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Giving meaning to the social world in autism spectrum disorders: Olfaction as a missing piece of the puzzle?

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ABSTRACT

Altered social cognition is a core feature of Autism Spectrum Disorders (ASD). These impairments have been explained as the consequence of compromised social motivational mechanisms that limit social interest and activate a cascade of social deficits. Following this rational, we argue that approaches capable of surpassing ASD usual restraints (e.g., deficits in verbal abilities), and able to assign social meaning, could be more effective at responding to these difficulties. In this framework, we propose that olfaction, as well as cross-modal integration strategies involving both visual and olfactory domains, may have such potential. In fact, most of socioemotional processing deficits in ASD have been shown in an uni-modal perspective, mainly with visual stimuli. However, the social environment involves other modalities and is typically multisensorial. Given the potential of olfaction as a gateway for socioemotional information in ASD, we argue in favor of studying olfactory perception, as well as visuo-olfactory integration, given the potential of these approaches to drive effective interventions and give the access to a meaningful social world in ASD.

1. Introduction

Autism Spectrum Disorders (ASD) are characterized by early core impairments in the social domain, accompanied by restrictive and repetitive behaviors and interests (American Psychiatric Association, 2013). Dysregulations in social cognition are paramount in ASD and play a vital role in patients' inadequate social functioning. Social cognition refers to the processes through which people perceive and give meaning to the social world by understanding and managing self and other's emotions, beliefs, intentions and behaviors, which is crucial to respond successfully to the complexity of social situations (Beer and Ochsner, 2006; Frith, 2008; Frith and Frith, 2008). These abilities have been shown to be compromised in ASD, as reflected in impaired recognition of emotional expressions (Harms et al., 2010; Uljarevic and Hamilton, 2013), abnormal emotion regulation (Mazefsky et al., 2013), difficulties in sharing feelings and experiences (e.g., Kasari et al., 1990) and difficulties in working out people's intentions (Baron-Cohen, 2000). Concomitantly, individuals with ASD often present difficulties in imitation behavior (Williams et al., 2004), as well as abnormal non-verbal communication, including poor eye-contact (Dawson et al., 2004; Senju and Johnson, 2009), and overall difficulties in engaging in relationships with others (Orsmond et al., 2004). These impairments involve significant psychosocial, occupational and economic burdens (Cappadocia and Weiss, 2011; Leigh and Du, 2015), as they seem to be present across the spectrum and do not improve spontaneously with time (Smith et al., 2010; Williams White et al., 2007).

Since vision may be the most significant way to effectively interact with the world (Pazzaglia, 2015), especially in the context of complex social interaction, most research focused on social cognition in ASD have only relied on this sensory modality. In the present article we argue, based on a large bulk of studies published in the last decade (Semin and Groot, 2013; Stevenson, 2010), that olfaction may be an important mean of conveying social information in ASD, one that may surpass the barriers of language and intellectual impairments. As such, we propose that olfaction should be considered in the context of social cognition in ASD, either by using a cross-modal visuo-olfactory approach in which olfactory cues may act as contextual cues that give meaning to visual social information or as an exclusive sensory cue that provides social information, which is of high relevance to ASD individuals adequately adjust to the social world.

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2. Social cognition in ASD: from vision to olfaction

2.1. Social cognition impairments in the visual domain

Research in social cognition in ASD seems to be consistent in showing that ASD individuals have an apparent lack of spontaneous interest in people and social interaction (Chevallier et al., 2012; Senju, 2013), with decreased visual attention to social stimuli across development, when compared to typical developing (TD) population (Chita-Tegmark, 2016; Guillon et al., 2014). This atypical attentional performance seem to impact face processing (Dawson et al., 2005), as well as the development of a larger spectrum of social skills, such as joint attention, i.e., the ability to share and coordinate orientation of attention to an object with another person (Dawson et al., 2004; Mundy and Newell, 2007), and theory of mind, which reflects the ability to attribute and represent mental states of other people (Baron-Cohen, 1991).

Most of the research in social cognition in ASD use human faces as social stimuli, as they convey important cues about the social environment and facilitate communication with others (Haxby et al., 2000). Being able to successfully extract meaningful information from others' faces, such as the individual's identity, intentions or emotional state, can help to predict their behavior and adjust self-behavior accordingly, hence providing valuable social advantages (Leopold and Rhodes, 2010). Although social information carried by faces seems to be crucial and salient enough to capture TD individual's attention (Palermo and Rhodes, 2007; Theeuwes and Van der Stigchel, 2006), that does not seem to be the case in ASD. Studies examining social attention in ASD observed a general lack of spontaneously directing eye-gaze for faces in children and adolescents (Riby et al., 2013; Riby and Hancock, 2009, 2008), as well as increased eye-gaze to the mouth and decreased eye-gaze to the eye region of the face in adults (Neumann et al., 2006; Pelphrey et al., 2002), reduced orienting to eye-gaze cues in adolescents and adults (Ristic et al., 2005) and overall reduced eye-contact (Senju and Johnson, 2009). Interestingly, children with ASD seem to be faster than TD (e.g., Kikuchi et al., 2011) and developmentally delayed peers (e.g., Chawarska et al., 2010) at disengaging their attention from a social stimulus. Despite being scarce, studies with adults report a similar pattern (e.g., Vlamings et al., 2005), suggesting that this difficulty may be stable across development. In visual exploration tasks, children with ASD also seem to look more and/or longer to objects of high interest rather than other objects (Sasson et al., 2011) or social stimuli (Sasson et al., 2011, 2008). Furthermore, the lack of spontaneous attention to faces seems to be even more evident when there are non-social stimuli competing for attentional resources, independently of whether the faces are relevant for the task or not (Klin et al., 2002; Remington et al., 2012; Riby et al., 2012). Together, this literature suggests a weaker engagement by social features (Kikuchi et al., 2011; Sacrey et al., 2014). Yet, there is also literature suggesting normative social orienting and disengagement in children (Fischer et al., 2016, 2014; Pruett et al., 2011) and adults with ASD (Kuhn et al., 2010; Skripkauskait, 2018). These discordant results may be driven essentially by sample and methodological differences across studies (Sacrey et al., 2014).

