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The (overgrown) body in social context: how atypical body features shape cognitive and socio-emotional development in overgrowth syndromes

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Summary

Embodied cognition accounts have provided striking evidence of how cognitive, affective and social processes are deeply rooted in the embodied experience. The way an individual perceives his/her own body has crucial, but often neglected, implications for social interaction and for psychological development. This thesis is composed by two research projects that investigate body perception and its impact on psychosocial functioning in healthy adults and in children and adolescents with overgrowth syndromes, respectively. A first project is aimed at investigating affective touch, a specific dimension of body perception that plays a primary role in conveying emotions and in forming social bond. Vicarious perception of affective touch is assessed in healthy adults through behavioural and neurophysiological experiments. The main research project addresses how cognitive and socio-emotional development is influenced by being born with an overgrowth syndrome, specifically Beckwith-Wiedemann (BWS), Malan and Sotos syndromes. Body perception, cognitive and emotional-behavioural development are investigated by means of a series of experiments and standardized assessments, involving children and adolescents with overgrowth syndromes as well as individuals with other genetic disorders and healthy participants.

The first chapter offers a narrative review of previous research on the multidimensional construct of body perception. The emergence of embodied cognition theories provides a theoretical and empirical framework for understanding the complex interactions between body, emotion and cognition in healthy and clinical populations.

The second chapter presents the results of the project aimed at investigating vicarious perception of affective touch in healthy adults. Two consecutive studies provide behavioural and neurophysiological evidence of how we understand the affective and social meaning of touch during observation of interpersonal interactions.

The third chapter offers an overview of the project on overgrowth syndromes and then investigates the neuropsychological profiles and educational outcomes in children and adolescents with BWS,

Sotos and Malan syndromes. Two studies explore the neuropsychological profiles of other genetic disorders, namely Williams syndrome and Joubert syndrome. The results and the indirect comparison with these disorders provide indications on cognitive development and the interplay between body, cognition and social context in overgrowth syndromes.

The fourth chapter is aimed at investigating body perception in adolescents with overgrowth syndromes compared to healthy peers through a multidimensional assessment. Specifically, body image disturbances, body-related representations of action and social spaces, interoceptive sensitivity to cardiac signals, and bodily illusions of ownership over a virtual body are assessed.

The fifth chapter examines the presence of emotional-behavioural problems and autistic traits in children with BWS, Sotos and Malan syndromes. A study investigating psychosocial difficulties in preschool-age children with BWS is presented as well. The findings highlight the socio-behavioural phenotypes of BWS, Sotos and Malan syndromes, which are discussed considering socio-cognitive abilities and clinical features of each condition.

Lastly, the results of the two projects and their implications for future research and for clinical management of overgrowth syndromes are discussed.

Contents

Chapter 1. The body in mind: a narrative review of the relationship between body, emotion and cognition

Chapter 2. The body in social touch: behavioural and neurophysiological evidence of how we understand others through the observation of interpersonal (affective) touch

Chapter 3. Cognitive development in children and adolescents with overgrowth syndromes: neuropsychological profile and educational outcomes of Beckwith-Wiedemann, Sotos and Malan syndromes

Chapter 4. Body perception in adolescents with overgrowth syndromes: results from a multidimensional assessment

Chapter 5. Socio-emotional development in children and adolescents with overgrowth syndromes: emotional-behavioural problems and autistic traits in Beckwith-Wiedemann, Sotos and Malan syndromes

1. The body in mind: a narrative review of the relationship between body, emotion and cognition

1.1 Introduction

"The ego is first and foremost a bodily ego; it is not merely a surface entity but is itself the projection of a surface" (Freud, The Ego and the Id, 1923).

"The object of the idea constituting the human mind is the body" (Spinoza, Ethics part 2 proposition 13, 1677).

These famous quotations of Freud and Spinoza attest that the role of the body in one's psychological experience has been well acknowledged in philosophy of mind and psychoanalysis. The body is indeed the primary interface through which we interact in the world, directly and often, without awareness. Because of its immediacy and obviousness, and also due to the traditional philosophical dichotomy between body and mind, how bodily experiences influence cognition and emotion has long been neglected. This oversight has occurred despite the increase in neurological disorders in the XX century, affecting the perception of one's body, such as phantom limbs, somatoparaphrenia and other alterations of body awareness (Brugger & Lenggenhager, 2014). These clinical phenomena suggest that alterations in the somatosensory representations of the body strongly impact cognition and emotions. However, in the last 25 years the body has gained attention in psychological and neuroscientific research (Berlucchi & Aglioti, 1997, 2010; de Gelder et al., 2010; Slaughter et al., 2002). The discoveries of selective body areas in the occipito-temporal cortex (Downing & Peelen, 2011; Urgesi et al., 2004) have highlighted that our brain is specialized in perceiving body stimuli. Processing another person's body is inherently linked with our embodied sensorimotor experience (Thomas et al., 2006). This stream of research has mainly focused on visual perception of bodily stimuli. More recently, studies on infants and children have documented that a primitive sense of body ownership starts forming early in life through the integration of visual information with that conveyed by other senses, such as auditive and tactile stimulation (Blanke et al., 2015; Filippetti et al., 2015). To develop an appropriate awareness of the own body, the processing of signals from internal organs and neurovegetative activity, called interoceptive perception, is as important as the one derived from exteroceptive sensorial information (Tsakiris, 2017). These contributions suggest that body perception is a complex, multifaceted construct, underlined by processes that begin from the very first months of life. So what happens when the early body experience is inherently biased due to a neurodevelopmental disability or other congenital disorders such as overgrowth syndromes? When body perception is affected early in these conditions, how does this alteration impact on cognitive and socio-emotional development? In this chapter, research contributions about body perception in the fields of cognitive neuroscience and developmental psychology are reviewed, with the aim of clarifying how body perception has been conceptualized. As well, new areas of research that still need to be fully addressed are presented. Lastly, the relationship between body, cognition and psychosocial functioning is considered in conditions characterized by altered bodily experience.

1.2 Evolution of the concept of body perception

There is not a unique meaning of body perception in literature, since authors have used this term or similar definitions, such as body representation and body awareness, to describe quite different processes referring to the perception of either one's own or another's body. With the aim of clarifying what I refer to as body perception, two main streams of research are offered that have investigated body perception as, respectively, the (multiple) representation of the body in the brain and the bodily contributions to the sense of Self.

Evidence of disorders of body perception in neurological and psychiatric patients has brought clinicians and researchers to investigate how and where the human brain represents body stimuli (de Vignemont, 2010). At the beginning of the XX century Head and Holmes proposed the first, classic distinction between body schema and body image (Head & Holmes, 1911). This dyadic classification has been widely adopted up to the present day. The body schema is considered as a dynamic, sensorimotor representation of the one’s own body that drives action and movement even when simulated internally. Body image is a static internal representation of one’s own as well as others’ bodies adopted for perception, recognition and judgement, thus includes both a perceptual and a conceptual component (Berlucchi & Aglioti, 2010). Studies on deafferented patients have reported evidence of a double dissociation between these representations (Anema et al., 2009; de Vignemont, 2010; Gallagher & Cole, 1995). However, diverse discriminative criterions have failed to show reliability in providing an unambiguous definition of these constructs, and particularly of body image (de Vignemont, 2010). A further classification was proposed to overcome the ambiguity of body image by splitting it into two components. The first is a perceptual, visuospatial component, called body structural description. The second is a conceptual, emotionally engaged, fully conscious representation called body semantics (Schwoebel & Coslett, 2005; Sirigu et al., 1991). The body structural description is involved in the detection and recognition of visual body stimuli, as research has demonstrated that bodies just like faces are processed through refined visual-perceptual strategies (Butti, Finisguerra, et al., 2022; Minnebusch & Daum, 2009). The category-specific areas in the occipito-temporal cortex respond selectively to the visual presentation of body stimuli (Cazzato et al., 2015; Urgesi et al., 2007). Conversely, the definition of body semantics has remained ambiguous because most studies continued to adopt the term body image in referring to the conscious body representation that is strongly influenced by cultural and social norms (McLean & Paxton, 2019; Slade, 1994). Importantly, body image in both its components represents one’s own as well as another’s body, thus it is an object of perception. Body schema is intrinsically linked to the subjective experience of one’s own body.

The difference between the body as object and subject of experience could be ascribed to the classic distinction between the I and the Me proposed by Williams James (James, 1890). While the philosophical disputes on this topic fall outside the scope of this thesis, the distinction between the Self as subject or object of experience has brought scholars of different disciplines to sustain the presence of a primitive, minimal, sense of Self, in contrast to a reflective, narrative Self (Damasio, 2003; Gallagher, 2000). There is a wide agreement that this minimal sense of Self is essentially embodied since it is grounded on the complex, multisensory experience of the one's own body (Ciaunica & Crucianelli, 2019). The term bodily Self acknowledges the contributions of cognitive sciences (Legrand, 2006) as well as of psychoanalysis and infant research (Stern, 1985, 2009). The sense of ownership, the sense of self location, and the sense of agency have been emphasized as core aspects of the bodily Self (Gallagher, 2000; Legrand, 2006; Serino et al., 2013). The sense of agency has gained interest with the discovery of the so-called mirror neurons system, which are activated during both action execution and action observation (Rizzolatti & Craighero, 2004). This discovery has provided evidence of a prominent role of motor intentionality in posing the foundation of our bodily self-awareness (Gallese & Sinigaglia, 2010). A new theoretical framework has been born to bridge the gap between the two related, but different concepts of body schema and bodily Self (Ferri et al., 2012; Frassinetti et al., 2011; Legrand, 2006). This framework has allowed the linking of what the famous neurologist Oliver Sacks had defined "a soulless neurology and a bodiless psychology" (Sacks, 1985).

1.3 The embodied cognition framework: how the body shapes cognition and emotion

Embodied cognition usually defines a wide and heterogeneous group of theories linked by the role of the body experience in cognition. By assuming a continuity between cognition, somatosensory and motor functions, this framework overcomes the classical mind-body dichotomy (Foglia & Wilson, 2013). Research has provided compelling evidence of mirror-like activations in the somatosensory and motor cortices, which have been integrated in the embodied cognition framework to account for cognitive and socio-emotional abilities (Schmidt et al., 2021; Urgesi et al., 2014). Indeed, by simulating others' actions into the observer's motor and somatosensory systems, people rely on their own bodily states to represent and understand others' mental states and feelings in a pre-reflective, embodied way (Ciaunica, 2019). The engagement of sensorimotor networks even in the absence of direct sensory stimulation or behavioural output indicates that basic mechanisms of cognition such as knowledge representation and retrieval are supported by patterns of embodied responses (Foglia & Wilson, 2013; Hétu et al., 2013). Thus, the body constitutes an intrinsic constraint that regulates and shapes our cognitive, emotional and social processes (Ciaunica, 2019).

Recently, embodied cognition theories have been integrated with predictive coding accounts of neural activities. The main assumption of predictive coding is that the brain constantly generates predictions about incoming events (Friston, 2012). Perception is seen as the result of recurrent interactions between bottom-up sensorial information and top-down expectations called priors. These processes drive the selection of the most probable cause for that specific sensorial input (Kilner et al., 2007). The integration of embodied cognition and predictive coding accounts has drawn attention to aspects of body perception formerly overlooked, such as interoception, (affective) touch, and multisensory integration (Friston et al., 2011; Petzschner et al., 2021; Seth, 2013).

1.4 The hidden sense of the body

Interoception refers to the ability to detect the feelings associated with the state of the internal body and its visceral organs (Craig, 2003; Tsakiris, 2017). Despite the existence of diverse definitions and conceptualizations, interoception is usually considered as distinct from exteroception (perception of the external environment) and proprioception (signals from the skin and musculoskeletal apparatus reflecting the position of the body in space) (Garfinkel et al., 2015). According to embodied cognition accounts, interoception is seen as the homeostatic state that drives the perception of our own and other people’s emotions (Allen & Tsakiris, 2018). Past research has documented the involvement of interoceptive abilities in empathy (Fukushima et al., 2011), emotion regulation (Füstös et al., 2013) and generally in social cognition (Gao et al., 2019), as well as in cognitive abilities like decision making (Dunn et al., 2010) and memory (Garfinkel et al., 2013). Importantly, altered interoceptive abilities have been associated with anxiety and social impairments in psychiatric and neurodevelopmental disorders, such as autism spectrum disorders (ASD) and eating disorders (ED) (Herbert & Pollatos, 2012; Palser et al., 2018; Schauder et al., 2015). Structural alterations of the body, such as in the case of overgrowth syndromes, may affect interoceptive processing, and thus impact emotional perception and regulation.

1.5 The power of caress

Recently, literature in neuroscience and developmental psychology has explored the link between interoception and a specific type of touch, called affective touch. This stream of research finds its foundation in the discovery and growing popularity of specific tactile afferents, called CT fibres, that optimally respond to slow, gentle, caress-like touch (see Chapter 2 for a detailed description). The pleasant feelings elicited by stimulation of the CT system promote social bonding and affiliative behaviours, thus play a pivotal role in socio-emotional development (Cascio et al., 2019; Fairhurst et al., 2014; Morrison et al., 2010). Notably, the CT afferents project to the posterior insula, which is considered the main hub of interoceptive processing (Craig, 2003; Kirsch et al., 2020), so that affective touch per se has been described as a subtype of interoception invested of social functions (Björnsdotter et al., 2010). Affective touch has been proposed as a basic mechanism that promotes the development of the bodily Self through early caregiver-infant interactions (Crucianelli & Filippetti, 2018; Montirosso & McGlone, 2020). Alterations in perception of affective touch have been documented in the same clinical populations that show interoceptive deficits, such as ASD and ED (Cazzato et al., 2021; Croy, Geide, et al., 2016; Crucianelli et al., 2016; Frost-Karlsson et al., 2022). In line with the assumptions of the embodied cognition, research has documented behavioural and neurophysiological mirror-like responses during the observation of interpersonal affective touch (Morrison et al., 2011; M. Schaefer et al., 2023; Walker et al., 2017). However, past studies have focused on the receiver of the touch action. How we perceive observed tactile interactions, as if we were the toucher, has still to be explored. This topic is addressed in Chapter 2.

1.6 Greater than the sum of sensory channels: multisensory integration and the bodily Self

Multisensory integration is the neurobiological process through which information conveyed by the sensory modalities are combined into a single percept (Noel et al., 2018). Beyond the specificity of each sensorial channel, it is through the integration of multisensory bodily information that infants develop coherent representations of their own bodies. This constitutes the core of the bodily Self (De Klerk et al., 2021; Zaidel & Salomon, 2023). Experimentally, various multisensory paradigms have been developed to manipulate the sense of body awareness. From the classic rubber-hand illusion to innovative methods including interoceptive signals (Cowie et al., 2016; Heydrich et al., 2018; Porciello et al., 2018), a wide range of experiments has provided evidence that the bodily Self is rooted in multisensory integration processes, with implications for our understanding of social relationships (Tsakiris, 2017). Indeed, different susceptibility to bodily illusions has been found in clinical populations characterised by altered social behaviour, such as ASD (Schauder et al., 2015). Interventions based on the manipulation of body ownership have been proposed to improve body image alterations in patients with ED (Keizer et al., 2016; Scarpina et al., 2019). While altered sensory processing has been reported in overgrowth syndromes (Mulder et al., 2020; Smith et al., 2023), how these conditions affect multisensory integration and the sense of body awareness has not been studied before.

1.7 The multisensory body (schema) in action and social spaces

In its motor and social functions, the body schema is strictly related to specific multisensory representations of space surrounding the body (Cardinali et al., 2009; D’Angelo et al., 2018). Although theoretical and empirical disputes about these terms continue (de Vignemont & Iannetti, 2015), these body-related representations have been defined as peripersonal space (PPS) and interpersonal distance (IPD). PPS has its neurobiological foundation in the discovery of the so-called bimodal neurons, responding similarly to somatosensory and visual stimuli only when they are presented in space regions near the body (Rizzolatti et al., 1981a, 1981b). These neurons thus encode a multisensory representation of the space surrounding the body, linking the sight of objects to expected tactile events and preparing the subject to act. Due to these features, peripersonal space is usually defined as the “grasping” space, in which the individual can reach any object by hand without locomotion (di Pellegrino & Làdavas, 2015). PPS is also conceptualized as the action space, a multisensory interface that prepares the body for voluntary object-directed movements or for defensive actions in case of threat (Coello & Cartaud, 2021). This action space is flexible, as it adjusts according to characteristics of the approaching stimulus, internal traits or the use of tools, as well as to the emotional and social context (di Pellegrino & Làdavas, 2015; Serino, 2019). However, an intertwined but dissociable body-related representation of space is more strictly related to social interaction. This interpersonal space or IPD defines the area around the body that individuals maintain with others during social interaction (Candini et al., 2021). IPD permeability refers to how individuals tolerate intrusion by others. Flexibility indicates how easily this space changes depending on internal and external factors (Candini et al., 2017). IPD is usually larger than PPS, as it contains the action space plus a ‘buffer space’ that helps maintain a feeling of comfort and security in social interaction (Coello & Cartaud, 2021). Dissociable alterations of these spaces have been reported in autism and other neurodevelopmental disorders characterised by abnormal social behaviours (Candini et al., 2019; Lough et al., 2015, 2016). However, no prior studies have investigated IPD and PPS and their relationships with social functioning in conditions of overgrowth.

1.8 Conclusions and aims of the project

This chapter has highlighted the complex, multifaceted nature of body perception, a term that includes the classic body representation models of body schema and body image, as well as the traditional and new contributions concerning the bodily Self.

Previous studies have investigated how altered early body experience or brain lesions acquired in developmental age may impact body perception, with likely consequences on cognitive and socio-emotional abilities. A study on children and adolescents with spastic diplegia documented that early perinatal damages to sensorimotor areas affect visual processing of bodily stimuli and mental imagery when the body schema is engaged. These alterations may at least partially account for social perception deficits shown by these patients (Butti et al., 2019). The same paradigm was adopted to study body perception in children born preterm, a condition associated with atypical exposure to visual, sensorimotor, vestibular, and proprioceptive stimulation in the early phases of life. Results indicated that preterm birth interferes with the development of body representations at the levels of body visual perceptual processing and of body schema, with effects even on visuospatial abilities for non-bodily stimuli (Butti, Montirosso, et al., 2020). Another study documented that traumatic brain injuries affected perception of the one's own and another's body (Corti et al., 2022). However, this research does not consider the multifaceted nature of body perception. As well, these studies do not characterise the cognitive and emotional-behavioural profiles of the recruited clinical populations.

The main project of this thesis, in collaboration with the Associations of families and patients with Beckwith-Wiedemann (Associazione Italiana Sindrome di Beckwith-Wiedemann – AIBWS), Sotos and Malan syndromes (Associazione Sindrome di Sotos Italia – ASSI Gulliver), was developed to fill this gap. The conditions of overgrowth syndromes inherently involve a biased body experience. But these rare genetic syndromes have not been fully characterised in their neuropsychological and emotional-behavioural functioning. These syndromes thus allow a more direct investigation of the relationship between body perception, cognitive and socio-emotional development. This project has three main aims: i) to describe the neuropsychological profiles of these syndromes in developmental age, also considering the profiles of other genetic disorders associated with abnormal social behaviour; ii) to examine different dimensions of body perception in adolescents with overgrowth syndromes compared to healthy peers; iii) to investigate socio-emotional development of children and adolescents with overgrowth syndromes.

