *Law of the Effect* (Thorndicke, 1911), other studies showed how implicit learning processes, based on reinforcement, affect the motivational valence of a stimulus. The motivational cue determines indeed the deployment of attentional resources on features or locations associated with satisfying outcomes (Chelazzi et al., 2013). For instance, Anderson et al. (2014) found that target features (i.e., color) carrying information about subsequent reward, predicted more attentional capture than features not associated to any reward (Anderson et al., 2014). These motivational effects have been described in light of two different mechanisms. The first mechanism refers to a process by which monetary reward acts as a feedback on participant performance by increasing the individual level of cognitive monitoring on the task (O'Doherty, 2004; Schultz, 2006). The second mechanism refers to conditions in which the reward is randomly associated to particular stimuli throughout the task, by inducing an implicit association between the stimulus and the associated reward (Chelazzi et al., 2013). In line with other studies, this latter mechanism can be interpreted as the result of a classic conditioning (Pavlov, 1927), in which the association stimulus-reward is created without the participant being aware of this contingence (Buchel et al., 1998; Pessiglione et al., 2008; Seitz et al., 2009).

Aims of the study

While previous studies focused on the reward modulation in guiding visual attention orienting to non-social stimuli, they did not explore whether this effect also emerges when considering social stimuli. In other words, to the best of our knowledge, previous evidence mainly examined the motivational effect of monetary stimuli by designing paradigms in which the monetary reward interacted with non-social cues with a neutral valence. Accordingly, no studies investigated whether monetary reward can modulate the effect of social cues on attention. To fill this gap in the literature, the present study was aimed at examining whether a non-social incentive (i.e., monetary reward) can modulate the gaze cueing effect.

To this end, a paradigm inspired by Chelazzi et al. (2014) was created. The procedure consisted of three phases: *i.* participants were required to carry out a gaze cueing task (*baseline*); *ii.* they performed an implicit learning task that was targeted at creating an implicit association between gaze and monetary reward *(learning)*; iii. the gaze cueing task was presented again to examine the impact of reward on the GCE. No reward was delivered in the baseline and in the test phase. Two hypotheses were taken into consideration, based on stimulus valence:

i.) The relevance of social stimuli (i.e., gaze direction) cannot be modulated by an external non-social rewarding stimulus (i.e., monetary reward). The GCE is not modulated by monetary reward.

ii.) The relevance of highly rewarding stimuli, such as monetary stimuli, is capable of modulating the effect of social stimuli (i.e., gaze direction). The GCE is modulated by monetary reward. According to this prediction, the modulatory effect of reward should enhance the GCE in congruent (faster reaction times) and incongruent (slower reaction times) trials, when the reward is delivered to the same side where the eyes are looking at, whereas it is expected to mitigate the GCE in incongruent trials when the reward is delivered in the opposite side.

Methods

Participants

Ninety (N = 90) participants (37 females, mean age = 23.61) took part in the study. Participants were randomly assigned to two experimental conditions (30 for each condition), whereas a third group (N=30) was assigned to a control condition. All participants were students of the University of Milano-Bicocca. They were all right-handed, had normal or corrected-to-normal vision and had no history of neuropsychiatric disorders. They received 5 Euros for their participation in the study. The participants gave their written informed consent before starting the experiment. The study was conducted in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki and fulfilled the ethical standard procedure recommended by the American Psychological Association (APA). The experiment was approved by the Ethics Committee of the University of Milano-Bicocca.

Procedure and tasks

The experiment was carried out in the Experimental Psychology Lab of the Department of Psychology at the University of Milano-Bicocca. Stimuli presentation and responses registration were controlled through the software E-Prime 2.0 Professional (Psychology Software Tools1). The participants sat approximately 57 cm away from a 15-inch LCD monitor. A standard Italian keyboard was used to register the participants' responses. The experiment was conducted in a dark room without windows. The experimental condition included three sessions: the baseline session, in which participants performed a gaze cuing task; the implicit learning task session, in which the association between gaze direction and reward was fostered by repeated implicit learning; the test session, in which the same gaze cueing task of session 1 was presented again. Two experimental conditions based on reward presentation side (A = reward on the right, B = reward on the left). In the control condition, a simple perceptual task was presented instead of the implicit learning task. The three tasks are described more in detail in the next three paragraphs.

Gaze Cueing Task

The task comprised 256 trials split into two blocks (128 trials each). A short break was inserted between the two blocks. Each trial was composed of the following events: (1) a fixation cross appearing at the center of the screen for 1000 ms; (2) a gaze-cue looking straight was presented; 3) after 1000 ms from its onset, the gaze-cue randomly gazed toward the left or the right; (3) an upper-case letter (L or T) appearing on the right or on the left side of the screen (Fig 1). Participants were required to press the V-key whenever the letter L appeared on the left side of the screen and, respectively, the B-key whenever the letter L appeared on the right side of the screen. The letter T's appearance did not require any type of response, but it was included to create a go/no-go condition in order to increase the task difficulty and investigate whether reward reduced response inhibition toward the reinforcing gaze directions. SOAs were manipulated in a way that the target letter could appear either after 250 or 750 ms, that is a time window often reported in the literature which usually gave robust GCE (Driver et al., 1999; Ricciardelli et al., 2002; Takao et al., 2018). The target appeared either in the location cued by the gaze (congruent trials) or on the opposite location (incongruent trials). RTs and accuracy were recorded. This task was used as both a baseline and test measure.

Implicit Learning Task

The task consisted of 200 trials (100 reward trials and 100 no-reward trials). Participants were informed that they were engaging in a monetary exchange with another agent (Participant B), who had to choose to split 10 cents, or to keep the entire amount for her/himself. Participants' task was to predict Participant B's decision, that was independent from their guess. Participant's B decision was indeed communicated by the gaze cue direction, that could shift to the right or left side of the screen. The agent did not exist in reality since the procedure was entirely controlled by a computer program. The scope of creating an association between gaze and the delivery of monetary reward was to make gaze direction a conditioned stimulus. Indeed, the assumption of this task was that participants implicitly learnt that the gaze cueing towards a specific location was associated to a win or not. Participants were assigned to two conditions: condition A (monetary reward predicted by gaze shifts to the right side; N = 30, female = 19) and condition B (monetary reward predicted by gaze shifts to the left side; N = 30, female = 18).

The trial sequence was the same of the gaze cueing task, that only differed for the target presentation. Instead of a letter, the picture of a coin indicating the reward condition (5 cents) or the no-reward condition (0 cents) appeared in one of the two sides of the screen. A proper images manipulation program (GIMP 2.8) was used to create realistic pictures of the coins (Figure 1). The total amount gained until that moment was displayed at the end of each trial. Group A's participants were required to predict the win by pressing the H-key on the keyboard, and the N-key when no win was expected. Group B's participants were asked to do the opposite. At the end of the experiment, all the participants received the same amount of money (i.e., 5 euros) for their participation.

Perceptual Discrimination Task

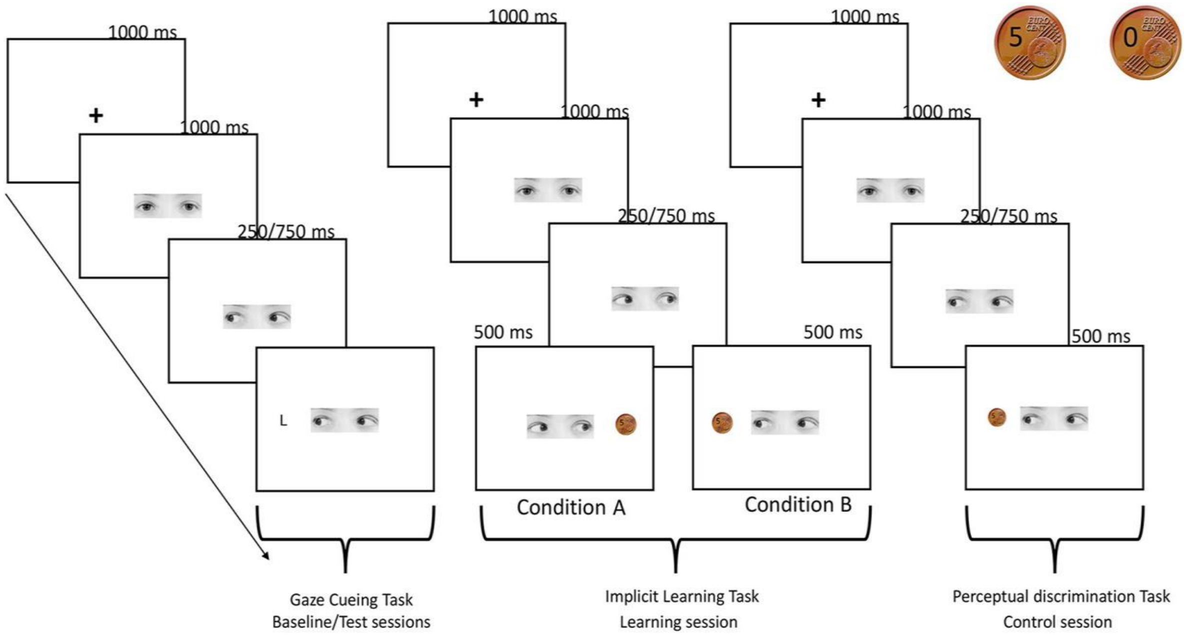
Only participants in the control condition performed this task. The task consisted of 200 trials, and had the same structure of the implicit learning task. The only difference was that, in this case, participants were told that they were engaging in a game in which they had to predict the moves of a Participant B (Figure 1). In particular, Participant B gaze could predict the appearance of the number 5 or the number 0, based on the side in which Participant B was looking at. The side of coin presentation was balanced between participants. Specifically, 50 % of the participants was informed that a 5 coin would have appeared when Participant B's gaze shifted to the left, whereas the other half was informed about the opposite (i.e., 5 coin appeared when the gaze shifted to the right). As in the implicit learning task, participants were asked to predict Participant B's choice pressing the H or N-keys. Importantly, in this case no reward was presented in association with the coin presentation.

Data preprocessing and analysis

Five participants were removed from the analysis. Data of four participants were not included in the analysis because of a technical error. Data of one participant was removed due to the high percentage of incorrect responses (error rate > 35 %). The mean and the standard deviation (SD) of correct trials' RTs were computed for each participant and each condition – i.e., congruency (2: congruent vs incongruent), SOA (2: 250 ms vs 750 ms) and side (2: right vs left). The 2 SD rule was applied to remove outliers (Ratcliff, 1993). The technique consists of excluding trials with RTs greater or lower than 2 SD from each participant individual mean. Overall, the 6,51 % of the trials were removed by applying this technique.

Data Analysis was conducted by combining a frequentist and a Bayesian approach. While traditional significance level (i.e., p-value) was taken into account in frequentist analyses, the Bayes Factor (BF) was used as output of Bayesian analysis. The BF is a measure of how likely data are to arise from one model, compared to another one (Wagenmakers et al., 2018). Mathematically, the BF is the ratio between the likelihoods of the two models (Pastore, 2009). Usually, the two models are the null model H0 (i.e., parameters do not statistically differ in the population) and the alternative model H1 (i.e., parameters statistically differ in the population). Therefore, the higher BF, the more likely are the data given one of the two models. Unlike frequentist analysis, which only allows to dichotomously reject or not the null hypothesis, Bayesian analysis enables to quantify evidence for H0 or H1. In other words, frequentist analysis relies on a dichotomous measure of evidence, whereas Bayesian statics relies on a continuous one. An advantage of Bayesian approach is that it allows to distinguish between uncertainty (BF = 1) and evidence for H0 (BF = 0) (Dienes, 2011).

Figure 1. *Experimental procedure. The first timeline displays the gaze cueing task administered before and after the implicit learning task. The central timeline shows the implicit learning task with the delivery of monetary reward. The reward was expected to appear whenever participant's B gazed at the right (condition A) or left side of the screen. The timeline on the right displays the perceptual discrimination task, in which no reward was delivered.*



When computing the BF, prior odds need to be calculated. Prior odds refer to how much plausible H_0 and H_1 are before observing the data. Since no prior information related to this experiment existed, the prior distribution was set as non-informative (r scale fixed effect = 0.5, r scale random effects = 1, r scale covariates = 0.354), as recommended by Wagenmakers et al. (2018). The BFs were computed by referring to the Mathôt method which takes into account the probability of models containing the effect of interest compared to the probability of equivalent models stripped of the effect (Wagenmakers et al., 2018; JASP Team, 2018). Statistical analyses were conducted using JASP Software (JASP Team, 2018), an open-source software in which it is possible to run both frequentist and Bayesian analyses. Six ANOVA models aiming to investigate different effects were run.

The first two models (Analysis 1 and Analysis 2) were run to investigate whether the GCE was present in the baseline session. Specifically, the first model (Analysis 1) was conducted by performing a frequentist analysis, while the second one (Analysis 2) was conducted by performing a Bayesian analysis. The two models consisted of a full factorial model including the three independent factors: congruency (2 levels: congruent vs incongruent; within-subject), SOA (2 levels: 250 vs 750 ms; within-subject) and the conditions (3 levels: A, B, control; between-subject). The dependent variable was the average of RTs across correct trials. No error analysis was conducted due to the low percentage of uncorrected responses (4.83%).

The models 3 and 4 (Analysis 3 and Analysis 4) were run to investigate whether monetary reward had an effect on the GCE. The first model (Analysis 1) was conducted by performing a frequentist analysis, while the second one (Analysis 2) was conducted by performing a Bayesian analysis. An *ad-hoc* three-levels factor named reward was created. The first level, named rewarding gaze direction, included conditions in which gaze predicted a win by shifting to either the right (condition A) or the left (condition B) side of the screen. The second level, named no rewarding gaze direction, included conditions in which did not predict any win. In contrast to the first level, the gaze shifting to the right or to the left could predict no win. The third level, named control condition, referred to the perceptual discrimination task in which no reward was delivered. The two models consisted of a full factorial model including the three independent factors: time (2 levels: baseline vs test; within-subject), SOA (2 levels: 250 vs 750 ms; within-subject) and reward (3 levels: rewarding gaze condition vs no rewarding gaze condition vs control condition; between-subject). The dependent variable was the average of RTs across correct trials.

The other two models (Analysis 5 and 6) investigated the same effects of the third and fourth model, by adding the side effect to explore if the rewarded side interacted with the side where the gaze was looking at. The reward factor was replaced by the “conditions” factor used in the first two analyses. The first model (Analysis 3) was conducted by performing a frequentist analysis, while the second one (Analysis 3) was conducted by performing a Bayesian analysis. The two models consisted of a full factorial model including the four independent factors: time (2 levels: baseline vs test; within-subject), SOA (2 levels: 250 vs 750 ms; within-subject), side (2 levels: left vs right; within-subject) and conditions (3 levels: A, B, Control; between-subjects). The dependent variable was the average of RTs across correct trials. The analyses were conducted separately for the two SOAs.

Results

Analysis 1

The first analysis investigated the presence of the GCE in the baseline session by adopting a frequentist approach. The ANOVA showed significant main effects of congruency [$F(1,82) = 32.535$, $p < 0.001$, partial-$\eta_2 = 0.284$), SOA [($F(1,82) = 82.491$, $p < 0.001$, partial-$\eta_2 = 0.501$)] and conditions [($F(2,82) = 5.893$, $p = 0.004$, partial-$\eta_2 = 0.126$)], whereas no significant interaction was found (all $p > 0.4$). As concerns the congruency effect, RTs were faster in congruent trials (M = 421.28, SD = 45.16) than in incongruent trials (M = 433.49, SD = 48.79), whereas the effect of SOA revealed faster RTs for SOA = 750 ms (M = 418.26, SD = 48.74) than for SOA = 250 ms (M = 436.50, SD = 45.22). As regards the conditions' effect, post hoc analysis, performed by applying Bonferroni's correction, showed that participants assigned to conditions A (M = 436.26 ms, SD = 54.54, t = 2.725, $p = 0.024$) e B (M = 441.79, SD = 45.45, t = 3.137, $p = 0.007$) were significantly slower than participants assigned to the control condition (M = 406.31, SD = 35.03).

Analysis 2

The first analysis investigated the presence of the GCE in the baseline session by adopting a Bayesian approach. Specifically, the Bayes Factor (BF_{10}) was computed for each effect. The effects are displayed in Table 1. Results showed that the effects of congruency, SOA and conditions were more likely to be the alternative than the null hypothesis. In contrast, results on interaction effects indicated absence of evidence for H_1, and anecdotal to moderate evidence for H0.

Analysis 3

The third analysis investigated the influence of monetary reward on the GCE, by adopting a frequentist approach. The ANOVA showed that the interaction of interest (i.e., time x reward x congruency x SOA) was not significant [$F(2,172) = 0.302$, $p = 0.74$, partial-$\eta 2 = 0.026$)]. Therefore, no difference was found between the baseline vs the test session with respect to each reward condition (Figure 2).

Table 1. *BF_{10} computed for main and interaction effects.*

Effect	**BF_{10}**	**Evidence for H0**
Congruency	2.051e + 7	Extreme
SOA	1.304e + 16	Extreme
Conditions	9.029	Moderate
Other interactions	< 0.4	No evidence for H1, anecdotal and moderate evidence for H0

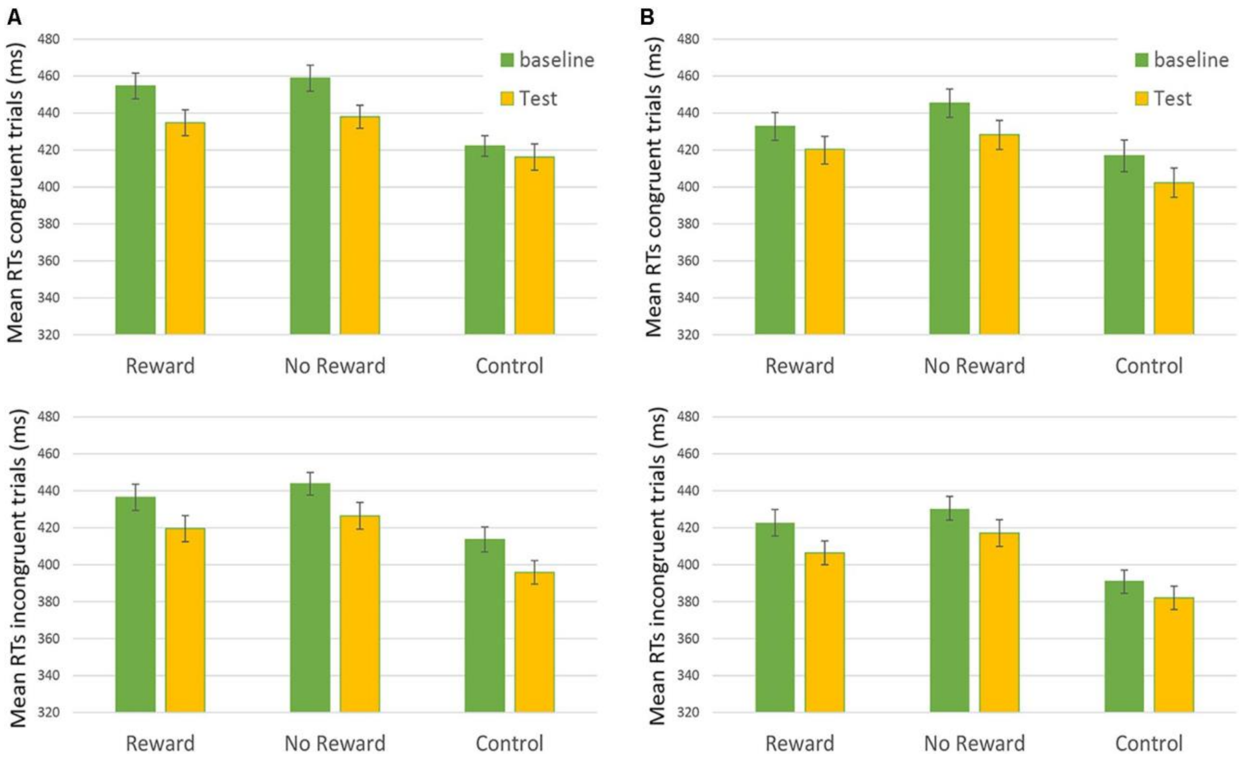
Analysis 4

The third analysis investigated the influence of monetary reward on the GCE, by adopting a Bayesian approach. Unlike Analysis 2, BF_{01} (i.e., $BF_{01} = 1/BF_{10}$) was used, instead of BF_{10}, as a metrics of the likelihood of the data given H0 compared to H1. Results showed that the the time ∗ reward ∗ congruency ∗ SOA interaction had a $BF_{01} = 14.493$. In other words, data were approximately fourteen times more likely to occur given the null than the alternative hypothesis, indicating a strong evidence for the H0 (Figure 2).

Analysis 5

The fifth analysis investigated the interaction time x side x condition x congruency interaction, by adopting a frequentist approach. The ANOVA showed that the interaction was not significant neither for SOA = 250 ms [F(2,81) = 0.135, p = 0.874, partial-η2 = 0.003)], nor SOA = 750 ms [F(2,80) = 0.647, p = 0.526, partial-η2 = 0.016)]. Therefore, no difference was found between the baseline vs the test session with respect to each reward condition by considering the side (Figure 3).

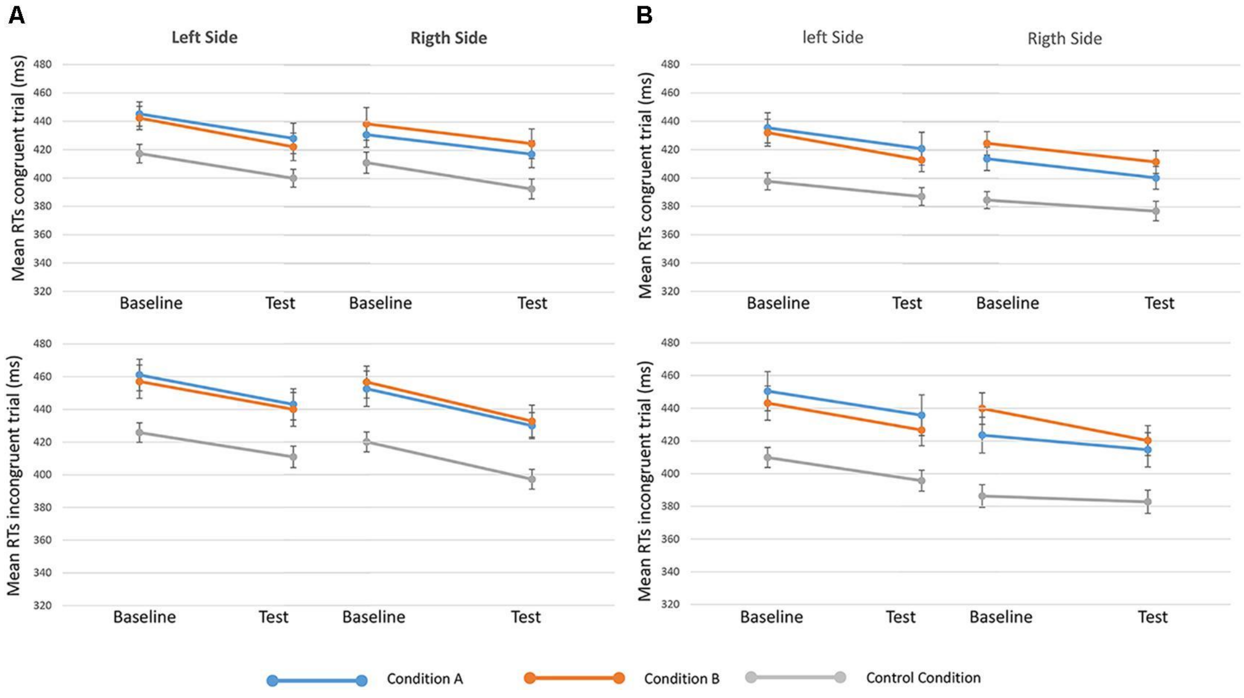
Fig 2. *Mean RTs of congruent and incongruent trials are computed for the time*reward*congruency*SOA interaction. Plots on the left (A) refer to SOA = 250 ms, whereas the two plots on the right (B) refer to SOA = 750 ms.*



Analysis 6

The sixth analysis investigated the interaction time x side x condition x congruency interaction, by adopting a Bayesian approach. BF01 was used as a metrics of the likelihood of the data given H0 compared to H1. This analysis showed that the interaction effect had a BF01 = 13.33, for SOA = 250 ms, and a BF01 = 3.16, for SOA = 750 ms. This evidence indicates that data were, respectively, thirteen times and 3 times more likely to occur given H0 than H1, resulting into strong (SOA = 250 ms) or moderate (SOA = 750 ms) evidence for H0.