Importantly, it is not the case that people with ASD are unable to attend to social cues. Instead, they seem not to attend to such cues in a spontaneous fashion, as observed in TD people (Senju, 2013). This is in line with the assumption that diminished social motivation, present since very early in development, may be subserving socioemotional deficits in ASD (Chevallier et al., 2012; Dawson et al., 2005). According to this approach, since social information, such as human faces, do not seem to carry the same rewarding nature for people with ASD as it does for TD people, they are hence less attended and, thus, the experience with these stimuli remains limited. This, in turn, impacts both the development of specific social skills and the normative cortical specialization for face processing (Dawson et al., 2005).

Indeed, a significant number of studies in the area support altered face processing, especially concerning face recognition in children and adolescents with ASD (Boucher and Lewis, 1992; de Gelder et al., 1991; McPartland et al., 2011; Wolf et al., 2008), as well as facial emotional processing in children (Farran et al., 2011; Gross, 2008) and adults with ASD (Ashwin et al., 2006; Baron-Cohen et al., 1997; Pelphrey et al., 2002). Yet, studies have been showing that ASD individuals process face identity in a similar fashion as TD people but have an overall weaker performance (Weigelt et al., 2012), especially in face memory tasks (Boucher and Lewis, 1992; McPartland et al., 2011) and face perception tasks requiring the discrimination of the eye region (Wolf et al., 2008).

In addition, the ability to rapidly and correctly detect and recognize emotions in other's faces, which is crucial to coordinate social interaction by helping to predict other's intentions and behavior and to adjust oneself accordingly (Keltner and Kring, 1998; Niedenthal and Brauer, 2012), is also dampened. Difficulties in this domain are thought to be linked to other crucial socioemotional processes, such as empathy and mimicry behavior (Atkinson, 2007), abilities also known to be impaired in ASD (Clark et al., 2008; McIntosh et al., 2006; Schulte-Rüther et al., 2011; Williams et al., 2004). Regarding emotional processing in particular, some studies suggest that dysregulations may be confined to certain social and complex emotions and mental states, with impact recognition of basic emotions both in children (e.g., Baron-Cohen et al., 1993) and adults with ASD (e.g., Adolphs et al., 2001; Baron-Cohen et al., 1997). However, other studies suggest impairments in processing basic emotions, particularly negative emotions such as fear, both in children (e.g., Farran et al., 2011) and adults with ASD (e.g., Ashwin et al., 2006). In comparison with the facial expressions of fear, the emotional processing of happy faces seems to be only slightly impaired in ASD (Uljarevic and Hamilton, 2013). Difficulties with the processing of fear can be hypothesized as the consequence of a lack of attention to the eye region, crucial for fear processing (Pelphrey et al., 2002), as well as the consequence of abnormalities in amygdala functioning (Ashwin et al., 2006). Some studies further corroborate this idea, by observing evident difficulties posed by children and adults with ASD when processing emotional information of the eye-region of the face (Baron-Cohen et al., 1997; Gross, 2008).

Importantly, face processing in ASD seems to depend on the nature of the employed stimuli (e.g., human faces vs. cartoon, animal or robot faces). For instance, children (Grelotti et al., 2005; Rosset et al., 2008; Sedeyn, 2017), and adolescents with ASD (Brosnan et al., 2015) seem to respond similarly to their TD peers when processing cartoon faces, possibly due to greater interest in this type of stimuli (Rosset et al., 2008). This interest in certain types of stimuli may incease expertise and specialization, facilitating their processing (Grelotti et al., 2002). Similarly, a study analyzing motivational approach and avoidance responses in adolescents with ASD also found that, for positive stimuli, these individuals showed faster avoidance from photographs of people but increased approach to cartoons (Silva et al., 2015). The authors interpreted these results as difficulties in assigning reward to socio-emotional stimuli in ASD. Some studies further suggest that animal faces may be also processed differently from human faces in ASD (Cross et al., 2019; Davidson et al., 2019; Whyte et al., 2016). For instance, children and adolescents with ASD seem to be better at recognizing emotions in animal faces rather than in human faces (Cross et al., 2019; Davidson et al., 2019). Adolescents with ASD have been also shown to have decreased neural activation for human but not for animal faces (Whyte et al., 2016). Additionally, individuals with ASD seem also to process robot faces similarly as their TD peers (Jung et al., 2016). Lastly, it is also suggested that adults with ASD respond differently to unfamiliar and familiar faces, being the latter associated with a stronger neural activation, specifically of the fusiform face area (e.g., Pierce et al., 2004). The nature of the stimuli seems to also play an important role in social attention. For instance, some studies suggest that differences between children with ASD and their TD peers emerge when using more ecologically valid stimuli (Chevallier et al., 2015; Saitovitch et al., 2013). Furthermore, a review and meta-analysis of eye-tracking studies inspecting social attention in ASD suggested that the latter is, in fact, diminished in ASD, and this seems to not depend on the complexity of the used stimuli but rather on the quantity of social content. This suggests that individuals with ASD have more difficulties when more people is included in the presented stimulus (e.g., in a social situation scene; Chita-Tegmark, 2016). Therefore, it is important to consider the nature of the stimuli when studying face processing and social attention in ASD, and also when designing interventions, given the potential of more motivating stimuli to enhance face processing and social skills in ASD (Cross et al., 2019; Jung et al., 2016).

Yet, independently of the nature and extension of the impairments, general difficulties in human face processing have been observed and they may have significant consequences for the social functioning of people with ASD (Dawson et al., 2005; Uljarevic and Hamilton, 2013; Weigelt et al., 2012). Herein, we argue that, given the diminished social motivation in ASD, possibly associated with other cognitive and neural impairments that disrupt general socioemotional processing, ideal interventions should include strategies that carry socioemotional meaning on their own and/or that are also able to orient attention and assign meaning to certain social stimuli, such as faces, that alone may not have an inherent rewarding nature for this population. Given the recent evidence in favor of the striking role of olfaction as an important channel of socioemotional communication (de Groot et al., 2017; Stevenson, 2010), we regard olfaction as a privileged candidate to facilitate socioemotional processing in ASD and to reduce the social deficits observed in this population.