Moreover, in Chapter 2 I present a specific project that investigates vicarious perception of affective touch through behavioural and neurophysiological techniques. This research integrates previous knowledge on this important dimension of body perception within the embodied cognition framework, with the aim of exploring the strict relationship between vicarious perception of affective touch, interoceptive awareness and empathy. The project was developed and conducted in collaboration with the Liverpool John Moores University as part of the visiting experience.

2. The body in social touch: behavioural and neurophysiological evidence of how we understand others through the observation of interpersonal (affective) touch

2.1 Introduction

Interpersonal tactile interactions are pervasive in the early stages of life and play a pivotal role in forming social bonds and communicating emotional information throughout the life span (Cascio et al., 2019; Montirosso & McGlone, 2020). At a somatosensory level, touch pleasantness correlates with the activity of slow-unmyelinated afferents, called CT fibres (Olausson et al., 2010; Vallbo et al., 1999). CT fibres, predominantly innervating hairy skin, respond optimally to touch delivered at velocities of 1-10 cm/s, at a temperature similar to human skin (Ackerley, 2022; Ackerley, Backlund Wasling, et al., 2014), eliciting a pleasant sensation that decreases for faster and slower touch following a typical inverted-U shaped pattern (Löken et al., 2009; McGlone et al., 2014). Through their projections to the dorsal posterior insula (Kirsch et al., 2020; Morrison, 2016), CT afferents support the processing of affective information entailed by social touch. Accordingly, recent research has documented the functional role of the CT afferents in affect regulation and social development (Fotopoulou et al., 2022), highlighting, for instance, the role of affective touch reception in modulating parasympathetic activation (Pawling et al., 2017; Van Puyvelde et al., 2019), in reducing pain (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017), and in buffering feelings of social exclusion (Von Mohr et al., 2017).

Beyond the somatosensory effects of touch, there is evidence of affective responses also when interpersonal gentle touch is just ‘observed’. Within the framework of the ‘embodied simulation theory’ of touch (Gallese & Ebisch, 2013), individuals can map others’ tactile events by re-using their own motor, somatosensory and interoceptive representations. As a result, this tactile mapping would allow an observer to perceive the touch as if receiving the same kind of tactile stimulation, thus facilitating the understanding of how the other person is ‘feeling’ that touch (Keysers et al., 2010). In line with this hypothesis, functional neuroimaging evidence reports the activation of the dorsal posterior insula during vicarious observation of CT-optimal touch (Morrison et al., 2011; M. Schaefer et al., 2023), suggesting a similar hedonic response to directly felt and vicarious touch experiences. Furthermore, observation of vicarious interpersonal touch is rated as more pleasant when delivered at CT-optimal compared to non-CT optimal velocities (i.e., slower or faster touch), eliciting the typical inverted-U function between vicarious pleasantness ratings and velocities (Bellard et al., 2022; Devine et al., 2020; Haggarty et al., 2021; Walker et al., 2017). These findings suggest that the human brain may be attuned to “see” CT-specific features when watching others performing interpersonal touch actions (Morrison et al., 2011).

Little is known, however, about the vicarious representation of *giving* gentle touch. Indeed, observing others’ actions triggers an inner simulation of the movements in the observer’s motor system (Fadiga et al., 1995; Gazzola & Keysers, 2009). This simulative representation includes not only movement kinematics, but also the affective valence of movement (Craighero & Mele, 2018; Finisguerra et al., 2021; Urgesi et al., 2020; Vicario et al., 2019). At a higher-order socio-affective level, affective touch may have important social meaning for both those who give and those who receive it (Schirmer et al., 2023). Evidence suggests that affective touch has a beneficial effect also for the person delivering the stroking gesture (i.e., toucher), given that those who give touch may convey feelings of closeness and care toward a touchee, who in turn may feel bonded and safe (Debrot et al., 2021; Jakubiak & Feeney, 2017). In primates, social interactions involving social touch are of critical importance for group life, so that delivering social touch is associated with desirable individual and social benefits (Jablonski, 2021). Furthermore, stroking other’s skin is perceived as pleasant by the toucher (Triscoli et al., 2017), is associated with more positive sensory experiences when delivered at CT-optimal velocities (Gentsch et al., 2015), and is spontaneously targeted to activate CT afferents (Croy, Luong, et al., 2016).

Despite these similarities between touch receiving and giving, there are profound perceptual differences which arise from the body parts that an individual normally uses to give and receive touch. Typically, most of the touching actions, like hand-holding, cradling and embracing, are performed with the toucher’s palm contacting a touchee’s arm, shoulder, or back (Schirmer et al., 2021; Triscoli et al., 2017). Notably, while CT afferents are widely represented in the hairy skin, the palm is densely innervated by fast-conducting Aβ fibres rather than CT afferents (Watkins et al., 2021). Thus, the tactile systems might receive more readily benefits from CT signalling when activated by touch receiving than by touch execution (Schirmer et al., 2023), suggesting a preference for reception over the hairy skin, compared to execution, with the palm, of affective touch (Triscoli et al., 2017). Additionally, giving compared to receiving touch more likely involves motor mechanisms and generates predictions about the somatosensory consequences of the stroking movements (Blakemore et al., 1998; Boehme et al., 2019). These sensorial predictions are associated with inhibitory processes that dampen the awareness of emerging somatosensory impressions (Boehme & Olausson, 2022).

Taken together, these studies corroborate the importance of interpersonal gentle touch for positive tactile interactions and suggest that the experiences and consequences of affective touch may differ between those who give and those who receive touch, even when touch is only observed. Yet, the commonalities and differences between the vicarious appreciation of touch giving and of touch receiving are unclear.

Here, in two consecutive studies, I sought to fill this theoretical gap by investigating toucher- and touchee-related pleasantness ratings of interpersonal CT-optimal touch (Study 1), and by exploring whether and how the motor system selectively captures CT-optimal stroking when watching interpersonal touch interactions (Study 2).

In line with previous research (Bellard et al., 2022; Walker et al., 2017), the first, behavioural study adopted a perspective manipulation to assess differences in bottom-up and top-down processing of vicarious social touch by asking participants to provide pleasantness ratings of self-directed and other-directed touch. Judging touch pleasantness in a first-person (i.e. pleasantness for the participant) was compared to the third-person (i.e. pleasantness for the model) perspective. Indeed, the appraisal of other-directed touch might rely more on the learned expectations about the rewarding pleasantness elicited by interpersonal stroking (Peled-Avron & Woolley, 2022). Even though one may not like to be stroked, he or she should still be able to acknowledge the hedonic, universally recognised, positive value of interpersonal touch. Previous studies documented higher vicarious preferences for other-directed compared to self-directed touch (Bellard et al., 2022; Walker et al., 2017). No previous research has investigated the effect of perspective on vicarious social touch execution. For both perspectives, participants were asked to rate the pleasantness for the partner who receives or gives gentle touch.

The second study directly addressed motor simulation of observed interpersonal touch events. A widely adopted index of motor simulation processes is "motor resonance", since it reflects the mirror activation of the motor system during the observation of other's movements (Bekkali et al., 2022; Naish et al., 2014). Motor evoked potentials (MEPs) are measured via electromyography (EMG) after transcranial magnetic stimulation (TMS) is administered over the primary motor cortex (M1), obtaining an index of corticospinal excitability (CSE; (Fadiga et al., 1995). Modulation of CSE is thought to represent dynamics of motor facilitation or suppression and correspond to an increase or decrease of motor simulation processes for the observed action (Amoruso et al., 2016; Liuzza et al., 2015). Given the acknowledged social and affective valence of CT-optimal touch, it is presumable that observation of stroking targeting or non-targeting the CT-fibres system might affect motor resonance.

A second aim of both studies was to explore individual differences in interpersonal touch due to childhood experiences and attitudes, and interoceptive awareness, as these might facilitate (or hinder) the experience of vicarious social touch (Bellard et al., 2022). The negative effects of childhood neglect/abuse and later life experiences on perception of affective touch are well known (Field, 2010; Keizer et al., 2022), with a recent study reporting blunted responses to vicarious affective touch in young adults who have experienced early life adversity and consequently spent time in foster care (Devine et al., 2020). Awareness of internal bodily states, namely the sense of interoception, may play a role in vicarious social touch, with individuals with higher levels of interoceptive awareness found to show higher responses in somatosensory areas for vicarious touch perception (Adler & Gillmeister, 2019).

2.2 Behavioural evidence of vicarious perception of affective touch[1]

2.2.1 Materials and methods

2.2.1.1 Participants

Based on a Repeated Measure ANOVA model with two agents, two perspectives, two body sites, and three stroking velocities, an a-priori power analysis using the G*Power 3.0.10 software (Faul et al., 2007) indicated that a sample > 50 allowed detecting a large effect size ($n^2_p = 0.14$), with 95% power and alpha set at 0.05 (two tailed). Fifty-three participants (31 females, 22 males; age mean = 28.6 years, SD = 4.8) were recruited for the study. Of these, 45 participated remotely, while 8 participants completed the experiment at the Body Image Lab of Liverpool John Moores University (LJMU).When assessing vicarious touch preferences, online collected data were reported to be comparable to those of lab-based studies (Haggarty et al., 2023), and data obtained from both modalities were analysed together in a recent work (Ali et al., 2023). Participants were recruited using posters, social media advertisements, and emails. Inclusion criteria included: i) normal or corrected-to-normal vision (with glasses/contact lenses) ii) right-handedness, iii) no history of or any form of neurological and psychiatric disorders, iv) no history of or any clinical condition of chronic pain and skin diseases. Participants for the lab-based study were compensated for their time with a £5 gift voucher and granted course credits if undergraduate psychology students. All procedures were approved by the LJMU Research Ethics Committee (reference number: 22/PSY/078). Informed consent was obtained by asking all participants to tick the relative box after reading the participant information sheet. The study recruitment started on the 12th of February and was completed by the 16th of April 2023.

2.2.1.2 General procedure

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[1] This study is reported in a preprint publication (Butti, Urgesi, et al., 2023).

All participants were asked to complete a vicarious affective touch task through the E-Prime 3® software (Psychology Software Tools, Pittsburgh, PA, USA), which allowed controlling stimuli administration and randomisation. The E-Prime Go® package was used for remote data collection. Then, self-report questionnaires were administered via Qualtrics® (Provo, UT, USA). Background information (e.g., age, sex, gender) was also collected, and participants were asked to confirm that they were right-handed by completing the Edinburgh handedness inventory (Oldfield, 1971). Only right-handed individuals were recruited as the displayed touchers' movements in the vicarious social touch task were all executed with the right hand, thus potentially triggering sensorimotor representations for the same hand (Marzoli et al., 2013). Online participants were asked to sit in a quiet room and to complete the task and questionnaires in a single session. All procedures required about 30 minutes to be completed. Upon completion of the procedure participants were debriefed about the aims and instruments of the study.

2.2.1.3 Affective touch video clips

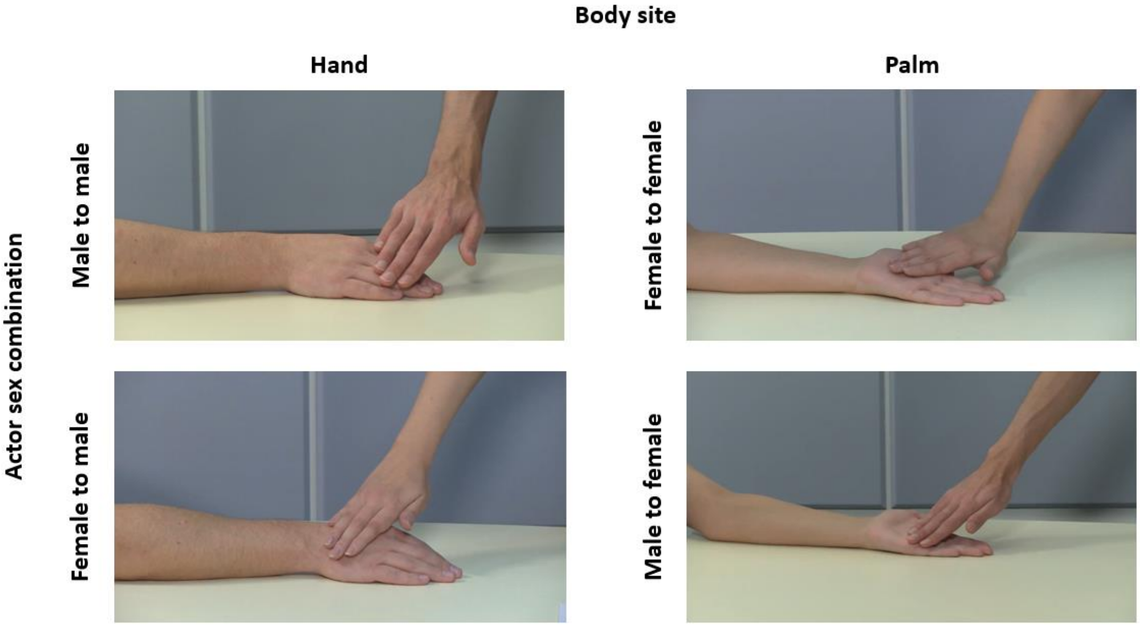
An adapted version of a previously published task was administered (Bellard et al., 2022; Walker et al., 2017). The task consisted of 6-second-long videos of both males and females applying touch with their right hand to female and male actors. Touch was delivered with CT-optimal (5 cm/s) and non-CT optimal velocities (static: 0 cm/s, fast: 30 cm/s) on the hand-dorsum and on the palm. These two body regions were selected as they were matched in terms of size and, thus, observed movements, whereas they represented areas with different density of CT-fibres, respectively, a hairy and a glabrous skin site. Moreover, the hand is considered a body part that strangers are allowed to touch (Suvilehto et al., 2015), thus pleasantness ratings of this site should be less influenced by top-down modulations related to the toucher's identity. After viewing each video, participants were asked a series of questions concerning touch delivering and reception, which were designed to probe expectations of how touch is perceived by oneself and by others. The questions for the toucher were as follows: "How much would you like to touch like that?" (self-directed toucher perspective) and "How pleasant do you think that action was for the person touching?" (other-directed toucher perspective); for the touchee, “How much would you like to be touched like that?” (self-directed touchee perspective) and “How pleasant do you think that action was for the person being touched?” (other-directed touchee perspective). Participants answered through a Visual Analogue Scale (VAS) scale ranging from 0 = “Not at all” to 100 = “Extremely”, for self-directed touch, and from 0 = “Very unpleasant” to 100 = “Extremely pleasant”, for other-directed touch. Separate blocks were administered for the toucher and the touchee, and within each block, self- and other-directed touch perspectives were presented in separate blocks, for a total of 4 blocks. This way, participants only answered one type of question per block (see Table 1).

Table 1. Task questions for each block.

		Agent	
		Toucher	**Touchee**
Perspective	**Self**	*“How much would you like to touch like that?”*	*"How much would you like to be touched like that?”*
	Other	*“How pleasant do you think that action was for the person touching?”*	*“How pleasant do you think that action was for the person being touched?"*

The order of administration of the four blocks was counterbalanced among participants. Considering a 2 agent × 2 perspective × 2 body site × 3 velocity design, 24 videos were presented once within each block in a completely randomised fashion. These videos represented all possible combinations of biological sex of actors with body sites and velocities. Overall, across all conditions and blocks, a total of 96 (i.e., 24 videos x 4 blocks) videos was presented. Examples of video stimuli are reported in Figure 1.

Figure 1. Examples of video stimuli representing touch delivered on two body sites with all combinations of biological sex of actors.



2.2.1.4 Self-report questionnaires

Multidimensional Assessment of Interoceptive Awareness

The Multidimensional Assessment of Interoceptive Awareness (MAIA)(Mehling et al., 2012) is a 32-item questionnaire which investigates eight dimensions of interoceptive bodily awareness: noticing (4 items), not distracting (3 items), not worrying (3 items), attention regulation (7 items), emotional awareness (5 items), self-regulation (4 items), body Listening (3 items) and trusting (3 items). Questionnaires are answered using a 6-point Likert scale ranging from 0 = "Never" to 5 = "Always". Each individual dimension is scored by the average of scores from questions corresponding to that subscale, with some questions being reversed scored. Good internal consistency was reported for the MAIA questionnaire (Cronbach α = 0.90) (Valenzuela-Moguillansky & Reyes-Reyes, 2015). For this study, the noticing and trusting scales were selected, as these variables were more congruent with the hypothesis that the more a person is aware of the own bodily signals, the more this person may feel the sensations elicited by observed interpersonal touch (Ebisch et al., 2011).

Touch Experiences and Attitudes Questionnaire

The short 37-item version of the Touch Experiences and Attitudes Questionnaire (TEAQ) (P. Trotter et al., 2018; P. D. Trotter et al., 2018) assesses current and childhood experiences of positive touch and an individual’s attitude towards interpersonal touch. Questions are answered using a 5-point Likert scale ranging from 1 = “Disagree strongly” to 5 = “Agree strongly”. A mean score is calculated for each of the five subscales: attitude to friend and family touch (7 items), attitude to intimate touch (10 items), childhood touch (8 items), attitude to self-care (7 items), and current intimate touch (5 items), with negatively worded questions reversed scored. The TEAQ short version was found to have a good internal consistency (Cronbach $\alpha = 0.93$). In line with the hypothesis that individual experiences and attitudes towards interpersonal touch should bias pleasantness ratings of vicarious touch, the childhood touch and the attitude to friend and family touch scales were selected as variables of interest, excluding the others as they focused on stroking the one own body and intimate touch, aspects that were less compatible with the adopted videos.

2.2.1.5 Data handling and statistical analysis

The pleasantness ratings attributed to each condition of the vicarious touch task were inserted into a Repeated Measure (RM) ANOVA with 2 agent (toucher vs. touchee) × 2 perspective (self vs. other) × 2 body site (hand vs. palm) × 3 velocity (3 levels: 0 cm/s, 5 cm/s and 30 cm/s) as within subject variables.

In keeping with previous research (Bellard et al., 2022; Croy, Luong, et al., 2016), two indexes of touch pleasantness were calculated, namely the Overall Touch Pleasantness (OPT) and the Pleasant Touch Awareness (PTA). Since agent (i.e., touch vs. touchee) and perspective (i.e., self- vs. other-directed) represented the two main manipulations of the task, the OPT and PTA were calculated separately for agent and perspective. Indeed, for each of the four conditions (i.e., toucher, touchee, self, other) the pleasantness ratings across the different conditions of the other variable (i.e., agent, perspective) were collapsed into a single value, regardless of the two body sites (i.e., palm, hand) while considering separately the three different velocities. As an example, for the toucher condition, pleasantness ratings in the other- and self-directed blocks for both the hand and the palm were collapsed, obtaining an averaged value of the pleasantness ratings expressed for the toucher separately for static, CT-optimal and fast touch. Then, the OPT was computed as the average rating across the three velocities, thus representing an index of individual pleasantness for interpersonal touch that is not CT-specific. As a proxy of individual preference towards CT-optimal velocity, the PTA index was calculated using the following formula: (CT-optimal – non-CT optimal fast velocity)/OPT. Spearman's r correlations were run between both OPT and PTA corresponding to the four different conditions, and the selected scales of the questionnaires, namely, noticing and trusting for the MAIA, and attitude to friend and family touch and childhood touch for the TEAQ.