Fig 3. *Mean RTs of congruent and incongruent trials are computed for the time x side x condition x congruency divided by SOA. In detail, plots in the left side (A) refer to SOA = 250 ms, whereas plots on the right side (B) refer to SOA = 750 ms.*



Discussion

The present study was aimed at investigating whether a non-social stimulus with a high incentive value, i.e., monetary reward, modulated attentional orienting induced by gaze direction. In other words, this study was addressed to respond to the first research question of the present dissertation, that is understanding whether social stimuli are prioritized even when they attentively compete with other relevant non-social stimuli. Specifically, two possible outcomes were hypothesized. The first one assumed that the GCE was not modulated by monetary reward, meaning that monetary stimuli do not exert more interference than social stimuli. The second scenario assumed that the GCE was modulated by monetary stimuli, by proving that the relevance of highly rewarding non-social stimuli is capable of modulating the effect of social stimuli. Monetary reward was chosen as rewarding stimulus due to its valence in the Western society and to previous studies showing effects of monetary reward on non-social stimuli processing (Anderson et al., 2014; Engelmann et al., 2009; Pessoa and Engelmann, 2010; Chelazzi et al., 2013). Previous research indeed mainly focused on the motivational role of reward associated with non-social stimuli in guiding selective visual attention (Della Libera and Chelazzi, 2009).

To answer this research question, a paradigm inspired by Chelazzi et al. (2014) was designed. Participants were required to perform a gaze cueing task before and after a task designed to deliver (implicit learning task; conditions A and B) or not (perceptual discrimination task; control condition) a monetary reward in one of the two spatial locations where the gaze was looking at. The goal of this paradigm was to investigate whether, or not, the repeated earning of money associated to a specific gaze direction (left or right) was able to modify the magnitude of the GCE in the test session compared to the baseline session. Frequentist and Bayesian analyses were conducted to examine how much robust the studied effects were.

Results of the baseline session showed faster RTs in congruent trials than incongruent trials, by replicating the existence of the GCE. Importantly, the gaze effect was not influenced by the condition (A, B, Control) or by the SOA. These results further corroborate the substantial number of evidence showing that gaze cue and, in general, social stimuli represent highly salient stimuli for human beings (Baron-Cohen et al., 1997; Driver et al., 1999; Frishen et al., 2007). This attentional pattern emerges both for adaptive and for motivational reasons. In line with the social motivation theory (Chevallier et al., 2012), attention to social stimuli, such as gaze direction, is also explained by the human tendency to seek value and pleasure (i.e., reward) in social interactions, as well as to maintain bonds with other individuals.

As concerns the main research question of the present study, no evidence of a modulation of GCE related to rewarding gaze direction (conditions A and B), as compared to non-rewarding gaze direction (control conditions), was found. Also, no significant interaction between reward side and gaze direction effect emerged. Therefore, it is possible to conclude that the monetary reward did not modulate the GCE. This result is in contrast with findings from studies with non-social stimuli and, likewise, strengthens the concept of saliency of social stimuli.

The most coherent interpretation of this effect is that the valence of the monetary reward is not relevant enough to mitigate or enhance the effect of powerful social signals such as gaze direction. Money represents one of the most important incentives of our society. However, money does not have the same biological valence as social stimuli, since the motivation to obtain money does not result from an evolutionary process begun at human birth (Lea and Webley, 2006). Contrarily, this motivation develops throughout the influence of the external world and culture. In other words, monetary reward is likely to be less powerful than gaze direction in automatically capturing and orienting attention in humans. In relation to the hypotheses of the present study, these results support the first hypothesis according to which monetary stimuli are not perceived as more salient than social stimuli. This result brings further evidence on the salience and priority that social stimuli have for TD individuals, even when competing when strongly salient non-social stimuli.

Beyond the adaptive and social motivation-related explanations of this effect, a cognitive interpretation of this effect can be given. As reported in the introduction of this study, many authors have supported the idea according to which the GCE would be purely automatic

(Friesen & Kingstone, 1998; Driver et al., 1999; Friesen et al., 2004). Accordingly, the reflexive nature of the GCE may have limited the influence of higher order motivational effects. However, as seen in the introduction, other authors came to opposite conclusions, by indicating that attentional orienting induced by gaze direction can be modulated by top-down processes (Bayliss et al., 2010; Wykowska et al., 2014; Perez-Osorio et al., 2017; Hayward & Ristic, 2018; Dalmaso et al., 2020).

As concerns the limitations, two possible limitations can be considered in the present study. The first limitation concerns participants' individual differences, namely the individual valence that each participant attributed to monetary stimuli. According to the Reinforcement Sensitivity Theory of Personality (Corr, 2004), individuals present different levels of reward sensitivity based on their history, culture and biology. In line with the first limitation, the second limitation concerns the lack of a manipulation check indicating whether participants implicitly learned, or not, the association between reward and gaze direction. In other words, one may speculate that that the training simply did not take place, thus determining the null effect, due to the scarce valence attributed to the monetary reward. However, as stated by classical condition theorists, the repeated exposure to stimulus-reward pairing should be sufficient to determine implicit learning (Pavlov, 1927; Buchel et al., 1998; Pessiglione et al., 2008; Seitz et al., 2009). Future studies should address this issue by evaluating participants' individual sensitivity to reward, and by carrying out stimuli manipulation check to insert in the models as a covariate.

Conclusion

The present study revealed that the modulatory effect of monetary stimuli, which emerged in studies using non-social stimuli, does not emerge if the attentional cue is a relevant social and biological stimulus (i.e., gaze direction) with high adaptive, social and motivational valence. In other words, this study strengthens the strong relevance that social stimuli have for TD individuals. Even though money has a prominent value in the Western society, gaze direction effect "resisted" its influence. Gaze and, more generally, social stimuli play a key role in human adaptation and development that probably cannot be mitigated by the influence of another relevant, but non-social, stimulus as a monetary incentive. This study enables to provide some evidence to answer the first research questions of this dissertation (i.e., investigating whether social stimuli are prioritized even when they attentively compete with other relevant non-social stimuli) supporting the attentional priority and relevance of social stimuli for TD individuals. The rest of this work will be addressed to examine if specific individual (i.e., ASD) and interstimulus differences can mitigate this perceived salience of social stimuli, by taking into account both cognitive and physiological processes.

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CHAPTER 2

Attention to social vs non-social stimuli in individuals with Autism Spectrum Disorder: A systematic review of the literature

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by difficulties with social communication (e.g., eye-contact, joint attention and social gestures), social interaction (e.g., developing, maintaining and understanding relationships), and by the presence of restricted, repetitive patterns of behavior, interests or activities (APA, 2013).

As shown in Chapter 1, social stimuli, more particularly human eyes, have a strong valence for human beings, even when attentively competing with salient and rewarding non-social stimuli such as money. In spite of this strong relevance of social stimuli for TD individuals, previous literature consistently indicated that the same saliency is not perceived by ASD individuals.

In Chapter 1, a specific task (i.e., the gaze cueing task) was used to investigate attentional sensitivity to human gaze. However, attention to social stimuli can be also examined by taking other processes into consideration. For example, some social attention tasks concurrently present pairs or matrixes of social and non-social stimuli to study the facilitation effect due to the presentation of social stimuli vs non-social stimuli. These types of task enable to shed light on the higher preference and on the faster processing of social stimuli in typical development (e.g., Goren et al., 1975; Bard et al., 1992; Ro et al., 2001; Conte et al., 2020). In detail, this pattern reflects the construct of attentional bias (AB), namely the tendency to selectively attend to certain categories of stimuli (i.e., most relevant stimuli) while ignoring others (MacLeod et al., 1986; MacLeod et al., 2002). The AB to social stimuli emerges very early in human development, as documented by studies on nine-minute-old newborns who already tend to prefer stimuli with a face pattern rather than non-human-like stimuli (Goren et al., 1975). Studies on adults corroborated this evidence, and showed that this attentional pattern remains stable throughout the entire lifespan (Ro et al., 2001; Ro et al., 2007; Bindemann, et al., 2007). For instance, Ro et al. (2001) analyzed reaction times and accuracy in detecting changes in human faces and objects in a change blindness paradigm. Results pointed out that changes were detected significantly faster and more accurately in faces than in object, and that this AB emerged only when faces were presented upright (canonical) (Ro et al., 2001). Also, Ro and colleagues (2007) arrived to the same conclusions – human faces detected faster than objects – by administering a modified version of the Visual Search paradigm (Ro et al., 2007). Similar conclusions came from studies using the Dot-Probe task. For example, Bindemann and colleagues (2007) used a version of the Dot-Probe task in which participants had to detect the spatial position of a target probe appearing after two stimuli presented in pair (i.e. a face vs non-social object). Participants were faster at detecting the target when it appeared in the spatial location of the face cue than in the non-social object's one (Bindemann et al., 2007). This facilitation effect illustrated that participants were more captured by the spatial location where the social stimulus appeared.

Evidence on individuals with ASD

Experimental studies indicated that the AB to social stimuli found in TD individuals is less prominent in ASD individuals. Specifically, some studies reported slow face changes' detection (Kikuchi et al., 2009), reduced attentional orienting to human face (Moore et al., 2012), faster disengagement from face stimuli (Katarzyna et al., 2010; Kliemann et al., 2012) and atypical visual exploration of face stimuli (Bar-Haim et al., 2006; Klin et al., 2002) in the ASD population. This atypical attentional bias can be partially explained by abnormalities in the amygdala found in ASD participants (see Sasson, 2006 for review). In fact, the amygdala is the brain region recruited to early evaluate the stimulus saliency (Adolphs, 2010; Brothers, 1990;1996), by triggering reward and avoidance mechanisms that are, respectively, activated during social interactions and in presence of danger (Dawson et al., 2002). The reduced orienting to social stimuli leads to the deployment of attentional resources towards other categories of stimuli. Specifically, individuals with ASD were found to pay more attention to non-social stimuli, and, more in detail, to specific objects' categories defined as High Autism Interest objects (HAI) (Sasson et al., 2008; Sasson et al., 2011). These objects include mechanical and electronic devices (e.g. play station console, phones, TV) as well as means of transport (e.g. trains, cars, airplanes), namely objects fulfilling the drive to systematically analyze or construct systems as documented in ASD individuals (Baron-Cohen et al., 2003). Likewise, this pattern reflects the tendency to perseverate on images of interest and to explore them in an extremely detail-oriented manner (Sasson et al., 2008). In two eye-tracking experiments, Sasson and colleagues (2008; 2011) presented an array containing a set of stimuli matched for social and non-social content. The non-social content was further balanced to include both stimuli eliciting circumscribed interests and systematic processing and purely neutral stimuli. Children with autism performed greater exploration behavior and sustained attention on HAI objects than TD children. Interestingly, the visual exploration of these objects positively correlated with the severity of repetitive behavior symptoms (Sasson et al., 2008; 2011).

Aim of the present review

The present systematic review is aimed at analyzing behavioral and/or eye tracking evidence examining the atypical AB to social stimuli in ASD individuals. Furthermore, it will be addressed at understanding whether this atypical social bias emerges along with an increased attentional orienting to specific non-social stimuli categories. In detail, the following areas will be investigated:

i.) Investigating which non-social categories (e.g., HAI stimuli) contribute to increasing attentional orienting to non-social stimuli in ASD individuals;

ii.) Investigating if the atypical bias to social stimuli is generalized or specifically emerges for certain types of social stimuli (e.g., face, eyes, parts of the body);

iii.) Analyzing the types of paradigms which are most frequently used to study these attentional effects;

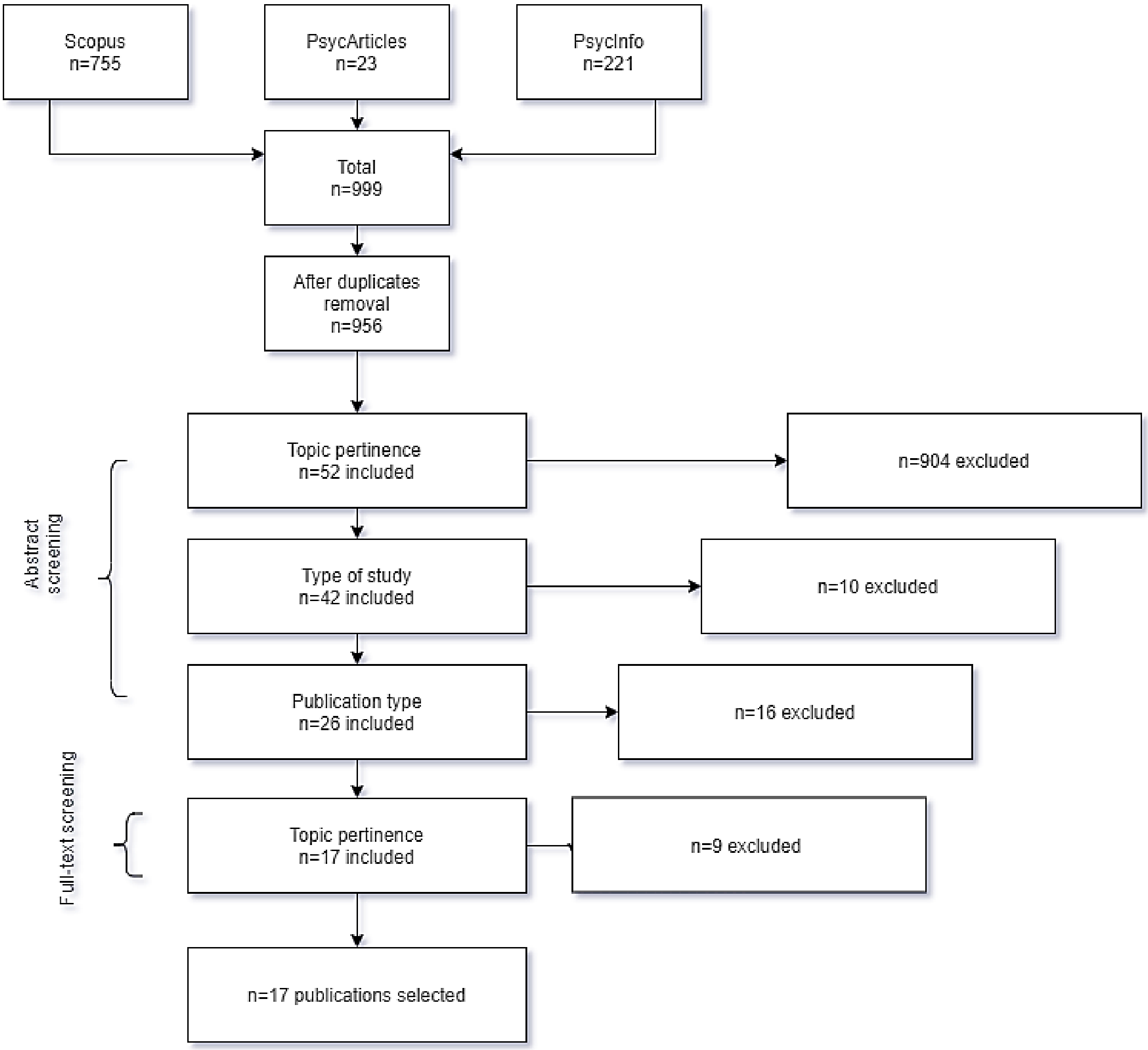
iv.) Analyzing the main theoretical and methodological issues emerging from the selected literature sources;

v.) Analyzing the impact of this pattern on ASD symptomatology.

Method

The systematic review followed the guidelines for systematic reviews in social and human sciences (Petticrew e Roberts, 2006), and was conducted on three databanks: Scopus (n=755), PsycInfo (n=221), PsycArticles (n=23). The total number of records was equal to 999. The research was carried out in July 2020. The search strategy was based on keywords filters and Boolean operators. Specifically, the filter included the key-words “autism” (OR ASD, OR Autism Spectrum Disorder), AND “attention*bias*”, AND “social stimuli”, AND “high autism interest object*”, AND “non*social stimuli”. Forty-three duplicates were identified and removed from the total resulting into a number of n=956 records. During abstract screening, further sources were removed on the basis of three criteria: topic (i.e., removal of studies not examining AB or ASD population), type of study (i.e., removal of non behavioural or eye-tracking studies), and publication type (i.e., removal of non-scientific articles). Respectively, n=904 studies were removed for lack of topic pertinence, n=10 did not meet the type of study criterion, and n=16 did not meet the publication type criterion. The remaining 26 records were further full-text screened for topic pertinency, that conducted to the exclusion of 9 records and, therefore, to the selection of 17 records. The selection process has been summarized in the selection diagram (Figure 1).

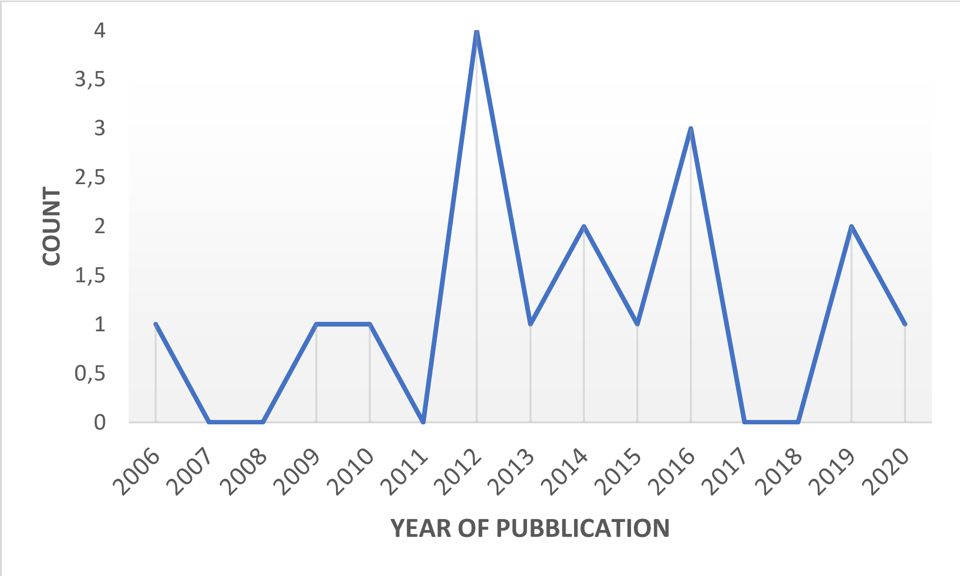
Figure 1. *Diagram of the selection process conducted in July 2020.*



Results

Seventeen (N=17) articles were selected after applying filters. Four (N=4) of them were published in 2012, whereas the other sources were published in 2016 (N=3), 2019 (N=2), 2014 (N=2), 2020 (N=1), 2015 (N=1), 2013 (N=1), 2010 (N=1), 2009 (N=1), 2006 (N=1) (Figure 2). Articles have been analyzed by extracting relevant information in line with objectives specified in the aim section. In detail, four areas have been explored in each article, that are the designed paradigm, the stimuli, the main findings, and the main limitations and issues. Results are summarized in Table 1.

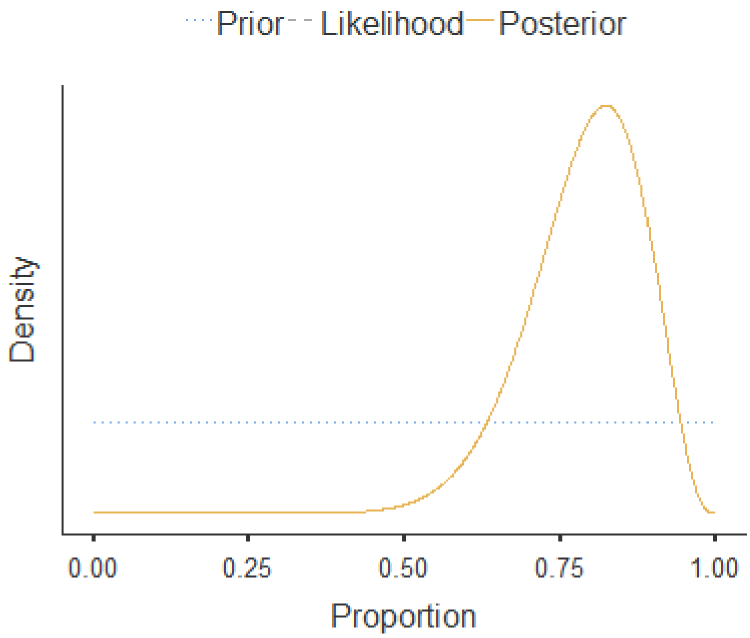
Figure 2. *Number of articles published from 2006 to 2020.*



Fourteen study (N=14) out of 17 (82,3 %) reported a reduced AB towards social stimuli in ASD individuals compared to TD individuals. A binomial test, conducted on Jamovi (The jamovi project, 2020), showed that this percentage was significantly different from a random population value (50 %) ($p = 0.013$, $g = 0.32$, $BF_{10} = 10.7$). Interestingly, the Bayes Factor (i.e., 10.7) supported the evidence of this conclusion. The prior probability was set by referring to a beta-binomial distribution with parameters a=1 and b=1 used as priors. The computed posterior probability is shown in Figure 3.

The most of the studies used human faces as prototype of social stimulus (13/17: 76,4 %). Eight studies (N=8) of the 14 using non-social stimuli in the experimental paradigm (57,14%) found an atypical bias towards non-social stimuli in ASD individuals. In this case, the binomial test did not support the significance of the difference between this value and a 50% population value ($p = 0.43$, $g = 0.07$, $BF_{10} = 0.36$), probably due to the lower number of observations. Importantly, four (N=4) of these studies included HAI stimuli in their paradigms, and three (N=

Figure 3. *Bayesian posterior probability relative to the frequency of studies finding a lack of AB towards social stimuli in ASD individuals.*



3) of them found an AB towards HAI stimuli in ASD participants (75%). As concerns the paradigm, the most of the studies designed free-viewing eye tracking paradigms (7 out of 17; 41,11%), whereas other studies implemented paradigms that mainly were modifications of Posner's paradigm (e.g., Dot-Probe) or Stroop paradigm. Two studies investigated impacts on symptoms severity by finding a link between atypical AB and atypical language and general symptoms severity. Finally, the most common reported limitations are, respectively, the lack of samples covering the entire autism spectrum (3/17; 17,64 %; for more details see the discussion) and the use of HAI stimuli non-targeted at specific participants' interests (3/17; 17,64%).