2.2. What makes olfaction special in this context?

The human olfactory system and its relevance in daily life has been receiving exponential attention in last decades (Heymann, 2006). This system is involved in the detection, identification, recognition and memory of a wide range of odors around us (Boudjarane et al., 2017), which can be non-social, coming from a variety of sources such as food, flowers or perfumes, or social, i.e., originating from human body fluids. These chemical signals constitute a valuable source of information about the world, providing important cues about available resources, opportunities and threats, influencing emotion, cognition and behavior (de Groot et al., 2012; Seo et al., 2010; Smeets and Dijksterhuis, 2014; Spehr, 2017) and, more importantly in this context, communicating crucial social information that mediates social interaction (Pause, 2012; Spehr, 2017). Thus, relying in olfactory information may be crucial, especially in ambiguous situations wherein the other senses may fail (Pause, 2012; Pazzaglia, 2015).

Olfaction encompasses a set of particularities that make it somewhat special in comparison with other modalities (Gottfried, 2006). First, the sense of smell develops very early in the development, being already present before birth (Schaal et al., 1998). Also, chemical signals are able to surpass physical barriers, having the potential of travelling for long distances (Pause, 2012). Furthermore, olfactory information is able to influence cognition, emotion and behavior subliminally or without the awareness of the receiver (Keller, 2011; Merrick et al., 2014; Sela and Sobel, 2010), directly accessing structures of the olfactory cortex without a thalamic relay (Gottfried, 2006). Also, structures involved in olfactory processing often overlap with others involved in emotional processing (e.g., amygdala), creating a strong interplay between olfaction and emotion. Indeed, odors are able to induce emotions, as well as emotions are also able to influence our olfactory perception (Chen and Dalton, 2005; de Groot et al., 2012).

Importantly, social communication is pointed as one of the main purposes of the human olfactory system (Stevenson, 2009). Each human carries a unique body odor (BO), receiving both genetic (Penn et al., 2007) and environmental influences, including reproductive status, diet, and general health (Havlicek and Lenochova, 2008). Many studies support the remarkable role of BOs as effective communicative agents in the social domain (de Groot et al., 2017). Human social chemosignals carry unique information about its owner's, such as age (Mitro et al., 2012), gender (Penn et al., 2007), genetic relatedness and compatibility (Porter et al., 1985; Ruff et al., 2012), hormonal variations (Miller and Maner, 2011), disease (Olsson et al., 2014), personality traits (Sorokowska et al., 2012), and emotional state (Chen and Haviland-Jones, 2000). This information is thought to modulate the dynamics of social interaction by, for instance, recruiting empathy-related neuronal areas in the receiver (Prehn-Kristensen et al., 2009), influencing interpersonal trust (Quintana et al., 2019) and social judgement (Dalton et al., 2013), inducing pro-social behavior (Camps et al., 2014), cooperative behavior (Huoviala and Rantala, 2013), risk behavior (Haegler et al., 2010), generosity (Perrotta et al., 2016), and by influencing pivotal social processes, such as the mother-child bonding (Lübke and Pause, 2015; Schaal, 2015, 1988), and sexual functioning and behavior (Alves-Oliveira et al., 2018; Havlicek et al., 2008; Herz and Inzlicht, 2002). Furthermore, there is evidence that social and biologically relevant stimuli, such as human BOs, have a differential and preferential processing, by recruiting brain structures related to emotional processing (e.g., the amygdala), attentional regulation (e.g. anterior cingulate cortex), visual processing (e.g., occipital cortex), processing of social stimuli (e.g., fusiform gyrus) and creation of a basic perception of a human body (e.g., the angular gyrus), contrasting with the more traditional olfactory areas recruited by common odors (COs), such as the medial orbitofrontal cortex and the piriform cortex (Lundström et al., 2008; Prehn-Kristensen et al., 2009). Nevertheless, even if human chemosignals seem to be a critical means of receiving information about the social environment, COs also play an important role in the way we interact with the world, by influencing, for instance, pro-social behavior, interpersonal trust and social relationships (e.g., Baron, 1997; Guéguen, 2012a, 2012b; Sellaro et al., 2014).

Independently of the social or non-social nature of an odor, odors have certain properties that determine how they will be further processed and attended, such as familiarity and valence (Seubert et al., 2017). For instance, evidence suggests that the BO of a kin elicit differentiated responses, compared to the BO from strangers (Lundström et al., 2008) and, accordingly, familiarity also seems to facilitate the detection of chemosensory emotional cues (Zhou and Chen, 2011). On the other hand, odor valence is similarly important to signal potential threats or positive and safe chemical signals, eliciting congruent emotions and behaviors (Seubert et al., 2017). Therefore, emotional-congruent responses are elicited in the receivers following different COs presence (Alaoui-Ismaïli et al., 1997; Bensafi, 2002). Crucially, BOs collected in specific socioemotional situations, such as fear (de Groot et al., 2012), disgust (de Groot et al., 2012), happiness (de Groot et al., 2015), anxiety (Prehn et al., 2006), competition (Adolph et al., 2010) and aggression (Mutic et al., 2016), have also demonstrated the ability to induce congruent affective responses in the receivers, including changes in the activity of certain facial emotional muscles (de Groot et al., 2015, 2012), inhalation magnitude (de Groot et al., 2012), eye-scanning behavior (de Groot et al., 2012), as well as motor (Prehn et al., 2006) and psychophysiological responses (Adolph et al., 2010; Ferreira et al., 2018). These results indicate that odors, especially BOs, indeed carry important social information that is effectively processed and produces compatible emotional and behavioral changes in the receiver, possibly to increase the chances to deal adaptively with the social environment.