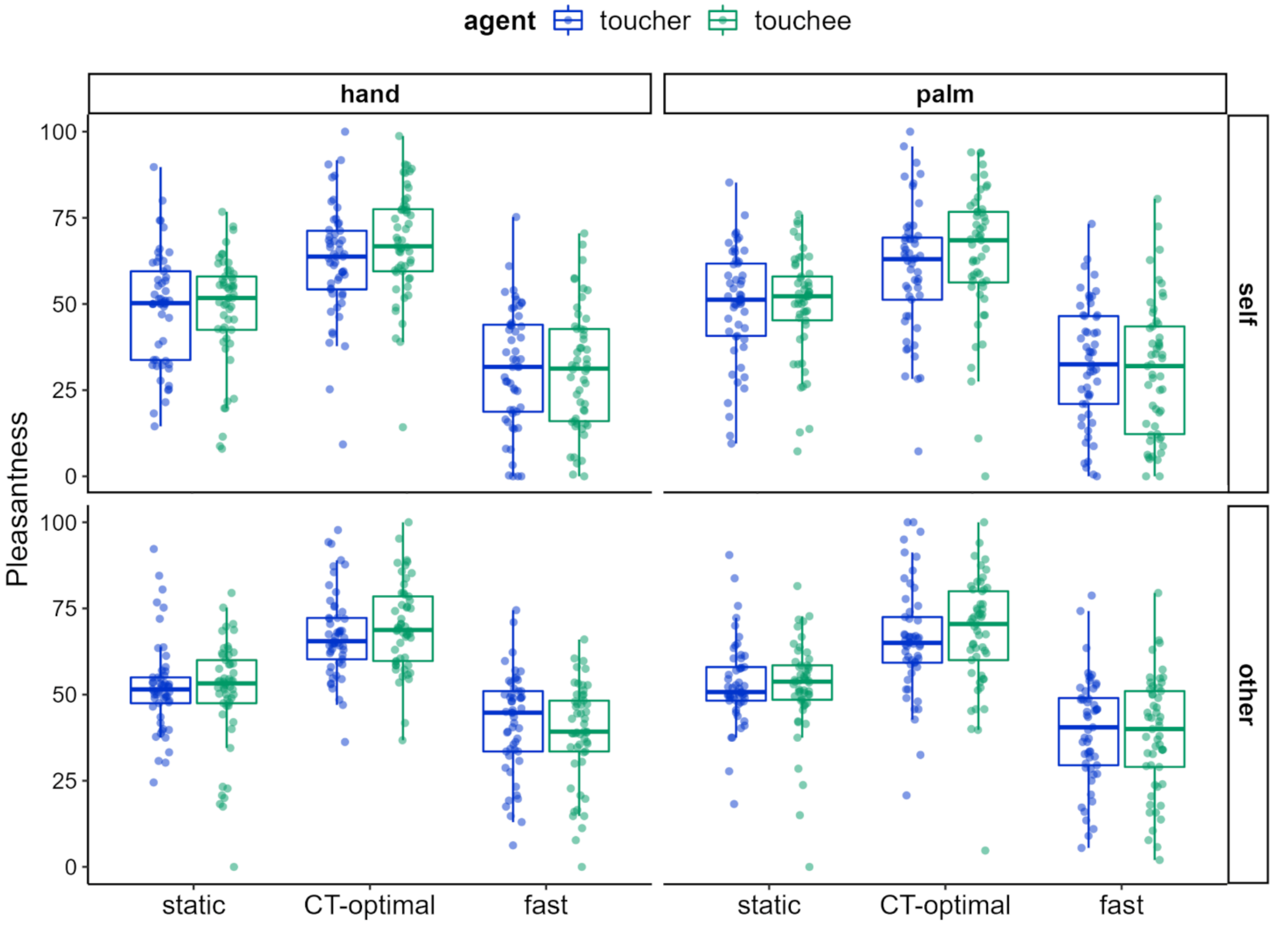
All analyses were performed with Statistica 8.0 (Statsoft, Tulsa, OK), and data were reported as mean ± Standard Error of the Mean (SEM). The significance threshold was set at $p < 0.05$ for all effects. Significant interactions were analysed with Duncan's post-hoc test correction for multiple comparisons, which allows testing effects of different size in the same design (Duncan, 1955; McHugh, 2011). For the correlations, the Bonferroni correction was adopted to adjust the standard p-value according to the number of comparisons (corrected $p = 0.013$). Effect sizes were estimated and reported as partial eta squared (n^2_p) for ANOVA designs, adopting conventional cut-off of 0.01, 0.06, and 0.14 for small, medium, and large effect sizes, respectively, and as Cohen's d for pairwise comparisons, adopting conventional cut-off of 0.2, 0.5, and 0.8 for small, medium, and large effect sizes, respectively, (Lakens, 2013).

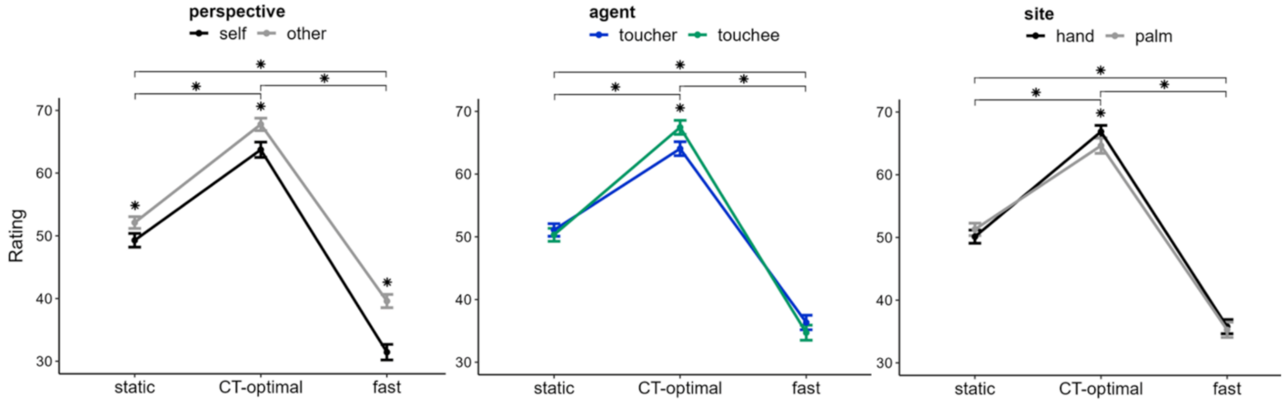
2.2.2 Results

2.2.2.1 Comparisons of vicarious touch ratings

The analysis yielded significant main effects of perspective (self: 48.15 ± 1.32, other: 53.16 ± 0.98; $F_{1,52} = 39.51$, $p < 0.001$, $n^2_p = 0.43$) and velocity (0 cm/s: 50.70 ± 1.63, 5 cm/s: 65.75 ± 1.74, 30 cm/s: 35.52 ± 1.86; $F_{2,104} = 81.72$, $p < 0.001$, $n^2_p = 0.61$), which were further qualified by a significant 2-way interaction of perspective × velocity ($F_{2,104} = 5.67$, $p = 0.005$, $n^2_p = 0.10$). Post-hoc tests indicated that, across perspectives, CT-optimal touch was preferred than both non-CT optimal velocities, with fast stroking being judged as less pleasant than static touch (all $p < 0.001$; all Cohen's d > 1.01). In addition, across velocities, higher ratings were attributed to other-directed compared to self-directed touch (all $p < 0.018$; Cohen's d: static = 0.23, CT-optimal = 0.30, fast = 0.56). Moreover, a significant agent × velocity interaction ($F_{2,104} = 5.23$, $p = 0.007$, $n^2_p = 0.09$) revealed lower pleasantness for toucher- than touchee-referred ratings only for CT-optimal velocity (5 cm/s: 64.05 ± 1.88 vs. 67.45 ± 1.82; $p = 0.005$; Cohen's d = 0.25), while such a difference did not emerge for static (0 cm/s: 51.09 ± 1.74 vs. 50.32 ± 1.80; $p = 0.513$; Cohen's d = 0.06) and fast touch (30 cm/s: 36.34 ± 1.91 vs. 34.71 ± 2.08; $p = 0.169$; Cohen's d = 0.11). Preferences for CT-optimal stroking compared to non-CT optimal velocities, and for static compared to fast touch, were detected for either agent (all $p < 0.001$; all Cohen's d > 0.98), indicating that both toucher- and touchee- referred ratings yielded the typical inverted-U shaped pattern. The velocity × body site interaction was also significant ($F_{2,104} = 4.24$, $p = 0.017$, $n^2_p = 0.08$), with a preference for touch received on or delivered to the hand compared to the palm detectable only for CT-optimal velocity (5 cm/s: 66.87 ± 1.61 vs. 64.64 ± 2.13; $p = 0.008$; Cohen's d = 0.16), and no differences between body sites for static (0 cm/s: 50.12 ± 1.78 vs. 51.28 ± 1.65; $p = 0.162$; Cohen's d = 0.09) and fast touch (30 cm/s: 35.78 ± 1.85 vs. 35.27 ± 2.00; $p = 0.539$; Cohen's d = 0.04). Neither the 3-way agent × velocity × body site nor any other main and interaction effects were significant (all $F < 1.87$, all $p < 0.159$). The pleasantness ratings attributed to each condition and the significant two-way interactions are represented in Figure 2.

Figure 2. Boxplot of pleasantness ratings in the vicarious touch task and line graphs of the two-way significant interaction effects. Dots represent observations; asterisks indicate the velocity level at which the interaction effects were significant.



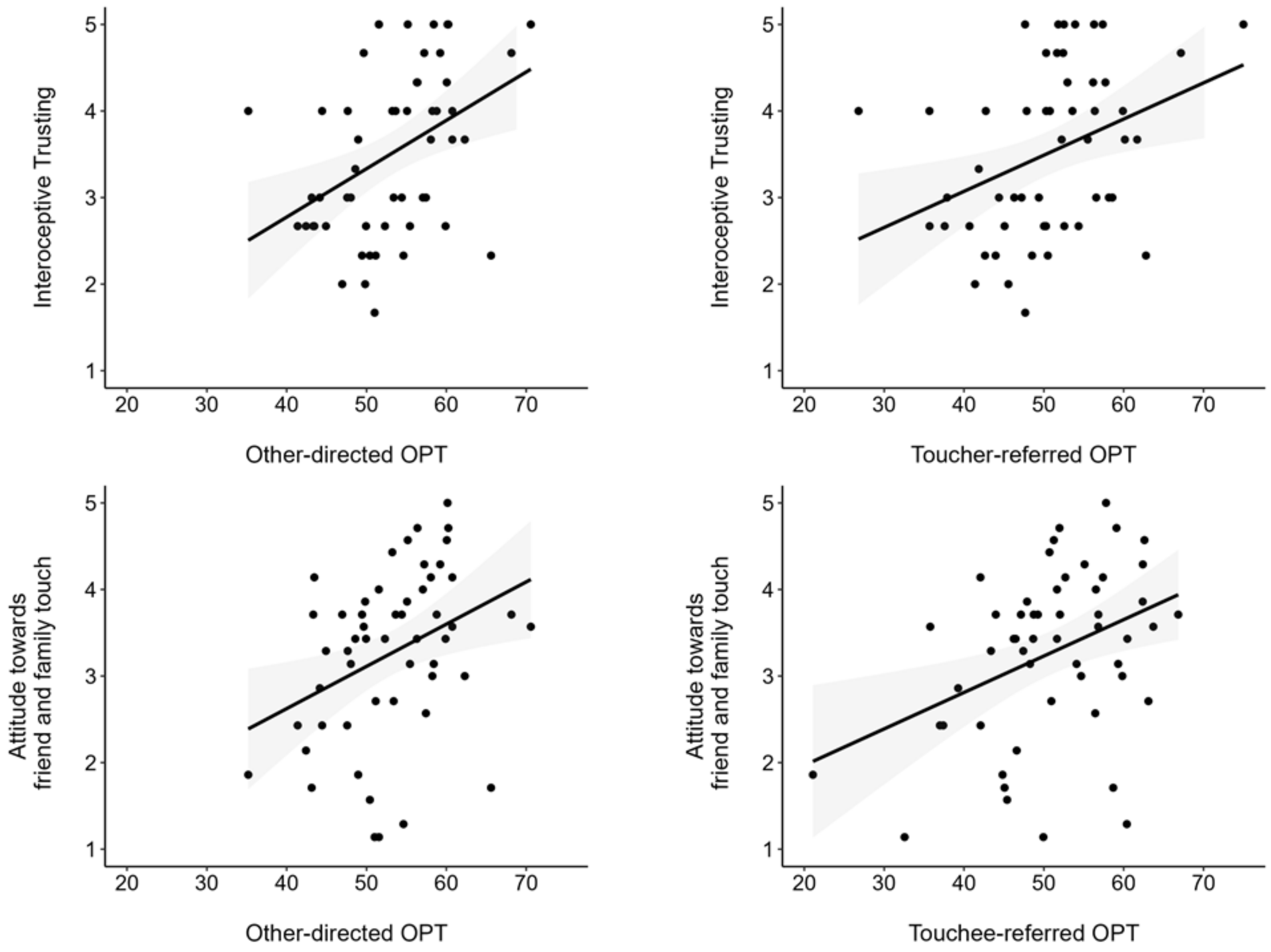


To sum up, participants expressed higher pleasantness for touch delivered at CT-optimal vs. non-CT optimal velocities. This was the case for both self- and other-directed ratings of touch execution and reception, and when CT-optimal touch was delivered to the hand-dorsum compared to the palm. Furthermore, higher pleasantness was attributed to the touchee- compared to toucher-referred ratings only for CT-optimal touch velocities (5 cm/s). Finally, the other-directed pleasantness ratings were higher than the self-directed ones across all conditions.

2.2.2.2 Correlation analyses

For the OTP indexes, higher scores obtained at the MAIA trusting scale were associated with higher pleasantness for other- ($r = 0.41$, $p = 0.002$) and toucher-referred ($r = 0.36$, $p = 0.008$) ratings. These correlations indicate that the more participants trusted their own body to be a safe place, the higher they tended to appraise the touch pleasantness for another person, and for the person delivering the touch. In a similar vein, a more positive attitude towards friends and family touch correlated with higher ratings for other-directed ($r = 0.36$, $p = 0.009$) and touchee-referred ($r = 0.39$, $p = 0.004$) ratings. Namely, the more positive attitude to receive interpersonal touch by family and friends, the more they judged positively the observed stroking for another person, and for the person receiving the touch. All other correlations were non-significant (all $r < 0.34$, all $p > 0.013$). The significant correlations are reported in Figure 3.

Figure 3. Scatter plots representing the significant correlations between OPT indexes and the questionnaire scales. Dots represent observations; the shaded grey areas represent SE.



No significant correlations emerged between PTA and any of the questionnaire scales (all $r < 0.24$, all $p > 0.084$).

2.2.3 Discussion

Previous research has found that reception of touch delivered at CT-optimal, compared to slower of faster stroking velocities, is judged as more pleasant, both when the participants directly receive the touch and when they observe another person receiving it (Bellard et al., 2022; Devine et al., 2020; Haggarty et al., 2021; Walker et al., 2017). This evidence documents an inverted-U function for the relation between pleasantness and stroking velocities for both real and vicarious touch reception. The present study aimed to compare the pleasantness ratings of vicarious touch execution and reception. Participants rated as more pleasant a touch delivered at CT-optimal than non-optimal stroking velocities when they had to embody either the partner receiving the touch or the partner delivering it. This is the first study documenting the typical inverted-U function characterising pleasantness ratings and velocities not only for vicarious reception (Haggarty et al., 2023), but also for vicarious delivering of interpersonal touch. These findings are in line with the hypothesis that humans are inherently ‘wired’ to receive and deliver affective touch (Croy, Luong, et al., 2016; Schirmer et al., 2023), as well as to distinguish CT-optimal stroking when observing the reception and delivery of interpersonal touch (Morrison et al., 2011), suggesting that vicarious perception of others both receiving and giving interpersonal touch is critical for adaptive behaviour in social contexts (Peled-Avron & Woolley, 2022).

Importantly, results point to a preference for vicarious touch reception compared to execution, which is specific for CT-optimal velocity. This preference mirrors, at a vicarious representation level, a previous study documenting that receiving strokes was perceived as more pleasant than stroking at CT-optimal velocities (Triscoli et al., 2017). Accordingly, such difference might depend on the scarce presence of CT fibres in the palm, so that vicarious reception would benefit more directly from CT-optimal stroking compared to vicarious execution. This view is also supported by present and previous (Walker et al., 2017) results that vicarious affective touch is perceived as more pleasant when received on or delivered to the hand-dorsum compared to the palm, according to a different distribution of CT fibres between hairy and glabrous skin (Löken et al., 2011; Watkins et al., 2021). That is, even though the inverted-U shaped pattern could be similarly elicited in glabrous and hairy skin sites (Cruciani et al., 2021), there is a functional difference between the skin typically involved in touch reception and the skin through which reaching out to touch (Ackerley, Carlsson, et al., 2014; Ackerley, Saar, et al., 2014). This critical distinction, supported by evidence of dissociable somatosensory responses to touch on hairy and glabrous skin (Schirmer et al., 2022), might result in the CT-specific advantage for touchee-related compared to toucher-related ratings reported here.

Correlation results partially support the hypothesis that not only different somatosensory processes, but also diverse socio-affective mechanisms might underlie vicarious reception and execution of touch. The positive correlation between attitudes towards friends and family touch and touchee-referred ratings is in line with the rewarding value of social touch for the touchee (Morrison et al., 2010), so that the more an individual is keen to engage in interpersonal tactile interactions with people close to him/her, the more touch reception gains a positive salience, and rated as more pleasant (Suvilehto et al., 2015). In keeping with a previous study showing that interoceptive signals affect touch delivery (Bytomski et al., 2020), higher toucher- referred ratings is also reported by individuals with higher trust in their own-body signals. Indeed, the way a person perceives his or her own bodily signals plays an active role in driving behaviour and predicting the consequences of one’s actions (Seth & Friston, 2016). Hence, higher interoceptive awareness might help to understand which touch stimulation may match the touchee’s expectations, leading to increased pleasantness judgments of interpersonal touch. It should be noted, however, that these correlations are not specific for CT-optimal velocity, since only the OTP (collapsing pleasantness rating across velocities), but not the PTA (reflecting selective pleasantness for CT-optimal vs. non optimal velocities) index shows significant correlations. The associations might be related to general top-down mechanisms influencing vicarious touch perception rather than to the selective mapping of touch features related to the physiology of CT afferents (Peled-Avron & Woolley, 2022).

As expected from previous studies (Bellard et al., 2022; Walker et al., 2017), a general advantage for other- compared to self-directed pleasantness ratings of touch emerged for both toucher- and touchee-related judgments. This finding is in line with the idea that humans can rely on the learned value of social touch when judging touch pleasantness for a third person (Peled-Avron & Woolley, 2022). Notably, other-directed ratings were significantly associated with both attitudes towards family and friend touch and interoceptive trusting. These results confirm that, even for vicarious delivery of touch, third-person perspective judgements are influenced by top-down expectations on the pleasantness of interpersonal tactile stimulations (Ellingsen et al., 2016). However, the difference of pleasantness ratings according to the perspective might be due to the stimuli used. Indeed, only videos viewed from a third-person perspective were presented, which might have facilitated the embodiment and relative pleasantness judgement of other- vs. self-related states.

This study had limitations that should be carefully considered. First, although the perspective manipulation was in accordance with previous studies (Bellard et al., 2022; Walker et al., 2017) and aimed to assess differences in self- and other-directed judgements, videos were not presented from a first-person viewing perspective. Future research should consider to add videos recorded from a first-person viewing perspective, so that participants would be shown the touch event as if they were the toucher or the touch receiver, thus likely facilitating embodied simulations of the observed action (Kessler & Thomson, 2010). Furthermore, the task was designed to avoid giving any clues about the context in order to focus on CT-related manipulations (i.e., velocity, body site). However, this way it did not consider contextual and social factors that may affect vicarious touch perception (Sailer & Leknes, 2022).