Table 1. *Results including the main characteristics and findings of the extracted sources*

Authors	Year	Sample	Paradigm	Stimuli	Main Findings	Limitations
Annaz et al.	2012	70 ASD children and 17 TD children matched for age (5.5 years old)	Point-light displays paradigm and eye-movements recording	Phase scrambled motion, top spinning motion, human walker motion	ASD did not attend to biological motion compared to phase-scrambled motion, whereas preferentially attended to a point-light display of a spinning top rather than biological motion.	Sample age limiting the conclusions around the mechanisms underlying this atypical bias
Antezana et al.	2016	49 ASD children (12.73 years old) and 29 TD children (13.27 years old)	Social-Emotional Inhibition of Return Task (IOR)	Neutral and angry faces. Non-social stimuli not included	ASD children exhibited a stronger IOR effect than the TD children. The IOR effect positively correlated with social impairments	Study did not cover the entire autism spectrum (no children with intellectual disability)
Ashwin et al.	2006	17 ASD adults (26 years old) and 17 TD adults (27 years old)	Emotional Stroop Task	Angry facial expressions, neutral expressions, or non-social objects	ASD participants had not longer latencies to angry vs neutral male faces, compared to TD individuals, whereas they exhibited slower latencies to facial expressions compared to non-social objects	No measures of anxiety, mood or hormone level. Lack of a control group other than ASD

Chawaraska et al.	2010	42 ASD children (32 months old), 31 children with developmental delays (DD) (29 month old), 46 ASD childen (29 months old)	Gaze Cueing Paradigm with both social and non-social cues (scrambled image)	Human face and non-social stimuli (scrambled images)	DD and TD children had more difficulties disengaging attention from faces than ASD children. This effect was not present when non social stimuli were presented.	Not reported
Chawaraska et al.	2012	54 ASD children (21 months old), 20 children with developmental delays (DD) (20 month old), 48 TD childen (20 months old)	Free viewing paradigm	Actress explicitly interacting or not (e.g., making a sandwhich) with the child, and presentation of non-social distractors (toys)	In not-explicit interactions (no direct speech and eye contact), attention to social stimuli in ASD children was comparable to that in DD and TD controls. When explicit dyadic cues were introduced, ASD children showed decreased attention to speaker’s face and increased attention to non-social objects. Decreased monitoring of speaker's face was associated with atypical language.	No data on speech and eye-contact unique contribution to the regulation of attention. Performance variability of ASD chilren not taken into account

Chevallier et al.	2013	24 ASD and 24 TD, all males and adolescents (age range : 10-16)	Modified version of the Stroop Task	Color names, social stimuli (eye region), non-social stimuli (flowers pictures)	The Stroop interference for social versus nonsocial stimuli was greater in TD, whereas the opposite pattern occurs in ASD. The superiority effect of direct gaze, reported iby previous studies, was not found	Only two social distracters (open vs closed eyes). Causes underlying this atypical bias were not investigated. Study did not cover the entire autism spectrum (no children with intellectual disability)
DiCriscio et al.	2016	19 ASD (13 years old), 19 TD (14 years old), 9 obsessed compulsive disorder (OCD) (15 years old)	Eye movement task in which participants were asked to look at peripherical targets (prosaccade) or to look at the opposite side (antisaccade)	Social stimuli (faces), Low Autism interest (LAI) objects, High Autism Interest (HAI) objects	No differences in the prosaccade condition were found. In the antisaccade condition, the ASD group made more errors than the control groups for HAI stimuli, but not for LAI and social stimuli. Antisaccade errors predicted symptoms severity	CI stimuli were not person-specific. Male-female unbalance in the sample

Elison et al.	2012	51 ASD children and 43 TD children ranging from 2 to 18 years old	Visual exploration task with eye-movements recording	Social stimuli (faces), Low Autism interest (LAI) objects, High Autism Interest (HAI) objects	ASD exhibited attentional bias for HAI stimuli from very early in life. Disproportionate visual attention to certain HAI objects, compared to social stimuli, spanned from early to late childhood in ASD	No Longitudinal design
Fischer et al.	2014	44 ASD children (9 years old) and 40 TD children (8 years old)	Free viewing paradigm	Social stimuli (faces) and nonsocial stimuli (e.g., fruits, vegetables)	No impairment in attentional disangagement from nonsocial stimuli and orienting to social stimuli	Non ecological paradigm
Greene et al.	2019	26 ASD (15 years old) and 18 TD (15 years old) adolescents	Expectancy outcome eye tracking tasks (modified version of Posner's paradimg)	Social stimuli (faces) and nonsocial stimuli (images not containing faces and bodies)	ASD participants gazed more on stimuli presented on locations violating the learned association and less on locations corresponding to the learned association. This effect was not moderated by stimulus type - i.e. social vs non-social stimuli	Gaze latencies to areas of interests not examined
Guillon et al.	2016	17 ASD (41 months old) and 23 TD (44 months old)	Preferential looking task	Upright and inverted face-like objects	TD children looked first towards upright face-like objects more than ASD children	No non-social stimuli presentation

Harrison et al.	2020	16 ASD and 20 TD children aged 6 to 17 years old	Visual Paired Preference Task with eye movements recording	Social stimuli (faces), HAI objects and control objects	Non-social stimulus type affects the proportion of dwell time on faces only in the TD group, and not the ASD group. Interest for faces among children with ASD is diminished regardless of whether the non-social stimulus is HAI or neutral	Personalized interest for HAI object was not taken into account and controlled as a covariate
Harrop et al.	2019	42 ASD children (9 years old) and 32 TD children (8 years old)	Free viewing paradigm	Socially rich scenes (dyadic play) and lean social scienes (parallel play)	Gender effect. ASD females oriented more to faces than ASD males in the social lean condition. ASD males oriented less to faces in all social contexts. ASD females only attended less to faces than TD females in the socially rich condition. TD males and ASD females did not differ in their attention to faces in both conditions.	Small sample of females. ASD children attened less overall (possible generalized inattention pattern in ASD)
Kikuchi et al.	2009	EXP1: 16 ASD children (13 years old) and 16 TD children (12 years old). EXP 2: 16 ASD children (12 years old) and 22 TD children (11 years old)	Change blindness paradigms	Array with social stimuli (faces) and non-social stimuli	ASD children had a reduced attentional bias toward' faces, which could be at the basis of their atypical social orienting	Low number of trials

Moore et al.	2012	19 ASD adults (26 years old) and 19 TD adults (28 years old)	Dot-probe task	Social stimuli (faces) and non-social stimuli	No attentional bias emerged in either groups when stimuli were presented at sub-threshold levels. Converselt, at supra-threshold presentation (200 ms), a face bias was found for TD participants but not for ASD participants	Only high-functioning individuals were tested
Sasson and Touchstone	2014	15 ASD children (46 months old) and 15 TD children (40 months old)	Free viewing paradigm similar to the Dot-Probe	Emotional faces, HAI objects and LAI objects	ASD participants did not differ from controls in their visual attention to faces presented with LAI objects, but attended less than TD participants to faces presented with HAI objects. This effect was replicated across three metrics: preference, prioritization and duration	Small sample size. Personalized interest for HAI object was not controlled
Wang et al.	2015	20 ASD (31 years old) and 19 TD (32 years old) participants	Free viewing paradigm	Natural scence social and non-social stimuli	ASD participants reduced saliency for faces and for locations cued by social gaze. On the other hand, they exhibited a general increase in pixel-level saliency (contrast) at the expense of semantic-level saliency	Stimuli likely not representative of how ASD individuals look at the world since they were not choosen by autistic individuals

Discussion

The selection process led to the selection of seventeen research articles addressing the main goals of the present systematic review. The next paragraphs will critically discuss the following four key-points created to answer the research questions of this work: i. examining the presence of the atypical AB towards social stimuli in ASD individuals and, likewise, whether this atypical bias emerges along with an increased attentional orienting to specific non-social stimuli categories (i.e., HAI stimuli); ii. analyzing the paradigms most frequently designed to study these patterns; iii. analyzing the recurrent issues retrieved from the selected articles; iv. Analyzing the impact of the atypical AB on ASD symptomatology.

Attentional Bias towards social vs non-social stimuli in ASD individuals

82,3 % reported a significant reduced AB towards social stimuli in ASD individuals compared to TD individuals. Interestingly, this pattern emerged regardless of the type of social stimulus presented to participants and not only with human faces. For instance, Annaz et al. (2012) compared attentional orienting towards biological and non-social motion in ASD and TD children. They found that ASD children did not exhibit an attentional preference to biological vs non-social motion and, contrarily, preferentially attended to point-light display of a spinning top rather than a human walker (Annaz et al., 2012). This may have an impact on other higher level skills, as shown by another study involving participants from general population with high autistic traits and exhibiting a low advantage for motion kinematics in the recognition of some emotions (Actis-Grosso et al., 2015). On the other hand, other two studies designed more ecological paradigms presenting naturalistic scenarios (Chawaraska et al., 2012; Wang et al., 2015). For example, Chawarasaka and colleagues (2012) presented a video of an actress in a setting with toys and ingredients for making sandwiches, whereas Wang and colleagues (2015) a set of pictures depicting performing naturalistic task (e.g., playing football at the beach). These paradigms provide more information on how ASD individuals explore the external environment and how their atypical AB emerges in social contexts. For instance, in the study conducted by Chawarasaka et al. (2012), the authors found that the decreased AB to social stimuli was only observed when explicit dyadic cues were introduced in the scene. In other words, in non-explicit interactions (e.g., actors making sandwiches and not looking participants straight in the eye) ASD participants' attention to social stimuli was comparable to TD participants, whereas in explicit interactions (i.e., actors explicitly looking participants straight in the eye) ASD participants' attention to social stimuli dramatically decreased (Chawarasaka et al., 2012).

An increased AB to non-social stimuli in ASD participants was observed in the 57,14 % of the studies containing non-social stimuli in the experimental paradigm. Although it is not a significant number, probably due to the low number of observations sample, this is a substantial evidence which deserves to be discussed. First of all, a variety of non-social objects was demonstrated to capture ASD participants' attention (Aswhin et al., 2006; Annaz et al., 2012; Chawaraska et al., 2012; Chevallier et al., 2013; Wang et al., 2015). However, it is interesting to note how three of four studies including HAI stimuli found a significant AB towards these stimuli in ASD participants (Sasson and Touchstone, 2014; DiCriscio et al., 2016; Elison et al., 2012). Conversely, Harrison et al. (2020) found that the type of object impacted the preference for social stimuli only in the TD group and, moreover, no difference related to the non-social object type (i.e., neutral or HAI) was observed. One possible speculation is that, unlike other studies involving young children (e.g., Sasson and Touchstone, 2014), the sample size of this study covered a relatively wide age range (6 to 17 years old). In fact, almost the totality of ASD children undertake rehabilitation treatments determining an improvement of their social and communication skills throughout adolescence. Another possible explanation of the null effects observed in more than the 60% studies (Chawaraska et al., 2010; Moore et al., 2012; Fischer et al., 2014; Kikuchi et al., 2009; Greene et al., 2019; Harrison et al., 2020) may be related to the choice of non-social stimuli. Although HAI stimuli are standardized on an ASD population sample, it is assumable that also individual preferences and differences (e.g., participant’s age) may have an effect on AB magnitude.

Paradigms

Free viewing eye tracking tasks represent the most frequent paradigms in this field. In these paradigms, participants are presented with a set of stimuli or videos and they are simply required to look at the screen while their eye-movements are recorded. In spite of the diminished experimental control, the main advantage of these tasks is given by the lack of artificialism increasing experiment’s ecological validity. Other paradigms consisted of modified versions of either the Posner’s paradigm or the Stroop’s paradigm.

The paradigms involving modifications of the Posner’s paradigm included the Social-Emotional Inhibition of Return Task (Antezana et al., 2016), the Dot-Probe task (Moore et al., 2012), and the Gaze Cueing Paradigm (Chawaraska et al., 2010). In the Social-Emotional Inhibition of Return Task, a cue-stimulus is presented respectively either on the left or the right side of the screen. Participants are required to ignore this stimulus and to detect the spatial position of a target appearing after the cue presentation. Specifically, two kind of trials are presented that are valid trials, in which the cue and the target are presented on the same side, and invalid trials, in which the cue and the target are presented on the opposite side. The Dot-Probe paradigm is an attentional task in which participants are asked to detect the spatial position of a dot after the presentation of a pair of stimuli that have to be ignored. The underlying logic is to compare response times (RTs) of probes replacing a “cue of interest” (e.g., social stimuli), i.e., congruent trials, and those related to probes replacing a “neutral cue” (e.g., non-social stimuli), i.e., incongruent trials (Williams et al., 1988). As seen in chapter 1, the Gaze Cueing Paradigm is a modified version of the Posner’s paradigm where participants are required to detect a target appearing either to the left or to the right of a centrally presented face (Friesen and Kingstone, 1998; Driver et al., 1999; Ricciardelli et al., 2002).

The paradigms involving modifications of the Stroop's paradigm (Stroop, 1935) consisted in the presentation of the Emotional Stroop Task (Ashwin et al., 2006; Chevallier et al., 2013). The Emotional Stroop Task is a modified version of the traditional Stroop task in which participants are required to name the ink-color of words with emotional or neutral valence, or of pictorial stimuli (Williams et al., 1996; De Angelis & Ricciardelli, 2017). For instance, Ashwin and colleagues (2006) used a pictorial version of the Stroop task in which colored images of emotional, neutral faces and non-social objects were presented (Ashwin et al., 2006). Also, Chevallier and colleagues (2013) presented a version of the task that was the traditional version of the paradigm including the addition of social and non-social distractors. The aim of this task is to investigate which stimuli exerted most interference to participants' performance as an index of AB (Chevallier et al., 2013).

Common Issues

The two most common issues concern the presence of samples non-covering the heterogeneity of the autism spectrum (Moore et al., 2012; Chevallier et al., 2013; Antezana et al., 2016), and the use of non-person specific HAI stimuli (Sasson and Touchstone, 2014; DiCriscio et al., 2016; Harrison et al., 2020). The autism spectrum included a variety of profiles that differ on the basis of cognitive and linguistic skills. Three of the selected studies pointed out that only participants without intellectual disabilities were tested (Moore et al., 2012; Chevallier et al., 2013; Antezana et al., 2016). Importantly, it should be important to control for participant's cognitive profile to understand how and whether the atypical AB emerges across the cognitive spectrum (Antezana et al., 2016). Moreover, the inclusion of control variables, to be added as covariates in statistical models, was suggested by other authors. Ashwin and colleagues (2006) indeed stressed the necessity to include measures of anxiety, mood and hormone levels, given the influence of these variables on the performance in tasks assessing AB (Ashwin et al., 2006).

Another issue raised from selected sources concern the use of HAI stimuli non-targeted at participants' personal interests and everyday life use. HAI stimuli were selected from the dataset validated by Sasson and colleagues (Sasson et al., 2008; Sasson et al., 2012). However, as reported by DiCriscio et al. (2016), HAI objects are typically person-specific in ASD individuals' everyday life and, therefore, the use of standardized non-social pictures likely resulted in a loss of study's ecological validity (DiCriscio et al., 2006). This issue was also reported by Sasson and Touchstone (2014) wo underlined the need to include CI personalized stimuli in future research designs (Sasson and Touchstone, 2014).

Impact of the atypical AB on ASD symptomatology

Only two studies took into account the impact of atypical AB on ASD symptoms severity, by revealing an association between atypical AB and atypical language and general symptoms severity (Chawarasaka et al., 2012; DiCriscio et al., 2016). Chawarasaka and colleagues (2012) found that decreased exploration of speaker's face, during explicit dyadic interactions, was associated with atypical language skills, by replicating developmental studies' evidence showing a correlation between attention to sensitive social cues and language development (Kuhl, et al.,1992; Thiessen et al., 2007). Interestingly, the atypical language profile was more extensive in those children paying less attention to speaker's mouth (Chawarasaka et al., 2012). On the other hand, DiCriscio and colleagues (2016) did not found any association between atypical AB to social stimuli, whereas they showed a negative correlation between antisaccade errors for HAI stimuli and, respectively, reciprocal social interaction scores and restricted interests' scores, measured by ADOS.

In light of these studies, the reduced AB to social stimuli is likely to predict difficulties with the communication-language domain, whereas the increased AB to HAI objects seems more associated with difficulties related to social behavior and repetitive/restricted behavioral patterns. It is important to note that other research should address the analysis of the consequences of atypical attentional processing in ASD. In fact, understanding these patterns may contribute to identifying new potential targets for ASD treatment in infancy.

Conclusion

The present systematic review has analyzed behavioral and eye tracking evidence aimed at examining the presence of reduced AB to social stimuli in ASD individuals compared to TD individuals and, likewise, the presence of increased attentional orienting to certain non-social stimuli categories (e.g., HAI stimuli). Seventeen research articles addressing the main goals of the present systematic review were selected. 82,3 % of the selected studies indicated a reduced AB towards social stimuli in ASD individuals compared to TD individuals, whereas 57,14% showed an increased bias towards non-social stimuli in ASD individuals. Among the studies including HAI in their paradigms, 75% reported an AB towards HAI stimuli in ASD participants. Free viewing paradigms and modified versions of the Posner's paradigm and the Stroop's paradigm are the most used to examine AB in the ASD population. Two of the selected studies pointed out a link between these atypical attentional patterns and ASD symptomatology. Finally, as indicated by the selected sources, further research will be required to deal with the most common issues that mainly concern the use of HAI person-specific stimuli, the sampling of heterogeneous ASD populations, and the inclusion of relevant covariates (e.g., anxiety, mood, hormone levels) in the statistical models.

The present work has clearly shown that social stimuli do not capture ASD individuals' attention to the same extent as TD individuals. This evidence strengthens Chapter's 1 conclusions about the attentional priority of social stimuli for TD individuals and, on the other hand, indicates an opposite pattern in ASD individuals (i.e., increased attention to non-social stimuli). The following chapters will deepen these findings by examining whether i. these differences in the processing of social vs non-social stimuli are also present at a physiological level; ii. these differences in social vs non-social stimuli processing may be the expression of a familiar phenotype; iii. whether the salience of social stimuli, and the atypical bias observed in ASD participants, can be changed through the intervention of external factors such as attentional trainings (i.e., AMBT training).

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CHAPTER 3

Physiological responses to anticipated and real pain of social vs non-social agents in ASD individuals:

A deep learning psychophysiological study

Introduction

Results reported in previous chapters have shown that social stimuli exert different levels of attentional capture in ASD and TD individuals. Specifically, ASD individuals consistently orient less to social stimuli and, on the other hand, more to non-social objects than TD individuals. However, while this evidence has particularly focused on the role of attentional processes, the physiology and the visceral components of the atypical processing of social vs non-social stimuli, observed in ASDs, is not completely clear yet. Previous computational models (Scherer, 2009), neuroscientific findings (Gallese et al., 1996; Oosterwijk, 2012; Barrett, 2017; Azzalini et al., 2019), and pioneer theories (Damasio et al., 1991; Damasio, 2006) have stressed indeed the importance of considering physiological processing as an active part of stimulus processing and response, due to the strong connectedness between physiological and cognitive systems. To this purpose, physiological responses to pain observed in other humans vs non-social agents (i.e., robotic agents) have been examined for several reasons, specifically: i. the presence of strong paradigms developed in the field of psychophysiology (e.g., Romano et al. 2014) that could be employed in the ASD research to fill-in the gap in the literature investigating pain experience in this population; ii. the increasing focus on ASD non-social symptoms among which sensory processing abnormalities such as hyper/hypo reactivity to sensory inputs (APA, 2013).

Pain perception, pain anticipation and responses to pain of others

Pain is a complex phenomenon resulting from the interaction of neuroanatomic and neurochemical systems, as well as of cognitive, sensory and affective processes (Garland, 2012). At a bottom-up level, pain is modulated by neurophysiological and neurochemical factors allowing the transduction and the transmission of the information related to the painful source, through the peripheral nervous system, to the central autonomic nervous systems (Garland, 2012). This process can be triggered by the mediation of specific receptors called nociceptors which give rise to the type of processing defined nociception (Garland et al., 2012). This bottom-up processing terminates at a neural level with the involvement of several cortical and subcortical regions involved in the sensory and affective experience of pain, that are the thalamus, the amygdala, the hypothalamus, the periaqueductal grey, the basal ganglia, and the insula (Sherman & Guillery, 1996; Willis & Westlund, 1997; Tracey & Mantyh, 2007). The involvement of cortical and subcortical areas determines the trigger of top-down processes that are able to modulate the sensory experience of pain. For instance, pain experiences can be conditioned by cognitive appraisal, whereby the individual evaluates the meaning of internal or external sensory signals (Garland, 2012). Therefore, pain cognitive processing is at the basis of the high heterogeneity and subjectivity of painful experiences. Interestingly, the cognitive appraisal of painful sources is strongly interconnected with the affective component of pain processing. The evaluation of a painful stimulus may indeed dramatically change based on the level of unpleasantness attributed to the stimulus (Price, 2002). From a neurobiological perspective, change in pain intensity results in altered activations of the somatosensory cortex, whereas change in pain unpleasantness results in an altered activation of the anterior cingulate cortex (Rainville et al., 1999; Fuchs et al., 2014). This is the reason why experienced runners perceive the “burn” in the muscles as a pleasant indicator of increasing strength, whereas beginners perceive the same sensation as unpleasant (Garland, 2012).

The cognitive dimension of pain is also reflected by the ability to anticipate the negative consequences of a potentially harmful stimulus. Previous studies have indeed demonstrated that the autonomic nervous system does not respond only to real painful stimulations but also to harmful stimuli approaching the skin without touching it. This type of anticipatory response has been called pain anticipation (Porro, et al. 1998; Brown and Jones 2008). Pain anticipation involves many brain areas triggered in pain perception, although in absence of a real harmful stimulation. For example, Porro and colleagues (2002) found an anticipatory response in the primary sensory cortex, anterior cingular cortex, insula and prefrontal medial cortex (Porro et al. 2002). Pain anticipation plays a key adaptive function that is to allow the avoidance of harmful stimuli through the initiation of protective behaviors (Palermo et al. 2015). Even though the mechanisms underlying pain anticipation are not completely clear yet, there is evidence suggesting that it may depend on the sense of body ownership and on the own body representation (Tsakiris 2010; Rohde et al. 2011; Romano et al. 2014). For instance, Romano et al. (2014) found a significantly low anticipatory response when a threatening stimulus approached the controlesional hand in patients with somatoparaphrenia. On the other hand, the effect did not emerge in patients with anosognosia for sensory deficits and hemiplegic patients with no deficits of ownership or sensory awareness (Romano et al., 2014).

An increasing evidence has shown the existence of an overlap between the responses to self-experienced pain and pain observed in others. Specifically, it was reported a similar pattern of brain responses described in the anterior cingulated cortex, anterior insula cortex, somatosensory and inferior frontal regions (Morrison et al., 2007; Singer et al., 2004; Jackson et al., 2005; Fallon et al., 2020). According to pioneer models, this empathetic response would result from the automatic activation of mirroring responses during the observation and perception of another person’s state (Preston & deWaal, 2002). However, other evidence showed that higher-level cognitive processes can intervene to modulate the responses to others’ pain. In particular, several factors able to modulate pain empathetic responses have been identified, which include contextual factors, intentionality, relevance, biases, and in/out-group status (Singer, 2006; Chen et al., 2007; Akitsuki & Decety, 2009; Azevedo et al., 2014; Fallon & Stancak, 2015). Another crucial component involves the ability to distinguish self-experience from other-experience (Lamm et al., 2016). This ability results from the awareness that own state has been triggered by the observation of another target person (Singer & Lamm, 2009). According to the Russian-Doll model, this self-other distinction process fosters the developmental change from primordial (i.e., emotional contagion) to evolved forms of social and emotional processes such as sympathy or perspective taking (de Waal, 2008). This developmental process was demonstrated to rely on the maturation of the temporoparietal junction (de Waal & Preston, 2017), although other studies found also supramarginal and lateral occipitotemporal activations related to this function (see Fallon et al., 2020 for a review).

Pain experience and anticipation in ASD

The perception of pain in individuals with ASD represents a very complex area of research due the small number of evidence and contradictory findings. In principle, clinical case studies pointed out that children with ASD would exhibit reduced pain sensitivity compared to neurotypically individuals (Allely, 2013). These conclusions were mainly based on clinical observations showing that ASD participants respond with less intensity to painful stimulations that TD participants. However, these clinical findings were demonstrated not to be in line with experimental results reporting complete opposite patterns. For instance, Tordjman and colleagues' study (2009) revealed higher heart rate and elevated plasma beta-endorphin in response to venipuncture in individuals with autism, which is an indicator of enhanced physiological stress (Tordjman et al. 2009). On the same end, a more recent study came to very similar conclusions. In this study, participants were required to select a level of stimulation, on a 5-points Likert scale, that they would have perceived as moderately painful. ASD participants chose a significantly lower level of stimulation, compared to TD participants, reflecting a lower pain tolerance threshold (Gu et al. 2018). Other behavioral studies reported increased pain sensitivity in both children (Nader et al. 2005) and adults (Cascio et al. 2008) with ASD. A plausible interpretation about the discrepancy between clinical and experimental evidence is that ASD individuals would not express and report their discomfort to painful stimulations as TD individuals would (Allely 2013). Therefore, this atypical pain expression would lead caregivers and professionals to misinterpret pain signals by labelling them as pain insensitivity.

Despite the importance of studying pain anticipation to better understand the cognitive components of pain processing, the study of pain anticipation in ASD is another under-investigated area. Understanding physiological anticipatory responses can indeed provide a better view on the mechanisms of pain experience in this population. Pain anticipation depends both on the interception of pain physical experience (somatosensory marker) and on the recognition of possible painful sources (cognitive representation of pain), fostering faster escaping and avoidance protective responses from the noxious stimulus (Ploghaus et al. 1999). From a clinical perspective, the underestimation of the consequences of a painful stimulus can lead to dangerous self-harm behaviors, as in the case of ASDs (Maddox et al. 2017). For example, previous literature findings revealed that adolescents with non-suicidal self-injury exhibit low physiological arousal before painful stimulation (Koenig et al. 2017) and that, more generally, individuals who do not show aversion towards anticipated pain are more likely to engage in self-injury (Nock 2010). To the best of my knowledge, there is only one study examining pain anticipation in ASD individuals. Specifically, this study analyzed pain anticipation in adults with high functioning ASD by developing a pain anticipation Functional Magnetic Resonance Imaging (fMRI) paradigm (Gu et al., 2018). Results indicated greater activation of the rostral and dorsal anterior cingulate cortex in ASD participants, compared to TD group, whereas no insular activation was found. According to the authors' interpretation, this effect might be an indicator of augmented cognitive processing in ASD participants during pain anticipation experience (Gu et al., 2018). However, it is possible that these results are partially due to the nature of the task where participants were continuously under cognitive effort – i.e., predicting whether a stimulus was harmful or neutral by relying on cues preceding the stimulation. On the other hand, other two studies reported an atypical sense of body ownership and difficulties in integrating visuo-tactile information in ASD population (Cascio et al. 2012; Paton et al. 2012) that, as shown by the literature mentioned before ahead, usually results into a reduction of anticipatory responses.