2.3. Olfactory (dis)abilities in ASD

Alterations in olfactory abilities and their impact in social and occupational functioning and health have been studied and documented across populations (Boesveldt et al., 2017; Croy et al., 2014b; Hummel et al., 2016). Impairments in these abilities may affect not only health, safety and work ability but also important dimensions of social functioning (Croy et al., 2014b, 2012; Hummel et al., 2017). Olfactory dysfunction also often occurs in neurodegenerative disorders, such as Parkinson disease (Haehner et al., 2009) and psychiatric disorders, such as schizophrenia (Moberg et al., 2014), and some studies have been suggesting that olfactory alterations are present in children and adolescents (Dudova et al., 2011; Hrdlicka et al., 2011; Rozenkrantz et al., 2015), as well as in adults with ASD (Ashwin et al., 2014; Galle et al., 2013; Suzuki et al., 2003; Wicker et al., 2016).

Atypical sensory processing is a well-established feature of ASD (American Psychiatric Association, 2013). It seems to be pervasive across development (e.g., Leekam et al., 2007) and involves distinct and frequently co-occuring response patterns that may include hyperresponsiveness (heightened sensitivity or response to a stimulus), hyporesponsiveness (diminished response to a stimulus) and sensory seeking (persistent search for stimulation; Baranek et al., 2006; Miller et al., 2007). Although evidence suggests that these sensory abnormalities extend to multiple modalities, most of the studies target visual or auditory perceptual processing, with very few literature addressing how individuals with ASD process olfactory cues (Baranek et al., 2014; Baum et al., 2015; Marco et al., 2011). Furthermore, although informative, studies about olfactory perception in ASD are still inconclusive, given the great heterogeneity in crucial aspects, such as the sample's characteristics (e.g., age of participants) and the type of tasks and olfactory stimuli used to measure olfactory function (Larsson et al., 2017; Martin and Daniel, 2014; Tonacci et al., 2015). For instance, the literature suggests lower ability to detect odors in children with ASD (Dudova et al., 2011; Muratori et al., 2017), but also points to normal (Galle et al., 2013; Suzuki et al., 2003; Tavassoli and Baron-Cohen, 2012) or enhanced (Ashwin et al., 2014) olfactory detection abilities in adults. Olfactory discrimination, the ability to distinguish odors considering their disctint qualities (Doty, 2017), seems to be unimpaired either in children (Muratori et al., 2017) and adults with ASD (Galle et al., 2013). Lastly, the ability to identify odors seems to be impaired both in children (Bennetto et al., 2007; Legisa et al., 2013; Muratori et al., 2017) and adults with ASD (Galle et al., 2013; Suzuki et al., 2003).

Importantly, in the socioemotional domain there is also some evidence of altered perception and emotional responses to odors, especially regarding subjective ratings of COs valence in children and adolescents with ASD (Hrdlicka et al., 2011; Legisa et al., 2013), as well as regarding perception and physiological response towards "fear BOs" in adults with ASD (Endevelt-Shapira et al., 2018). For instance, children and adolescents with ASD seem to perceive the pleasantness of some COs, such as cinnamon and sweat, in a significantly more "neutral" way than their TD peers (as less pleasant and less unpleasant, respectively; Hrdlicka et al., 2011; Legisa et al., 2013). On the other hand, Endevelt-Shapira et al. (2018), who performed the only study, to our knowledge, that evaluated the processing of BOs in adults with ASD, observed that emotional BOs, specifically BOs collected during emotional induction of fear, significantly increased electrodermal response in TD people but not in ASD. Additionally, these "fear BOs" reduced measures of trustworthiness in TD people but displayed the opposite effect in ASD (Endevelt-Shapira et al., 2018). The authors argued that ASD people may process social odors in a distorted fashion (which they called "social dysosmia"), similarly to what happens in other sensory modalities, such as vision. This social distortion is further argued as a potential mechanism behind the emotional processing deficits observed across modalities in ASD. Nevertheless, despite these dysregulations, adults with ASD seem to be as able as TD individuals to spontaneously sample BOs, adjusting their sniffing pattern and being able to detect and discriminate them (Endevelt-Shapira et al., 2018).

On the other hand, and interestingly in the context of olfactory abilities, Rozenkrantz et al. (2015) observed impairments in the adjustment of the sniffing pattern according to CO valence, in children with ASD. The adjustment of the sniffing response is important because it may reflect the adaptive functioning of sensory acquisition and rejection mechanisms that allows and regulates the amount of information that is received when a potential contaminant, threat or positive chemical signal is encountered (de Groot et al., 2012). One could argue that having a compromised functioning of these mechanisms can be a serious limitation and, in ASD particularly, may be favoring the observed social deficits (Rozenkrantz et al., 2015). On the other hand, we can also argue that an undifferentiated sniffing pattern can actually be an opportunity rather than a deficit, because it allows people with ASD to obtain the maximum of socioemotional information as possible from an odor, even if negative. This is especially meaningful in the context of impaired visual emotional processing in ASD (Uljarevic and Hamilton, 2013) because, when vision fails, olfaction may be an important, if not the only one, way to access the available socioemotional information in the environment (Pazzaglia, 2015). The research of Parma et al. (2013) may provide an additional and important reinforcement of this potential. These authors conducted a study to examine if an olfactory social cue would be able to facilitate social behavior in ASD, particularly imitation behavior. The results showed that children with ASD were able to imitate the action of a model only when a socially meaningful BO, namely the odor of their own mother, was present in the scene, reinforcing the role of socioemotional meaningful olfactory cues as facilitators in social context.