2.3 Neurophysiological evidence of vicarious perception of affective touch

2.3.1 Materials and methods

2.3.1.1 Participants

Based on the effect size (n^2_p = 0.157) reported by a previous TMS-MEP paper on interpersonal-action observation and adopting a similar design (Betti et al., 2022), considering a RM-ANOVA model with two muscles, two body sites, and three stroking velocities, an a-priori power analysis using the G*Power 3.0.10 software (Faul et al., 2007) indicated a target sample size >28, with 80 % power and alpha set at 0.05 (two-tailed). Hence, 30 participants (17 females, 13 males; age mean = 27.1 years, SD = 5.7) completed the experiment at LJMU. Participants were recruited through posters, social media advertisements, and emails to research panel lists. Inclusion criteria were the same as the behavioural study; however, participants were screened also for TMS exclusion criteria through a safety screening questionnaire (Rossi et al., 2009, 2021). None of them had contraindication to TMS and complained of discomfort or adverse effect during the experimental session. Participants were compensated for their time with a £10 gift voucher and granted course credits if undergraduate psychology students. All procedures were approved by the LJMU Research Ethics Committee (reference number: 22/PSY/078). Written informed consent was obtained by all participants before starting any procedures.

2.3.1.2 General procedure

Volunteers were asked to complete a preliminary TMS screening questionnaire to check for eligibility to the study via email and/or any way that was suitable to them. Only eligible participants were then contacted to arrange the single-session experiment. On the scheduled date, participants were asked to re-complete the safety screening questionnaire, to ensure no changes have occurred. Participants were comfortably seated in a recliner chair with their right arm resting on a pillow and asked to remain relaxed while watching the video clips presented on a 24″ monitor (resolution 1920 x 1200 pixels, refresh rate 60 Hz) set at an eye-level distance of about 100 cm. Then, participants executed the experimental task in which interpersonal touch videos were presented during MEP recording. MEP baseline measurements were also taken before and after administration of interpersonal touch videos. After this procedure, participants were asked to report demographic data (e.g., age, gender), and to fulfil the same self-report questionnaires adopted in the first study to assess interoceptive awareness (i.e., MAIA) and touch attitudes and experiences (i.e., TEAQ). In line with the behavioural results, the selected variables of interests were the trusting and emotional awareness scales for the MAIA, attitude towards friend and family touch and childhood touch experience for the TEAQ. Right-handedness was also verified by completing the Edinburgh handedness inventory (Oldfield, 1971). All procedures required about 70 minutes to be completed, and then participants were debriefed about the aims and instruments of the study.

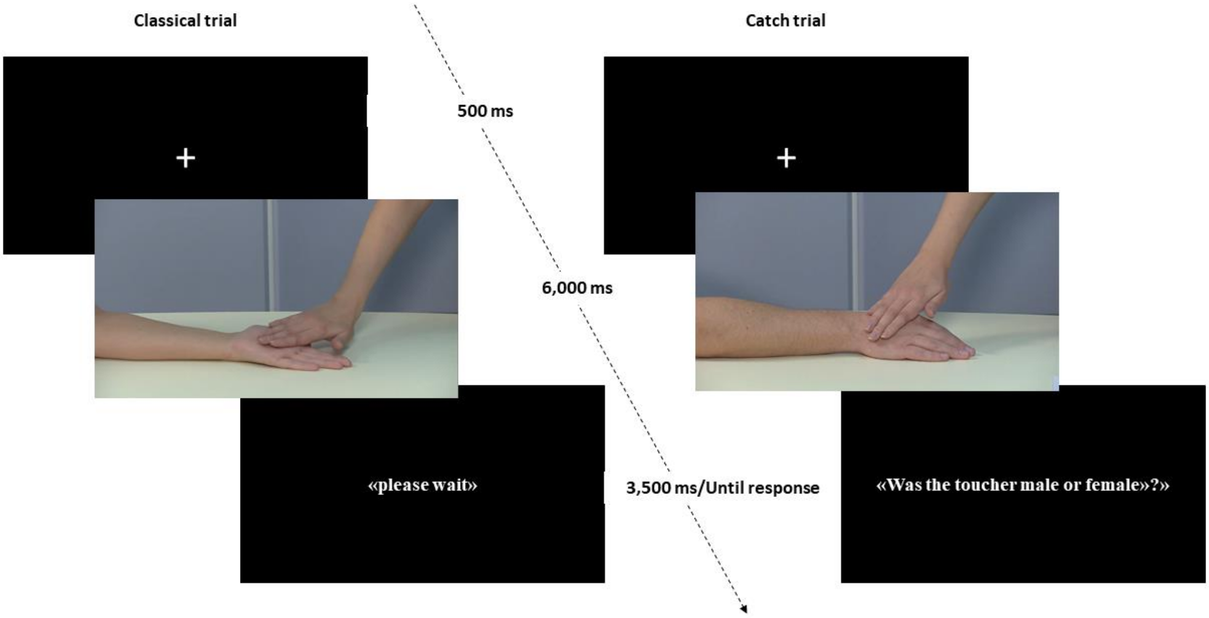
2.3.1.3 Stimuli and task structure

During the experimental task, participants were presented with the same 24 interpersonal touch video clips adopted in the first study, which represented all possible conditions of actor sex combinations, velocities (static, CT-Optimal, fast) and body sites (hand-dorsum as hairy skin, palm as glabrous skin).

Before video presentation, an instruction slide informed participants that they would be presented with interpersonal touch videos while receiving single-pulse (sp) TMS. Moreover, the instructions required participants to pay attention to the biological sex of the toucher because in some trials they would be asked to verbally indicate whether the toucher was male or female. This explicit sex judgement task was thought to engage participants during video presentation and to prompt them to focus on the actor delivering interpersonal touch and, thus, on the touch action. A verbal, rather than a motor response was chosen to avoid MEP contamination due to hand-response preparation (Betti et al., 2022).

Each trial started with a fixation cross lasting 500 ms, followed by the 6-second-long interpersonal touch videos. The spTMS was administered in the last second of video presentation, in order to ensure participants were exposed to full action unfolding (details below). At the end of the video, “classical” trials displayed a black background screen reporting “please wait” in white letters for 3500 ms. This way, the whole trial lasted 10 s. Conversely, in “catch” trials the last slide reported the question “Was the toucher male or female?”, written in white letters on a black background. Participants had to answer verbally (i.e., “male”, “female”) and the experimenter recorded verbal responses by pressing the m or f tab on a wireless keyboard. The response accuracy (mean = 95%, SD = 5%) confirmed that participants were engaged in the task. The response slide lasted until a response was recorded and its duration across participants was roughly equivalent to the “please wait” slide in classical trials (mean = 2894 ms, SD = 454 ms). Examples of a classical and a catch trial are reported in Figure 4.

Figure 4. Trial structure. Examples and timeline of classical and catch trials.



On the basis of a 2 muscle × 3 velocity × 2 body site design, and to obtain 16 observations per cell, a total of 192 trials were presented. Of them, 48 were catch trials (25%). This way, each of the 24 video stimuli was displayed six times in classical trials and two times in catch trials. The order of video and trial presentation was completely randomized. The E-Prime 3® software (Psychology Software Tools, Pittsburgh, PA, USA) controlled task administration and response recording.

2.3.1.4 TMS and MEP recording procedure

TMS was performed by means of a 70-mm figure-eight stimulation coil (Magstim D70 alpha flat coil), connected to a Magstim SuperRapid2 Stimulator (The Magstim Company, Carmarthenshire, Wales, UK) producing a magnetic field up to 0.8 T at the surface of the coil. During task presentation, single TMS pulses were administered in the last part of the video according to one of five time-delays after video onset (5100, 5200, 5300, 5400, 5500 ms). Delay variability prevented any anticipatory effect of the stimulation (Betti et al., 2022; Tran et al., 2021). Single TMS pulses were delivered to left M1 in order to elicit MEPs in the contralateral target muscles, thus obtaining a reliable index of excitatory and inhibitory corticospinal responses to the observed action. Prior to MEP recording, participants were tested for their resting motor threshold (rMT), which is the minimum stimulus intensity able to evoke MEPs from both the muscles with amplitude of at least 50 μV in 50% of 10 trials (rMT mean = 72%, SD = 14%). The stimulation intensity was then set at 120% of the individual rMT. Moreover, for each participant, the optimal position of the coil was determined by moving the coil in approximately 0.5 cm steps around the scalp position corresponding to the left motor hand area and by delivering TMS pulses at constant intensity until recording maximal amplitude MEPs from both muscles. The determined position was marked on a tight-fitting cap wore by participants, and the coil was held securely to the scalp ensuring the magnetic pulses were only given to the area of interest. In line with previous studies (Amoruso & Urgesi, 2016; Borgomaneri et al., 2015), the coil was placed tangentially on the scalp, with the handle pointing backward and approximately 45° lateral from the midline.

MEPs were recorded simultaneously from the Extensor Carpi Radialis (ECR) and the First Dorsal Interosseous (FDI) of the right limb. These muscles were chosen as they represent, respectively, a proximal and a distal muscle involved in interpersonal touch movements (Schieppati et al., 1996; van Kuijk et al., 2009). Surface Ag/AgCl disposable electrodes (1 cm diameter) were placed in a belly-tendon montage for each muscle. Electrode positions were determined by palpation during maximum voluntary contraction for each muscle, with reference electrodes placed over the ipsilateral interphalangeal joint for the FDI and over the ulnar styloid process for the ECR, while the ground electrode was positioned over the right elbow. A Biopac MP-36 system (BIOPAC Systems, Inc., Goleta, CA) was used for signal amplification, band-pass filtering (5-1000 Hz) and digitalization (sampling rate 10000 Hz). The TMS pulse was also recorded as digital input channel starting when the TMS was triggered and lasting 15 ms. Before and after the experimental task, MEPs were recorded during 10 baseline trials in which participants were presented with a fixation cross while receiving the single TMS pulse at the 120% of the rMT. TMS stimulation and EMG recording were controlled by the E-Prime 3® software. Offline analysis of EMG data was executed by means of the AcqKnowledge software (BIOPAC Systems, Inc., Goleta, CA).

2.3.1.5 Data handling and statistical analysis

For each muscle and condition, MEPs were calculated as peak-to-peak EMG signal (in mV) from the end of the digital input representing the TMS pulse for the following 40 ms. With the aim to control for muscle preactivation and artefact, trials in which the peak-to-peak signal from 70 to 10 ms before the TMS pulse was higher than mean + 2 SD were discarded and excluded from further analyses. Across all subjects and for both muscles excluded trials were less than 10 % (ECR: mean = 3.6%, SD = 1.8%; FDI: mean = 4.8%, SD = 1.8%), thus ensuring EMG data reliability. Changes in basal CSE during the experiment were examined by comparing the pre- and post-baseline raw MEPs through paired-sample *t*-tests (two-tailed). Post-baseline MEPs of three subjects were not recorded due to technical issues. As concerns the experimental task, for each participant and separately for the two muscles, the raw MEP amplitude of each trial was normalized according to the distribution of all trials (Z-score). Transformation into Z-scores was chosen to control for interindividual variability and to insert the two muscles in the same analysis. The Z-scores were inserted into a RM-ANOVA with 2 muscles (ECR, FDI), 2 body sites (hand, palm) and 3 velocities (static, CT-optimal, fast) as within-subject variables, and post-hoc analysis was performed using Duncan's test correction. Then, planned linear and quadratic polynomial contrasts were run between the three velocities. Indeed, a linear trend would point to the direct mapping of stroke velocity, whereas a significant quadratic model would indicate a MEP modulation for the CT-optimal velocity in favour of affective touch mapping.

Separately for each muscle, an Affective Touch Sensitivity (ATS) index was calculated with the following formula: ((CT-optimal – fast) + (CT-optimal – static))/2. Higher positive values would indicate greater MEP facilitation for CT- optimal compared to non-CT-optimal velocities, while higher negative values would point to greater MEP suppression for CT-optimal touch. A Pearson's correlation analysis was then conducted between the ATS indexes and the selected scale of interoceptive awareness (i.e., trusting and emotional awareness) and of individual differences in touch attitudes and experiences (i.e., attitude towards friend and family touch and childhood touch experience), adopting Bonferroni correction for multiple comparisons.

Analysis methodology was the same of the behavioural study, with the exception of the R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) used to perform polynomial contrasts.

2.3.2 Results

2.3.2.1 MEP modulation

The comparisons between the MEP amplitudes recorded as pre- and post-task baseline yielded no significant results either for the ECR (t_{26} = 0.52, p = 0.606) and the FDI (t_{26} = 1.13, p = 0.270), probing that the TMS per se did not change basal MEPs across the experiment. The normalized MEPs for each condition are reported in Table 2.

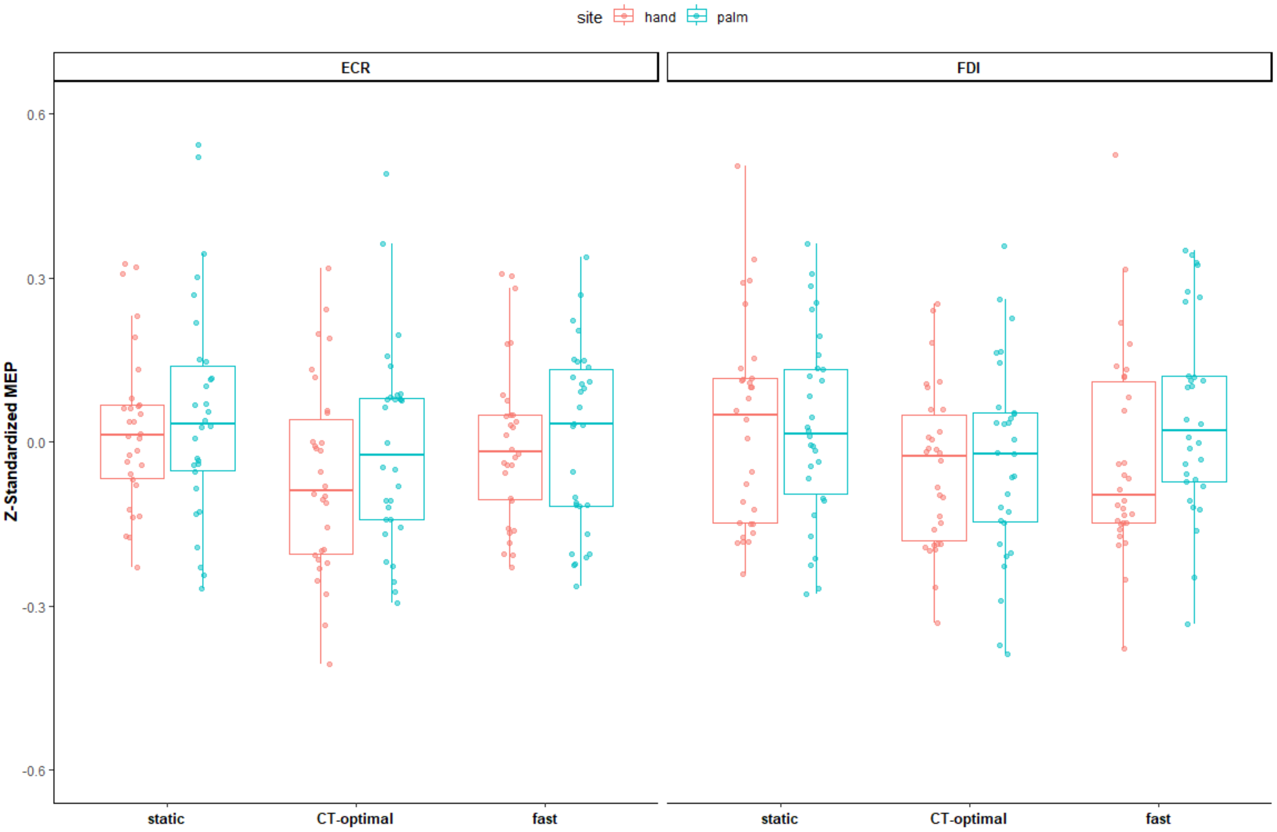
Table 2. MEP Z-scores. Means (± SEM) of Z-scores for the ECR and FDI muscles according to the body site on which touch was delivered and stroking velocities.

Muscle	Body site	Velocity	Z-score
ECR	Hand	Static	0.024 ± 0.026
ECR	Hand	CT-optimal	-0.066 ± 0.032
ECR	Hand	Fast	-0.003 ± 0.027
ECR	Palm	Static	0.055 ± 0.037
ECR	Palm	CT-optimal	-0.011 ± 0.034
ECR	Palm	Fast	0.006 ± 0.031
FDI	Hand	Static	0.029 ± 0.034
FDI	Hand	CT-optimal	-0.047 ± 0.027
FDI	Hand	Fast	-0.031 ± 0.034
FDI	Palm	Static	0.027 ± 0.032
FDI	Palm	CT-optimal	-0.034 ± 0.033
FDI	Palm	Fast	0.048 ± 0.033

The RM-ANOVA revealed a significant main effect of velocity, with a medium-to-large effect size ($F_{2,58}$ = 3.51, p = 0.036, n^2_p = 0.11). Post-hoc analysis indicated a significant, large difference in MEP amplitudes between static and CT-optimal touch (0.034 ± 0.016 vs. -0.040± 0.014; p = 0.015, Cohen's d = 0.89), while such a difference was not significant between static and fast touch (0.005 ± 0.018; p = 0.306, Cohen's d = 0.31) and between CT-optimal and fast stroking (Cohen's d = 0.51). Neither the main effects of muscle and body site nor the interaction effects were significant (all F <

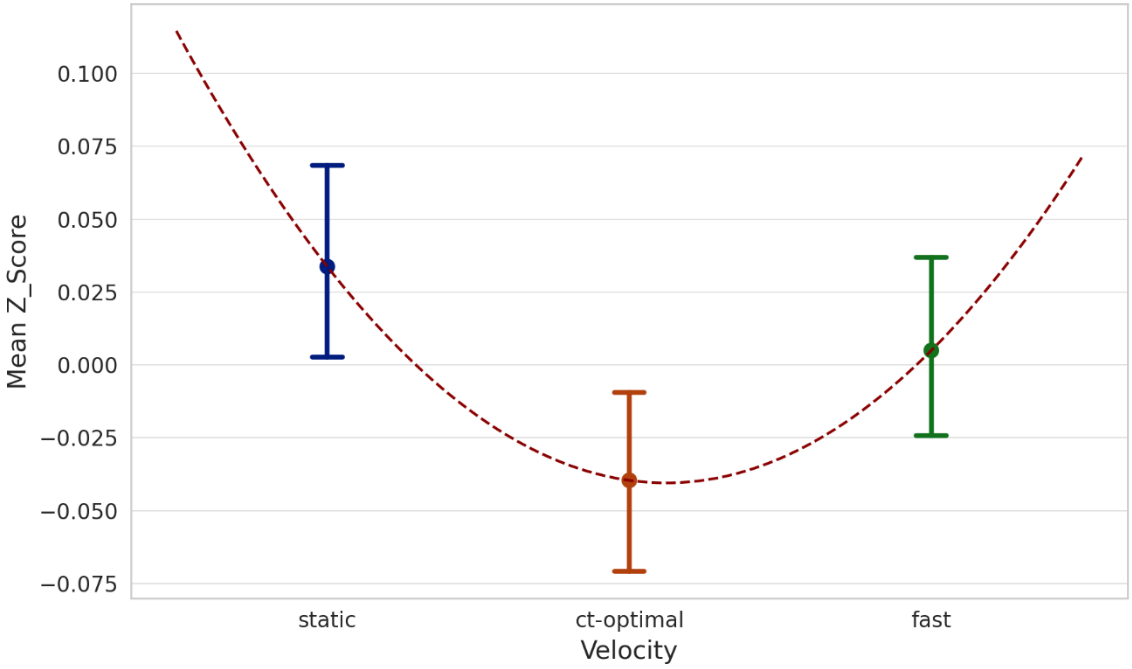
4.02, all *p* > 0.054). These findings pointed to lower MEP amplitudes for CT-optimal velocity compared to static touch, detected in both the muscles and regardless of the body site (Figure 5).