Physiological responses to pain of others in ASD

As well as literature on pain anticipation and perception, there is also a certain degree of inconsistency related to evidence on the perception of others' pain in ASD. On the one hand, atypical responses to others' pain in individuals with ASD were reported. For instance, Minio-Paluello and colleagues (2009) found an absence of embodied isomorphic reactions to others 'pain, as measured by the motor-evoked potentials (MEP; Minio-Paluello et al. 2009), in ASD participants that is an indicator of absent empathic pain responses. Specifically, ASD participants' responses were not congruent to the saliency of the pain attributed to the agent, meaning that ASD participants coded others' pain by taking a self-oriented instead of an other-oriented stance. A study by Gu et al. (2015) revealed heightened SCR and increased neural activity in the Anterior Insular Cortex (AIC) reflecting an abnormal neurophysiological overreaction related to others'pain processing (Gu et al. 2015). On the other hand, another study reported intact empathetic responses in ASDs (Hadijkhani et al., 2014). In detail, this study did not find differences in the levels of activation in the areas involved in pain sharing during the view of video clips of actors in pain. It has to be noted that this result may be affected by the fact that only facial expressions, and not body cues, were shown. Finally, to the best of my knowledge, no studies considering the very early stage of empathy for pain process, that is when a noxious or harmful stimulus is approaching another human skin before touching it, have been published so far.

Physiological responses to pain of humanoid non-social agents in ASD

In Chapter 2, a systematic examination of the AB towards non-social stimuli in ASD individuals was reported. Previous studies have also focused on the high sensitivity and interest in robotic stimuli in ASD individuals (Kim et al. 2013; Kajopoulos et al. 2015; Kuzamaki et al. 2018). For instance, Kim and colleagues (2013) found that ASD participants prefer speaking and interacting with robotic agents rather than human or computer game interaction partners (Kim et al., 2013). In addition, robotic-based interventions were reported to lead to better social and communication outcomes in ASD than TD children (Kuzamaki et al. 2018), by reflecting a specific preference for this type of non-social stimuli in children with ASD (Klin et al. 2009; Kuzamaki et al. 2018). However, these findings have been mainly raised by studies testing the level of social cognitive engagement between the autistic person and the robot, by relying on parameters such as joint attention and interactions' frequency. Contrarily, to the best of my knowledge, no previous literature considered physiological reactions related to the processing of these stimuli, for instance, in situations of pain or possible painful conditions.

Aims of the present study

In light of the theoretical background described before ahead and the purposes of the present dissertation, the present study was targeted at comparing physiological responses to the observation of painful stimuli touching or approaching social (humans) and non-social (robots) agents in ASD and TD individuals. Physiological responses were measured through the detection of the Skin Conductance Responses (SCR). Both pain anticipation and pain perception were measured to provide a complete analysis of the pain experience in these two populations.

To answer these research questions, a traditional statistical approach (General Linear Model) was combined to a more advanced analytics approach combining deep learning (Artificial Neural Networks, ANNs) and data mining techniques. Specifically, after running

GLM analyses, the most emerging relevant patterns were explored by performing complex computational analyses.

ANNs are computational systems, inspired by the functionality of the human brain, that simulate the structure and the functioning of biological neurons (Baldini et al. 2018). ANNs mimic this functionality to process inputs and generate outputs. For instance, a typical application of ANNs in healthcare and neuroscience analytics is to allow the prediction of output labels (e.g., clinical diagnoses) inputted into the system and to find patterns or anomalies in complex datasets. The use of deep learning and Machine Learning (ML) techniques has been increasing both in medical and the psychological research (Orrù et al. 2019; Topol 2019). One of the main advantage of these techniques is indeed to minimize the replicability issues that often occur when adopting inferential approaches, by relying on complex validation algorithms. These algorithms are indeed based on strict validation procedures in which different subset versions of a dataset are randomly selected and tested. In the case of the present study, the ANN approach was performed along with an innovative data mining approach aimed at understanding the specific connections among the variables of the study. This mapping method, called Minimum Spanning Tree (MST), is able to detect connectivity traces (i.e. associations) among variables through an artificial adaptive system (Buscema et al. 2008).

Method

Participants

Twenty-two (N = 22; mean age = 26, SD = 2.67; Females = 7; mean education level = 2.23, SD = 0.53, where 0 was ‘primary school degree’ and 4 was ‘PhD/Master’) TD neurotypical participants and twelve (N = 12; mean age = 30, SD = 11.50; Females = 5, mean education level = 2.42, SD = 0.79, where 0 was ‘primary school degree’ and 4 was ‘PhD/Master’) participants with ASD took part in the study. The two groups were matched for age (t(32) =

1.19, p = 0.25), gender ($\chi^2(1) = 0.33$, p = 0.56) and education (t(32) = -0.835, p = 0.41). All the ASD participants have received an official ADOS-2 (Autism Diagnostic Observation Schedule, Second Edition; Lord et al. 2003) diagnosis by a multidisciplinary team of the Italian National Health System (Sistema Sanitario Nazionale), in accordance with the Italian Society of Child and Adolescence Neuropsychiatry guidelines (Società Italiana di Neuropsichiatria Infantile e dell'Adolescenza; SINPIA, 2017). In the eventuality participants were not diagnosed through ADOS-2 assessment, an ad-hoc ADOS-2 Module 4 administration was carried out by the laboratory's PI (Professor Paola Ricciardelli, chartered psychologist who attended a dedicated training). The ADOS-2 scores of experimental group participants are reported in Table 1. ASD participants were recruited through the collaboration with clinical institutions and non-profit organizations in the Milan area.

ASD participants had not psychiatric comorbidities or cognitive impairment diagnosis. Plus, they were all either university students or individuals performing high-skill jobs (e.g., computer engineers, technology consultants, etc.). Control group participants were adults with typical development and without any history of psychiatric, neurological or medical disorders. Both ASD and TD participants filled out the Autism Quotient (AQ; Baron-Cohen et al. 2001) before taking part in the study to assess the presence of autistic traits in the two groups, that served as a further manipulation check of participants' assignment to the two groups.

Participants gave their written informed consent before starting the experiment. The study was conducted in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki and fulfilled the ethical standard procedure recommended by the American Psychological Association (APA). The experiment was approved by the Ethics Committee of the University of Milano-Bicocca.

Table 1. *ADOS-2 Module 4 scores of experimental group participants; *ASD cut-off = 10*

ADOS-2 – Module 4 scores	**M**	**SD**
Language and communication	4.12	1.12
Social Interaction	6.62	1.92
TOTAL	10.74*	2.43

Stimuli

Seventy-two (72) stimuli combinations were administered to each participant while SCRs were recorded. Stimuli consisted of either painful/noxious stimuli (i.e., a sterilized needle) or neutral ones (i.e., cotton bad) (Forgiarini, et al. 2011; Romano et al. 2014). Neutral stimuli were administered to provide a baseline stimulation to compare with painful stimulations. Two types of stimulation were delivered: real (i.e., needle touching the skin) or anticipated (i.e., needle approaching the skin without touching it). In the real stimulation, the stimulus actually touched the skin of the hand in the area corresponding to the proximal phalanx of the middle finger. In the anticipatory condition, the stimulus approached the same region of the hand but without touching it. In detail, the stimulation was stopped at a distance of approximately 0.5 from the skin (Romano et al., 2014). These stimulations were delivered to three different targets, namely the hand of the participant (self-condition), another human agent's hand (other-condition) and a robotic arm of human-like size (robot – condition).

Experimental set-up and procedure

Participants sat at a table in front of the experimenter with their hands resting on the table (Figure 1). Three paper panels were located on the right, left and in front of the participant. The panels were positioned in a way that only the hand of the other social agent (i.e., male confederate), positioned on the right, and the anterior section of the robotic arm, could be seen. The panel located in front of the participant had to shield the experimenter's hands and the stimuli selected by the experimenter in each trial (Romano et al., 2014). Accordingly, participants could not predict the kind of stimulation (noxious or neutral) they were going to receive until the experimenter showed the stimuli (i.e., needle or cotton bad) from behind the panel.

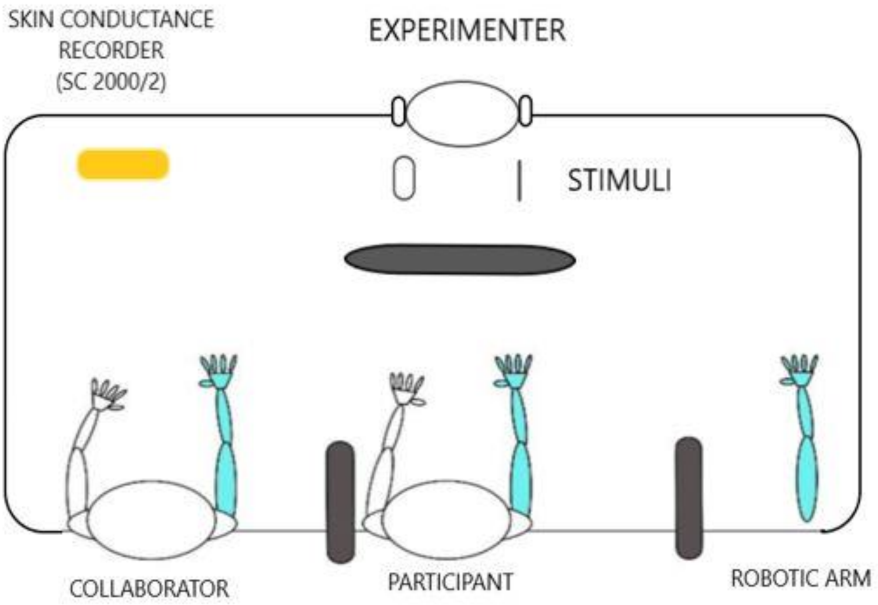
After receiving all the instructions, participants were blindfolded to allow the entry of the confederate inside the laboratory and to put the robotic arm in position. Participants were instructed to remain as still as possible and keep regular breathing throughout all the experiment. They were also required to keep their gaze toward a fixation point indicated at the center of the panel positioned in front of them. Stimulation was carried out by the experimenter who was properly trained to maintain the same trajectory for all the stimulation trials. Participants were asked to follow the stimulus trajectory with their gaze for the whole trajectory duration in order to avoid to get distracted.

SCRs were recorded using a SC2000/2 amplifier (Simple Scope, UFI). The amplifier was connected to the computer through a parallel port. The gain parameter was set at 10 µmho/V and the signal sampled at 100 Hz. The signal was acquired by applying two electrodes (1081 FG) placed on the first phalanx of the index and ring fingers of the left hand. The signal was obtained by means of the two electrodes. With the aim to improve signal-to-noise ratio, a saline conductive paste was applied to the electrodes. Data were digitalized using the SC-2000 software. The experimenter sent the event-related trigger at the beginning of each trial by using a keyboard connected to the amplifier. The trigger was sent whenever the stimulus appeared from behind the panel. At the end of the experiment, to rate the perceived noxious valence of the needle, participants were asked to report how much noxious the needle stimulation was on a scale from 0 to 10.

Research design

The experiment was structured into a 2 (type of stimulation: real, anticipated) x 2 (type of stimulus: needle, cotton bad) x 3 (self, other social agent, robot) experimental design with 12 conditions. Each condition was repeated 6 times for a total number of 72 trials. Trials were divided into six blocks, each one including twelve trials. Each condition was within-blocks randomized. The randomization was performed to control for autonomic response adaption which is a very common phenomenon emerging in the presence of constant and repetitive stimulations (Levinson and Edelberg 1985). Each block was divided by a short break (30 sec).

Figure 1. *Experimental set-up.*



Data preprocessing

The analysis of SCRs was conducted by adopting a peak-to-base approach. (Lyken and Venables 1971; Rhudy et al. 2007; Rhudy et al. 2010; Breimhorst et al. 2011). The difference between the maximum value detected in 7-seconds-post stimulus and the baseline (i.e. average value of the 0.3 sec pre-stimulus time window) was computed. Peak-to-base responses were within-subject normalized and transformed into z-scores (Rhudy et al. 2007, 2010; Romano et al. 2014). Data preprocessing was conducted with R software by implementing a dedicated code (R Core Team 2017). SCRs were extracted for each experimental condition both in a across-blocks aggregated form and blocks-separated form (e.g. Pain Self Block 1, Pain Self Block 2 etc.). Pain perception (real stimulation) and anticipatory responses (anticipated condition) were separately analyzed.

Data analysis

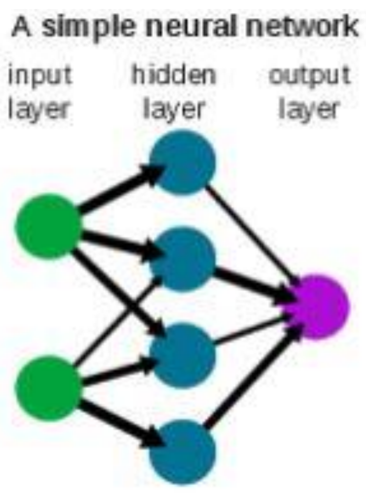
Data analysis was divided in three steps. At first, t-tests were conducted to compare AQ and self-pain rating responses in the two groups. Secondly, General Linear Models (GLMs) were applied to investigate the effect of the independent variables on the dependent variable (SCRs). Thirdly, the most relevant results obtained through GLM were further analyzed by relying on a sophisticated computational approach combining deep learning (Artificial Neural Networks, ANNs) and data mining.

GLMs consisted of two full factorial Analysis of Variance (ANOVA) models with four independent variables, that are the type of stimulus (2 levels: painful vs neutral; within-subjects), the type of target (3 levels: self-hand, other-hand, robotic-hand; within-subjects), and the groups (2 levels: ASD vs TD; between-subjects). The dependent variable was the SCRs in both models. In detail, real perceptual responses were analyzed in the first model, whereas anticipated responses were considered in the second model. Before running the models, a check of the assumptions was conducted to correctly perform GLM analysis.

Artificial Neural Networks

After performing GLM statistics, AANs were used to predict the diagnostic class (ASD vs Control) starting from features-variables of the study. ANNs are computational systems that simulate the structure and the functioning of biological neurons. As well as biological neurons, neural networks receive input signals that are processed and then transformed in output signals transferred to other neurons. The typical ANN architecture is a layer structure in which each layer contains specific nodes with specific computational roles (Figure 2). The first layer is defined input layer, and it consists of nodes receiving inputs to feed into the network. After passing through the input layer, the information is passed to intermediate layers called hidden layers. In these layers, signals received from the input layer are processed and then forwarded to the output layer. The output layer may consists of one or more nodes, and, in the lexicon of traditional statistics, corresponds to the dependent or outcome variable. It is important to note that each layer's node can activate one or more nodes of the subsequent layer. The activation is set by numerical values defined weights. In other words, weights enable to determine the strength of the connection between different layers' nodes. More precisely, the weighted sum of different weights conveys to an activation function determining whether a node will be activated or not. Weighted associations are learnt through backpropagation algorithms, namely a process which error rate (i.e., loss function) is minimized through the correction of weights' values through the application of optimization algorithms.

Figure 2. *An example of basic AAN architecture (Maind & Wankar, 2014)*



In the current work, AAN architecture consisted of one input layer containing nine nodes (i.e., predictors), one hidden layer containing four nodes, and one output layer containing two nodes (i.e., ASD vs TD group). The selection of nine nodes in the input layer resulted from the application of an evolutionary algorithm, called TWIST (Training With Input Selection and

Testing), which is an evolutionary algorithm serving as both a dimensionality reduction and a validation technique (Buscema et al., 2010; 2013; Rotondano et al., 2011). TWIST evolutionary system is constituted by a population of Multilayer AANs. Each ANN is subjected to the learning of a subset of the global dataset, and it is blindly tested with another subset. At this point, some of the original attributes are selected and two optimal subsets for training and testing, with a reduced number of variables, are generated. In detail, the validation process was performed to contain the risk of data overfitting by evaluating the model's generalization and replication capabilities. Validation was structured into the following five steps:

i. Dataset splitting into two subsets: subset A (used for training) and subset B (used for test).

ii. ANN performed on the Training Set. ANN is trained to associate the input variables with outcome variables (diagnostic group).

iii. At the end of the training phase, the weights matrix compute by the algorithm is saved and frozen together with all of the other parameters used for the training.

iv. The Testing Set (subset B) is shown to a virgin twin (same architecture and base parameters) ANN with the same weights matrix of the trained ANN, acting as final classifier. This operation takes place for all records in the testing set and result (right or wrong classification) is not communicated to the classifier. This allow to assess the generalization capability of trained ANN.

v. In a second run, another virgin ANN is applied to subset B which is used as training subset and then to subset A which is used as a testing subset.

Minimum Spanning Tree

Despite the strong computational relevance and prediction power, the complexity of AANs often results in a lack of interpretability and explicability. To overcome this issue, other techniques can be applied to deepen the associations emerging from the computed network. In the present work, a specific algorithm called Minimum Spanning Tree (MST) was implemented to identify the most reliable data association structure. The MST algorithm was originally described by the Czech scientist Otakar Boruvka (1926), and then readapted as a deterministic algorithm by Kruskal (1956) and last decades' research (e.g., Buscema, 2008; Drenos et al., 2015). MST provides a view of the associated variables. The importance of the variables in the graph is given by number of links. Specifically, hubs can be defined as the variables with the maximum number of connections in the graph. The clustering distance among two variables is related to their separation degrees. In other words, the association among variables varies as a function of the distance separating them. The general assumption is that, since all systems naturally tend to minimum energy state, the graph generated by MST expresses the fundamental information of the system. It is important to note that distances are not computed through a unique formula, but optimal distance metric function has to be identified before applying MST. In the case of the present study, the metric function with the best clustering accuracy, based on clinical group distinction (i.e., ASD vs TD), was selected. In detail, four metric functions were tested: Euclidean, Linear Correlation, Contractive Map, Prior Probability. As shown in Table 2, the Prior Probability resulted to be the best solution.

Table 2. *Performance of metric functions*

Metric function	**No. incorrect links**	**Clustering accuracy**	**Map reliability**
Euclidean	13	61.70%	Low
Linear correlation	12	64.70%	Fair
Contractive map	10	70.60%	Good
Prior Probability	8	76.50%	Very good

Prior Probability is given by the ratio of probabilistic concordance and discordance among pairs of variables. Firstly, the prior probability of co-occurrence between any couple of variables of the assigned dataset has to be calculated:

$$A_{i,j} = -\ln \frac{\frac{1}{N^2} \cdot \sum_{k=1}^{N} x_{i,k} \cdot (1 - x_{j,k}) \cdot \sum_{k=1}^{N} (1 - x_{i,k}) \cdot x_{j,k}}{\frac{1}{N^2} \cdot \sum_{k=1}^{N} x_{i,k} \cdot x_{j,k} \cdot \sum_{k=1}^{N} (1 - x_{i,k}) \cdot (1 - x_{j,k})};$$

$$-\infty \leq A_{i,j} \leq +\infty; \quad x \in [0,1]; \quad i, j \in [1, 2, ..., M]$$

where :

$A_{i,j} =$ Association strenght between any couple of variables x_i and x_j of the assigned dataset;

$x_i =$ value of any variable scaled between 0 and 1;

$N =$ Number of records of the assigned dataset;

$M =$ Number of variables of the assigned dataset.

Then, it is possible to transform the matrix of the variables association into a non-linear distance matrix, and to convert the assigned dataset is transformed in an undirected weighted graph, where MST is applicable:

$$d_{i,j}^{[A]} = MaxA - A_{i,j}; \quad \text{where } MaxA = \text{Maximum A matrix value.}$$

Results

AQ and pain rating responses

T-tests revealed that ASD participants had significantly higher AQ scores than control participants (t = 9.01, SE = 2.31, p < .001 , Cohen's d = 3.23), and that no control group participant resulted to have AQ greater than 25 (first risk cut-off). As concern the rating of pain experience, ASD participants reported to have experienced the needle as less painful than control participants (t = 3.23, SE = 0.63, p = .003 , Cohen's d = 1.16).

General Linear Models

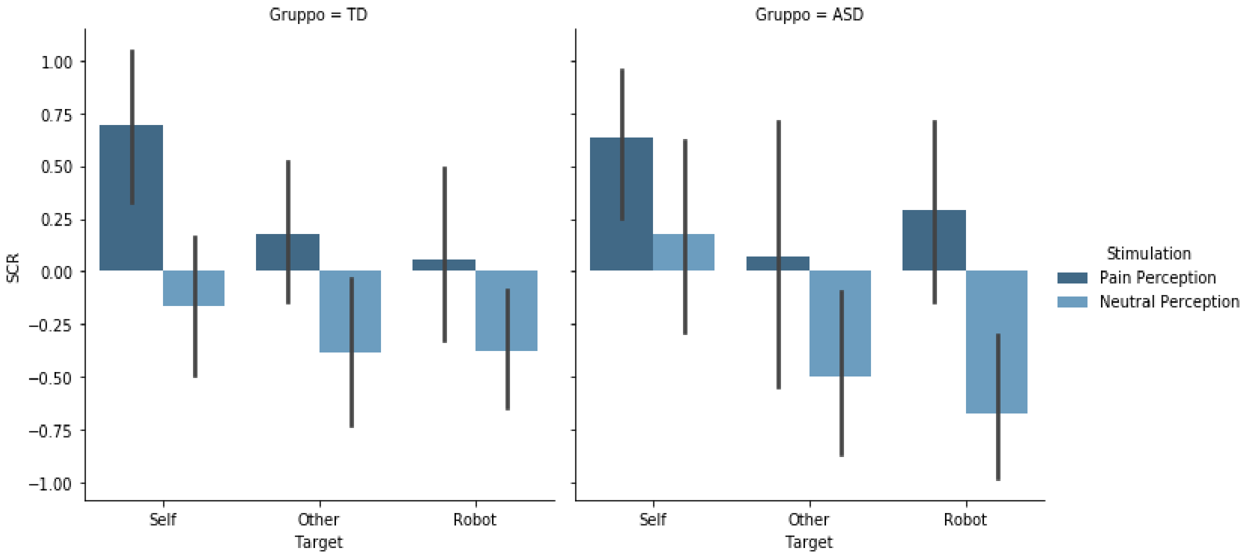
The first ANOVA model was conducted on real perception data (Fig. 3). Two main effects were found to be significant, that were, respectively, the effect of type of stimulus (F(1,64) =

29.103; $p < .001$; partial-$\eta 2 = 0.476$) and the effect of the type of target ($F(2,64) = 5.203$; $p = .010$; partial-$\eta_2 = 0.134$). These effect were further investigated by conducting post-hoc analyses through the application of Bonferroni's correction. Post-hoc analysis on the type of stimulus effect showed greater SCR responses related to the painful ($M = 0.316$) stimulation than neutral ($M = - 0.950$) stimulation ($t(32) = 5.390$; $p < .001$). As regards the target effect, post-hoc showed a significant difference between SCR responses related to the Self condition ($M = 0.671$) and the Other human agent ($M = 0.139$) condition ($t(64) = 2.681$; $p = 0.028$), and between the Self condition and the Robot agent ($M = 0.140$) condition ($t(64) = 2.773$; $p = 0.022$). No main effect of group variable and interaction effects were found to be significant (all $p > 0.340$).

The second ANOVA model was conducted on pain anticipation data (Fig. 4). One main effect was found to be significant that was the type of stimulus effect. $F(1,64) = 6.515$; $p = 0.016$; partial-$\eta 2 = 0.169$). Post-hoc analysis with alpha corrected through Bonferroni's correction Post-hoc analysis on the type of stimulus effect revealed greater SCR responses related to the painful ($M = 0.206$) stimulation than neutral ($M = - 0.619$) stimulation ($t(32) = 2.550$; $p = 0.016$). Plus, a substantial trend towards significance related to the group x type of stimulus x type of target was found ($F(2,64) = 2.849$; $p = 0.065$; partial-$\eta 2 = 0.082$). No other main effect or interaction effect were found to be significant (all $p > 0.430$).

Descriptive trends and GLM analyses suggested the presence of a relevant trend related to pain anticipation responses, whereas no substantial effect emerged when analyzing and exploring pain perception data. Therefore, only pain anticipation data were considered for the development of computational models.

Figure 3. *Catplot depicting pain perception responses in the two groups.*



Artificial Neural Networks

First of all, the TWIST algorithm enabled to remove noisy variables by selecting 8 attributes that comprised aggregated, data split based on the block in which the stimulation was delivered and the subjective rating of the painful stimulus. The eight variables were: Painful Stimulus Block 5 (Pain Self 5), Painful Stimulus Block 6 (Pain Self 6), Painful Stimulus Robot Aggregated (Pain Robot AGG), Neutral Stimulation Robot Aggregated (Neutral Robot AGG), Neutral Stimulus Self 4 (Neutral Self 4), Neutral Stimulus Other social agent Block 3 (Neutral Other 3), Neutral Stimulus Other social agent Block 4 (Neutral Other 4), Neutral Stimulus Robot Block 4 (Neutral Robot 4), and the subjective rating of pain (Reported pain). Accordingly, the new data set was composed by 9 variables by determining a neural network architecture containing one input layer (9 inputs), one hidden layer (4 nodes) and one output layer (2 nodes). Figure 5 shows the final ANN architecture. It has to be noted that the number of hidden layers equal to one, as well as the low number of hidden layer nodes (n=4), was chosen due to the low number of records in order to avoid overfitting.