2.4. The role of olfaction in visual processing

We live in a multisensory world, which constantly provides us an unimaginable amount of diversified information. Hence, it is not surprising that the information coming from the different senses interact to provide a faster and clearer experience of the environment, directing also our focus of attention (Driver and Noesselt, 2008; Driver and Spence, 1998; Pazzaglia, 2015). Cross-modal interactions occur when a stimulus from one modality influences the processing of another stimulus from other sensory modality (Spence, 2018). When stimuli from different modalities are presented approximately in the same spatial location and time window, multisensory integration processes may occur, resulting in a distinct percept that may facilitate performance (Holmes and Spence, 2005; Spence, 2010; Stein and Rowland, 2020). These processes may be especially relevant when the information coming from the individual sensory channels is ambiguous or little informative (De Gelder and Vroomen, 2000; Zhou and Chen, 2009). Indeed, according to the principle of inverse effectiveness (Holmes and Spence, 2005; Meredith and Stein, 1986), the less effective the individual stimuli are, the most pronounced and beneficial multisensory integration is.

Much research has, therefore, been interested in studying cross-modal interactions, especially between vision, audition and touch (Driver and Noesselt, 2008). More recently, the interest in studying the role of olfactory cues in cross-modal interactions has also been growing. For instance, in the non-social domain, olfactory cues have been showed to enhance visual perception (Frassinetti et al., 2002; Ohla et al., 2018), to orient attentional resources to congruent objects or images (Chen et al., 2013; Seigneuric et al., 2010; Seo et al., 2010), to influence visual distraction and visual attentional capture (Michael et al., 2005, 2003), as well as the salience of congruent images during attentional blink (Robinson et al., 2013). Moreover, studies have shown that olfactory cues seem to influence reaction time in visual and auditory tasks (Millot et al., 2002) and subjective ratings of valence regarding pictures (Banks et al., 2012). They also seem to facilitate the localization of sounds (La Buissonnière-Ariza et al., 2012), the processing of auditive and visuo-auditive stimuli (Ohla et al., 2018), and have the ability to change the pleasantness of touch (Croy et al., 2014a). Hence, in the social domain, olfactory cues do represent a promising socioemotional context when interacting with the visual domain.

In fact, social communication and social interaction are multisensory-based. To effectively disentangle the cues imbued in a social situation, we may have to rely on vision, but it is unlikely that this is the only information we receive and rely on (de Groot et al., 2017; Pause, 2012). For instance, speech cues, touch and chemical signals interact and possibly integrate to provide us a better understanding and, hence, an adaptive responding to social interaction demands. Thereupon, and corroborating this assumption, anxiety chemical signals have been shown to boost attentional allocation, to induce stronger startle responses following the presentation of fear facial expressions in high social anxiety (Adolph et al., 2013), to enhance the perception of fearful faces (Wudarczyk et al., 2016), to decrease the priming effect of positive facial emotional expressions (Pause et al., 2004), to facilitate dynamic facial emotional recognition (Rocha et al., 2018), and to decrease subjective ratings of pleasantness of ambiguous faces (Zernecke et al., 2011). Similarly, fear chemical signals seem to modulate the appraisal of ambiguous faces (Zhou and Chen, 2009) and to facilitate the detection of congruent fearful facial expressions but not other negative expressions (Kamiloglu et al., 2018).

Furthermore, a set of studies have crossed social and non-social domains of olfactory and visual stimuli, by demonstrating that COs also affect subjective ratings of human faces (Cook et al., 2017, 2015), modulates neural responses towards faces (Cook et al., 2017, 2015; Leleu et al., 2015b), facilitates the perception of emotional faces, either emotionally congruent (Leppänen and Hietanen, 2003) or not (Seubert et al., 2010), guides affective decision-making towards faces in children (Cavazzana et al., 2016) and facilitates the perception of ambiguous facial expressions (Leleu et al., 2015a; Novak et al., 2015). Together, this evidence supports the notion that olfactory cues, both social and non-social, are able to act as special primes in visual processing, orienting attention for congruent visual stimuli and enhancing facial perception, especially when a stimulus is ambiguous or congruent with the emotional tone of the odor.

3. Olfaction as a unique contextual socioemotional cue for ASD?

3.1. The arguments

By merging pieces of evidence together, and although the nature of olfactory abilities in ASD remains far from uncovered, we argue that the promising results obtained in the last decades unravel new opportunities for developing comprehensive and integrative research about the relevance of social information imbued in olfactory cues for the social behavior in ASD. We aim to further support this idea, by arguing that olfaction may be a privileged channel of socioemotional communication in ASD, and also a strong candidate to surpass the difficulties often observed in visual domain by means of cross-modal visuo-olfactory integration of information. Our arguments are the following:

1. Olfaction is unique in its privileged relationship with emotional brain structures (Gottfried, 2006), and emotionally relevant cues exert great influence in general attentional and perceptual processes (Pourtois et al., 2013). Also, some of these structures have been showed to be abnormally functioning in ASD (e.g., the amygdala and fusiform gyrus) in facial processing tasks (Schultz, 2005). Hence, we believe that olfaction may be able to easily and rapidly recruit these areas, enhancing emotional communication in ASD. Furthermore, since visual stimuli may fail to properly recruit these areas in ASD, possibly due to lack of socioemotional salience (Dawson et al., 1998), olfaction may be able to directly influence the structures involved in socioemotional processing (Gottfried, 2006; Schultz, 2005) and, thus, provide the salience that visual stimuli is lacking (Michael et al., 2003).

2. Olfaction can be used as an effortless and subliminal aid in ASD (Merrick et al., 2014; Parma et al., 2013). This is absolutely critical for these population, since it helps to deal with the verbal language, severity, sensory hypo and hyper-sensibility, intellectual functioning and compliance problems often described by researchers and clinicians (Kasari and Patterson, 2012; Larsson et al., 2017; Martin and Daniel, 2014; Watkins et al., 2015).

3. Olfaction may provide social meaning and disambiguation of other modalities, including the visual system, by being able to recruit areas related to both visual and social perception (Lundström et al., 2008), since it has been suggested that integrating redundant information by two or more modalities may reduce ambiguity (Ohla et al., 2018). This assumption is corroborated by the research in cross-modal visuo-olfactory integration conducted with TD population, that highlights the role of olfactory cues as a facilitator in the perception of ambiguous faces (Leleu et al., 2015a; Zernecke et al., 2011) and in visual attention to congruent stimuli (Seo et al., 2010).