Figure 5. Boxplot of MEP amplitudes. Dots represent observations.



Polynomial-contrast analysis further clarified this MEP modulation related to touch velocities, with a significant effect for the quadratic contrast (coefficient = -0.020, *p* = 0.003) but not for the linear model (coefficient = -0.014, *p* = 0.204). These results suggested that there was a U-shaped relationship between touch velocities and MEP amplitudes, where the CT-optimal touch resulted in lower Z-scores (Figure 6).

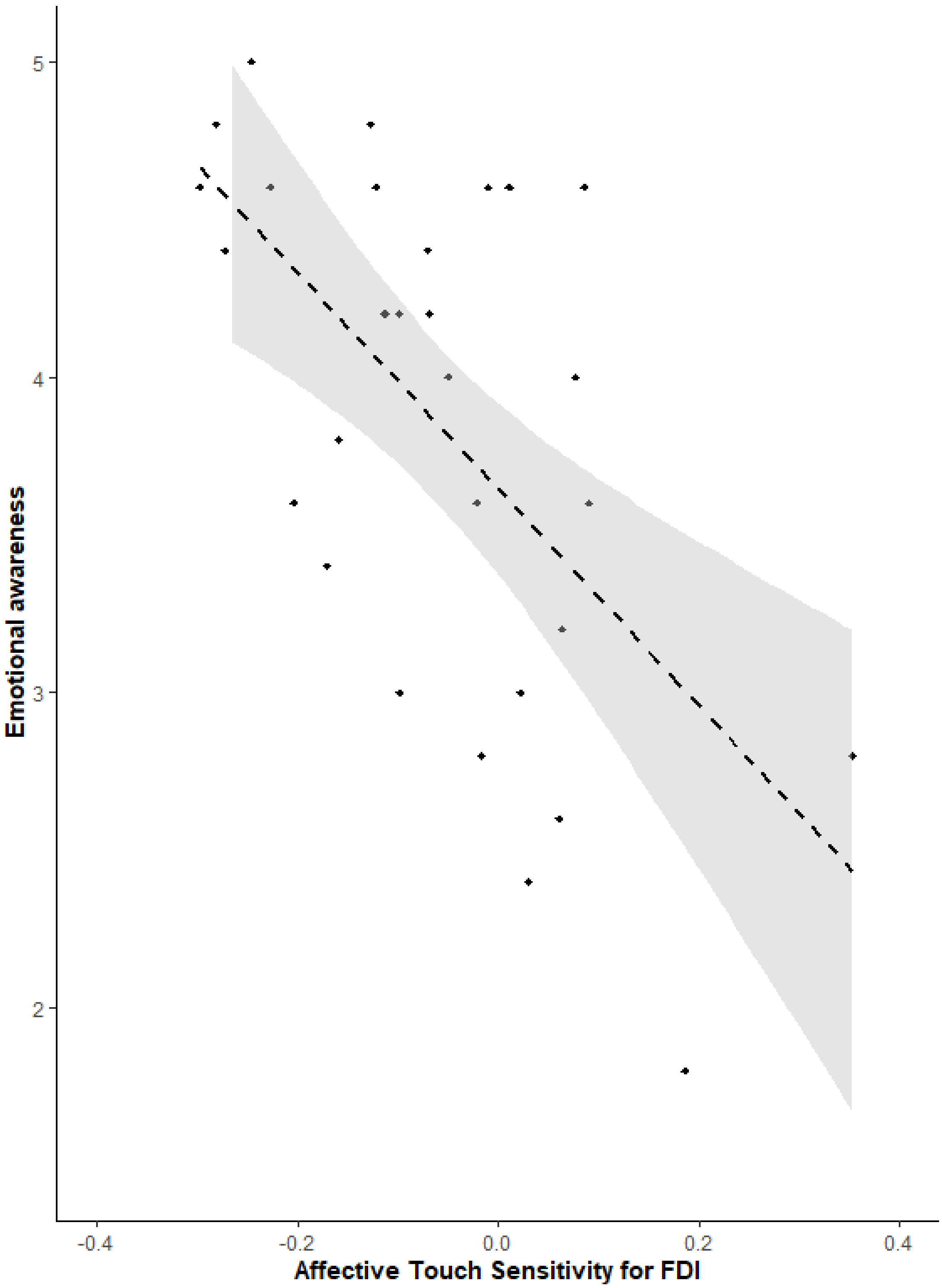
Figure 6. Relationship between MEP amplitudes in Z-score. Bar lines represent SEM; the dotted red line represents a quadratic regression model fitting the data.



2.3.2.2 Correlation analyses

A strong, negative correlation emerged between the ATS for the FDI and the MAIA emotional awareness scale ($r = -0.60$, $p < 0.001$). This correlation indicated that the more participants used their bodily cues to be aware of their emotional states, the greater the MEP suppression for CT-optimal compared to non-CT optimal velocities. Conversely, individuals with low scores of emotional awareness showed positive PTA values, corresponding to MEP facilitation for CT-optimal touch (Figure 7).

Figure 7. Scatterplot of correlation between emotional awareness and affective touch sensitivity for the FDI. Dots represent observations; dotted black line represents regression line; shaded grey area represents 95% confidence interval.



Any other correlation was non-significant (all $r < |0.35|$, all $p > 0.063$).

2.3.3 Discussion

Motor resonance to interpersonal touch was found to be modulated by stroking velocities, and specifically by CT-optimal vs. static touch. This result confirms that the human brain is attuned to distinguish CT-optimal stroking during observation of the reception and delivery of interpersonal touch (Morrison et al., 2011). Noteworthy, this motor resonance modulation was represented by lower MEP amplitudes for the CT-optimal velocity compared to static touch, while no difference emerged between these touches and fast, non-CT-optimal stroking. The presence of a significant, quadratic rather than a linear relationship between the three touch velocities and MEP amplitudes rules out that the difference between CT-optimal and static touch might represent per se a motor mapping of stroking velocities. These findings indicate that the observer's motor cortex selectively codes CT-optimal velocities during observation of interpersonal touch, resulting in diminished CSE in the arm muscles. In other words, the motor cortex would be sensitive to the observation of affective touch, but this sensitivity would lead, to some extent, to a reduced motor simulation of affective touch. Accordingly, a previous fMRI research reported that passively observing interpersonal touch increased the activation in somatosensory and socio-cognitive networks but not in the motor cortex, even though in that study a preference for CT-optimal touch was not systematically investigated (Lee Masson et al., 2018).

Contrary to the findings of the behavioural study, no differences were found between hairy (i.e., hand back) and glabrous (i.e., palm) skin sites, which are differently innervated by CT-fibres (Ackerley, Carlsson, et al., 2014; Watkins et al., 2021). This finding ensures that participants were exposed to similar movements on both skin sites, which were chosen to match in size, ruling out results that might depend on different kinematics for touch delivery on the hand or the palm. This finding suggests that the motor system is attuned to the execution of CT-optimal touch but not to the body site on which the touch is delivered. A possible speculation is that this information would be more easily retrieved by somatosensory simulation of the observed touch, as it is suggested by previous evidence of dissociable somatosensory responses to touch on hairy and glabrous skin (Schirmer, Lai, et al., 2022).

A significant, moderate-to-high, negative correlation emerged between emotional awareness and the ATS, an index that reflects the MEP modulation for CT-optimal compared to non-CT optimal touch. Specifically, higher reliance on bodily cues to be emotionally aware was associated with greater motor suppression for CT-optimal compared to non-CT-optimal velocities. This correlation could be interpreted within the earlier mentioned speculation, namely that a suppression of motor resonance to affective touch might aid in understanding the touchee's feelings during vicarious interpersonal touch. Since simulation processes are rooted in the own embodied representations of the observed action (Gallese & Ebisch, 2013), it could be that participants more aware of their bodily signals are better able to perceive the observed touch as if they were the touchee, and may benefit from a suppression of motor resonance to facilitate somatosensory simulations. Previous research has documented that individuals with higher levels of interoceptive awareness show higher responses in somatosensory areas for vicarious touch perception (Adler & Gillmeister, 2019). Overall, this result adds to previous literature pointing to a link between vicarious touch, interoceptive awareness and empathy (Lamm et al., 2015; Peled-Avron et al., 2016, 2019; M. Schaefer et al., 2013; Smit et al., 2023).

This correlation was significant for the FDI but not for the ECR. The FDI was chosen as proximal muscle and it directly belongs to the hand, the body part through which we usually reach out to touch. Thus, it might provide further feedback regarding motor intentions of the toucher, which could be decreased for CT-optimal touch to facilitate somatosensory simulation. However, the main analysis did not highlight an interaction effect of muscle with velocity, suggesting that the quadratic relation between MEP amplitudes and velocities was similar in the two muscles. Previous research has indicated that a non-muscle-specific modulation of motor resonance might reflect a rapid and automatic processing related to social and emotional functioning (Lepage et al., 2010). The absence of muscle specificity might depend on the methodological choice to assess CSE well after the video onset. While this choice ensured that participants were exposed to the full action unfolding, this way did not disentangle different stages of the CSE modulation (Naish et al., 2014).

Limitations must be acknowledged when interpreting the results of this study. The speculations advanced to explain results should be confirmed and further tested in future research, e.g., using repetitive TMS on somatosensory vs. motor cortices (Bellard et al., 2023). As cited above, to disentangle specific stages of CSE modulation and muscle-specific effects, future studies may explore distinct contributions of emotional reactivity and motor simulation to vicarious touch by investigating different time windows (Borgomaneri et al., 2012; Finisguerra et al., 2021). The videos adopted here were previously validated and adopted to assess vicarious pleasantness in the first behavioural study, but in this experiment, participants were not asked to rate pleasantness for the observed touch. How motor simulation processes may affect mechanisms of touch execution appraisal should be clarified by future research.

2.4 General discussion

The two, consecutive studies provide behavioural and neurophysiological first evidence of vicarious processing of touch delivery.

In the first study, the results of a CT-specificity for pleasantness ratings of vicarious delivery of touch suggest that observation of delivery of affective touch may activate embodied motor simulation of the stroking gesture, which would help individuals with understanding what kind of tactile stimulation may be more appropriate to match the touchee’s needs (Kirsch et al., 2018). Accordingly, a modulation of the Mu and Rolandic EEG rhythms, which are considered neural markers of sensorimotor simulation, was reported during vicarious touch perception (Addabbo et al., 2020; Peled-Avron et al., 2016; Schirmer & McGlone, 2019) and when participants had to carry out a consoling touch on the partner (Peled-Avron et al., 2018). However, the findings of the first study point to a preference for vicarious touch reception compared to execution, which would be specific for CT-optimal velocity.

The second study helped to clarify this first study’s results by documenting that the motor system would selectively respond to the observation of affective touch with a mechanism of motor-resonance suppression. Given this modulation of motor resonance to interpersonal touch, the question is why the motor excitability decreases for CT-optimal stroking. Interestingly, the quadratic, U-shaped relation between touch velocities and MEP amplitudes indicates an opposite pattern compared to the typical inverted-U-shaped trend widely documented for CT-fibre firing and for pleasantness rating (Ackerley, 2022; Löken et al., 2009; McGlone et al., 2014).

A potential explanation for this dissociation and the higher ratings attributed to vicarious reception vs. delivery of affective touch in the first study, is the reduction of motor simulation facilitating somatosensory simulation of observed (affective) touch, a mechanism that helps individuals capture the hedonic value of CT-optimal stroking and “resonate” with another’s affective experience of being touched (Lee Masson et al., 2019; Peled-Avron et al., 2016; M. Schaefer et al., 2012). This hypothesis is in line with an increasing number of studies documenting a relationship between vicarious touch reception and affective processing, with a wide network of socio-cognitive and somatosensory areas contributing to understanding and, more importantly, feeling the observed touch (Bolognini et al., 2011, 2012; Keysers et al., 2004, 2010; Peled-Avron et al., 2019; Peled-Avron & Woolley, 2022; Rigato et al., 2019; M. Schaefer et al., 2023). In this vein, somatosensory simulation would be advantaged over motor simulation of the observed touch as it is the touchee’s experience to determine whether the stroking is perceived as pleasant, adequate to the context and matched to the toucher’s purpose, thus providing more information than vicarious execution to infer affective and social values conveyed by interpersonal touch (Kirsch et al., 2018; Sailer & Leknes, 2022).

In keeping with the hypothesis that the own bodily signals play an active role in driving perception of external stimuli (Seth & Friston, 2016), both studies reveal significant associations between interoceptive awareness and vicarious touch perception. The interplay between interoceptive signals and perception of external stimuli may be particularly important for interpersonal touch, as the posterior insula is a critical hub for both CT-afferents and interoceptive processing (Craig, 2003; Kirsch et al., 2020). Of note, embodied simulation in the insula and somatosensory cortices, which would subtend the “feel” of the touch, is thought to capture the social meanings of stroking gestures (Ebisch et al., 2008; Lee Masson et al., 2018; Morrison et al., 2011; Schirmer & McGlone, 2019), a mechanism that would help us to “resonate” with other’s affective experience of being touched (Lee Masson et al., 2019; Peled-Avron et al., 2016; M. Schaefer et al., 2012).

The two studies had limitations described in detail above, and particularly that pleasantness ratings were not assessed in combination with motor resonance. Limitations notwithstanding, these studies are the first to provide evidence that human brain is selectively attuned to affective touch during observation of touch reception and delivery. The findings hint different cognitive and affective mechanisms that subserve simulation of vicarious reception and execution of social touch. They also may pave the way for a deeper understanding of vicarious touch processing, with potential implications for psychopathological disorders showing altered touch perception and social cognition deficits such as ASD (Haggarty et al., 2020; Peled-Avron & Shamay-Tsoory, 2017), ED (Cazzato et al., 2021; Bellard et al., 2022; Crucianelli et al., 2016) and schizophrenia (Ebisch et al., 2013). A better understanding of how vicarious touch reception and execution are processed in these disorders might indeed help finding new target for rehabilitation treatments, also considering the potential use of virtual reality to provide multisensory stimulation that can shape touch processing, overcoming at the same time social anxiety often present in these conditions (Della Longa et al., 2022; Spence, 2022).

3. Cognitive development in children and adolescents with overgrowth syndromes: neuropsychological profile and educational outcomes of Beckwith-Wiedemann, Sotos and Malan syndromes

3.1 Overview of the project on overgrowth syndromes

Overgrowth syndromes are a heterogeneous group of rare genetic syndromes that, beyond the specific clinical features, involve the excessive growth of the whole body or of specific body parts (Brioude et al., 2019). The current project recruited participants with three overgrowth syndromes: Beckwith-Wiedemann syndrome (BWS), Sotos syndrome, and Malan syndrome.

BWS is a human imprinting disorder that leads to overgrowth, with an estimated prevalence of 1:10,500 newborns (Wang et al., 2020). The clinical manifestation varies greatly, with cardinal features including macroglossia, abdominal wall defects, hemihyperplasia (i.e., lateralized overgrowth), hyperinsulinism and a heightened risk of developing embryonal tumours. Secondary features involve enlarged abdominal organs, birthweight greater than two standard deviations above the mean, and a facial nevus simplex. BWS is not usually associated with intellectual delay, unless specific at-risk conditions are present, such as severe hypoglycemia and prematurity (Brioude et al., 2018; McElroy et al., 2023) (see Section 3.2 for further details). BWS is linked to genetic and epigenetic changes in the 11p15 chromosome region. Approximately 60% of BWS patients have an altered expression of the growth suppressor gene *CDKN1C*, mostly due to loss of methylation of the *KCNQ1OT1* differentially-methylated region (DMR) (also known as IC2) in the maternal allele of the centromeric domain. Less frequent causes are known to be a gain in methylation in the *H19/IGF2* DMR (also known as IC1), associated with increased expression in the growth promoter gene *IGF2* in the paternal allele of the telomeric domain and Uniparental Paternal Disomy (UPD) of 11p15.5.

Sotos syndrome is a rare congenital, autosomal dominant disease, with an estimated prevalence of 1: 14,000 newborns. Cardinal features of these syndrome are facial dysmorphism characterized by acromegalic appearance, childhood overgrowth of excessive height and/or head circumference, advanced bone age, and intellectual disability, even though a wide variability of cognitive functioning has been reported (Lane et al., 2016; Siracusano et al., 2023). Other common features are multiple organic malformations, seizures and joint hyperlaxity. Sotos syndrome is associated with intragenic mutations or microdeletion of the *NSD1* gene in 5q35 chromosomal region.

Malan syndrome is thought to be a ultra-rare disorder as less than 100 affected individuals have been reported (Macchiaiolo et al., 2022; Priolo et al., 2018). This condition presents clinical features similar to Sotos syndromes, such that, in absence of *NSD1* alterations, it was previously defined as Sotos-2 or a Sotos-like syndrome. However, in the last years an increasing number of studies have started to further characterise the clinical, cognitive and behavioural phenotype of Malan syndrome (Alfieri et al., 2022; Mulder et al., 2020). It is now acknowledged that the Malan syndrome is due to aberrations in the *NFIX* gene, located at chromosome 19p13.2 (Malan et al., 2010).

The project aimed at investigating the neuropsychological profiles, multiple dimensions of body perception and socio-emotional development in children and adolescents with BWS, Sotos and Malan syndromes. All participants aged 5-18 years underwent a comprehensive neuropsychological assessment, whose results are presented in the current chapter. Adolescents aged 11-18 years and a control group of healthy peers were administered with experiments assessing diverse dimensions of body perception. The procedures and results are reported in Chapter 4. Standardized questionnaires were used to assess autistic traits and emotional-behavioural problems in children and adolescents with overgrowth syndromes aged 6-18 years. The results of this assessment, along with a previous study on preschool-age children with BWS, are presented in Chapter 5.

The families affiliated with AIBWS and ASSI were informed of the possibility of participating in the project. All interested families were then contacted by the experimenter to be further informed about aims and procedures of the project and to arrange their visit to the Scientific Institute Medea, where all studies were carried out. Families of four children with BWS, twelve participants with Sotos syndrome and two with Malan syndrome preferred to be hospitalised in the neuropsychiatry and neurorehabilitation unit, but the remaining families opted for daily access to the Institute. All procedures were usually conducted over two or three consecutive days. Parents were asked to sign an informed consent form before starting any procedures. All procedures of the project were in accordance with the Declaration of Helsinki and were approved by the Ethical Committee of the Scientific Institute, IRCCS E. Medea (Prot. 18/21 CE).

3.2 Cognitive functioning in overgrowth syndromes, Williams syndrome and Joubert syndrome

BWS, Sotos, and Malan syndromes involve quite different intellectual functioning, although they are classified as overgrowth disorders (Brioude et al., 2019).