Figure 4. *Catplot depicting pain anticipation responses in the two groups.*

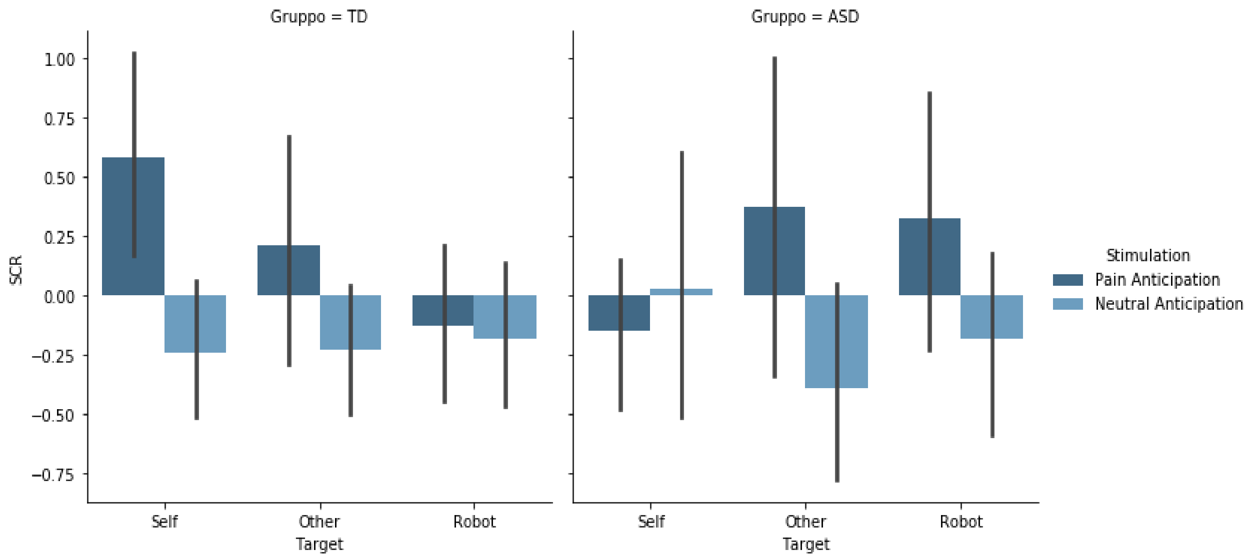


Table 4 shows the metrics obtained through the Twist and ANN implementation, and Figure 6 the related receiver-operating characteristic (ROC) curve. Global accuracy was about 91.25%, whereas sensitivity, specificity and ROC area under the curve (AUC) were, respectively, 91,67%, 90,83% and 89%.

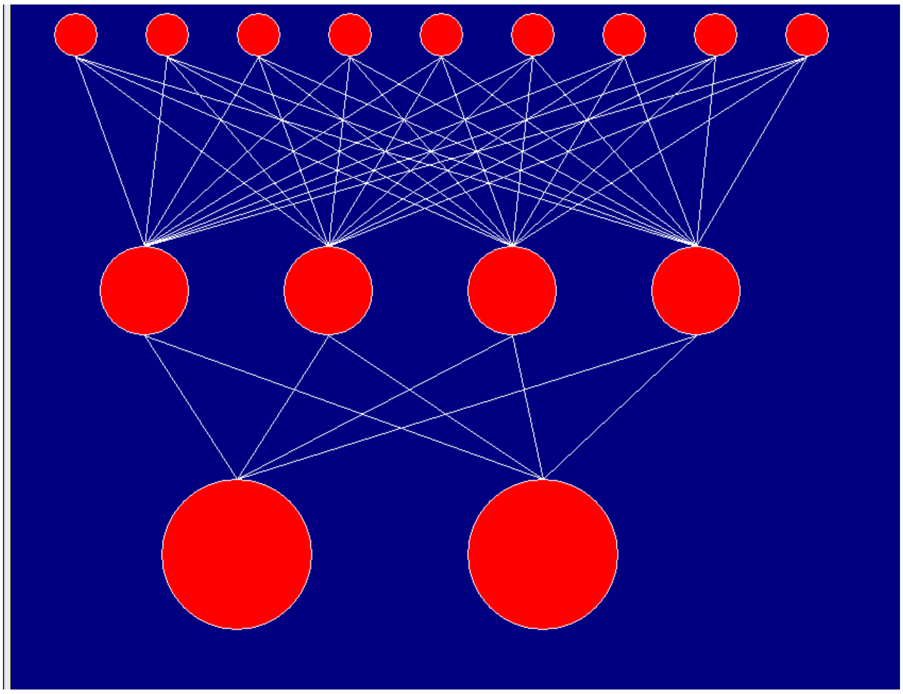
Minimum Spanning Tree

The semantic connectivity map provides a view of the associated variables (Fig 7). As mentioned before ahead, hubs can be defined as the variables with the maximum number of connections in the graph, whereas the clustering distance among two variables is related to their

Table 3. *AAN metrics.*

Neural network	Sensitivity (%)	Specificity (%)	Overall accuracy (%)	ROC AUC
4 hidden units (ab sequence)	83.3	91.67	87.5	0.83
4 hidden units (ba sequence)	100	90	95	0.93
Average	91.67	90.83	91.25	0.89

Figure 5. *AAN architecture with 9 inputs units (input layer), 4 hidden units (hidden layer) and 2 output units (output layer).*



separation degrees. It is important to note that the number of input variables in the map has increased from 9 to 18. This is due to the application of a method aimed at avoiding the fuzzy positioning of the scaled variables pointing out to the higher values. By subtracting the scaled value from 1 (e.g. 0 becomes 1), the system is allowed to project and point out the fuzzy position of the variable also according to its lower values. In the map these two different forms were named as "high" and "low". This scaling method was necessary to make possible a proportional comparison among all the variables, and to understand the existing links of each variable when the values tended to be high or low. Complement values (binarization) were obtained for each of the 9 variables considered for data mining within the database.

It is possible to note from Figure 7 that the two target variables (ASD and Controls) are clearly separated and, thus, hubs of the system, each one in association with six variables. ASD nodes results to be connected with low reported pain, low pain anticipation in blocks 5 and 6, high pain anticipation in the robot condition with data aggregated across-blocks, low pain anticipation in the in the third and the third blocks of the other condition when the stimulus was neutral. In contrast, TD nodes are connected with high reported pain, high pain anticipation in blocks 5 and 6, low pain anticipation in the robot condition with data aggregated across-blocks, low pain anticipation in the third and the fourth blocks of the neutral condition when the target was the other human agent. Taken together, these results suggest the existence of two clearly distinct patterns at the basis of the differences between the control group and the ASD group. Theoretical details on the implications for the understanding of social vs non-social stimuli physiological processing will be presented in the discussion.

Discussion

The aim of the present study was to compare physiological responses to real painful stimuli (pain perception) or anticipatory painful stimuli (pain anticipation) touching or approaching social (humans) and non-social (robots) agents in ASD and TD individuals. An ecological Skin Conductance paradigm was designed to answer the main research questions. Participants were required to focus on the trajectory of either a painful stimulus (a needle) or a neutral stimulus (cotton bad) touching (perception) or approaching (anticipation) their own hand (self condition), another's person hand (other condition) or a robot's hand (robot condition). Skin conductance response (SCR) was measured in each condition. Data analysis relied on the integration of GLM statistics (i.e., ANOVA) and computational methods. Specifically, computational analysis consisted of the combination of ANNs and a data mining technique called Minimum Spanning Tree (MST). The present works has focused on both pain perception and pain anticipation so as to provide a complete view of pain experience in the ASD population, by aiming at disentangling physiological responses to real pain and anticipatory responses to a painful stimulus, that are more related to an internal representation of the pain experience (Brown et al., 2008).

Figure 6. Receiver Operating Characteristic (ROC) curve of the two experiments. The ROC curve is a performance measurement metric for classification problems considering different cut-off points (i.e., in this case the cut-off is a 50 % probability). It is plotted with the specificity (SP) against the sensibility (SE). The plot below clearly shows how the SP and SE are both consistently high.

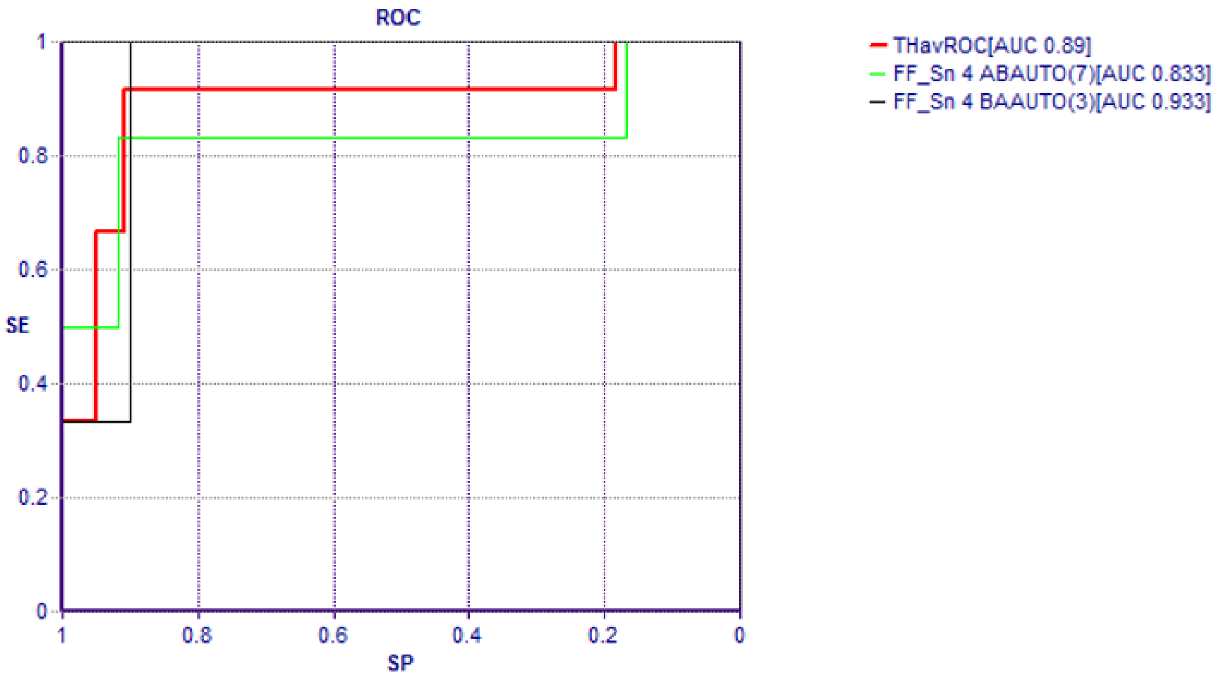
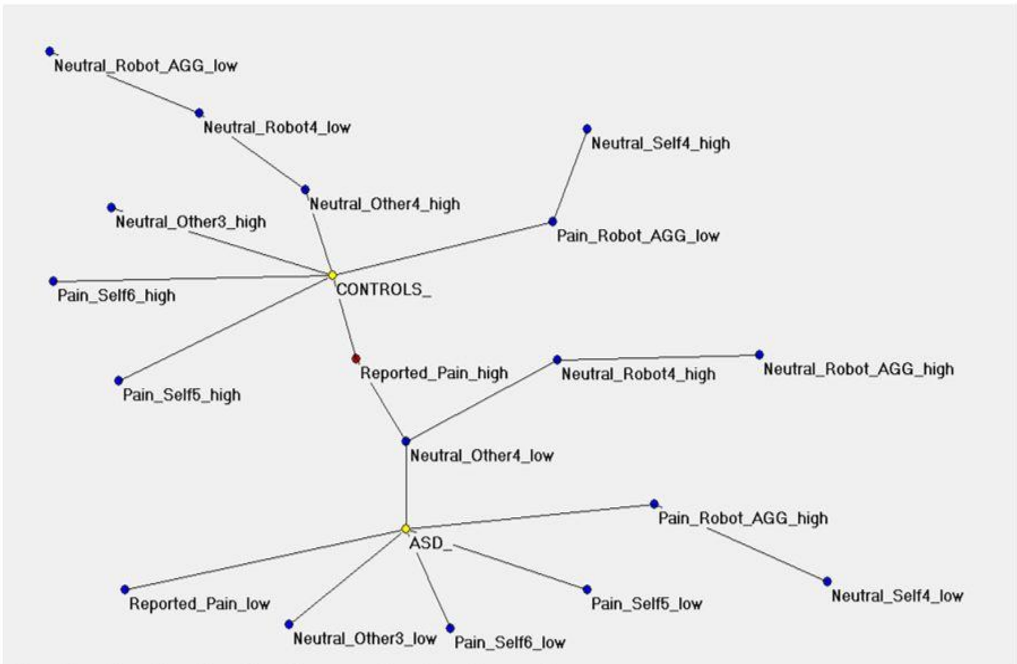


Figure 7. *Semantic Connectivity Map depicting variables' association*



General Linear Models did not reveal any statistical difference between groups when the painful stimulus was delivered to the participants (i.e., pain perception), whereas a substantial trend to significance was identified when participants observed the painful stimulus approaching the skin without touching it (i.e., pain anticipation). This discrepancy further stresses the need to distinguish pain perception and pain anticipation which are partially different mechanisms. Specifically, the effect of interest was the three-way interaction among the type of stimulation, the stimulation target, and the three groups. Accordingly, only pain anticipation responses were taken into account for computational analysis. The evolutionary TWIST algorithm enabled to extract nine relevant features which were used as inputs of the model. The predictive AAN was 91% accurate in classifying participants in the two groups (ASD vs TD). Finally, the MST enabled to better understand the specific patterns at the basis of groups' differences, by generating a semantic connectivity map (Auto-CM). Since the aim of the present study was to investigate SCRs to social (other humans) and non-social (robot) agents, only this part of evidence will be discussed in the following paragraphs.

Pain anticipation related to social agents (humans)

The anticipation of others 'pain was not found to be relevant to distinguish ASD cases from TD cases. This evidence is in line with findings on empathy in autistic population which showed that the affective-visceral component of empathy is preserved (Jones et al. 2010; Hadjikhani, et al. 2014; Rueda et al. 2015), although probably in a rudimentary form as shown by the Minio-Paluello et al. study (2009). In particular, these findings are coherent with Hadijkhani and colleagues fMRI evidence (2014), that did not reveal any significant difference in the activation of areas involved in pain sharing during the view of video clips of actors in pain (Hadijkhani et al., 2014). Unlike these studies, and Minio-Paluello et al. (2009) and Gu et al. (2015), the present research did not focus only on real perceptual responses but also on anticipatory responses. Accordingly, these findings add a piece of evidence on how ASD individuals process pain of other social agents, by revealing the lack of substantial differences from neurotypical individuals when anticipating pain and harm in others. It is reasonable to speculate that, unlike other populations characterized by affective empathy deficits such as individuals with high psychopathic traits (Decety et al. 2013), the ability to anticipate the harmful consequences of a painful stimulus approaching another person seems to be preserved in individuals with ASD. Conversely, the atypical responses to real stimulation in others, found by other studies (e.g. Minio-Paluello et al. 2009), are likely to describe abnormal sensorimotor responses reflecting a difficulty to bodily mirror what another person is feeling when perceiving pain. It has to be highlighted that no differences related to real painful stimulations have been spotted by the present study. Although it may depend on the low sample size, it is highly assumable that this discrepancy relies on the different research paradigms and techniques (i.e., SCR vs MEP) used in the present study and in the Minio-Paulello's one. Furthermore, it is possible that disentangling real and anticipatory responses has enabled to shed light on two separated mechanisms of physiological processing that were not taken into account in the Minio-Paluello et colleagues' study (2009).

Although focusing on responses to neutral stimulations was not among the goals of the study, an interesting finding deserving deeper consideration emerged. Specifically, data mining analysis revealed lower SCRs in ASD compared to TD participants when the stimulation approaching the other human being was neutral. To the best of my knowledge, there is no previous literature addressing this topic. A possible interpretation is that TD participants tried to overinterpret the other participant's sensation and emotion related to the experience of being touched by the cotton bad. It is indeed well known that touch experience is very subjective and that different stimuli and materials can be differently experienced. Therefore, it is possible that control group participants were more aroused since they were not completely aware of how the other participant was perceiving the cotton bad. On the other hand, previous literature has reported ASD individuals more inclined to process information more systematically (Baron-

Cohen 2006), and less able to cope with stochastic variables or responses in complex systems such as the social world of other minds. This issue should be addressed by future studies address, for instance, by investigating how ASD individuals react to different types of stimulation sources.

Pain anticipation related to non-social agents (robot)

ASD participants showed greater SCRs, compared to TD participants, when the painful stimulus approached the robotic hand. This pattern emerged across the experimental blocks. This interesting evidence may be linked to the increasing number of evidence showing a special interest and motivation to interact with robots in individuals with ASD (Kim et al. 2013; Kajopoulos at al. 2015; Wykowska et al. 2015). The motivation to interact with robotic tools may, in turn, determine an increased attunement with these agents. Given their predictability fulfilling ASD' individuals systematic cognitive style, robots are likely perceived as more predictable and reassuring by this population (Alcorn et al. 2019). Accordingly, it is assumable that ASD individuals tend to attribute a greater sense of agency and intentionality to these inanimate agents. According to the Intentional Stance Model, social cognitive functions, such as mentalizing, empathizing, rely on the fundamental assumption that the other agent is actually capable of having mental states (Dennett 2003; Wykowska et al. 2014). Assuming that inanimate agents have mental states means to attribute the Intentional Stance towards that entity (Wykowska et al. 2014). Adopting an Intentional Stance towards an agent represents a prerequisite to engage and feel attuned with that agent. For example, observing agents considered as intentional activates social brain areas such as those involved in empathy, prosocial behaviors and action understanding (see for a review, Wiese et al. 2017). Plus, previous findings showed that responses to the pain of robots can be observed at later stages of the top-down process of empathy (Suzuki et al. 2015). In other words, taking the cognitive and emotional perspective of a non-social agent requires more cognitive effort and takes longer than for other human beings (Suzuki et al. 2015). It is reasonable to speculate that empathetic responses to robotic agents are not automatic processes but they are modulated by top-down beliefs and individual representations of the agent. Accordingly, ASD individuals would be more likely to represent robots as more "social" than other human beings. Other studies should address these issues to clarify this result.

Limitations of the present study

The small sample size represents a limitation of the present work. The difficulty to find a homogeneous and large sample population is a frequent problem when using a computational approach with a relatively rare condition like ASD (Grossi et al. 2017) in adults. However, the use of such a rigorous validation protocol should have mitigated the impact of this issue, essentially for three reasons. Firstly, the main goal of cross-validation techniques is to prevent overfitting (i.e. a condition that usually occurs when training data records are low) by testing prediction accuracy in a different subset (validation or test set) from the training set (Cawley and Talbot 2010). Unlike traditional training-test protocols using one training set and one test set, our methodology (Buscema and Grossi 2008) implied the use of two sequences of training testing protocol, that are A-B and B-A. Secondly, the TWIST input selection algorithm was implemented so as to reduce the risk of high unbalanced inputs/records ratio, since it was demonstrated a potential source of overfitting (Defernez and Kemsley 1999). In addition, Artificial Neural Networks (ANNs) are based on the principle of functional estimation, namely a condition that intrinsically overcomes the problem of dimensionality (Grossi et al. 2017). Finally, this methodology has been already applied in other studies with modest sample sizes by providing good outcomes in ASD research (Fulceri et al. 2019; Grossi et al. 2017). However, future research should test the replicability of these findings on a larger sample.

Conclusion

The aim of the present study was to examine how ASD and TD individuals physiologically respond to real and anticipated pain of social vs non-social agents. SCRs were measured in a paradigm which consisted of an administration of a noxious stimulus (i.e., needle) which could approach (pain anticipation) or touch (pain perception) participants 'own hand, the hand of another human (other-condition) or a non-social robotic hand (robot-condition). Results showed a close to significance interaction only in the pain anticipation condition, which was further explored through the implementation of computational analysis combining classificatory AANs and data mining techniques. The computational analysis did not show any between-groups difference concerning the physiological responses to pain of other social agents. On the other hand, ASD participants showed a higher response when the robotic hand was approached by the painful stimulus.

With respect to the aims of the present dissertation, these findings add evidence on how ASD individuals process information coming from social (humans) and non-social (inanimate objects) stimuli. In this sense, these results show that the reduced attentional orienting to social stimuli (see evidence presented in Chapter 2), observed in ASD participants, does not necessarily emerge together with a decreased physiological response toward these stimuli. Accordingly, this pattern also contributes to further clarifying the dissociation between the different mechanisms at the basis of social difficulties observed in ASD individuals and other clinical population such as individuals with psychopathic traits (Jones et al., 2009; 2010). On the other hand, the great response to robotic stimuli supports the conclusion that the high attentional priority attributed to non-social stimuli – HAI and mechanical stimuli in particular – can also emerge together with a strong physiological response related to these stimuli. In other words, non-social stimuli (more likely HAI stimuli) are likely to both capture attentional orienting and determine a higher physiological activation in ASD than TD individuals.

The following chapter will continue to examine the mechanisms underlying the different processing of social vs non-socials stimuli in ASD and TD participants, by investigating whether these differences may be the expression of a familiar phenotype or not.

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CHAPTER 4

Attentional biases toward social vs non-social stimuli in parents of children with ASD:

A Dot-Probe study

Introduction

The systematic review of the literature presented in Chapter 2 has pointed out an atypical attentional pattern in ASD individuals, which consists in a reduced attentional bias (AB) towards social stimuli and in increased attentional orienting towards non-social stimuli (i.e., 57 % of the examined papers). In addition, the findings reported in Chapter 3 have indicated how social stimuli can determine a physiological response in ASD participants, which is comparable to the one observed in control participants. Contrarily, an atypical higher physiological activation was observed when ASD participants were anticipating pain in non-social agents.

Autism phenotype was demonstrated to depend on a substantial genetic susceptibility (Schaaf & Zoghbi, 2011; Masi et al., 2015). Around 400-1000 genes were found to be related to increased risk of autism (He et al., 2013). In particular, these genes would explain abnormalities in the developmental stages of the brain leading to neurostructural problems (Krishnan et al., 2016; Masi et al., 2017). However, an exclusive genes-based explanation is still not comprehensive since it was demonstrated to be able to explain only 30% of cases of autism (Schaaf & Zoghbi, 2011; Masi et al., 2015). The remaining part of the variance is likely to rely on concurrent environmental factors emerging throughout prenatal growth and/or postnatal development. Among these aetiologic factors, maternal infection was assumed as a possible prenatal environmental risk factor for ASDs (Malkova et al., 2012) as well as the use of substances such as valproate (a medication primarily used for the treatment of epilepsy and migraine) (Gardener et al., 2011).

The genetic component at the basis of ASDs was also demonstrated to have a phenotypic expression in the so-called Broader Autism Phenotype (BAP; Baron-Cohen & Hammer, 1997; Gerdts & Bernier, 2011). The BAP refers to a consistent number of parents and siblings of children with ASD who manifest behavioural and cognitive features that are comparable to some of the symptoms of ASDs, although in a milder form (Baron-Cohen & Hammer, 1997; Gerdts & Bernier, 2011; Perasso & De Angelis, 2020; Sasson et al., 2013). These characteristics include peculiar linguistic and social-communication skills, repetitive and circumscribed interests, difficulties with social-cognitive abilities, atypical attentional skills and personality traits (for a review see Sucksmith et al., 2011). It is not completely clear whether this broader phenotype can be considered as a behavioural expression of a shared genetic pattern, or the consequence of parenting strategies that parents of ASD children adopt to feel more attuned with their children. In this sense, a recent review by Crowell and colleagues (2019) has pointed out a possible environmental explanation according to which parents of ASD children would tend to adapt to their child's atypical interaction and communication by modifying their own one (Crowell, Keluskar & Gorecki, 2019).

A very few studies have examined attentional orienting patterns to social stimuli vs non-social objects in parents of ASD children. Scheeren and Stauder (2008) addressed this topic by comparing a group of parents of autistic children with a group of parents of TD children on a spatial cueing task where the cue could be either social (eye gaze) or non-social (arrow). Results showed that only fathers of ASD children responded slower in the social cues condition than control parents (Scheeren & Stauder, 2008). An ERP study found similar patterns, although in both members of the dyad. Specifically, parents of autistic children did not exhibit the typical N170 latency advantage for face stimuli, by mirroring the same pattern shown by individuals who received a diagnosis of autism (Dawson et al., 2005). The majority of other studies shed light on face processing mechanisms in parents of ASD individuals, by detecting difficulties to discriminate subtle differences between faces (Wallace et al., 2010), to show sensitivity to direct vs adverted eye-gaze direction (Wallace et al., 2010), and to orient to the eye region by, instead, spending more time fixating the mouth region (Adolphs et al., 2008). Importantly, the reduced relevance attributed to human face was found to emerge together with an increased orienting to HAI objects in only the 20 % of the studies (see Sucksmith et al., 2011 for review), which is a consistently low percentage.