4. Adding information about two or more modalities not only facilitates perception (Ohla et al., 2018), but is closer to how reality works. Notwithstanding the robust difficulties observed in ASD regarding spontaneous allocation of attention to visual social cues and in face processing (Dawson et al., 2005, 1998; Klin et al., 2002), human faces are rarely (if not never) encountered alone in a social interaction, but instead show up together with more information coming from the other senses. As human BOs are highly informative about its sender, communicating striking information in the context of the social encounter and modulating receiver's emotions and behaviors (de Groot et al., 2017; Semin and Groot, 2013), they possibly constitute a key element for understanding social processes in ASD. To close the argument, authors have been claiming that the context matters when studying social attention in ASD (Chawarska et al., 2013), highlighting the need to employ more ecological social stimuli when addressing social processing in ASD. Indeed,when more ecologically valid visual stimuli are used (e.g., complex scenes involving more than one person), the differences between ASD people and TD people seem to be more salient (Chevallier et al., 2015; Chita-Tegmark, 2016; Risko et al., 2012). Moreover, people with ASD are able to look at faces when told to, but instead do not seem to do that spontaneously (Senju, 2013), and are also able to learn emotion recognition strategies and other social skills, but often do not know how to apply them to multiple settings (Kasari and Patterson, 2012). These results seem to suggest that, in fact, ASD people present social difficulties in real-life, complex, social interactions, and, still, we may have been failing to assign and adjust this social and ecological meaning with the adopted approaches. Adding olfactory cues to improved paradigms would mimic more closely the complexity of real-life.

5. Finally, olfaction does not depend on a thalamic relay (Gottfried, 2006). Yet, the existence of a direct route connecting olfactory receptors with the cortex does not necessarily imply that the thalamus is not involved in olfactory processing at all (Courtiol and Wilson, 2015). In fact, the role of thalamus in olfaction is still underexplored, but some studies suggest that it may be involved in olfactory attentional processing, as well as in cortico-cortical communication, hedonic processing, learning and memory (for reviews see Courtiol and Wilson, 2015; Gottfried, 2010; Tham et al., 2009). Furthermore, this structure seems to be compromised in ASD (e.g., Nair et al., 2013; Tamura et al., 2010), Although the impact of these abnormalities in olfactory processing is still unknown. Nevertheless, the fact that at least not all olfactory information relies in a thalamic stay, thus being able to directly access the olfactory cortex, confers a more direct and rapid processing (Gottfried, 2006).

By putting these arguments together, we hypothesize that olfactory stimuli, used as an emotional prime or context, may facilitate socioemotional processing in ASD, especially concerning the orientation of attentional resources to social cues and socioemotional perception, which is critical in this population.

3.2. Implications of the present work

We would like to make some considerations, starting by the point of this framework, which does not aim to propose ungrounding new research or to directly propose new interventions in ASD without evidence, but rather: 1) to review the actual knowledge about social cognition in ASD, with particular focus in visual social attention and face processing, which have been showing impairments across the spectrum and may be linked to broader social deficits; 2) to review the knowledge about olfactory processing in ASD, which remains a very under-explored area for the potential we show that effectively exists for olfaction and socioemotional communication; and 3) to present evidence-based arguments to support why olfactory processing, as well as cross-modal and visuo-olfactory integration approaches could be used to study social perception and behavior in ASD. Thus, we intend to provide new opportunities to further investigate the role of olfaction in socioemotional processing in ASD, as well as its role in cross-modal and multisensory integration processes in ASD, which have the potential to critically drive effective practices.

More than providing answers, we sought to open a new avenue of questions. For instance, until date, no research had addressed the use of COs in comparison to BOs in visual social processing, and the research using them in separate have demonstrated very similar abilities to influence facial perception (Leleu et al., 2015a; Zernecke et al., 2011). It would be interesting to investigate if the presence of an olfactory cue is sufficient to facilitate visual social processing or if the socioemotional meaning of the odor is important in this context. Also, what are the remaining odor properties that guide the effect? Does familiarity, intensity and valence play equally important roles in facilitation effects? Parma et al. (2013), for instance, observed that only familiar odors (maternal BOs) facilitated imitation in ASD children. This suggests that familiarity may be an important property, especially in this population, but we keep unaware of what would have happened if the BOs had a strong emotional content (e.g., being collected in different emotional induction situations). May the effect of these properties be modulated by the characteristics of the spectrum as, for instance, the existence of anxiety symptoms? For instance, Parma et al. (2019) found that ASD and anxiety are associated with differentiated patterns of psychophysiological response. These findings support that measuring anxiety is relevant when addressing, for instance, responses to emotional stimuli, and that this variable may be modulating some of the mixed results observed in uni-sensorial emotional research in ASD.

To test the role of olfaction as a facilitator in social cognition processes in ASD, it is possible to adapt multiple experimental paradigms, some of them typically used in visual perception research in ASD. These include eye-gaze cueing, spatial attention and scene viewing paradigms (for a review see Ames and Fletcher-Watson, 2010). Tasks already employed in cross-modal visuo-olfactory interaction studies in TD population, such as facial emotion recognition/categorization tasks (e.g., Leppänen and Hietanen, 2003; Rocha et al., 2018; Wudarczyk et al., 2016), can also be explored in ASD. For instance, analyzing eye movements in scene-viewing paradigms (Klin et al., 2002) in which visual social stimuli are presented after and/or during an olfactory cue, would allow to evaluate differences in the scanning behavior of visual social stimuli between both sensory conditions. Based in previous research in visual domain, we would expect less spontaneous scanning of social features in the absence of an olfactory cue, in people with ASD (e.g., Klin et al., 2002). Additionally, we hypothesize that the presentation of an olfactory stimulus could approximate the performance of people with ASD and TD individuals by orienting their attention to congruent visual cues (Kamiloglu et al., 2018; Seo et al., 2010). We further expect these effects to be more robust in the presence of BOs, since they would be socially relevant and congruent with the visual stimuli (Seo et al., 2010), and that affective congruency between visual and olfactory stimuli would guide or augment the effects (Kamiloglu et al., 2018). Considering research in more applied settings, it would be also interesting to study specific components of social behavior/interaction in ASD by using odors as a context in semi-realistic and real-life settings, similarly to the approach employed by Parma et al. (2013). It would be also interesting to understand if, assuming that olfaction does have a facilitation effect in visual domain and social behavior in ASD, a visuo-olfactory training would have benefits regarding facial processing, social attention and social functioning in general.