BWS is not usually associated with intellectual delay, unless specific at-risk conditions are present, such as severe hypoglycaemia, prematurity, unbalanced chromosome rearrangements and paternal genome-wide UPD (Brioude et al., 2018; McElroy et al., 2023). However, a recent study (Butti, Castagna, et al., 2022) found that developmental difficulties in language and motor skills for preschool-age children with BWS may depend on typical features of BWS – macroglossia and hemihypertrophy (see Chapter 5 for details). As well, a recent survey-based study reported learning difficulties in almost 20% of adult patients with BWS (Drust et al., 2023). Other research has pointed to a potential role of epigenetic mechanisms associated with BWS in the emergence of learning difficulties (Choufani et al., 2021; Slavotinek et al., 1997). This evidence asks for a further characterisation of cognitive development and educational outcomes in children and adolescents with BWS.

The presence of intellectual disability is a common feature of Sotos syndrome. Nevertheless, only in recent years research has started to shed light on specific cognitive profiles of this syndrome (Lane et al., 2016). Relative strengths in verbal abilities and visuospatial memory, and relative weaknesses in non-verbal abilities and quantitative reasoning have been documented in a sample that included children and adults with Sotos syndrome (Lane, Milne, et al., 2019). The first study to compare genotypes associated with Sotos syndrome has found that microdeletions in *NSD1* result in lower intellectual functioning independently of age and behavioural problems (Siracusano et al., 2023). However, a full description of the neuropsychological profile of Sotos syndrome in developmental age is still lacking.

Less information is available on Malan syndrome, even given its recent identification as a distinct disease. Evidence of specific neuropsychological features is limited (Priolo et al., 2018). The studies on this topic have indicated that multiple cognitive domains are affected in this syndrome (Alfieri et al., 2022; Macchiaiolo et al., 2022; Mulder et al., 2020).

Distinct neuropsychological profiles have been previously described for many congenital syndromes, particularly for Williams syndrome (Mervis et al., 2000; Miezah et al., 2020). This condition can be seen as an optimal benchmark for Sotos and Malan syndromes, as all these syndromes often have comorbidities with ASD and attention deficit and hyperactivity disorder (ADHD) (Alfieri et al., 2023; Asada & Itakura, 2012; Lane et al., 2016; Riccioni et al., 2024; Sheth et al., 2015; Vivanti et al., 2018). Thus, differences and similarities in neuropsychological profiles may clarify distinct neurocognitive mechanisms underlying abnormal social functioning in these syndromes. For instance, a previous study compared Sotos and Williams syndromes on socio-communicative abilities, revealing differences in linguistic and pragmatic abilities (Lane, Van Herwegen, et al., 2019b). Nevertheless, social perception abilities present in individuals with Sotos, Malan and Williams syndromes have not been fully considered in the broader context of neuropsychological profiles.

A rare condition associated with specific neuropsychological impairments and autism-like behaviour is Joubert syndrome (Holroyd et al., 1991; Tavano et al., 2007). This syndrome is characterised by the so-called molar tooth sign, a set of malformations including cerebellar vermis hypoplasia, deepened interpeduncular fossa, and elongated superior cerebellar peduncles (Poretti et al., 2014; Romani et al., 2013). By comparing the neuropsychological profile of the Joubert syndrome with other congenital cerebellar malformations, it is possible to investigate associations between specific cerebellar areas and impairments in social and cognitive functions (Tavano & Borgatti, 2010). Importantly, a previous study documented abnormalities of the cerebellum in some individuals with BWS (Gardiner et al., 2012).

Most studies investigating cognitive ability have focused only on a few specific neuropsychological domains, such as language or visuospatial processing. They have often adopted tests from different batteries (Alfieri et al., 2022; Lane, Milne, et al., 2019; Menghini et al., 2010). Since cognitive functions are strongly interdependent, especially in children with intellectual delay (Ferrari et al., 2023), these issues limit the reliability of the results. A comprehensive assessment of different cognitive domains, including social perception, with a co-normed test battery might provide new insights into the neuropsychological profile of these syndromes.

Below, results of a comprehensive assessment are presented for the neuropsychological profile of BWS, Sotos and Malan syndromes. This assessment includes educational outcomes, reading, comprehension and mathematics, to further qualify the difficulties experienced by children with these syndromes. As well, the results of two studies adopting a similar neuropsychological assessment in Williams and Joubert syndromes are given. Differences in procedures and inclusion criteria do not allow a direct comparison between these conditions and overgrowth syndromes. Nevertheless, the results of the main project and these studies are discussed in order to highlight different profiles of socio-cognitive abilities in populations with rare genetic disorders.

A detailed description of the neuropsychological profiles of overgrowth syndromes not only has important clinical and rehabilitative implications but can shed light on the interplay between body and cognitive development.

3.3 Neuropsychological profile and educational outcomes in Beckwith-Wiedemann syndrome

3.3.1 Materials and methods

3.3.1.1 Participants

Twenty-nine children and adolescents were recruited in collaboration with AIBWS. Inclusion criteria were: i) confirmed clinical and/or genetic diagnosis of BWS spectrum (Brioude et al., 2019);

ii) age from 5 to 18 years. The sample included participants with comorbid diagnoses of neurodevelopmental disorders. Four had a diagnosis of learning difficulties, one of which was also affected by epilepsy. One had ASD and developmental delay. One had diagnoses of borderline intellectual functioning, attention deficit and learning disorder not otherwise specified. One had previously received a diagnosis of developmental delay. Demographic and clinical features of the recruited sample are reported in Table 3.

Table 3. Demographic and clinical features of the recruited sample with Beckwith-Wiedemann syndrome.

	Mean (SD)/N (%)
Sex (females)	18 (62%)
Age (years)	9.4 (3.5)
Genetic diagnosis	
Altered expression of *IGF2* (IC1)	2 (7%)
Altered expression of *CDKN1C* (IC2)	18 (62%)
Paternal Uniparental Disomy	6 (21%)
Other/unknown	3 (10%)
Clinical features	
Macroglossia	25 (86%)
Lateralized overgrowth	18 (62%)
Birthweight > 2 SD above the mean	9 (31%)
Omphalocele	4 (14 %)
Neonatal hypoglycaemia	12 (41%)
Tumour onset	3 (10%)
Preterm birth	10 (34%)
Neurodevelopmental disorders	7 (24%)

3.3.1.2 General procedure

Participants completed a comprehensive, standardized assessment including general intellectual functioning, multiple cognitive domains, and educational outcomes. Duration and number of sessions depended on characteristics of each child (e.g., age, behaviour, attention).

3.3.1.3 Classification of intellectual functioning

In order to obtain a classification of intellectual functioning (i.e., IQ), the Raven progressive matrices or the Raven coloured progressive matrices were administered according to the child’s age

(Raven, 1982). Raven matrices are considered a timewise, non-verbal instrument to assess IQ providing a classification of intellectual functioning similar to the gold standard Wechsler scales (Mungkhetklang et al., 2016). Participants were shown visual geometric design with a missing piece, and they were asked to choose among six to eight options to fill it in. On the basis of the raw score, the normative standardization manuals were used to classify each participant's intellectual functioning as above mean, mean, borderline, mild delay, moderate delay, or severe delay.

3.3.1.4 Neuropsychological Assessment

Participants were administered with selected subtests of the Italian NEPSY–II version, one of the widest adopted batteries of neuropsychological assessment in developmental age (Korkman et al., 2007; Urgesi et al., 2011). These subtests were selected to assess various neuropsychological domains, thus providing a detailed description of the neuropsychological profile and specific cognitive abilities (Table 4).

Table 4. Description of the selected NEPSY-II subtests. For each domain, subtest and sub-part, the age range of administration and the main assessed abilities are described.

Domain	Subtest	Part	Age	Main assessed abilities
Attention and executive functions	*Visual attention*		5-18	Visual, selective attention
	Auditory Attention and response Set	*Auditory attention*	5-18	Selective auditory attention and vigilance
		Response set	7-18	Establishment, maintenance, and change of a response set
	Inhibition	*Naming*	5-18	Control of verbal response
		Inhibition	5-18	Inhibitory control of verbal response
		Switching	7-18	Flexibility in control of verbal response
	Animal sorting		7-18	Categorisation
Language	*Comprehension of instructions*		5-18	Receptive language
	Speeded naming		5-18	Rapid semantic access and production

Memory and learning	*Memory for faces*		5-18	Encoding and immediate/delayed retrieval of facial stimuli
	Memory for designs	*Immediate*	5-18	Immediate visual-spatial memory
		Delayed	5-18	Delayed visual-spatial memory
	Word list interference	*Repetition*	7-18	Verbal working memory span
		Interference	7-18	Verbal working memory following interference
Sensorimotor functions	*Fingertip tapping*		5-18	Rapid motor programming
	Imitating hand positions		5-18	Imitation
	Manual motor sequences		5-18	Encoding and retrieval of rhythmic motor programmes
Social Perception	*Theory of Mind*	*Verbal part*	5-18	Understanding mental functions (e.g., belief, pretending etc.)
		Contextual part	5-18	Understanding others' emotional states related to social context
	Affect recognition		5-18	Facial affect recognition
Visuospatial processing	*Design copying*		5-18	Graphomotor control and visual-perceptual analysis
	Block construction		5-18	Visuospatial construction skills
	Picture puzzles		7-18	Recognizing part-whole relationships
	Geometric puzzles		5-18	Mental rotation

Raw scores at NEPSY-II subtests were converted into scaled scores (mean = 10, SD = 3, range 1-19) with respect to the values for the corresponding chronological age of the Italian normative sample (Urgesi et al., 2011). For the auditory attention and response set subtest, raw scores were transformed into percentile ranks (<2, 2-5, 6-10, 11-25, 26-50, 51-75, > 75) as per indications of the standardization manual. Scaled scores > 13 and percentile ranks > 75 indicate strengths, scaled scores < 4 and percentile ranks < 6 indicate weaknesses.

3.3.1.5 Assessment of educational outcomes

Reading, reading comprehension and mathematics were assessed by means of the Italian standardized tests MT-3 and AC-MT according to educational level (Cornoldi et al., 2017, 2020; Cornoldi & Carretti, 2016). For reading, both speed and accuracy were assessed; the reading comprehension test provided a single raw score. For all grades, arithmetical facts (i.e., calculation and knowledge of basic arithmetic rules), and accuracy as well as speed of mental calculation were assessed. Please note that calculation speed was considered only when the result was correct in at least one third of the items. Raw scores were used to classify the performance on the basis of normative standardization tables, providing a four-level classification: fully achieved criterion, sufficient performance, request for attention, request for immediate intervention. Even though these levels do not imply a diagnosis, they are widely used for screening children with learning difficulties (Barbiero et al., 2019).

These tests were administered to children already enrolled in primary school (N = 21).

3.3.1.6 Data handling and statistical analysis

For the Raven matrices, the percentage of participants for each level of intellectual functioning was calculated.

As regards the NEPSY-II, descriptive statistics and the percentage of children with strengths or weaknesses in specific subtests were calculated. For the domain and subtest analyses, scaled scores obtained at different parts of the same subtest (i.e., inhibition, memory for designs, word list interference) were collapsed into a single average scaled score. Similarly, a global score was computed as the mean scaled score on the subtests for each neuropsychological domain. A hierarchical analysis approach was used for describing the neuropsychological profile. Since the auditory attention and response set subtest only provides percentile ranks, it was excluded from these analyses. First, an RM-ANOVA was conducted inserting the six domain scores as dependent variables. Then, a series of RM-ANOVAs or paired-sample *t*-tests (for language and social perception) were run within each domain, inserting scaled scores of each subtest as within-subject variable. Note that some of the subtests (i.e., animal sorting, word list interference, picture puzzles) were administered from the 7th year of age. The analyses were first executed considering these subtests, thus excluding children younger than 7 years old (N = 9). The analyses were then repeated without these subtests, thus including also participants younger than 7 years old. Moreover, for each domain and subtest, the percentage of participants with individual strength (scaled scores > 13, percentile ranks > 75) or weakness (scaled scores < 4, percentile ranks < 6) were calculated.

The percentage of participants for each of the four levels of performance was calculated with regard to educational outcomes.

All analyses were performed with Statistica 8.0 (Statsoft, Tulsa, OK), with alpha set at $p < 0.05$ for all effects. Significant interactions in the RM-ANOVAs were analysed with Bonferroni post-hoc tests. Effect sizes were estimated and reported as partial eta squared (n^2_p) for ANOVA designs, and as Cohen’s *d* for pairwise comparisons, adopting conventional cut-offs (Lakens, 2013).

3.3.2 Results

3.3.2.1 Intellectual functioning

The performance at the Raven matrices indicated that one participant had a mild intellectual disability. This child had autism and had previously received a diagnosis of developmental delay. Two participants (7%) were classified with borderline intellectual functioning; both had a previous diagnosis of neurodevelopmental disorder (one with learning difficulties and epilepsy, one with borderline intellectual functioning, attention deficit and learning disorder not otherwise specified). None of these children had hypoglycaemia at birth, and only one was born preterm (late). Eighteen participants (62%) showed average intellectual functioning, and the remaining eight children (28%) had above-average intellectual abilities.

3.3.2.2 Neuropsychological profile

Scaled scores/percentile ranks and the percentage of participants showing individual strengths or weaknesses in each subtest and domain are reported in Table 5.

Table 5. Performance at the NEPSY-II of children with BWS. Scaled scores/percentile ranks and percentage of participants with individual strengths or weaknesses for each domain and subtest. Scaled scores are reported as mean (SD), percentile ranks as median.

Domain	**Subtest**	**Part**	**Scaled score/percentile rank**	**Participants with individual strength (%)**	**Participants with individual weakness (%)**
Attention and executive functions			9.5 (2.2)	0	0
	Visual attention		10.3 (3.6)	14	3.5
	Auditory Attention and response Set	*Auditory attention*	26-50	7	7
		Response set	26-50	5	10
	Inhibition	*Naming*	8.7 (2.6)	3.5	3.5
		Inhibition	9.2 (2.8)	7	0
		Switching	8.8 (2.4)	5	10
	Animal sorting		9.3 (3.3)	10	0
Language			8.7 (2.7)	3.5	3.5
	Comprehension of instructions		9.2 (2.8)	7	3.5
	Speeded naming		8.1 (3.1)	3.5	10.5
Memory and learning			8.9 (4.1)	10.5	0
	Memory for faces		10.7 (2.7)	14	0
	Memory for designs	*Immediate*	8.2 (4.3)	7	17.5
		Delayed	9.6 (4.6)	17.5	10.5
	Word list interference	*Repetition*	9.5 (2.5)	0	0
		Interference	9.5 (3.2)	10	5

Sensorimotor functions		10.2 (2.2)	14	0
	Fingertip tapping	11.8 (2.5)	24.5	0
	Imitating hand positions	9.5 (2.9)	3.5	7
	Manual motor sequences	9.6 (3)	10.5	0
Social Perception		11.2 (2.7)	10.5	0
	Theory of Mind	11.7 (2.4)	21	0
	Affect recognition	10.8 (2.4)	10.5	0
Visuospatial processing		10.3 (3.3)	21	7
	Design copying	9 (3.9)	14	7
	Block construction	10.4 (3.7)	17.5	7
	Picture puzzles	10.1 (4.3)	32	4.5
	Geometric puzzles	11.8 (3.5)	35	3.5

The comparison between neuropsychological domains highlighted significant differences ($F_{5,140} = 8.49$, $p < 0.001$, $n^2_p = 0.23$). Lower scores emerged in the linguistic domain compared to sensorimotor functions ($p = 0.005$), visuospatial processing ($p = 0.002$) and social perception ($p < 0.001$). The latter domain obtained higher scores than attention and executive functions ($p = 0.001$), as well as memory and learning ($p = 0.001$). Visuospatial processing showed the highest percentage of participants with strength (21%) on a domain level. Across domains, the percentage of participants with individual weaknesses was very low (range 0-7%).

The analysis within the attention and executive functions domain did not reveal significant differences between subtests ($F_{2,40} = 0.70$, $p = 0.501$, $n^2_p = 0.03$). However, when considering the whole sample, a better performance emerged in visual attention compared to inhibition subtest (t_{28} = 2.27, p = 0.031, Cohen's d = 0.51). Similarly, within the language domain, comprehensions of instructions obtained higher scores than speeded naming (t_{28} = 2.46, p = 0.020, Cohen's d = 0.39). Significant differences between subtests emerged in the memory and learning domain ($F_{2,40}$ = 4.50, p = 0.017, n^2_p = 0.18). A better performance was detected in memory for faces over memory for designs (p = 0.014), a result that was significant even when considering children younger than 7 years old (t_{28} = 2.55, p = 0.017, Cohen's d = 0.51). No difference emerged between word list interference and the other subtests (all $p > 0.399$). For sensorimotor functions, the significant within-subject effect ($F_{2,52}$ = 9.79, $p < 0.001$, n^2_p = 0.27) pointed to a better performance in fingertip tapping than in imitating hand positions and manual motor sequences (all $p < 0.001$). Conversely, similar scores were recorded in these two subtests ($p > 0.999$). No difference emerged between social perception subtests (t_{28} = 1.55, p = 0.132, Cohen's d = 0.40), indicating comparable abilities to understanding another's mental states and emotions from verbal, contextual and facial cues. Concerning visuospatial processing, a significant within-subject effect ($F_{3,60}$ = 7.44, $p < 0.001$, n^2_p = 0.27) indicated a better performance in geometric puzzles than with all other subtests (all $p < 0.023$). When considering children younger than 7 years old, significant differences between subtests were detected ($F_{2,56}$ = 13.49, $p < 0.001$, n^2_p = 0.33), with higher scores in geometric puzzles than all other subtests (all $p < 0.040$) and in block construction than design copying (p = 0.033). On an individual level, the highest percentage of participants with strengths was estimated in geometric puzzles (35%), picture puzzles (32%), fingertip tapping (24.5%) and theory of mind (21%). The percentage of participants with individual weaknesses was lower than 20% across all subtests (maximum: memory for design immediate 17.5%).

3.3.2.3 Educational outcomes

The percentage of participants for each performance classification is reported in Table 6.

Table 6. Performance at the educational-outcome tests of children with BWS. The percentage of participants for each performance classification is reported.

	Fully achieved	Sufficient	Request for attention	Immediate intervention
Word reading				
Accuracy	10	62	24	4
Speed	10	43	28	19
Reading comprehension	14	57	10	19
Mathematics				
Arithmetic facts	4	76	10	10
Mental calculation				
Accuracy	10	76	4	10
Speed	0	26	32	42

A high percentage of children with difficulties was observed in reading speed and calculating speed. In accuracy measures and in the other tests, a large majority of the sample showed sufficient-to-fully achieved abilities.

3.3.3 Discussion

This study confirms that BWS is not usually associated with cognitive impairments (Mussa, Di Candia, et al., 2016; Wang et al., 2020). Indeed, in terms of general intellectual functioning and specific neuropsychological domains, few participants show a performance lower than the age-expected mean. However, these findings also highlight strengths and weaknesses of the neuropsychological profile as well as slowness in reading and in mental calculation in the educational-outcome tests.

Relative strengths appear to be sensorimotor functions, visuospatial processing and social perception. The latter suggests that children with BWS are particularly able to understand others' emotions and mental states. It can be speculated that growing up with a condition that implies atypical body features and frequent hospitalization, combined with adequate intellectual functioning, may lead to increased sensitivity towards others' social and emotional reactions as coping strategy (Compas et al., 2012).