Another issue raising from the analysis of the previous literature regards the lack of studies taking into account how the cognitive profile of the child may contribute to clarifying this common autistic phenotype. An increasing number of evidence has been indeed showing that distinct genetic profiles are at the basis of autism emerging together with Intellectual Disability (ASD-ID) and without Intellectual Disability (ASD-NOID). For instance, according to Groves and colleagues' data, milder manifestations of autism (e.g., high-functioning autism, Asperger's Syndrome etc.) are more characterized by higher levels of hereditability than forms emerging with severe comorbidities such as Intellectual Disabilities (Grove et al., 2019). On the same hand, another study showed that ASD-ID is less heritable than ASD-NOID, since ASD-ID participants were found to have more *de-novo* gene mutations than ASD-NOID (Xie et al., 2020).

Aims of the present study

In light of the theoretical background described before ahead and, in accordance with the purposes of the present dissertation, the goal of the present study was to examine if parents of ASD children exhibit the same reduced AB to the human face observed in individuals with ASD diagnosis, and if this pattern emerges together with a high attentional preference for HAI objects. Specifically, despite the increasing number of genetic evidence showing specific genetic factors distinguishing ASD cases characterized by preserved cognitive and linguistic abilities from those characterized by a comorbidity with Intellectual Disability (Grove et al., 2019; Xie et al., 2020), this cognitive diversity has not deeply taken into account by previous studies on the autism phenotype. Accordingly, the present study was also aimed to examine to what extent this attentional patterns emerge in parents of ASD children with Intellectual Disability (ASD-ID) and parents of ASD children without Intellectual Disability (ASD-NOID).

A Dot-Probe paradigm was designed to answer these research questions. The Dot-Probe task is a validated task used to assess the presence of AB towards specific categories of stimuli (MacLeod et al., 1986). The task involves the presentation of stimuli's pairs, which have to be ignored, prior to the presentation of a target appearing in one of the two stimulus spatial positions, which has to be detected as fast as possible. The underlying logic is to compare response times (RTs) related to trials in which the probe spatially replaces "a cue of interest" (congruent trials), such as social stimuli (for parents of TD children) or HAI stimuli (for parents of ASD children), and those related to trials in which the probe replaces a "neutral cue" (incongruent trials), such as non-social objects. In other words, the cue of interests represents a type of stimulus which is supposed to capture more attention compared to a neutral cue in a given population. Since there are inter-individual variables, such as, for example, autistic traits and social anxiety that can modulate the magnitude of the AB towards social stimuli (Sasson, 2006; Mansell et al., 1999), and, thus, were controlled as a potential source of confounding by comparing the three groups on these two variables and, if significant, by inserting them as covariates of the model.

Method

Participants

Thirty-one (n = 31) parents of children with Autism Spectrum Disorder (ASD parents; mean age = 45, SD = 5.49, Females = 16) and sixteen (n = 16) parents of typically developed children (control parents; mean age = 48, SD = 9.59, females = 9, mean education level = 2.07, SD = 0.59) took part in the study. ASD parents were recruited through the collaboration with clinical institutions and non-profit organizations in the Milan area, and divided in two groups based on the eventual compresence of Intellectual Disability in the child: i.) the ASD-ID group including parents of children with Intellectual Disability (n = 19, aged = 45, SD = 5.30, Females = 8, mean education level = 2.25, SD = 0.62); ii.) the ASD-NOID group including parents of children with preserved cognitive abilities (n = 12, aged = 44, SD = 5.65, Females = 8, mean education level = 2.22, SD = 0.43). The specific IQ ranges of the ASD children are reported in the Table 1. The three groups were matched for age ($F(2,44) = 0.89$, $p = 0.42$), gender $\chi^2(2) = 3.26$, $p = 0.19$) ed education level ($F(2,44) = 0.41$, $p = 0.66$)

Only parents of children who received an official diagnosis according to the Italian Society of Child and Adolescence Neuropsychiatry guidelines (Società Italiana di Neuropsichiatria Infantile e dell'Adolescenza; SINPIA, 2017) made up by a multidisciplinary team of the Italian national health system, took part in the study. Control group participants were parents of children with no ASD, no Learning Disorder, no Intellectual Disability diagnosis or any other neurological/psychiatric condition. Before taking part in the study, all the participants filled out the Autism Quotient (AQ; Baron-Cohen et al., 2001) to further assess the presence of autistic traits in the three groups. In addition, the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998; Sica et al., 2007) was administered to participants. The three groups were matched for age ($F(2,42) = 1.08$, $p = .35$) and gender ($X^2(2)= 3.26$, $p = 0.19$).

The participants gave their written informed consent before starting the experiment. The study was conducted in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki and fulfilled the ethical standard procedure recommended by the American Psychological Association (APA). The experiment was approved by the Ethics Committee of the University of Milano-Bicocca.

Table 1. *Children of experimental group parents' s IQ range. ICD-10 (WHO, 2007): 50-69 "mild mental retardation"; 35-49 "moderate mental retardation"; < 34 "severe/profound mental retardation"*

IQ range	***Group***	***n***
IQ > 80	ASD-NOID	12
50 > IQ > 69	ASD-ID	9
35 > IQ> 49	ASD-ID	6
IQ < 34	ASD-ID	4

Stimuli

The stimuli consisted of two social stimuli (one male face and one female face), two Low Autism Interest objects (LAI; pictures of a chair and a plant), two High Autism Interest objects (HAI; pictures of a phone and a car) selected from the stimuli dataset developed and validated by Sasson and colleagues (Sasson et al., 2008; Sasson et al., 2012). The HAI stimuli were selected from categories that were reported to be the most commonly occurring circumscribed interests in ASD (South et al., 2005; Klin et al., 2007). In line with the Empathizing-Systemizing theory, presented in the Introduction of this dissertation, these stimuli are also likely to fulfill the systematic cognitive style reported in ASD individuals (Baron-Cohen, 2009; van der Zee & Derksen, 2020). Images size was 400x300 pixels. The selected images were simultaneously presented on a black background in the left and right visual field with a visual angle of 4°, separated by a central white cross. Stimuli selection was conducted with the collaboration of a psychologist expert of ASD rehabilitation and intervention, working in one the clinical institutions collaborating to the project. Stimuli were corrected and matched for low-level properties. Accordingly, original stimuli were converted to greyscale and corrected for luminance using MATLAB Shine Toolbox (Willenbockel et al., 2010) to avoid confounding effects of colors or light brightness.

Procedure

The experiment was set up and carried out in a quiet and dimly illuminated room. Stimuli presentation and responses' registration were controlled through the software E-Prime 3.0. The experiment was implemented into an ASUS laptop having the following technical features: Display 15.6″ (16:9) LED FHD (1920×1080) 60Hz Anti-Glare Panel, and Graphics NVIDIA GeForce 940MX 2GB GDDR5 VRAM. The participants comfortably sat approximately 57 cm away from the LCD monitor. A standard Italian keyboard was used to register participants' responses. Participants eye-movements were tracked through the VirtualDub software that was directly interfaced to E-Prime and the computer webcam. VirtualDub is an open-source video processing utility designed to process linear video streams (Lee, 2000). In the case of the present experiment, the software was used to mark each trial number, by enabling to re-watch each participant's video and manually remove trials where participants explicitly moved their eyes. The Dot-Probe (see next paragraph) is a covert attentional task that requires participants to keep their eyes fixated on the center of the screen throughout each trial. Research has indeed showed that explicitly eye-movements can affect Dot-Probe findings by being a potential source of noise (Petrova et al., 2013).

Dot-Probe Task

The Dot-Probe task is an attentional task developed by MacLeod and colleagues (MacLeod et al., 1986) to assess attentional biases – i.e., human beings' tendency to selectively attend to certain categories of stimuli while overlooking or ignoring others (Williams et al., 1988). In this task participants are asked to detect the target appearance, on either the left or the side of the screen, after the presentation of a pair of stimuli that have to be ignored. The underlying logic is to compare response times (RTs) related to trials in which the probe spatially replaces "a cue of interest" (congruent trials), i.e., social and HAI stimuli, and those related to trials in which the probe replaces a "neutral cue" (incongruent trials), i.e., LAI stimuli. Accordingly, the

Dot-Probe can be also considered as a modified version of the traditional Posner's spatial cueing task.

In the version of the task presented in the current study (Fig. 1), social and HAI stimuli were separately presented in pair with LAI stimuli for 250 ms after the presentation of a fixation cross, lasting 500 ms, and prior to the target presentation (i.e., a dot; until participants' response). Each stimulus of the pair was presented, respectively, on the left or on the right of the central fixation point. Therefore, LAI stimuli were used as neutral/control stimuli. The task included 8 types of trials (4 social-LAI and 4 HAI-LAI) that were presented 16 times during the experiment for a total number of 128 trials. Each cue stimulus had the same probability to appear on the right and left side of the screen. The target probe was programmed to replace each stimulus 50% of the time. Trials presentation order was counterbalanced across participants.

The participants' task was to indicate where the dot appeared by pressing a key (H or B) on the computer keyboard corresponding to the target location on the screen (right or left). The key order was reversed and counterbalanced across participants. Before the beginning of the session, participants performed a practice block composed of 8 trials to familiarize with the task and the response keys.

At the end of the task, participants were also required to provide an explicitly rating over the images they were presented during the task. Specifically, participants were required to rate how much they liked the presented images on a scale from 0 ('not at all') to 4 ('a lot'). This measure was included in order to provide a comparison between implicit and explicit responses, and replicate findings from Sasson and colleagues (Sasson et al., 2008; Sasson et al., 2012) about the higher TD participants' explicit preference for social stimuli and, on the other hand, the higher ASD participants' preference for non-social stimuli.

Other measures

Two self-report questionnaires were administered to control for inter-individual variability within the sample of participants. The Autism Quotient (AQ; Baron-Cohen et al., 2001) was administered to estimate the level of autistic traits in the three groups. The AQ is a screening measure intended to assess the presence of autistic traits in the general population. The test is composed of 50 items, each of which enables the participant to indicate how he/she agrees with the presented statement on a scale from "definitely disagree" to "definitely agree". The other questionnaire was the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998; Sica et al., 2007). This test was administered to control for a possible effect of social anxiety traits on the performance at the Dot-Probe task. Previous evidence has indeed stressed the presence of reduced AB to social stimuli in participants with social anxiety traits which reflect their overwhelming fear of social interactions (Chen et al., 2002; Pishyar et al., 2004). The SIAS is a self-report questionnaire assessing social anxiety in individuals by measuring how individuals feel distressed when meeting or talking with other people. The test is composed of 20 items on a 5 points Likert scale ranging from 0 ("not at all characteristic of me") to 4 ("extremely characteristic of me").

Data Preprocessing and Analysis

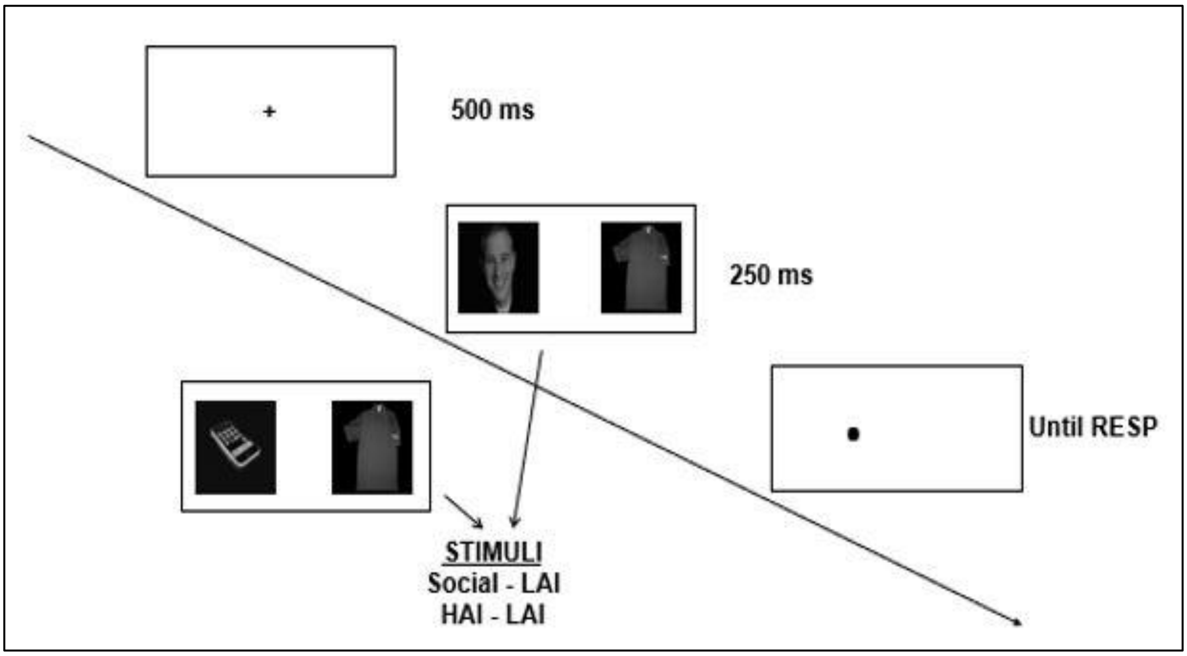
Two participants were excluded from the sample (one from the ASD-ID group and one from the control group) due to the high rate of incorrect responses (>10%) and of eye movements (> 15 %). Reaction times (RTs) slower than 1000 ms were removed from the analyses. In addition to this criterion, the median RT of each condition (congruence: congruent/incongruent; type of stimulus: social/HAI; probe side: right/left) was calculated since the median was demonstrated to be more robust to outliers than the mean parameter (Ulrich e Miller, 1994). These two outlier handling strategies were implemented for two reasons. Firstly, the modest sample size was likely to increase the weight of outliers within each participant's data distribution. The second reason, strongly connected to the first one, was related to the high inter-individuality of participants' responses, in particular of parents of ASD children.

Two separated attentional biases scores (AB scores), one for social stimuli and one for HAI stimuli, were calculated to control for the individual RTs differences between participants. The mean of the median RTs differences between incongruent trials (i.e., when the probe replaced the LAI stimuli) and congruent trials (i.e., when the probe replaced either social or HAI stimuli) was computed. The probe side was collapsed across conditions. Two separated facilitation indexes were computed for social and HAI stimuli (Table 2). Positive bias scores reveal an attentional preference for a category of stimuli (e.g. social or HAI), whereas negative scores indicate an avoidance tendency from a class of stimuli.

Before running statistical models, the possible moderating effect of parents' gender, AQ and SIAS scores was investigated to control for the effect of individual differences. To this aim, the following analyses were performed: i. two t-tests with gender as factor (i.e., male vs female) and, respectively, AB scores to social and HAI scores stimuli as dependent variables; ii. two one-way ANOVAs with group as factor (i.e., control/TD vs ASD-NOID vs ASD-ID) and, respectively, the AQ and the SIAS scores as individual variables; iii. a correlational analysis examining the correlation between questionnaires 'scores (AQ and SIAS) and the AB scores (to social and HAI stimuli). Since none of these individual traits' effects was found to be significant, these variables were not inserted in the final models (see next paragraph). Therefore, two one-way Analysis of Variance (ANOVA) models were applied to a model with 1 between-subject factor (Group: control vs ASD-NOID vs ASD-ID) and, respectively, either the AB scores to social stimuli or the AB scores to HAI stimuli as dependent variable. Plus, the same analysis was conducted by considering the explicit participants' responses, related to the degree of likeability attributed to each class of stimuli, to provide a comparison between implicit and explicit responses. Effect size measured with the partial eta-squared ($\eta 2$) was also computed.

Significant interactions were explored by computing post-hoc pairwise comparisons through Bonferroni's Correction. Data analysis was conducted with IBM SPSS 25.

Figure 1. *Dot-Probe Paradigm. Social and HAI (experimental) stimuli were separately presented in pair with the LAI (neutral) stimuli after the presentation of the fixation cross and prior to the target presentation (dot). The pair of stimuli was presented for 250 ms. The target probe was programmed to replace each stimulus 50% of the time. Participants were required to detect the probe position by pressing a key (H or B) on the computer keyboard corresponding to the target location on the screen (right or left). LAI = Low Autism Interest; HAI = High Autism Interest.*



Each frequentist analysis was integrated with Bayesian evidence investigating the likelihood of the data given the alternative and the null hypothesis (i.e., Bayes factor). In this way, Bayesian analysis served to quantify evidence for H_0 or H_1, and not only to provide dichotomous evidence for one of the two hypotheses. A better description of the rationale underlying Bayesian approach and Bayes Factor can be found in Chapter 1.

Table 2. *Means of the Attentional Bias scores (AB) of the three groups: parents of typically developed children (Control/TD group), parents of autistic children with no Intellectual Disability (ASD-NOID) and parents of autistic children with Intellectual Disability (ASD-ID). HAI = High Autism Interest.*

Group	***AB to Social Stimuli***	***AB to HAI Stimuli***
Control/TD	30.40 (48.20)	-18.60 (30.30)
ASD-NOID	19.50 (35.90)	9.73 (42.40)
ASD-ID	-22.60 (56)	1.56 (26.60)

Results

Gender, AQ and SIAS

The effect of Gender on the AB scores was investigated by performing two separated t-tests. Both t-tests did not reveal any significant difference between males and females related to AB scores to social ($t(43) = 0.228$, $p = 0.821$, Cohen's $d = 0.071$) and HAI stimuli ($t(43) = 0.918$, $p = 0.364$, Cohen's $d = 0.286$). The Bayes Factor computed for the AB to social ($BF_{10} = 0.304$) and HAI stimuli (0.418) revealed, respectively, substantial and anecdotal evidence for H_0, by supporting the null effects estimated by the frequentist analysis.

AQ and SIAS scores' comparison was investigated by applying two one-way ANOVA with group as independent variable and AQ and SIAS as separate dependent variables. No significant between-groups differences were found when the SIAS was the dependent variable ($F(2,42) = 1.860$, $p = 0.179$, partial-$\eta 2 = 0.081$), whereas a significant difference related to the AQ scores was observed ($F(2,42) = 3.730$, $p = 0.032$, partial-$\eta 2 = 0.150$). These effects were weakly supported by the Bayesian analysis, which showed anecdotal evidence for H_0, when the model comprised the SIAS as the dependent variable ($BF_{10} = 0.422$), and for H1, when the model comprised the AQ as dependent variable ($BF_{10} = 1.974$). Post-hoc analysis conducted through Bonferroni's correction revealed a significant difference between the AQ means of

ASD-NOID (M = 21.80) group and the ASD-ID group (M = 15) (t(42) = 2.515, p = 0.041), and a close to significance difference between the ASD-NOID (M = 21.80) group and the control group (M = 15.30) (t(42) = 2.330, p = 0.063). The AQ and SIAS means and standard deviations are reported in Table 3.

Finally, Pearson's correlation analysis did not show any significant correlation between AQ scores and AB scores to social (r = 0.090, p = 0.556) and HAI stimuli (r = - 0.021, p = 0.891), and between SIAS scores and AB scores to social (r = 0.116, p = 0.446) and HAI stimuli (r = - 0.027, p = 0.859).

In conclusion, none of these variables was inserted into the models as a covariate. Although the AQ scores were shown to be different in the three groups, with ASD-NOID participants having significantly higher AQ scores than other participants, the low BF_{10} and the null correlations with the AB scores showed that this variable could not modulate the AB magnitude.

Table 3. *AQ and SIAS scores descriptive statistics.*

	Control		***ASD-NOID***		***ASD-ID***	
	M	SD	M	SD	M	SD
AQ	15.30	4.91	21.80	7.95	15.0	8.40
SIAS	14.0	5.50	20.80	13.1	18.0	12.30

General Linear Models with AB scores

The group effect on AB scores was investigated by applying two one-way Analyses of Variance (ANOVA) to models with 1 between-subject factor (Group: control vs ASD-NOID vs ASD-ID) and, respectively, either the AB scores to social stimuli or the AB scores to HAI stimuli as dependent variable. Means are reported in Table 2, whereas the graphical representation of the effects is reported in Figure 2.

The first ANOVA, with AB scores to social stimuli as dependent variable, revealed a significant group effect (F(2,42) = 5.430, p = 0.008, partial-η2 = 0.205), which was further explored through post-hoc analysis with Bonferroni's correction. The Bayes Factor indicated substantial evidence for H_1 (BF_{10} = 6.853), by supporting the rejection of the null hypothesis estimated by the frequentist analysis. The post-hoc analysis revealed a significant difference between the control group and the ASD-ID group ($t(42) = 3.110$, $p = 0.009$), whereas a close to significance difference emerged when comparing the ASD-NOID and the ASD-ID group ($t(42) = 2.31$, $p = 0.065$).

The second ANOVA, with AB scores to HAI stimuli as dependent variable, did not reveal a significant group effect, although the p-value was rather closed to significant threshold ($F(2,42) = 2.810$, $p = 0.071$, partial-$\eta 2 = 0.118$). The Bayes Factor indicated anecdotal evidence for H_1 (BF_{10} = 1.114), by bringing weak evidence of H_1 hypothesis. From Figure 2, it is possible to observe a trend showing a clear difference between control parents and parents of ASD children, regardless of the child's cognitive level. This pattern was confirmed by performing a t-test with the two ASD parent groups merged into a unique group (i.e., ASD). The t-test showed a significant difference between the control group and the ASD group ($t(43) = 2.290$, $p = 0.027$, Cohen's $d = 0.277$). However, the Bayes Factor revealed anecdotical evidence for this conclusion (BF_{10} = 2.33), by bringing weak evidence of H_1 hypothesis.

General Linear Models with explicit stimuli ratings

The group effect on explicit stimuli rating scores was investigated by applying three one-way Analyses of Variance (ANOVA) to models with 1 between-subject factor (Group: control vs ASD-NOID vs ASD-ID) and, respectively, the mean score of social, LAI and HAI stimuli. Means are reported in Table 4, whereas the graphical representation of the effects is reported in Figure 3.

The first ANOVA, with social stimuli ratings as dependent variable, revealed a significant group effect ($F(2,42) = 4.030$, $p = 0.025$, partial-$\eta 2 = 0.161$), which was further explored through post-hoc analysis with Bonferroni's correction. The post-hoc analysis revealed a significant difference between the control group and the ASD-ID group ($t(42) = 3.110$, $p = 0.019$). The Bayes Factor indicated anecdotal evidence for H_1 ($BF_{10} = 2.709$), by weakly supporting evidence for this conclusion.

Table 4. *Means of stimuli explicit ratings in each group.*

Group	***Social stimuli***	***LAI stimuli***	***HAI stimuli***
Control/TD	2.61 (0.60)	1.68 (0.99)	1.93 (0.90)
ASD-NOID	2.21 (0.68)	1.46 (0.65)	1.83 (0.68)
ASD-ID	1.86 (0.88)	1.64 (0.66)	2.53 (0.86)

The second ANOVA, with LAI stimuli ratings as dependent variable, did not reveal a significant group effect ($F(2,42) = 0.294$, $p = 0.747$, partial-$\eta 2 = 0.013$). The Bayes Factor indicated substantial evidence for H_0 ($BF_{10} = 0.203$), by supporting the null effect estimated by the frequentist analysis.

Finally, the third ANOVA, with HAI ratings as dependent variable, revealed a significant group effect ($F(2,42) = 3.234$, $p = .049$, partial-$\eta 2 = 0.133$), which was further explored through post-hoc analysis with Bonferroni's correction. The Bayes Factor indicated anecdotal evidence for H_0 ($BF_{10} = 1.570$), by weakly supporting the alternative effect estimated by the frequentist analysis. The post-hoc analysis did not reveal any significant difference between the three groups, although the Figure 3's plot clearly show a trend consisting in ASD-ID participants rating better HAI stimuli than other participants.