Apart from the potential to facilitate visual processing, olfactory cues may also play a fundamental role in other dysfunctional processes and behaviors in ASD, such as eating behavior and food selection (Boesveldt, 2017). It has been reported that people with ASD presents more feeding problems than their TD peers, resulting in, for instance, nutritional intake deficits (Sharp et al., 2013). These feeding problems may be associated with variables including alterations in sensory processing (e.g., Cermak et al., 2010; Suarez et al., 2014), the emotional valence attributed to visual and olfactory food stimuli (Luisier et al., 2019a, 2015) and the child's family reported eating preferences (Schreck and Williams, 2006). For instance, Luisier and colleagues (2015) found an association between the valence attributed to olfactory food stimuli and food neophobia, the tendency to reject new food, in children with ASD. Furthermore, other study enrolled TD children and children with ASD in several sessions to allow an increase in familiarization with olfactory food stimuli (Luisier et al., 2019b). The authors observed not only a more positive appraisal of the "familiarized odors", but also that children tended to choose food associated with the "familiarized odor". These findings suggest that odors, especially familiar and positive odors, may facilitate food education and the expansion of food repertoire of children with ASD. Future research should further investigate if, for instance, familiarization with food odors brings long-term enhancement of eating behavior in ASD.

To conclude suggestions of future research, it would be also interesting to investigate sensory processing and cross-modal integration considering ASD in a dimensional perspective, including the manifestation of autism symptoms in the general population (Baron-Cohen et al., 2001; Constantino and Todd, 2003). These symptoms, often addressed as autism traits, seem to have a hereditary component (Hoekstra et al., 2007) and to be continuously distributed in the general population (Hurst et al., 2007). Importantly, differences in the manifestation of these traits have been associated with altered attention mechanisms (e.g., Dunn et al., 2016; Freeth et al., 2013; Muller Spaniol et al., 2018), sensory processing (e.g., Bayliss and Tipper, 2005; Cribb et al., 2016; Mayer, 2017; Robertson and Simmons, 2013) and multisensory integration (e.g., Donohue et al., 2012; Kawakami et al., 2018; van Laarhoven et al., 2019), in a similar fashion as observed in the clinical extreme of the spectrum. Nevertheless, there is limited knowledge about olfactory perception and cross-modal visuo-olfactory integration in the sub-clinical part of the spectrum. By studying these processes considering a dimensional perspective, we would have the opportunity to not only access their manifestation and variability in the general population (Donohue et al., 2012), but also to expand the knowledge about this subclinical phenotype of autism and its relationship with the clinical manifestation (Ingersoll and Wainer, 2014; Ronald and Hoekstra, 2011).

Extending research about olfactory and visuo-olfactory perception in ASD would, thus, allow to improve knowledge about if and how olfaction influence social cognition in this population and also how visual and olfactory stimuli combine to modulate attention, emotion and behavior in ASD. In addition to the theoretical and research value, we believe that investigating these processes may have a great impact for the development of new cost-effective and non-invasive intervention programs, with potential to generalize their effects to multiple contexts and to reach positive effects in a cascade of social skills.

3.3. Challenges and opportunities

Throughout the document we have been discussing why studying olfactory perception, as well as cross-modal and multisensory integration involving olfactory cues, may be relevant in the context of sensory and social processing difficulties in ASD. Yet, we disclose some challenges and opportunities regarding these topics that should be carefully considered in future research. First of all, as previously reviewed in this paper, people with ASD often presents altered visual perception (e.g., Behrmann et al., 2006) and may also exhibit either normal (e.g., Robertson, 2012), increased (Ashwin et al., 2006), decreased (e.g., Suzuki et al., 2003) or even distorted olfactory perception (e.g., Endevelt-Shapira et al., 2018). This could imply that, if both visual and olfactory cues are processed in an atypical fashion when isolated, the integration of both signals could also lead to a different, most likely maladaptive percept of the world. Still, the methodological and sample differences across studies strongly difficult direct comparisons, as well as the understanding of how individual differences in this spectrum, such as developmental stage, comorbid conditions (e.g., anxiety disorders) or symptoms' severity, could be associated with sensory processing. Although ASD comprise a complex condition, with great variability regarding symptoms and levels of functioning, efforts should be made to isolate as much as possible the effects of these variables to better understand sensory and social processing in this population.

Furthermore, some studies have been suggesting that the ability to combine information from multiple sensory channels is often compromised in ASD (for reviews see Baum et al., 2015; Beker et al., 2018; Feldman et al., 2018; Wallace et al., 2020). Nevertheless, these studies rely mostly in the integration of visual, auditory and tactile sensory information. Regarding the integration of information involving olfactory cues, little is known. To the best of our knowledge, only one study has, so far, addressed the behavioral effects of cross-modal integration of visuo-olfactory stimuli in ASD (Endevelt-Shapira et al., 2018). The authors examined olfactory perception of "fear BOs" in adults with ASD and TD people, including the influence of these olfactory cues in a face perception task and in a social judgement task. The authors did not found behavioral effects of exposure to BO in either group in the face perception task, but observed altered estimation of trustworthiness following the perception of fear social chemosignals in ASD. These results open a new avenue of questions about the processing of emotional odors, especially BOs, and their relevance in visual and social perception across contexts, in ASD. Still, conclusions are limited due to scarcity of literature, as well as by the fact that this study only tested adults, mainly male and only used BO, collected in specific emotional situations.