The advantage in the sensorimotor functions domain was mainly driven by the performance at the fingertip tapping subtest. This result integrates the evidence of lower gross-motor abilities compared to fine-motor in preschool-age children with BWS (Butti, Castagna, et al., 2022) (see Chapter 5 for details). While gross-motor functions may be affected by typical features of the syndrome such as hemyhyperplasia, fine-motor skills are on average or even above the age-expected mean.

Visuospatial processing obtained higher scores than attention and executive functions or language domains. The worst performance was at the inhibition and speeded naming subtests. Both are timed subtests, in which rapidity in semantic access and verbal response strongly contribute to the scaled scores. Macroglossia, a cardinal features of BWS, may affect speech speed (Drust et al., 2023; Shipster et al., 2012). But, speed was found to be low for word reading and mental calculation.

Rather than pointing to a presumed increased incidence of learning difficulties in BWS (Choufani et al., 2021; Slavotinek et al., 1997), the findings of reduced speed in word reading and mental calculation should be read in the light of a complex relationship between genetic predisposition, psychosocial factors and educational outcomes. As for other chronic illnesses and orofacial malformations (Dardani et al., 2020), learning outcomes may be influenced by social, familiar and individual emotional factors (Bell et al., 2016; Pinquart & Teubert, 2012). For instance, increased anxiety and social withdrawal may impact on learning abilities, and speed (Grigorenko et al., 2020; Passolunghi, 2011). Future research using wider samples should address the prevalence of learning difficulties in BWS and the underlying factors that can contribute to educational attainment.

3.4 Neuropsychological profile and educational outcomes in Sotos and Malan syndromes

3.4.1 Materials and methods

3.4.1.1 Participants

Twenty-nine children and adolescents with Sotos syndrome and six children and adolescents with Malan syndrome were recruited in collaboration with ASSI Gulliver. Inclusion criteria were: i) confirmed genetic diagnosis of Sotos or Malan syndromes; ii) age from 5 to 18 years. Demographic and clinical features of the recruited samples are reported in Table 7.

Table 7. Demographic and clinical features of the recruited samples with Sotos and Malan syndromes.

	Sotos syndrome Mean (SD)/N (%)	**Malan syndrome** Mean (SD)/N (%)
Sex (females)	10 (34%)	1 (17%)
Age (years)	12.3 (3.8)	12.9 (4.7)
Genetic diagnosis		
Intragenic mutation of *NSD1*	23 (79%)	
Microdeletion of *NSD1*	6 (21%)	
Alterations in *NFIX*		6 (100%)
Clinical features		
Macrocephaly	25 (86%)	6 (100%)
Height > 2 SD above the mean	22 (76%)	5 (83%)
Advanced bone age	15 (52%)	5 (83%)
Epilepsy	6 (21%)	2 (33%)
Intellectual disability	22 (76%)	6 (100%)
Speech impairment	4 (14%)	3 (50%)
Neurodevelopmental disorders	14 (48%)	1 (17%)

As expected, almost half of the participants with Sotos syndrome received a previous diagnosis of ASD (N = 7), ADHD (N = 4), or both (2), while one participant without intellectual disability had a diagnosis of severe dyslexia. For Malan syndrome, ADHD was reported for one participant. For four children with Sotos syndrome and in half of the sample with Malan syndrome, speech was absent or composed of a few words.

3.4.1.2 General procedure

The general procedure and instruments were exactly the same as those adopted for BWS (see Sections 3.3.1.2 – 3.3.1.5 for further details). One participant with Sotos syndrome did not complete any tests due to severe emotional-behavioural problems, and was thus excluded from analyses. The presence of severe intellectual delay and/or speech impairments prevented some participants from being administered the full neuropsychological battery. If scaled scores were available only from a single subtest of a domain (e.g., visual attention for attention and executive functions), the global score of that domain was not calculated. When applicable, educational outcomes were assessed with tests matched to each participant’s level of school competence, as all participants followed a differentiated and/or reduced school programme in accordance with Italian laws.

3.4.1.3 Data handling and statistical analysis

The Sotos syndrome statistical analysis plan mirrored the one adopted for BWS (see Section 3.3.1.6 for further details). To consider the impact of comorbid diagnoses of neurodevelopmental disorders (N = 14) on the neuropsychological profile, this factor (i.e., absence vs. presence of neurodevelopmental disorder) was inserted as a categorical variable in a follow-up mixed-model ANOVA with domain scores as within-subject variable. Most of the sample exhibited intellectual disability, so only the percentage of participants with individual weaknesses was computed for each subtest of the NEPSY-II.

Due to the limited size of the sample with Malan syndrome, only descriptive statistics were calculated for this condition.

3.4.2 Results

3.4.2.1 Intellectual functioning

All participants completed the Raven’s matrices (Sotos syndrome N = 28, Malan syndrome N = 6). For Sotos syndrome, results confirmed that one out of four participants had average intellectual functioning. Eight children had borderline intellectual functioning (29 %), four with mild intellectual disability (14%), five with moderate intellectual disability (18%), and four with severe intellectual disability (14%). All participants with *NSD1* microdeletion exhibited moderate-to-severe intellectual disability. For Malan syndrome, three participants had severe intellectual disability and three had moderate intellectual disability.

3.4.2.2 Neuropsychological profile

Table 8 reports the number of participants that completed each subtest and domain, the corresponding scaled scores/percentile ranks and the percentage of participants showing individual weaknesses in each subtest and domain for the Sotos syndrome.

Table 8. Performance at the NEPSY-II of children with Sotos syndrome. Scaled scores/percentile ranks and percentage of participants with individual weaknesses for each domain and subtest. Scaled scores are reported as mean (SD), percentile ranks as median.

Domain	Subtest	Part	Tested participants (N)	Scaled score/percentile rank	Participants with individual weakness (%)
Attention and executive functions			23	5.1 (2.8)	30
	Visual attention		26	5 (4.4)	54
	Auditory Attention and response Set	*Auditory attention*	27	11-25	37
		Response set	20	2-5	55
	Inhibition	*Naming*	23	4.5 (3)	39
		Inhibition	23	3.7 (3.3)	56
		Switching	18	4.3 (3.1)	50
	Animal sorting		18	5.9 (3.1)	17
Language			23	4.5 (2.5)	48
	Comprehension of instructions		28	4.6 (3.3)	39
	Speeded naming		23	3.9 (2.5)	52
Memory and learning			24	6 (2.8)	29
	Memory for faces		28	7.8 (4.7)	21
	Memory for designs	*Immediate*	24	3.6 (3.3)	58
		Delayed	24	4 (3.8)	58
	Word list interference	*Repetition*	21	5.7 (3.3)	24

	Interference	21	6 (3.3)	24
Sensorimotor functions		27	5.5 (3.2)	37
	Fingertip tapping	28	6.8 (4.5)	32
	Imitating hand positions	27	4.3 (3.7)	56
	Manual motor sequences	27	5.4 (3.3)	33
Social Perception		26	5.2 (3.1)	38
	Theory of Mind	26	4.9 (3.5)	42
	Affect recognition	28	5.4 (3.6)	36
Visuospatial processing		27	4.3 (2.8)	44
	Design copying	23	2.9 (2.5)	61
	Block construction	28	5 (3.5)	39
	Picture puzzles	22	4.3 (4)	59
	Geometric puzzles	25	5.1 (3.4)	32

The analysis highlighted significant differences between domains ($F_{5,110} = 4.07$, $p = 0.002$, $n^2_p = 0.16$). Post-hoc tests clarified that lower scores were detected in language than in memory and learning ($p = 0.009$) or sensorimotor functions ($p = 0.033$). The memory and learning domain had higher scores than visuospatial processing ($p = 0.038$). It is noteworthy that the group mean was lower than the normative range (scaled scores < 7) across all domains, and that the percentage of participants with individual weaknesses was higher than 25% (minimum: memory and learning 29%, maximum: language 48%).

Regarding comorbidity with neurodevelopmental disorders, neither its main effect ($F_{1,21} = 1.95$, $p = 0.178$, $n^2_p = 0.08$) nor the interaction with domain ($F_{5,105} = 0.62$, $p = 0.686$, $n^2_p = 0.03$) were significant. The within-subject effect of domain was still significant ($F_{5,105} = 3.24$, $p = 0.009$, n^2_p = 0.13). These results confirm that the differences between neuropsychological domains were observed regardless of the secondary diagnosis of neurodevelopmental disorders.

For attention and executive functions, no differences between subtests ($F_{2,34} = 1.43$, $p = 0.252$, $n^2_p = 0.08$) were revealed, even when considering children younger than 7 years old ($t_{17} = 0.52$, $p = 0.607$, Cohen's $d = 0.13$). In the linguistic domain, higher scores were obtained in comprehension of instructions compared to speeded naming ($t_{22} = 2.12$, $p = 0.045$, Cohen's $d = 0.56$). For memory and learning between-subtests differences ($F_{2,40} = 13.89$, $p < 0.001$, $n^2_p = 0.41$) pointed to better performance in memory for faces than in the other subtests (all $p < 0.022$). No difference emerged between word list interference and memory for designs ($p = 0.060$). In sensorimotor functions ($F_{2,52} = 7.49$, $p = 0.001$, $n^2_p = 0.22$), higher scores were recorded in fingertip tapping than in imitating hand positions ($p = 0.001$). No significant differences emerged for the manual motor sequences subtest (all $p > 0.076$). Comparable scores were observed in the two subtests of social perception ($t_{25} = 0.85$, $p = 0.406$, Cohen's $d = 0.17$). In the visuospatial processing domain, the significant subtest effect ($F_{3,54} = 5.76$, $p = 0.002$, $n^2_p = 0.24$) highlighted lower scores in design copying than in block construction ($p = 0.003$) and in geometric puzzles ($p = 0.006$). All other comparisons were non-significant (all $p > 0.058$). On an individual level, the lowest percentage of participants with weaknesses was observed in the animal sorting (17%), memory for faces (21%) and word list interference subtests (24%). In all other subtests, more than one out of four participants showed weaknesses, with the highest percentage in design copying (61%), picture puzzles (59%), memory for designs (58%), imitating hand positions (56%) and inhibition (56%). It is important to note that all participants with average intellectual functioning showed weaknesses in at least one of the subtests.

For Malan syndrome, the number of participants that completed each subtest and the corresponding scaled score/percentile rank are reported in Table 9.

Table 9. Performance at the NEPSY-II of children with Malan syndrome. Scaled scores are reported as mean (SD), percentile ranks as median.

Domain	Subtest	Part	Tested participants (N)	Scaled score/Percentile rank
Attention and executive functions	*Visual attention*		6	2.8 (2.1)
	Auditory Attention and response Set	*Auditory attention*	6	<2
		Response set	3	2-5
	Inhibition	*Naming*	3	4.7 (3.2)
		Inhibition	2	1 (0)
		Switching	1	1
	Animal sorting		2	1 (0)
Language	*Comprehension of instructions*		6	1 (0)
	Speeded naming		2	6 (1.4)
Memory and learning	*Memory for faces*		6	4.5 (5.1)
	Memory for designs	*Immediate*	6	1 (0)
		Delayed	6	1.8 (1.6)
	Word list interference	*Repetition*	3	3 (3.5)
		Interference	3	2 (1.7)
Sensorimotor functions	*Fingertip tapping*		2	2.5 (2.1)
	Imitating hand positions		6	1 (0)
	Manual motor sequences		6	1.2 (0.4)
Social Perception	*Theory of Mind*		6	1 (0)
	Affect recognition		6	1 (0)
	Design copying		2	1 (0)

Visuospatial processing	*Block construction*	6	1 (0)
	Picture puzzles	5	1.8 (1.8)
	Geometric puzzles	6	1 (0)

Overall, the performance across all subtests was low, in keeping with the moderate-to-severe intellectual delay observed in the sample. However, despite the number of tested participants did not allow statistical comparisons, better performances were observed in the naming condition of inhibition, in speeded naming and in memory for faces.

3.4.2.3 Educational outcomes

For Sotos syndrome, the percentage of participants for each performance classification is reported in Table 10.

Table 10. Performance at the educational-outcome tests of children with Sotos syndrome. The percentage of participants for each performance classification is reported.

	N	**Fully achieved**	**Sufficient**	**Request for attention**	**Immediate intervention**
Word reading					
Accuracy	16	0	81	6	13
Speed	16	0	37	19	44
Reading comprehension	18	0	50	33	17
Mathematics					
Arithmetic facts	18	6	22	11	61
Mental calculation					
Accuracy	18	6	28	0	66
Speed	6	0	33	50	17

Consistent with the prevalence of intellectual disability in the sample, the percentage of children with learning difficulties was relatively high across all tests. Nevertheless, half of the tested participants showed sufficient reading comprehension abilities, and a large part of the children were sufficiently accurate in reading. Conversely, more than half of the sample showed difficulties in mathematics.

In the group with Malan syndrome, only two participants were tested. As expected from their moderate-to-severe intellectual disability, comprehension was strongly affected in both participants. Still, although relatively slow, they showed good reading accuracy. In mathematics, all scores were in the ‘immediate intervention’ range with the exception of a sufficient performance in arithmetic facts by a participant who also showed preserved verbal working memory abilities in the neuropsychological assessment.

3.4.3 Discussion

In line with previous literature (Lane et al., 2016), the findings show a prevalence of intellectual disability in Sotos syndrome, even though a wide variability was observed and a quarter of the sample showed average cognitive functioning. As suggested by a recent study (Siracusano et al., 2023), microdeletion of *NSD1* seems to be associated with more severe intellectual delay. However, the limited sample size prevented statistical comparisons between participants with and without microdeletion on specific neuropsychological skills. Conversely, all children and adolescents with Malan syndrome showed moderate-to-severe intellectual disability (Mulder et al., 2020).

The neuropsychological assessment provides a first comprehensive description of the neuropsychological profile of Sotos syndrome in developmental ages. Differing from previous studies (Lane et al., 2016; Lane, Milne, et al., 2019), the language domain was not found as a relative strength. Rather, linguistic skills were lower than other domains. This inconsistency may depend on the use of different batteries, as classic IQ tests mainly consider comprehension abilities as proxy of general verbal abilities (Wechsler, 2003). Here, the analysis within the language domain indicates that verbal comprehension abilities are relatively spared compared to rapid semantic access and linguistic production. The findings from this study clarify that while verbal reasoning may be a relative strength, rapid verbal production is often impaired in children with Sotos syndrome. In the NEPSY-II battery some verbal abilities are included in other domains. Verbal working memory, a subtest in which less than one quarter of the sample showed individual weaknesses, belongs to the memory and learning domain. Interestingly, the latter domain appears to be a relative peak of the profile.

The previous characterization of the cognitive profile by Lane and colleagues (2019) indicated visuospatial memory as strength in Sotos syndrome. In the current study, visuospatial memory is found defective in more than half of the sample, while memory for faces is the most preserved ability both on a group and individual level. Considering that the visuospatial processing domain is also found as the relative valley of the profile, these findings suggest that the visual rather than spatial memory is more preserved in Sotos syndrome.

Basic abilities to maintain and repeat a motor program, assessed by fingertip tapping, are more preserved than imitation of hand position. This requires the integration of motor and visual-spatial information. Similarly, design copying is the most affected ability in the visuospatial domain. Although not conclusive, these findings hint at a specific difficulty in integrating sensory and motor information. This was also suggested by a recent study reporting abnormalities in sensory processing and proprioception (Smith et al., 2023).

In Malan syndrome, the general intellectual disability yielded a floor effect in almost all subtests, limiting the delineation of a specific profile. Given its importance in social functioning across different contexts (Zebrowitz, 2006), it is important to note that memory for faces appears to be a relative strength. For participants with spared speech, the non-defective performances at simple naming tasks indicate that semantic access and verbal production may be relatively preserved in Malan syndrome. This evidence is further supported by the standardized tests on educational outcomes. Only two participants had access to this assessment, but both showed good reading accuracy. That is, even in the presence of moderate-to-severe intellectual disability, children with Malan syndrome can effectively learn to read.

For children with Sotos syndrome, reading accuracy was preserved in most of the tested participants. Conversely, a wide part of the sample displayed difficulties in mathematics. Numeracy has long been described in Sotos syndrome (Cole & Hughes, 1994). But research on this topic is scarce and results are conflicting. The study of Lane and colleagues (2019) reported a deficit in quantitative reasoning as a feature of the Sotos syndrome cognitive profile. A study by the same group (Lane, Van Herwegen, et al., 2019a) sustained that the approximate number system, the rapid and intuitive sense for numbers, is not impaired but rather associated with a deficit in inhibitory control. In the current study, inhibition is found as an individual weakness in more than half of participants. The limited sample size prevented testing this hypothesis directly, which should be addressed by future research. By using specific standardized tests on educational outcomes, this study highlights a frequent deficit of mathematics and calculation skills, which should be acknowledged and considered for rehabilitation and school attainment purposes.

3.5 Neuropsychological profile and social perception in Williams syndrome

3.5.1 Materials and methods

3.5.1.1 Participants

Twenty-six individuals with a confirmed diagnosis of Williams syndrome (15 males), aged 11-41 years (mean = 21.9; SD = 7.9), were recruited in collaboration with associations dedicated to this condition (Associazione Famiglie Sindrome di Williams – AFSW; Associazione Persone Sindrome di Williams Italia – APW).

All participants and their parents/guardians were informed about aims of the study and were asked to sign a written informed consent. The procedures were approved by the local Ethics Committee of the Scientific Institute (IRCCS) E. Medea (Prot. N.34/18 – CE) and were in accordance with the Helsinki Declaration guidelines.

3.5.1.2 General procedure, assessment and analysis

The participants underwent a comprehensive neuropsychological assessment including the Raven's matrices and the NEPSY-II, while educational outcomes were not tested in this population. For the NEPSY-II, the same subtests administered to BWS, Sotos and Malan syndromes were used, with the exception of auditory attention and response set. To further consider possible dissociations between low- and high-level social perception abilities, here scaled scores were calculated separately for the verbal and contextual parts of the theory of mind subtest. Raw scores at the NEPSY-II subtests were transformed into scaled scores (mean = 10, SD = 3) but avoiding the approximation at the low extremes usually adopted in standard normative tables (Urgesi et al., 2011). This procedure was choice in order to limit the expected floor effect and to enhance score variability.

The analysis plan replicated the hierarchical approach adopted with BWS and Sotos syndrome, starting with comparisons across NEPSY-II domains and moving to comparisons across different subtests within each domain. Lastly the percentage of participants showing individual weaknesses in each domain and subtest was calculated.

3.5.2 Results

The performance at the Raven's progressive matrices indicated a mild to moderate intellectual disability on average, although approximately one of four individuals fell within the normal range.

The scaled scores and the percentage of participants showing individual weaknesses in each subtest and domain of the NEPSY-II are reported in Table 11.

Table 11. Performance at the NEPSY-II of individuals with Williams syndrome. Scaled scores and percentage of participants with individual weaknesses for each domain and subtest. Scaled scores are reported as mean ± SEM.