Figure 2. *Mean plots of the effects of group variable on AB scores to social and HAI stimuli.*

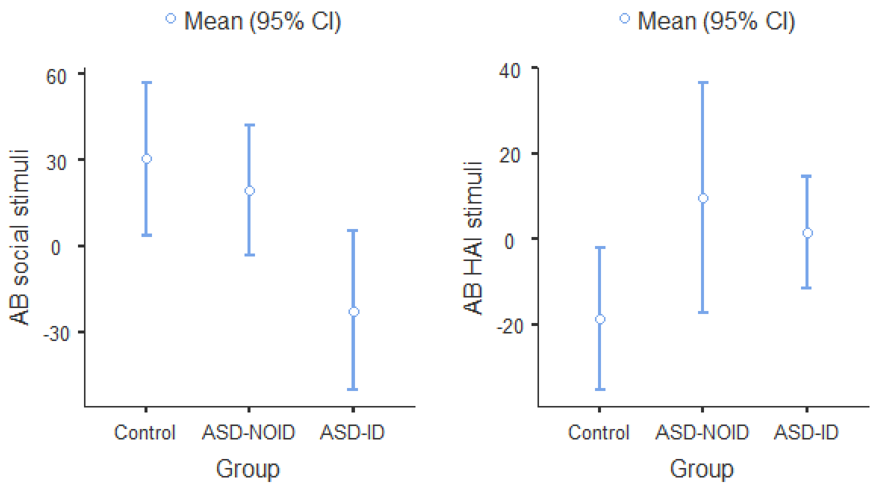
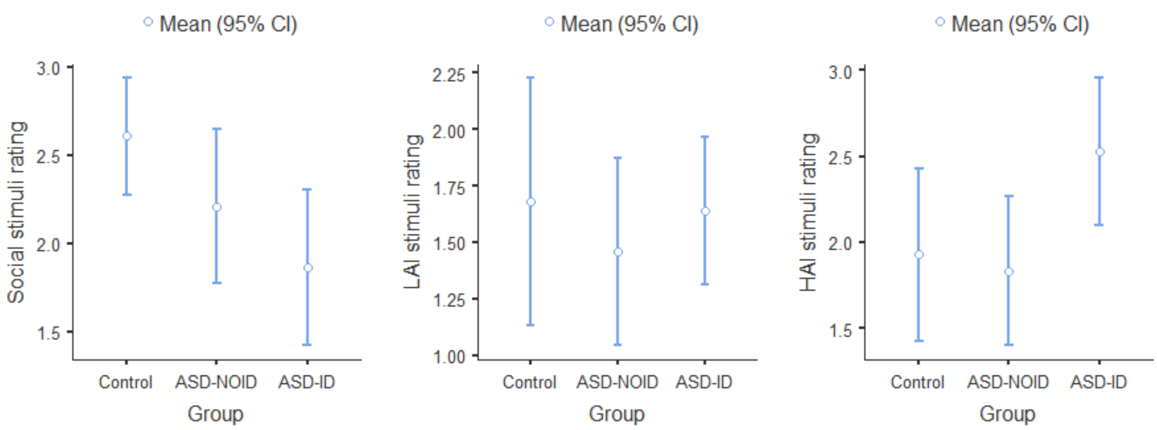


Figure 2. *Mean plots of the effects of group variable on stimuli ratings.*



Discussion

The present study was aimed at examining whether parents of ASD children exhibit the same attentional pattern (i.e., diminished AB to social stimuli and augmented AB to HAI objects) as observed in individuals with ASD diagnosis (see Chapter 2 of this dissertation for a review of the literature). Given the heterogeneity of ASDs and the distinctive genetic and phenotypic patterns between ASD individuals with and without an Intellectual Disability (Grove et al., 2019), the distinction between parents of children with ASD and Intellectual Disability (ASD-

ID) and parents of children with ASD and preserved cognitive abilities (ASD-NOID) was taken into account in the present study. To this aim, participants carried out a Dot-Probe task requiring them to detect the spatial position of a dot appearing after the simultaneous presentation of a pair of stimuli. Social (i.e., faces) and the HAI objects were separately presented in pair with LAI stimuli. Two Attentional Bias (AB) scores were computed for each stimuli of interest category – in this case social and HAI. The AB score is a quantitative index measuring the RTs difference between incongruent (dot appearing on the opposite side of the social or HAI stimulus) and congruent trials (dot appearing on the position of the social or HAI stimulus). Hence, the AB score provides a measure of the AB magnitude related to a particular class of stimuli.

No significant inter-individual differences possibly moderating the AB magnitude were found. The only significant difference concerned the AQ scores, which were higher in the ASD-NOID group than in the other two groups – the difference between the ASD-NOID and the ASD-ID was significant, whereas the difference between the ASD-NOID and the control group was only close to significance. Although not strictly relevant to the purposes of the present research, this result is of great interest since it adds a piece of evidence to the findings on the BAP. There is indeed a vast number of studies reporting high AQ scores in parents of ASD children (Bishop et al., 2004; Whitehouse et al., 2007; Wheelwright et al., 2010; Ruta et al. 2012; Taylor et al., 2013) but, to the best of my knowledge, none of these has considered the heterogeneity of the child cognitive profile as a possible moderating factor. In this sense, this result strengthens the idea that the BAP may differently manifest in parents of ASD children in relation to the child's profile severity. This evidence is also in line with recent aetiologic explanations provided by Groves and colleagues' study, which reported higher levels of hereditability related to milder forms of autism (e.g., high-functioning autism, Asperger's Syndrome etc.) respect to forms emerging with severe comorbidities such as Intellectual Disabilities (Grove et al., 2019). Despite the AQ is far from providing genetic clues around the aetiology of the ASD, the result from the current study seems to support the conclusions raised from Grove and colleagues (2019), by highlighting a greater phenotypic expression of autistic traits in parents of ASD-NOID children than parents of ASD-ID children.

As concerns the comparison of AB scores to social/HAI stimuli in the three groups, the main finding of the current study is that, unlike control group parents and parents of ASD-NOID children, parents of ASD-ID children exhibited a reduced atypical AB towards the face. Interestingly, this attentional pattern partially matched with the explicit stimuli rating that participants gave to each class of stimuli, with control group parents giving higher rate scores to social stimuli than ASD-ID parents. On the other hand, no significant differences related to the AB to HAI objects was found, although a clear and significant distinction emerged when collapsing the two ASD parents groups, revealing that parents of ASD children had a greater attentional preference for these stimuli than parents of TD children.

Taken together, these findings suggest the existence of two distinct phenotypes in parents of ASD-NOID and ASD-ID children. Parents of ASD-NOID children exhibit higher autistic traits but would not differ from parents of TD children based on their social attention pattern. By contrast, parents of ASD-ID children would do not have high autistic traits but would exhibit less attention to social stimuli and high attention to non-social stimuli in general (i.e., both LAI and HAI). The two groups would only share an attentional preference for HAI objects as documented by previous literature on individuals diagnosed with ASD (see Chapter 2 for literature review). Accordingly, given these results and recent evidence on the aetiology of ASD (Grove et al., 2019), the BAP explanation may falter in explaining the different social attention patterns observed in the three groups and the dissociations between the ASD-NOID and the ASD-ID group. In light of these considerations, the reduced attentional orienting to the face, observed in parents of ASD-ID children, may not entirely reflect the expression of a common broader phenotype, and the distinction between ASD-ID and ASD-NOI parents' groups suggests to revise the concept of BAP by taking into account this dissociation.

Some interesting clue may come from attachment and parenting psychology, which provides a more environmental explanation about ASD expression. Parenting literature indicated that parents of autistic children tend to adopt special communication strategies to engage with their children (Crowell et al., 2019). These strategies are usually learned during training sessions in which parents are trained to find proper communication channels to effectively respond to the child's cue (Perasso & De Angelis, 2020). Many interventions indeed work to boost parental sensitivity to increase the attunement level between members of the parent-child dyad, and to make parents more sensitive to the needs of their children without being too intrusive (Perasso & De Angelis, 2020). In this respect, non-social objects seem to play a key role to foster this type of interaction. For instance, Gulsrud and colleagues (2016) highlighted the importance to share and imitate the way the child plays with selected toys to increase children joint attention (Gulsrud, et al., 2016). Other parent-mediated interventions are explicitly targeted at enhancing parental sensitivity and responsiveness by using objects as a communication medium. Among these, the Infant Start is a program for parents and their children of 6-11 months old (Rogers et al., 2014) in which parents are asked to follow the child's leading gaze to find objects of interests (e.g., HAI objects) and then to share the child's emotion concerning that object (Rogers et al., 2014). Hence, it is clear how parents of children with autism are continuously asked to find communication and emotional strategies, which are different from ones adopted in dyads with TD children (Eisenberg et al., 1998; Leong et al., 2017; Vernetti et al., 2018). Accordingly, they are readily prompted to disengage from social stimuli, such as faces or eyes, and to enhance attention to non-social objects. In relation to the differences identified in the present study, one plausible explanation is that, given the substantial level of cognitive, communication and language impairment of ASD-ID children (Rapin & Dunn, 2003; Boucher et al., 2008; Weismer et al., 2010), the effort required to attune with these children is even higher than the effort required to interact with ASD-NOID children. This explanation would clarify why parents of both ASD children groups would exhibit an AB to HAI stimuli, and, on the other hand, the reduced AB to social stimuli observed only in parents of ASD-ID children. It is possible that the massive use of learned communicative strategies, based on diminished eye-contact and the use of a "third-element" (object) to capture child attention, determines this specific attentional pattern in parents of ASD-ID children. This assumption should be investigated more in detail by future studies.

The present study presents some limitations. The first limitation concerns the lack of a comparison with a group of parents with other developmental disabilities (e.g., ADHD, language or communication disorders etc.). Although most of the research investigating the Broad Autism Phenotype did not take this comparison into account, future studies should consider this issue so as to understand whether this pattern can be generalized to parents of children with other disabilities. The second limitation regards the low ecological validity of this experiment. Developing more naturalistic set-ups may be an approach to overcome this issue, for example, by including the use of mobile eye-tracking technology or virtual reality. Finally, a replication of the present findings with higher sample sizes is strongly recommended.

Implications

The present study is expected to contribute to increasing theoretical and empirical knowledge of autism. Although ASD is a very heterogeneous syndrome varying according to the individual cognitive profile, the cognitive level has been rarely taken into consideration as a possible modulating factor. To the best of our knowledge, this is indeed the first study examining the BAP construct by differentiating the ASD parents' group based on the child's cognitive level. These findings are also expected to provide hints for the development parent-mediated interventions. Furthermore, previous clinical research suggested that attentional biases can be modified by reallocating individual attentional resources on more adaptive stimuli and away from maladaptive ones (Bar-Haim, 2010; Hakamata et al., 2010; Kuckertz et al., 2014). In the case of parents of children with ASDs, this attentional bias modification (Bar-

Haim, 2010) may be helpful to increase attentional sensitivity to social cues, by consequently fostering parents' ability to recognize child's emotional expressions and to provide congruent and tuned responses.

Conclusion

The aim of the present study was to investigate whether parents of ASD children exhibit a reduced AB to the human face, as observed in individuals with ASD diagnosis, and whether this pattern emerges together with a greater attentional preference for HAI objects. In particular, given the evidence showing the existence of specific genetic factors at the basis of ASD individuals' cognitive profile heterogeneity (Grove et al., 2019), parents with TD children were compared with, respectively, parents of ASD children with Intellectual Disability (ASD-ID) and parents of ASD children without Intellectual Disability (ASD-NOID). To this purpose, participants were asked to perform a Dot-Probe task that was designed to assess the magnitude of AB towards social stimuli and HAI objects in three groups. Specifically, social stimuli (faces) and high-autism interest non-social objects (HAI; e.g. devices) were presented in pair with non-social neutral objects (e.g. t-shirt) prior to the target (i.e., a dot) presentation. Results showed a AB towards the face in parents of TD children and in parents of ASD-NOID, whereas it was absent in parents of ASD-ID children. Interestingly, both ASD parents' groups exhibited a significant AB towards HAI objects. These findings have important implications for the conceptualization of the BAP. In particular, they show that the different social attention patterns between ASD and TD participants, reported in previous chapters, may only partially be the expression of a familiar phenotype due to the heterogeneity of the results in the ASD-NOID and in ASD-ID parents' groups. Contrarily, it is possible that attention to social vs non-social objects in parents of ASD children is modulated by external variables such as, as shown in the current chapter, the level of child cognitive development affecting the parent-child interaction.

In the next chapter (Chapter 5) it will be investigated whether it is possible to modify the salience of social stimuli in ASD individuals through an Attention Bias Modification Treatment (ABMT) methodology. Specifically, the chapter will report a study aimed at understanding the degree of which attention to social stimuli is permeable to external modifications. A dedicated implicit learning and reward-based AMBT has been created and administered to a sample of ASD children. The study has been conducted on children participants since there is evidence reporting a high brain plasticity during childhood (Kolb & Gibb, 2011).

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CHAPTER 5

Increasing social attention in children with ASD: A Pilot Study based on the Attentional Bias Modification Treatment (ABMT)

Introduction

A meta-analysis by Frazier et al. (2017) has considered 122 independent studies on gaze patterns, overall including 1155 statistical comparisons between individuals with ASD and neurotypical controls. The meta-analysis has shown that individuals with ASD consistently presented abnormalities in eye fixation patterns reflecting ASD individual's failure to select socially relevant information. These results are in line with evidence, reported in the previous chapters of the present dissertation, that point out a difficulty to orient to and process social stimuli in individuals with ASD and their parents (in particular parents of children with preserved cognitive abilities).

An interpretative hypothesis attributes the cause of such attentional abnormalities in ASDs to a general lack of social motivation (i.e., lack of interest in the social world) (Chevallier et al., 2012). On the other hand, other authors have claimed that ASD individuals would tend to experience high social anxiety levels, therefore, as a consequence, they trigger defensive avoidance mechanisms leading to abnormal gaze-patterns (Corden et al., 2008; Cuve et al., 2018).

Another point raising from previous chapters is the preference exhibited by ASD individuals for non-social stimuli processing. In fact, unlike neurotypical controls, children and adults with ASD prefer orienting their gaze towards non-social stimuli (e.g., trains, cars, consoles, and electronics) than social images (Sasson et al., 2008, 2012; Sasson & Touchstone, 2014).

The idea driven from this theoretical and empirical background is that ASDs atypical attentional pattern is likely to be the basis of most of the social, communicative, and emotional impairments observed in this population. For example, social cognition literature has highlighted that the capacity of allocating attention towards social stimuli is a predictor of higher level social-cognitive skills (e.g., cognitive theory of mind, ToM) (Frirth & Happé, 2005; Happé & Conway, 2016), which are typically impaired in autistic individuals (Baron-Cohen et al., 1985; Stewart et al., 2020). Thus, the present chapter will investigate how gaze patterns could be modulated by external factors, shifting ASD children's visual attention from non-social objects and guiding it towards social stimuli.

Noticeably, we have already seen that human beings are prone to selectively attend to specific categories of stimuli (e.g., social stimuli) while overlooking or ignoring others (Williams et al., 1997). This automatic tendency sometime reveals atypical attentional biases (AB), a characteristic at the basis of many clinical conditions (e.g., psychopathologies or maladaptive behaviours). For instance, active smokers were reported to exhibit an AB for smoke-related stimuli (i.e., cigarettes) (Chanon et al., 2010) as individuals with alcohol use disorders show it for alcohol-related words (Field & Cox, 2008). Eating disorders are also characterized by AB in the perception of body related stimuli (Faunce, 2002), whereas individuals suffering from Generalized Anxiety Disorder exhibit an AB for threat-relevant information (Amir et al., 2009). Research on the association between personality disorders and AB also revealed that antisocial offenders present attention bias for violence-related stimuli (Domes et al., 2013), whereas borderline individuals present attentional bias for words related to negative emotions (Kaiser et al., 2016) and words related to negative life events (Wingenfeld et al., 2009). Additionally, attentional bias has been studied in association with post-traumatic stress disorder (Bryant & Harvey, 1997), psychosis paranoid functioning (Moritz & Laudan, 2007), and obsessive-compulsive disorder (De Mathis et al., 2020). Within a cognitive framework of psychopathology, the AB are thought to be the critical mechanism underlying the symptoms associated with some clinical conditions (e.g., symptoms, emotions, behaviours, beliefs).

Given the evidence on dysfunctional AB in many different psychopathological conditions, the Attention Bias Modification Treatment (ABMT; Hakamata, 2010; MacLeod & Matthews, 2012) was specifically developed to produce a change in the atypical attentional resources allocation. Specifically, the ABMT aims at re-orienting individual's attentional resources away from the maladaptive stimulus (i.e., threatening stimuli) towards the adaptive one (i.e., neutral stimuli). ABMT is usually designed on the basis of traditional cognitive tasks such as visual probes tasks (i.e., modified version of the Dot-Probe task), emotional spatial (or visual) cueing task (e.g., Fox et al., 2001), and visual search tasks (Treisman & Gelade, 1980). In the modified version of the Dot-Probe task, the person is required to discriminate the position of the target onset on a screen, after the presentation of a pair of stimuli (adaptive vs maladaptive) to which no response has to be made. Unlike traditional versions of the Dot-Probe task, in the ABMT version the probe replace the adaptive stimulus in almost the totality of the trials. On the other hand, the maladaptive stimulus does appear on the screen but it is never, or rarely, presented in the same position of the subsequent probe.

Although the meta-analysis by Mogoaşe et al. (2014) invites to cautiously interprete ABMT effectiveness in ameliorating patients' disorder, a wide range of Randomized-Control Trials (RCT) studies has supported the effectiveness of this treatment in different conditions, including generalized anxiety (Hakamata et al., 2010), social anxiety (Miloff et al., 2015; Ollendick et al., 2019), depression (Dai et al., 2019; Woolridge et al., 2020), eating disorders (Starzomska, 2017; Mercado et al., 2020), post-traumatic stress disorder (Wald et al., 2016), cigarette consumption (Elfeddali et al., 2016), and substance addiction (Cristea et al., 2016; Zhang et al., 2018). Across all of these disorders and conditions, the ABMT was shown to be effective in reducing symptoms, emotional reactivity, and craving (MacLeod & Mathews, 2012).

Given the above presented background and the goals of the present dissertation, the present study was aimed at:

i. investigating the effects of an ABMT intervention in fostering attentional orienting toward social stimuli and away from non-social objects in ASD children;
ii. understanding the degree of which attention to social stimuli is permeable to external modifications.

To answer these research questions, a dedicated implicit learning and reward-based ABMT intervention has been structured and administered to a sample of ASD children. The sample choice (i.e., primary school children) was based on the evidence reporting a high brain plasticity during childhood (Kolb & Gibb, 2011), which fosters the acquisition and the consolidation of new information and processes.

Method

Participants

Fifteen (n = 15) children with ASD diagnosis took part in the study. Children were randomly assigned to two groups, that were the experimental group (i.e., participants undergoing the treatment) and the control group (i.e., participants not undergoing the treatment). The random assignment was conducted by exploiting the Python Numpy function *random.randint* which returns random integers (0 = control, 1 = experimental) from a discrete distribution. Eight children (n = 8; mean age = 8.50, SD = 0.7; Females = 1) were assigned to the experimental group, whereas seven children (n = 7; mean age = 7.40, SD = 1.1; Females = 1) were assigned to the control group. The two groups were matched for age ($t(13) = 0.32$, $p = 0.75$) and gender ($X^2(1)= 0.01$, $p = 0.91$). Respectively, two children of the experimental group and one child of the control group's child presented a more severe profile due to the presence of cognitive delay (IQ < 70) and/or some language development delay. Children did not have any comorbidity with neurological, physical or psychiatric disorders, and all had normal or corrected-to-normal vision. Children were recruited through contacts with schools within the Greater London region, recognized by the UK National Autistic Society, which is the UK leading charity for people on the autism spectrum and their families. Only children with a certified NHS (National Health Service) diagnosis, or a diagnosis made by a recognized private professional, could take part in the research.

The parents of ASD children gave their informed consent before starting the experiment. The study was conducted in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki and fulfilled the ethical standard procedure recommended by the American Psychological Association (APA). The experiment was approved by the Ethics Committee of the Goldsmiths University of London.

Stimuli

The same stimuli described in Chapter 4 were used for this study. The stimuli consisted of two social stimuli (one male face and one female face), two Low Autism Interest objects (LAI; pictures of a chair and a plant), two High Autism Interest objects (HAI; pictures of a phone and a car) selected from the stimuli dataset developed and validated by Sasson and colleagues (Sasson et al., 2008; Sasson et al., 2012). Images size was 400x300 pixels. The selected images were simultaneously presented on a black background in the left and right visual field with a visual angle of 4°, separated by a central white cross. Stimuli were corrected and matched for low-level properties. Accordingly, original stimuli were converted to greyscale and corrected for luminance using MATLAB Shine Toolbox (Willenbockel et al., 2010) to avoid confounding effects of colors or light brightness.

Training procedure

The entire study was conducted and setup in a quiet and illuminated room located in the hosting institutions where the training took place. The training software was programmed in and run on E-Prime 3.0, and implemented into an ASUS laptop having the following technical features: Display 15.6″ (16:9) LED FHD (1920×1080) 60Hz Anti-Glare Panel, and Graphics NVIDIA GeForce 940MX 2GB GDDR5 VRAM. The training consisted of two sessions per day, and it was carried out throughout 7-days, for a total number of 14 sessions. Each session lasted approximately 30-minutes. The training was presented to the child under the form of a game so as to decrease the performance-related anxiety and to augment the motivation for the task. Only the experimental group participants underwent the real training procedure, whereas the control group participants carried out a similar task, which did not comprise neither the implicit learning or the incentive component (see next paragraph for a better description of the training task). The baseline/outcome measures were collected, respectively, two days before the training onset session and two days after the last training session. Both children and parents were naïve of the condition (experimental or control) the child was assigned to.

Training description

As stated in the introduction section of the present Chapter, the aim of ABMT is to re-orient user attention from maladaptive, or pathological, stimuli to the more adaptive ones, based on their clinical condition. For instance, users with anxiety disorders may implicitly learn to shift their attention away from threatening faces, triggering high levels of anxiety, and to orient to neutral faces (Bar-Haim, 2010). More technically, the ABMT can be defined as a modified version of the Dot-Probe task where the target readily appears in the same position where the more adaptive stimulus was presented in the previous frame. This repeated target-stimulus presentation is expected to trigger an implicit learning process fostering the attentional (re)orienting to the adaptive stimulus (e.g., neutral faces in anxiety). In the case of the present study, a paradigm similar to the one described in Chapter 4 was implemented. While in the original version of the task the target replaced the social and non-social stimuli exactly 50 % of the trials, in this adapted version the target replaced the social stimulus approximately 90 % of the trials (i.e., 115 out of 128 trials). It has also to be noted that in this version of the task both the LAI stimuli and the HAI stimuli were presented paired to the social stimuli in order to increase the number of times the social stimulus was presented throughout each session (128 instead of 64). Unlike the experimental group participants, the control group participants performed a standard version of the Dot-Probe task where target appearance side was equally distributed across trials, by not probing any implicit learning effect.

Importantly, a novelty of this training procedure is represented by the presence of a reward stimulus appearing at the end of each correct trial. The reward type was chosen by following the evidence, reported in the previous chapters, on the restricted interest towards mechanical and electrical objects in ASD participants. As in Chapter 3, a robotic stimulus was used since a preference for robotic stimuli in ASD individuals has been reported in the literature (Wiese et al., 2015; Wykowska et al., 2015; Kajopoulous et al., 2017). Specifically, the stimulus consisted of a 626x728 pixels picture of a robot toy with the thumb up (Figure 1). The reinforcer was presented at the center of screen (E-Prime X and Y positions set to 50%, aligned to the center). The reinforcer was only included in the experimental group training sessions.

Figure 1. *Picture of the robotic stimulus used as a reinforcer during the training*

Baseline and outcome measures

The baseline/outcome measures comprised an assessment of the AB change before and after the treatment, considering both implicit attentional responses and explicit rating responses, and qualitative data assessing the impact of the training on everyday child routine.

The evaluation of the AB change was performed by administering a standard version of the Dot-Probe with the target probe equally replacing social and non-social stimuli. As in Chapter 4, an attentional bias score (AB score) was computed to quantify the magnitude of the AB. An AB score for social stimuli resulting from mean of the median RTs differences between incongruent trials (i.e., when the probe replaced the non-social stimulus) and congruent trials (i.e., when the probe replaced either social stimulus) was computed. The non-social stimulus type (i.e., HAI and LAI) and probe side were collapsed. Positive bias scores revealed an attentional preference for social stimuli, whereas negative scores indicated tendency to orient more to non-social stimuli. The implicit evaluation of AB was accompanied by an assessment of the explicit ratings that participants gave to the social stimuli. In particular, participants were asked to both evaluate how much they liked the presented faces and, to evaluate the self-reported emotional response to those stimuli, to evaluate how much that stimulus made them anxious. Both questions had a response range on 5-points Likert scale, where 0 = "not at all", and 5 = "extremely".

Qualitative data consisted of three questions addressed to children's parents. The three questions were aimed at investigating how the parent perceived their child behavior in everyday life, in three critical areas of social communication and interaction. Specifically, the three questions were structured as follows:

i. "Do you think that your child pays more attention to objects than other people?" (circumscribed attention to objects area);

ii. “Do you think your child gets anxious when he/she is interacting with other people?” (fear of interaction area)

iii. “Do you think your child rarely makes eye-contact with you or other people? (eye-contact avoidance).