Regarding the neural correlates of multisensory visuo-olfactory integration, the scarcity of studies even in typical development greatly limits the knowledge about how the brain processes this information (e.g., Ripp et al., 2018; Sijben et al., 2018). In ASD, there is only one study analyzing brain activation following visuo-olfactory stimulation, suggesting that visuo-olfactory integration of congruent images and common odors (e.g., rose), is associated with a pattern very similar to that observed in audio-visual integration (Stickel et al., 2019). Furthermore, results evidenced similar brain activation for TD and adults with ASD, suggesting intact visuo-olfactory integration in adults with ASD (Stickel et al., 2019). Therefore, despite the evidence in favor of altered multisensory integration regarding other sensory modalities (which is not true for all the people with ASD and for all the types of sensory stimuli; see, for instance, Beker et al., 2018), it is very preliminary to assume that visuo-olfactory integration is also atypical in ASD. As argued throughout the paper, future studies should further investigate olfactory perception and visuo-olfactory integration in ASD (and also in typical development), to provide a better understanding of how the brain processes this information separatedly and together, and how this perception influences cognition, emotion and behavior in this population.

Despite inconsistent results regarding olfactory perception in ASD, olfactory cues have already been shown to have the potential to foster previously impaired adaptive behaviors in this population. For instance, the research of Luisier and colleagues (2019b) suggested that it is possible to increase familiarization with odors from food stimuli, allowing a more positive evaluation of these stimuli and a preference for the associated food. This may have important implications for future research regarding eating behavior and food refusal in ASD, but also hints that it may be possible, through the process of familiarization with odors, to use familiar olfactory stimuli to improve behavior in other contexts. Similarly, the research of Parma et al. (2013) also suggests that familiar and socioemotionally significant BO, such as the mother's BO, is able to promote social behaviors. Familiarity seems to be a central property to unlock previously impaired behaviors, yet further research is necessary to extend this results and explore other possibilities.

An additional important challenge is to understand how to transpose this laboratory research to daily life context, where people deal with the typical complexity of a real social interaction. In a real social interaction, we are overwhelmed with sensory information that we must be able to successfully filter, select, integrate and segregate to identify rapidly and correctly the presence of a kin, rivals and potential partners, as well as their emotions, thoughts, intentions and behaviors (Carretié, 2014; Keltner and Kring, 1998; Stein and Rowland, 2020; Vuilleumier, 2005). In addition to relevant social information, we also receive cues about nonsocial objects present around us, that may possess different properties and, therefore, signal events of distinct relevance in the environment. Even social information can be masked or modified by nonsocial cues, such as parfum or hygiene products, that mix with the BOs of people around us (Allen et al., 2019). It is up to our perceptual system to prioritize socially and evolutionarily relevant information, allowing an appropriated response to the challenges and opportunities posed by the environment (Carretié, 2014; Desimone and Duncan, 1995; Egeth and Yantis, 1997). This may be a challenge for people with ASD, that frequently report to be overloaded with sensory information (Jones et al., 2003; O'Neill and Jones, 1997). Considering that individuals with ASD may process social information in a nonsocial fashion, either due to motivational deficits (e.g., Chevallier et al., 2012), or broader atypical perceptual functioning (e.g., Mottron et al., 2006), or both, then we could argue that they may have difficulties in prioritizing and using relevant information to act accordingly, especially in more complex scenarios. Difficulties in multisensory integration may also play a significant role here, as previously described, as well as difficulties in effectively value and learn from prior sensory experiences and use this knowledge to deal with current sensory information (Pellicano and Burr, 2012). All these accounts seem plausible and may not be mutually exclusive in their role to explain sensory and social difficulties in ASD. Together, they may hint why olfactory cues, which are present in the environment together with other sensory information, do not help in face processing and social behaviors in ASD in everyday life. Therefore, it may be necessary to: 1) First, understand how cross-modal and multisensory integration processes work in ASD, in controlled and well-defined laboratory experiments, by isolating the stimuli of interest from other irrelevant sensory stimuli as much as possible; 2) Second, evaluate the feasibility and efficacy of sensory trainings that systematically combine relevant sensory information to improve, for instance, face processing and/or social attention. Starting with more motivating visual (e.g., cartoons and animal facial expressions; Rosset et al., 2008; Whyte et al., 2016) and olfactory (e.g., familiar and socioemotionally relevant odors; Luisier et al., 2019b; Parma et al., 2013) stimuli may help in the process; 3) And third, gradually transpose the experimental paradigms to more applied contexts, evaluating not only measures of social attention, but also how the sensory training improved social functioning in general. We hypothesize a long way to go with many challenges subserved by a complex and fascinating spectrum. Nevertheless, independently of the outcome and as argued before, we argue that investigating olfaction and cross-modal interplay in ASD will provide certainly several answers and, importantly, many other important questions.

4. Conclusion

In this article, we have reviewed evidence that supports that olfaction possesses a set of unique properties whose processing isworthy of stuying in ASD, and that olfactory cues can be helpful to disentangle social meaningless and ambiguity, as well as to overcome the consequent social deficits observed in ASD. Despite the still scarce literature in olfactory processing, studies suggest that the interplay between olfaction and emotion is, indeed, significant, and that odors may be an effective way to correspond to the complexity of social interaction. We also believe that the knowledge about olfactory abilities in ASD and how odors interact with other sensory modalities may be helpful to better understand how these modalities work alone, how cross-modal and multisensory mechanisms work in general, how the sensory profile of this population works in particular, and this knowledge may be crucial to design cost-effective, embracing, generalizable, inclusive and effortless intervention plans. We further suggest that this knowledge would be also capable of open new possibilities for other populations with deficits in social domain (e.g. schizophrenia). For now, this framework lights up new opportunities for research and, posteriorly,practice in social domain, by providing one more piece for the intriguing and complex puzzle of ASD functioning.

Declaration of Competing Interest

None.

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