The questions were structured on a cascade response type. At first, parents were required to indicate whether they agreed or not with the content of the question (i.e., binary response 0 = no, 1 = yes). In case of positive response, they were required to better describe the patterns and the dynamics explaining the answer to the question (i.e., response validation step).

Data Preprocessing and Analysis

Due to the population type, the accepted incorrect response threshold was increased to 15 % (i.e., with respect to the criterion set in Chapter 4). None of the tested children exceeded this threshold and only one control group child exceeded the 10 % threshold. Reaction times (RTs) slower than 1000 ms were removed from the analyses. The median RT of each condition (congruence: congruent/incongruent; type of stimulus: social/HAI; probe side: right/left) was calculated since the median was demonstrated to be more robust to outliers than the mean parameter (Ulrich e Miller, 1994). An attentional biases score (AB score) for social stimuli was calculated to control for the individual RTs differences between participants.

Two factorial mixed Analysis of Variance (ANOVA) models were applied to a model with 1 between-subject factor (Group: experimental vs control) and 1 within-subject factor (Treatment Sessions: baseline vs post-treatment). The dependent variable was the AB score for the social stimuli. The explicit participants’ responses, related to the degree of likeability and anxiety attributed to each class of stimuli, were also analyzed in two separated 2x2 factorial ANOVAs to provide a comparison between implicit and explicit responses. Effect size measured with the partial eta-squared (η2) was also computed. Significant interactions were explored by computing post-hoc pairwise comparisons through Bonferroni's Correction. Data analysis was conducted with IBM SPSS 25.

Qualitative data collected from questions asked to parents was analyzed by performing a Chi-Square association test to investigate the existence of an association between parents' responses and the child's group. Only cases who received a positive answer at the baseline (i.e., parent stating that the child presents the reported difficulty) were analyzed in order to evaluate whether, according to parents, the reported problematic was still present or not after the treatment.

At the end, a linear regression model estimating the predictors of treatment success was performed. Two reasons were behind the development of this model. Firstly, according to clinical research evidence, ANOVA results should be interpreted along with other alternative statistical approaches when managing clinical intervention data (Vickers, 2005). Secondly, the aim of this model was to analyze which factors, other than training, may concur to predicting AB changes. The model included six predictors (age, treatment group, level of functioning, AB scores at the baseline, stimulus anxiety rating at the baseline, and stimulus likeability rating at the baseline) and one continuous target (post treatment AB score).

Results

Dot-Probe

First of all, a t-test comparing baseline AB scores was performed to check whether the two groups were comparable at the baseline. The t-test revealed no differences between the baseline AB scores in the two groups ($t(13) = 0.504$, $p = 0.62$, Cohen's $d = 0.253$). The factorial mixed ANOVA model with AB score for the social stimuli (Figure 1) did not reveal any main effect of Group ($F(1,13) = 0.395$, $p = 0.541$, partial-$\eta2 = 0.029$)), whereas a significant Group x Session interaction emerged ($F(1,13) = 8.75$, $p = 0.011$, partial-$\eta2 = 0.402$). This interaction was further investigated by conducting post-hoc analysis through Bonferroni's correction. The post-hoc test showed a significant difference between baseline and post-treatment AB scores for the social stimuli only in the experimental group ($t(13) = 4.457$, $p = 0.003$), revealing significant higher post-treatment scores ($M = 83.70$, $SD = 89.70$) than baseline scores ($M = -40.50$, $SD = 52.60$).

Explicit ratings

The anxiety level and the likeability degree associated with the observation of social stimuli were derived from two distinguished questions rated on a 5-points Likert scale. Neither a significant main group effect nor a Group x Session effect emerged for both anxiety and likeability ratings. Contrarily, a significant main Session effect emerged only for anxiety ratings ($F(1,13) = 0.195$, $p = 0.034$, partial-$\eta 2 = 0.302$). Post-hoc analysis showed a significant decrease of anxiety ratings attributed to social stimuli at the end of the training ($t(13) = 2.37$, $p = 0.034$). Although not significant, a similar trend occurred also when considering likeability ratings. Means and standard deviations of explicit ratings are reported in Table 1

Figure 1. *Bar plots of the effects of Session x Group interaction on AB scores for the social stimuli.*

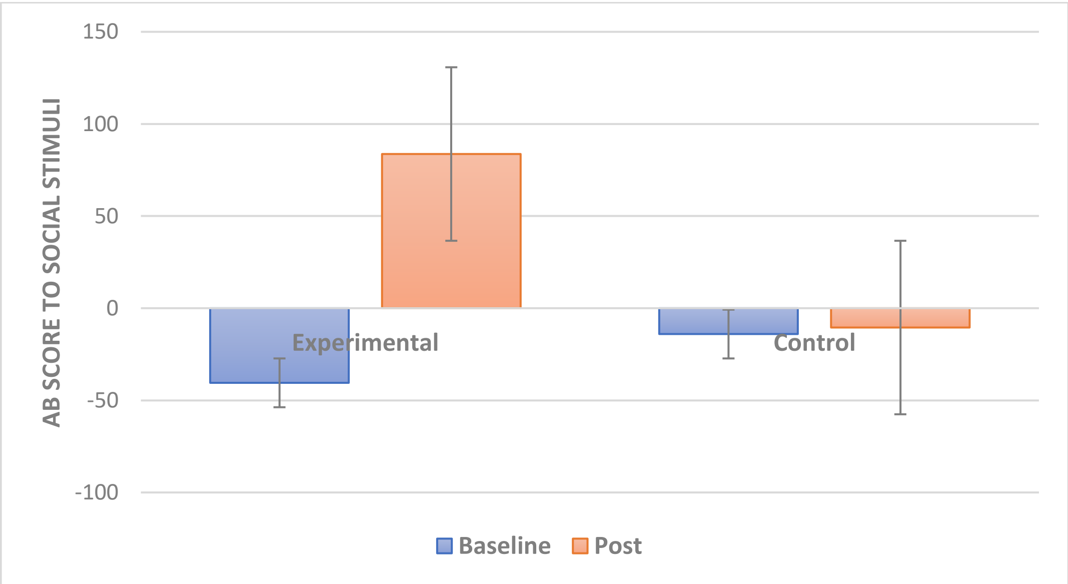

Table 1. *Means of stimuli explicit ratings in each group.*

Group	***Baseline Anx Face***	***Post Anx Face***	***Baseline Like Face***	***Post Like Face***
Control	1.57 (1.40)	1.14 (1.07)	1.71 (0.95)	1.86 (0.69)
Experimental	2.13 (1.13)	1.50 (0.92)	1.50 (1.07)	2.13 (0.83)

Qualitative data from parents

Figures 2,3,4 provide a comparison between parents' responses over the time in the three investigated areas. As it is possible to observe from figures, parents did not report any change in the "circumscribed attention to objects" and "fear of interaction" areas, whereas a slight decrease of "eye-contact avoidance" was reported by parents of the experimental group's children. Specifically, while 38 % of the parents reported a child difficulty in establishing eye-contact before the training, the percentage of parents reporting this difficulty dropped to 13 % after the training (Figure 4). This pattern was further investigated by performing a Chi-Square association test between child's treatment group and the proportion of children who were reported to be improved in that area according to their parents (i.e., binary variable: improved vs not-improved; Table 2). The Chi-Square test reported a significant association between these two variables ($\chi^2(1) = 5.830$, $p = 0.016$, phi-coefficient = 0.764). However, this effect should be carefully interpreted due to the small available sample size.

Prediction model of treatment effectiveness factors

The model investigating the factors underlying treatment success explained the 71 % of the variance, as measured by the determination coefficient ($R^2 = 0.711$). As shown in Table 3, two predictors resulted to be significant, those were the treatment group and the baseline AB score.

Table 2. *Contingency table describing the proportion of children improved in the "eye-contact avoidance" area, according to parents' report, as a function of the treatment group.*

	Improved		
Group	**No**	**Yes**	**Total**
Control	7	0	7
Experimental	1	2	3
Total	8	2	10

Figure 2. *Percentage of parents reporting "circumscribed attention to objects" before and after the training in the two groups.*

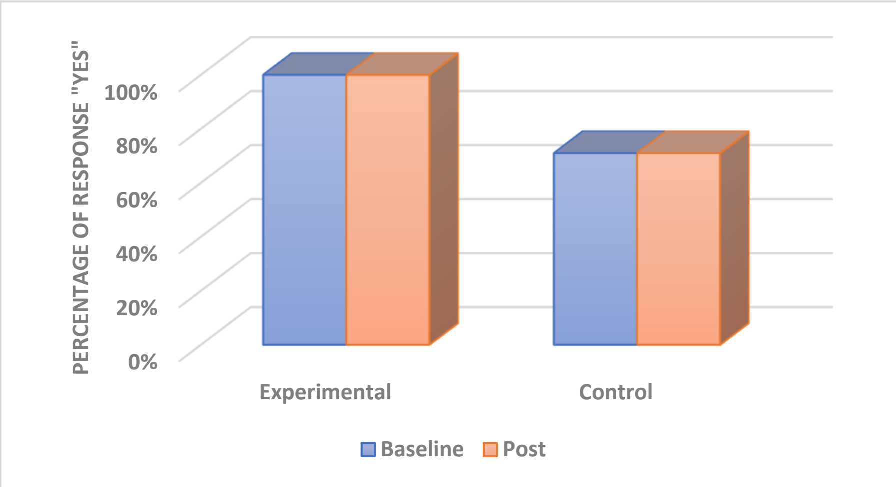

Figure 3. *Percentage of parents reporting "fear of interaction" before and after the training in the two groups.*

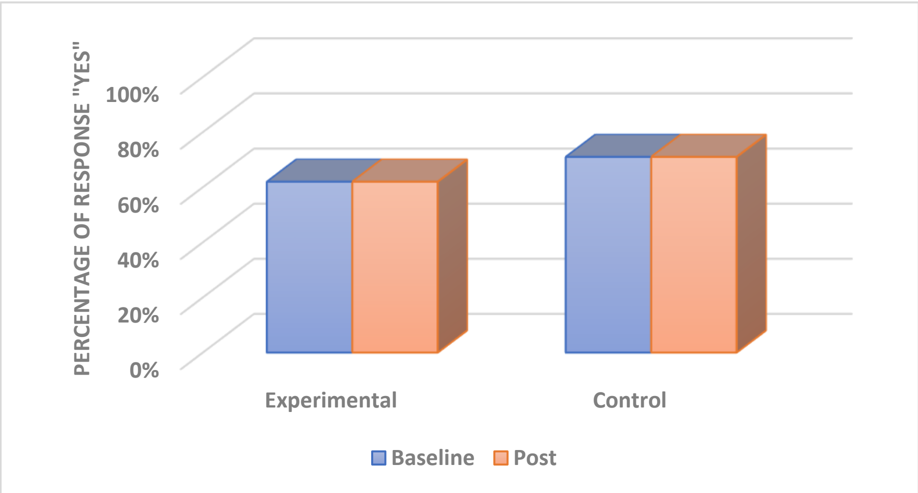

Figure 4. *Percentage of parents reporting "eye-contact avoidance" before and after the training in the two groups.*

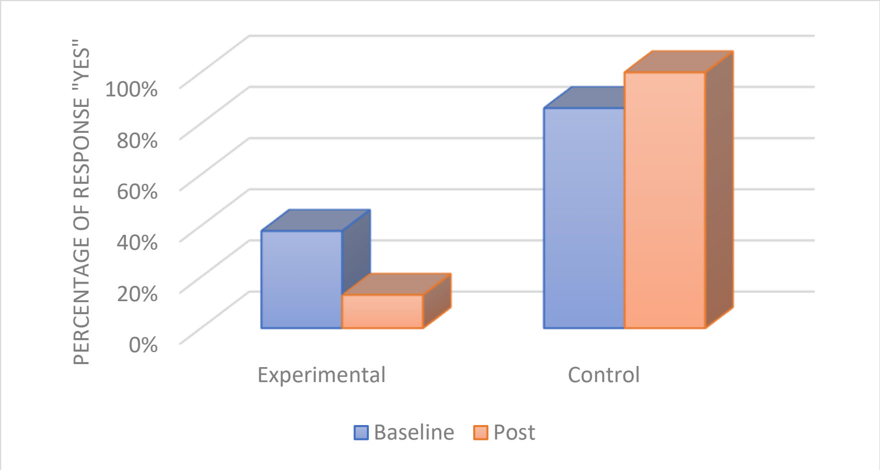

Table 3. *Regression model on factors predicting treatment success. Outcome variable is the AB score to social stimuli.*

						95% Confidence Interval	
Predictor	**Estimate**	**SE**	**t**	**p**	**Stand. Estimate**	**Lower**	**Upper**
Intercept	15.197	197.301	0.0770	0.940			
Age	-4.476	22.733	-0.1969	0.849	-0.0442	-0.5622	0.474
Treatment Group	**118.644**	**49.498**	**2.3969**	**0.043**	**0.4874**	**0.0185**	**0.956**
Level of Functioning	-62.437	62.185	-1.0041	0.345	-0.2056	-0.6779	0.267
Baseline AB score	**0.838**	**0.255**	**3.2805**	**0.011**	**0.6580**	**0.1955**	**1.121**
Baseline Anx face score	12.491	23.883	0.5230	0.615	0.1238	-0.4220	0.670
Baseline Like face score	7.257	28.644	0.2533	0.806	0.0569	-0.4610	0.575

Discussion

The present study was aimed at investigating the effects of an ABMT intervention in fostering attentional orienting toward social stimuli and away from non-social objects in ASD children.

Accordingly, the second aim was to understand the degree of which attention to social stimuli is permeable to external modifications. A dedicated implicit learning and reward-based ABMT has been structured and administered to a sample of ASD children. Children were randomly assigned to either an experimental or a control group. The training consisted of a modified version of the Dot-Probe task where the target readily appeared in the same position where the more adaptive stimulus (i.e., in this case the social stimulus) was presented in the previous frame. In the present adaptation of the ABMT, the social stimulus was presented paired to non-social objects, and the probe replaced the social stimulus 90 % of the trials. In addition to previous versions of the training, a reward stimulus was displayed following each correct response. The reward stimulus was a picture of a robotic toy, due to the evidence pointing out a special interest toward these stimuli in the population with ASD. Control group participants performed a standard version of the Dot-Probe task, with no reward, where target appearance side was equally distributed across trials, so as not to trigger any implicit learning effect. Treatment outcome measures included the AB score for the social stimuli, the participants' ratings on the level of anxiety and the likeability attributed to the social stimulus, and the parents' qualitative reports on child's behavior in three areas (i.e., circumscribed attention to objects, fear of interaction, eye-contact avoidance).

A significant increase of AB scores for the social stimuli was observed only in the experimental group after the training and with respect to the baseline measure. The treatment effect resulted to be also significant when including the treatment group variable as a predictor in the model of factors predicting treatment success. The same effect did not occur when considering the participants' explicit ratings on the level of anxiety and likeability attributed to the social stimuli. Contrarily, a significant main effect emerged only for anxiety ratings, that indicated a significant decrease of anxiety ratings attributed to the social stimuli at the end of the training in both groups. A similar non-significant trend occurred also when taking into account likeability ratings. This effect may be explained by a familiarization effect with the presented stimuli that took place in both groups due to the repeated exposure to the stimuli. This may be linked to what the previous literature defined as the “mere-exposure effect”. That is, a phenomenon by which participants develop a tendency to prefer certain stimuli only because they have been repeatedly exposed to them (Zajonc, 1968; 2001). Finally, the analysis of the parents’ reported qualitative data revealed a substantial change in one of the three investigated areas. Specifically, the parents of experimental group children claimed that the children were less prone to avoid eye-contact after the treatment with respect to the baseline. However, these results should be cautiously interpreted. Only a subsample of parents, in fact, reported a difficulty in one area at the treatment onset.

Taken together, these results provide five relevant indications. Firstly, the present pilot study has replicated the effectiveness of the ABMT intervention, although in a different domain with respect to previous research, which was mainly focused on anxiety, depressive and related disorders (e.g., Faunce, 2002; Amir et al., 2009; Domes et al., 2013; Kaiser et al., 2016). Secondly, the present findings show how attention to social stimuli is permeable to external modifications. In the previous chapters it was pointed out that social stimuli are prioritized when competing with other non-social stimuli, and that this pattern does not emerge, or emerges in different ways, in individuals with ASD. The present chapter adds further evidence to the topic by showing that attention to social stimuli can be modulated by exploiting implicit and reward based learning processes. Thirdly, the present results offer interesting hints for the rehabilitation of ASD. Although further evidence, including wider samples sizes is needed, the ABMT may represent a robust intervention tool to be included in the rehabilitation plan of ASD individuals presenting difficulties in social visual interaction and communication. Furthermore, the analysis of the factors predicting the treatment effectiveness has clearly shown how the AB change was selectively sensitive to the effects of the administered training, since no other variables predicted the AB score after the training. More precisely, except for the treatment group, only the baseline AB scores were found to predict AB scores at the end of the training. This effect may mean that the children with higher baseline scores kept the gap with children with lower scores also at the end of the training. This bias needs to be further addressed by future studies investigating the effects of this training. Fourthly, these results are in line, to the best of our knowledge, with the only previous study in which an ABMT intervention was administered to children with ASD (Alvares et al., 2019). In particular, Alvares and colleagues, by using eye-tracking measures and related eye-movements parameters, also found an increased tendency to orient attention to faces after a brief social attention ABMT training (Alvares et al., 2019). Finally, a key-issue, raising from the present results, relates to the scarce generalizability of the administered training effects in every-day life contexts, as measured by qualitative data collected from parents. This may partially be due to a lack of sensitivity of the used measures, or to the low ecological validity of our paradigm. This aspect highlights the need to design follow-up studies based on more naturalistic training materials and setups.

The present study presents some limitations. The first limitation regards the low sample size employed. Although this study was intended to provide preliminary evidence, a replication of the present findings, with a wider sample, is recommended. The second limitation concerns the outcome measures. In particular, despite the use of implicit measures (i.e., AB scores), no objective psychophysiological measures were included in the research design (e.g., eye-tracking). In addition, the use of self-report measures, such as stimulus ratings and qualitative data collected from parents' reports, carry the risk of inter-individual confounding factors such as acquiescence or social desirability. The third limitation concerns the use of the same stimuli for the training and the testing phase before and after the training. Future research trying to replicate these results should be addressed to use different stimuli for the training phase, in order to provide an evaluation of the training generalization effect over new stimuli. The last limitation concerns the research paradigm. At first, because of the pilot nature of the present research, the low sample size did not allow to include a wider range of experimental conditions. However, future studies may consider the inclusion of other two sub-groups, experimental and control, differing from the presence, or not, of the reward stimulus. These conditions would contribute to investigate further the role of the reward on the effectiveness of the training. Another important development of the present paradigm may regard the inclusion of more follow-up measures so as to monitor the effects of the training throughout a wider time window.

Conclusion

The present study was aimed at investigating the effects of an ABMT intervention in increasing attentional orienting toward social stimuli and away from non-social objects in ASD children. Secondly, the present study was designed to understand the degree of which attention to social stimuli is permeable to external modifications. To this purpose, an implicit learning and reward-based ABMT has been structured and administered to a sample of ASD children. The Attentional Bias (AB) scores to the social stimuli increased only in the experimental group after the training and with respect to the baseline. In addition, the parents of the experimental group children reported that their children avoided less eye-contact after the treatment with respect to the baseline. The present study provides preliminary evidence on the effectiveness of ABMT training to improve social attention in ASD children. Moreover, with respect to the topic of the present dissertation, the present findings support the assumption of permeability of attention to social stimuli to external modifications. Whereas the findings reported in the other chapters shed light on the processing priority of social stimuli, and on the lower relevance assigned to them by ASD individuals, the present chapter shows that the priority of processing of those stimuli can be augmented through implicit and reward-based learning processes.

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General conclusion

The aim of the present dissertation was to understand how social stimuli are processed by human beings by taking into consideration inter-individual and inter-stimuli differences. The results presented in Chapter 1 showed that social stimuli are attentively prioritized even when they compete with other relevant non-social stimuli such as money. However, findings from other chapters suggested that this pattern can be modulated by individual differences. Specifically, typically developed (TD) individuals were compared with participants with Autism Spectrum Disorder (ASD), who typically present difficulties in the social domain.

The systematic review presented in Chapter 2 shed light on the existence of two different attentional patterns between TD and ASD groups. While evidence supported the existence of a clear attentional bias (AB) to social stimuli in TD individuals, the opposite pattern was found in ASD individuals. Furthermore, 75 % of the selected studies reported an AB towards HAI stimuli in ASD participants, namely stimuli capable of fulfilling ASD participants' restricted interests and systemizing cognitive style.

Chapter 3 was intended to fill the gap of studies considering the physiology and the visceral components of the typical vs atypical processing of social and non-social stimuli. A naturalistic paradigm, combined to a deep learning and data mining approach, enabled to highlight a different pattern from the one reported by studies only focusing on the cognitive processing of social vs non-social stimuli. In this experiment, ASD participants exhibited similar physiological responses when anticipating the pain of others. On the other hand, results showed a higher physiological response to the impeding pain of non-social stimuli such as robotic agents (i.e., stimuli fulfilling ASD participants restricted interests) in ASD participants.

Due to the evidence collected in Chapters 2 and 3, Chapter 4' s study was designed to investigate if parents of ASD children exhibited the same reduced AB to social stimuli, as observed in individuals with ASD diagnosis, and if this pattern emerged together with a high attentional preference for HAI objects. Plus, the study was also addressed to examine to what extent these attentional patterns emerged in parents of ASD children with Intellectual Disability (ASD-ID) and parents of ASD children without Intellectual Disability (ASD-NOID). Results indicated the existence of an AB towards the face in parents of TD children and parents of ASD-NOID, whereas the same pattern was not found in parents of ASD-ID children. Both ASD parents' groups exhibited a significant AB towards HAI objects. Importantly, due to the heterogeneity of the results in the two groups, it was possible to conclude that these atypical ABs are not likely to be the expression of a common familiar phenotype (i.e., Broad Autism Phenotype), but they may be the expression of environmental variables such as the effort performed by parents to find effective communication channels to attune with their children.

Finally, Chapter 5 was primarily addressed to investigate whether the atypical AB to social stimuli, observed in ASD individuals, can be modified through the administration of implicit learning and reward based interventions. Accordingly, a version of the Attentional Bias Modification Treatment (ABMT) was administered to a sample of children diagnosed with ASD. Interestingly, children who underwent the training had an increase of their AB score to social stimuli throughout the treatment. This chapter has, therefore, emphasized the possible use of ABMT to increase ASD individuals' social attention and, on the same hand, that the processing stimuli can be augmented through the deployment of external resources such as implicit and reward-based learning processes.

The present dissertation is expected to provide three main implications: theoretical, methodological and clinical. As concerns the theoretical implications, the present work only partially supports Aristotle statement mentioned in the introduction. Indeed, the reported findings have clearly highlighted that, although social stimuli are usually prioritized, their valence may be affected by a variety of variables such as individual differences (e.g., autistic traits) or characteristics of the non-social stimuli presented in competition with the social ones (e.g., High Autism Interest stimuli). Finally, results presented in Chapter 3 stress the importance of considering the different stages of stimulus processing (i.e., cognitive vs physiological) when examining human responses to social vs non-social stimuli.

As regards the methodological implications, the present work provides important hints for future research on social vs non-social stimuli processing with TD and atypical development populations. In particular, future studies are encouraged to: i. take individual differences into account when developing study designs comparing responses to social vs non-social stimuli in human beings – for instance by adding covariates to the model; ii. take multiple levels of stimulus processing into account – for instance by disentangling cognitive and physiological processing; iii. integrate the use of traditional statistical approaches with more advanced data science techniques (e.g., machine learning, deep learning, data mining and Bayesian statistics) so as to better the describe the complexity present in the data.

As concern the clinical implications, this work has provided a rich examination of how children and adults of ASD children process social and non-social stimuli both at an attentional level and at a physiological level. The evidence presented in this dissertation can be also considered a further piece of evidence in favor of the social motivation theory and the Empathizing-Systemazing theory of autism that, respectively, explain the reduced interest of ASD individuals for the social world and the high interest for objects or activities fulfilling their systematic cognitive style (see the Introduction for a better description). Plus, as mentioned before ahead, it strengthens the importance of considering all the variables that may concur to modulate the investigated effects (e.g., cognitive abilities, environmental variables, characteristics of stimuli, stage of stimulus processing etc.). Secondly, it has contributed to further shedding light on the concept of BAP, by showing its limitations and the role played by environmental variables in shaping the parents of ASD children's behavioral responses. Finally, the treatment's results presented in Chapter 5 may represent a suggestive starting point for the development of rehabilitation interventions to increase social communication skills in ASD individuals.

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