Domain	Subtest	Part	Scaled score	Participants with individual weakness (%)
Attention and executive functions			-1.7 ± 0.8	85
	Visual attention		2.4 ± 1.3	62
	Inhibition	*Naming*	-0.4 ± 1.4	88
		Inhibition	-8.3 ± 2.4	85
		Switching	-4.7 ± 1.6	88

	Animal sorting		2.4 ± 0.5	58
Language			0.8 ± 0.7	85
	Comprehension of instructions		0.0 ± 1	81
	Speeded naming		1.6 ± 1.2	53
Memory and learning			-1.7 ± 0.6	96
	Memory for faces		7.1 ± 1	19
	Memory for designs		-9.9 ± 1.1	96
	Word list interference	*Repetition*	3.0 ± 0.4	46
		Interference	1.4 ± 1.3	46
Sensorimotor functions			-1.5 ± 1.2	92
	Fingertip tapping		-3.8 ± 2.2	85
	Imitating hand positions		-6.1 ± 1.5	96
	Manual motor sequences		5.5 ± 0.7	35
Social Perception			-0.8 ± 0.6	58
	Theory of Mind	*Verbal part*	-3 ± 1.2	88
		Contextual part	6.4 ± 0.9	27
	Affect recognition		4.3 ± 0.8	35
Visuospatial processing			-0.8 ± 0.6	88
	Design copying		-5.7 ± 1	92
	Block construction		1.1 ± 0.4	92
	Picture puzzles		-1.2 ± 1.1	77
	Geometric puzzles		2.8 ± 0.8	61

The analysis highlighted a significant difference between domains ($F_{5,125} = 9.87$, $p < 0.001$, $n^2_p = 0.28$), with social perception less impaired than all other domains (all $p < 0.001$) but language ($p = 0.390$). Language was less affected than attention and executive functions ($p = .022$) or memory and learning ($p = 0.027$). All other comparisons were non-significant (all $p > 0.052$). At individual level, social perception showed the lowest percentage of participants with weaknesses in that domain, even though across all domains more than half of the sample showed deficits.

Within-domain analyses revealed that, in the attention and executive functions domain, a worse performance was recorded in inhibition ($F_{2,50} = 17.17$, $p < 0.001$, $n^2_p = 0.41$) compared to both visual attention and animal sorting ($p < 0.001$). No difference emerged between these two latter subtests ($p > 0.99$). In the language domain, the performance of comprehension of instructions and speeded naming subtests was comparable ($t_{25} = -0.97$; $p = 0.341$). A significant difference between subtests ($F_{2,50} = 99.42$, $p < 0.001$, $n^2_p = 0.41$) emerged in the memory and learning domain. This indicated a relatively spared ability to memorize faces, with a mean score falling within the normative range, compared to verbal working memory ($p = 0.001$) and visual-spatial memory ($p < 0.001$). Significant differences were detected also between subtests of sensorimotor functions ($F_{2,50} = 21.87$, $p < 0.001$, $n^2_p = 0.47$), with manual motor sequences significantly better than both fingertip tapping ($p < 0.001$) and imitating hand positions ($p < 0.001$). The difference between fingertip tapping and hand imitation was non-significant ($p > 0.673$). As concerns social perception, significant effect of the RM-ANOVA ($F_{2,50} = 30.61$, $p < 0.001$, $n^2_p = 0.55$) pointed to stronger difficulties in verbal theory of mind compared to both contextual theory of mind ($p < 0.001$) and affect recognition ($p < 0.001$). Conversely, on these two latter subtests, participants obtained comparable scores ($p = 0.303$). Lastly, a significant effect of subtest emerged in the visuospatial processing domain ($F_{3,75} = 25.29$, $p < 0.001$, $n^2_p = 0.50$), with the worst performance detected on design copying compared to all other subtests (all $p < 0.001$). Moreover, a significant advantage emerged for geometric compared to picture puzzles ($p = 0.002$), while all other comparisons were non-significant (all $p > 0.190$). At individual level, almost all participants (> 85%) showed individual weaknesses in inhibition, memory for designs, imitating hand positions, the verbal part of theory of mind, design copying and block construction. The least impaired individual performances were observed in memory for faces (19%), the contextual part of theory of mind (27%), and affect recognition (35%).

3.5.3 Discussion

Even though individuals with Williams syndrome displayed poor performance across all the examined cognitive domains, social perception was a relative strength, both at group and individual levels. Still, an uneven profile was detected within this domain, with weaknesses in the verbal theory of mind subtest. Conversely, higher scores were recorded in affect recognition and contextual theory of mind, with only a third of our sample showing valleys in their individual profiles for one of these subtests. These results are in line with previous studies that suggested a differential impairment in high-level, explicit, socio-cognitive processes, partially overlapping with difficulties in narrative and pragmatic language (Alfieri et al., 2017; Lorusso et al., 2007; Marini et al., 2010; Van Den Heuvel et al., 2016), compared to relatively spared low-level, implicit, mostly non-verbal social perception skills (Campos et al., 2017; Tager-Flusberg, 2000; Weisman et al., 2017). Interestingly, a recent study has confirmed that Williams syndrome could be associated with an altered spontaneous judgment of face trustworthiness, but the ability to match emotional face expressions and social context descriptions appeared to be partially preserved (Gomez et al., 2020). Overall, our findings indicate that facial affect recognition and non-verbal theory of mind skills should not be considered as typical weaknesses in the neuropsychological profile of Williams syndrome, at least in adolescent and adult individuals. However, they might exhibit atypical developmental trajectories (Ibernon et al., 2018; Martínez-Castilla et al., 2015) and abnormal social attention patterns (Hanley et al., 2013; Vivanti et al., 2017).

As expected from previous literature (Martens et al., 2008; Mervis & Becerra, 2007), the language domain was found to be a relative strength. However, more than half of the sample showed weaknesses in comprehension of instructions. In some trials this subtest requires comprehension of spatial relationships between stimuli (e.g., above, left), which was reported to be a specific difficulty in the receptive language abilities of patients with Williams syndrome (Landau & Zukowski, 2003). It has been argued that apparently good expressive language in Williams syndrome might conceal comprehension difficulties, which may become more evident as task-demands increase (Royston et al., 2019). Given their inherent complexity, social interactions might represent one of the most likely contexts where receptive language problems arise, with potential detrimental effects on verbal theory of mind and pragmatic skills.

Overall, the results in the other domains were consistent with the established profile of Williams syndrome (Atkinson, 2022; Miezah et al., 2020; Royston et al., 2019). Within-domain analyses clarified that inhibition, visual-spatial memory, fine sensorimotor skills, and design copying were the most impaired abilities (Menghini et al., 2010; Rhodes et al., 2010; Vicari et al., 1996).

3.6 Neuropsychological profile of Joubert syndrome compared to other cerebellar malformations[2]

3.6.1 Materials and methods

3.6.1.1 Participants

Twenty-nine participants (19 males), aged 6-25 years, were recruited at the child neuropsychiatry and neurorehabilitation unit of the Scientific Institute, IRCCS E. Medea. All participants presented with congenital malformations of the cerebellum as revealed by T1- and T2-weighted images obtained through MRI. Exclusion criteria were: i) primary acquired brain lesions, ii) severe sensorial, motor, and phono-articulatory deficits that could interfere with the neuropsychological assessment administration. For each participant, the Full-Scale Intelligence Quotient (FSIQ) derived from the age-corresponding Wechsler Intelligence Scale (Wechsler, 2003) was assessed as a routine clinical procedure during the same hospital stay in which the patients were enrolled in this study. Based on clinical evaluation of neuroimaging findings by an expert paediatric

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[2] This study is reported in a published paper (Butti, Oldrati, et al., 2023).

neuropsychiatrist, 14 participants were classified as Joubert syndrome (JS) and 15 participants as other cerebellar malformation (CM). A resume of demographic information of the two groups is reported in Table 12.

Table 12. Demographic information of the groups with cerebellar malformations. Age and FSIQ data are reported as mean (SD).

	Joubert syndrome	Other cerebellar malformations	Statistical comparisons
Male: female	8:6	11:4	$\chi 2 = 0.28$, $p = 0.59$
Age in years	15.9 (6.6)	12.2 (2.7)	$t = 1.9$, $p = 0.07$
FSIQ	57 (16)	66 (15)	$t = -1.4$, $p = 0.15$

All participants and their parents were informed about study aims and provided verbal assent to participate in the study. Parents of underage children signed a written informed consent, while for participants aged 18 or over, written informed consent was obtained from them or their parents according to their legal status. The procedures were approved by the local Ethics Committee of the Scientific Institute (IRCCS) E. Medea (Prot. N.34/18 – CE) and were in accordance with the Helsinki Declaration guidelines.

3.6.1.2 Neuropsychological assessment

All participants were assessed with eight selected subtests of the Italian NEPSY–II version: visual attention (VA), comprehension of instructions (CI), memory for designs (MD), geometric puzzle (GP), imitating hand positions, manual motor sequences, theory of mind, affect recognition. These subtests were selected to assess all six cognitive domains (attention and executive functions, language, memory and learning, visuospatial processing, sensorimotor functioning, and social perception) and to be administered to children of different ages and cognitive levels. In a silent room, patients were tested individually in two separate sessions, each lasting approximately 45 minutes. Sessions were administered in two different days at intervals of less than 10 days.

3.6.1.3 Data handling and statistical analysis

Sex distribution in the two clinical groups was compared using the $\chi 2$ statistics. Their age and FSIQ were compared with Student's *t*-tests (two tailed) applying Welch's correction for unequal variance (Table 14).

As for Williams syndrome, raw scores at the NEPSY-II subtests were transformed into scaled scores avoiding the approximation at the low and high extremes that is inherent to the use of normative standardization tables. Neuropsychological outcome measures were the scaled scores obtained at the single subtests for each of the following neuropsychological domains: VA for attention and executive functions; CI for language; MD for memory and learning; GP for visuospatial processing. To reduce data dimensionality, scaled scores obtained at the subtests within the same cognitive domain were collapsed into a single measure. The scores obtained at the imitating hand position and manual motor sequence subtests were averaged into a sensorimotor domain (SM) index, and the scores obtained at the affect recognition and theory of mind subtests were averaged into a social perception domain (SP) index.

The six neuropsychological outcomes (VA, CI, MD, GP, SM and SP) were first entered into a multivariate analysis of variance (MANOVA) with diagnostic group (JS vs. CM) as a between-subject factor. The aim of this analysis was to examine whether the two clinical populations differed overall in relation to the selected outcome measures. The same differences were tested adding IQ scores as a covariate into a MANCOVA design, since group difference for IQ may be a potential explanation for group differences on the neuropsychological outcomes.

Next, a series of univariate ANOVAs were performed on each neuropsychological outcome separately, with diagnostic group (JS vs. CM) as a between-subject factor, to test for between-group differences in each neuropsychological domain. As with the multivariate analysis, these differences were also tested adding IQ as a covariate.

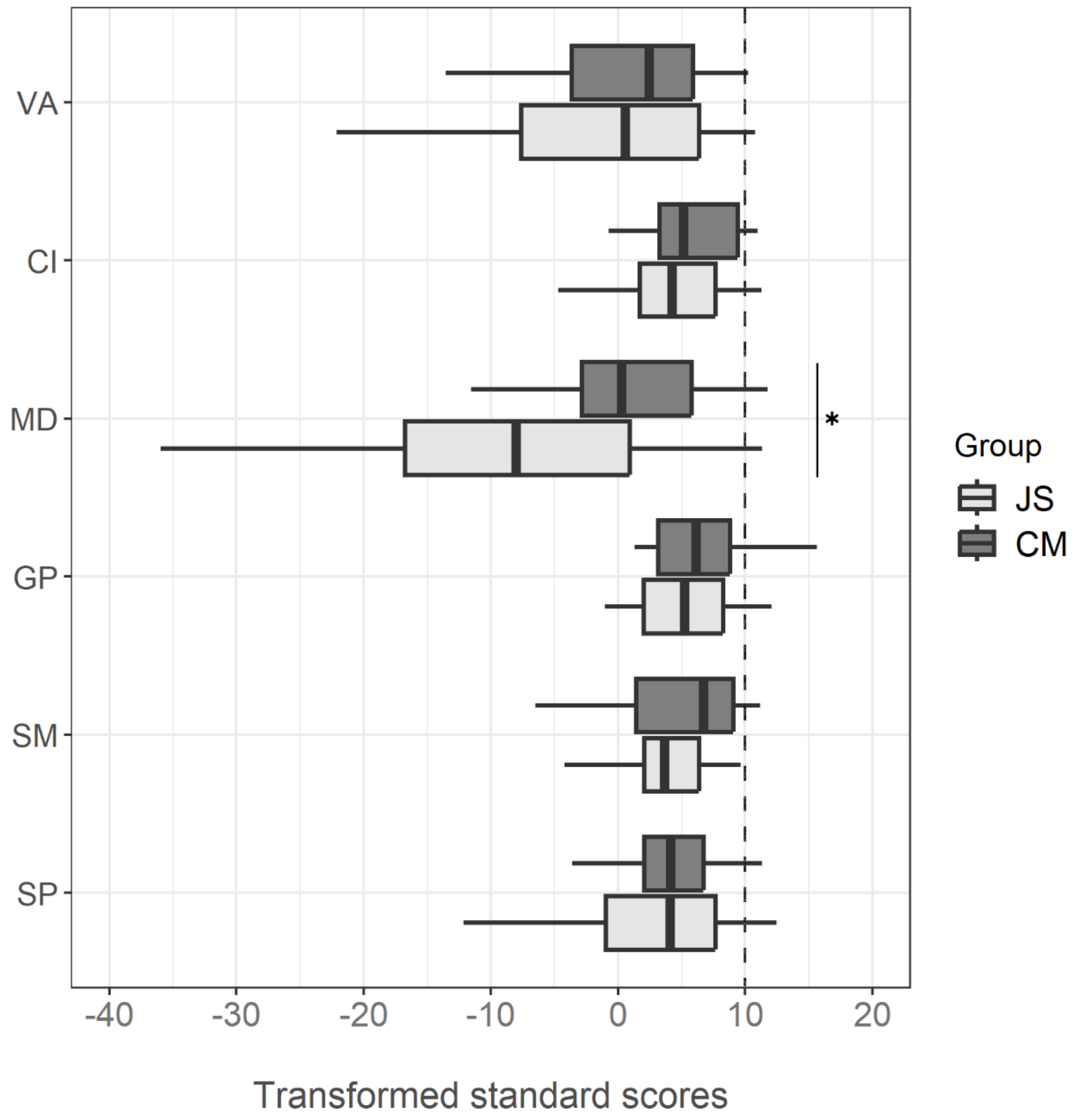
Statistical significance was obtained by a Type III of Sums of Squares. The level of statistical significance in all tests was set at $p < 0.05$. R software (version 4.0.3; R Foundation for Statistical Computing) was used to perform all the statistical analyses.

3.6.2 Results

The MANOVA on the neuropsychological outcomes yielded a non-significant effect of diagnostic group ($F_{6,22} = 0.91$, $p = 0.51$, $n^2_p = 0.19$), suggesting that the two groups had an overall similar neuropsychological performance. The MANCOVA with IQ as a covariate confirmed the non-significant effect of the diagnostic group ($F_{6,22} = 0.65$, $p = 0.69$, $n^2_p = 0.16$) and yielded a significant effect of IQ ($F_{6,22} = 5.76$, $p = 0.001$, $n^2_p = 0.62$), with better neuropsychological outcome in individuals with higher IQ.

Regarding the univariate ANOVAs, a significant effect of diagnostic group emerged in MD ($F_{1,27} = 5.62$, $p = 0.03$, $n^2_p = 0.17$). This result indicated that the memory outcomes differed between groups, with JS patients showing poorer performance as compared to CM (JS: mean = -8.4, SEM = 3.7; CM: mean = 1.0, SEM = 1.7). Non-significant effects of diagnostic group were found in the other cognitive outcomes (all $F < 1.16$, all $p > 0.28$) The ANCOVA with IQ as a covariate yielded only a trend of significance in MD ($F_{1,27} = 3.34$, $p = 0.08$, $n^2_p = 0.11$) and confirmed the non-significant effect of diagnostic group in VA, CI, GP, SM, and SP (all $p > 0.5$). Figure 8 depicts cognitive outcomes distributions among diagnostic groups.

Figure 8. Boxplot of cognitive outcomes scores by group (JS vs. CM). * indicates $p < 0.05$. The scaled score of 10, signalled by the dashed line, represents the normative mean.



3.6.3 Discussion

The findings of this study confirm and integrate previous contributions to the field in showing that non-progressive, paediatric ataxia due to either Joubert Syndrome or other congenital cerebellar malformations could result in multiple neuropsychological deficits (Bulgheroni et al., 2016; Schmahmann & Sherman, 1998; Tavano et al., 2007). Even though the profile of both groups was similar, displaying poor performance across all the examined cognitive domains, the patients with Joubert syndrome performed worse than patients with other cerebellar malformations in visual-spatial memory. This difference was partially detectable after the use of IQ as a covariate. These findings could not be attributed to a higher prevalence of visual deficits in Joubert syndrome compared to other cerebellar patients, since both groups were similarly impaired in visuospatial processing and visual attention. Thus, results of the current study provide evidence that a significant impairment of visual-spatial memory is inherently characteristic of the neuropsychological profile of Joubert syndrome.

A cerebellar contribution to visual-spatial memory has been widely considered in previous studies (Durisko & Fiez, 2010; Guell et al., 2018). Through its connections with basal ganglia and prefrontal cortex, the cerebellum might modulate filtering processes of incoming information in memory (Baier et al., 2010, 2014). The cerebellum could contribute to a cerebellar-frontal-parietal network in maintaining stimulus-specific representations of working memory items (Brissenden et al., 2021; Brissenden & Somers, 2019). These studies pointed to lobules VIIb and VIIIa in representing visual-spatial stimuli, with the pyramid of the vermis critically involved in filtering irrelevant information. Accordingly, it can be speculated that the absence or hypoplasia of the cerebellar vermis, which is characteristic of the molar tooth sign (Romani et al., 2013), might result into a more pronounced deficit of visual-spatial memory in Joubert syndrome through an enhanced susceptibility to distracting stimuli. However, it is to note that both groups were similarly impaired in the visual attention task. This result suggests that vermis malformations associated with Joubert syndrome might hinder the specific filtering function exerted during the recalling of task-relevant memories more than when distinguishing target stimuli from distractors. Indeed, distinct cortico-cerebellar loops for visual attention and visual memory have been reported (Brissenden et al., 2018). Nevertheless, the complex picture of malformations presented by our sample, affecting the cerebellum as well as other infratentorial and supratentorial areas, prevented disentangling the contribution of specific cerebellar areas. Furthermore, it is to note that also many participants with other cerebellar malformations presented with abnormalities of the vermis. Thus, the hypothesis of a link between vermis malformations in Joubert syndrome and their visual-spatial memory deficits should be investigated and confirmed in future research adopting functional neuroimaging techniques.

The differences in the profile of Joubert syndrome compared to other cerebellar malformations, and particularly the visual-spatial memory deficits shown by patients with Joubert syndrome, should be considered in identifying potential targets of rehabilitation. To date, only few studies have proposed interventions for cerebellum-related cognitive impairments, and only a single-case study addressed these deficits in Joubert syndrome (Gagliardi et al., 2015). In line with the hypothesis of a predictive contribution of the cerebellum to working memory (Stein, 2021), the cerebellar functions of maintaining internal models and signalling mismatches between the expected and the incoming information might be targeted by interventions aiming to boost filtering of irrelevant information and enhance learning. Accordingly, previous studies proposed the cerebellar functions of predictive coding and error-signalling could be directly targeted with interventions addressing motor impairments (Bhanpuri et al., 2014) and social cognition deficits (Butti, Biffi, et al., 2020; Urgesi et al., 2021).

3.7 General discussion

The studies presented in this chapter document a first characterisation of the neuropsychological profile of BWS, Sotos and Malan syndromes in the developmental ages. The findings for each of these conditions and the (indirect) comparison with other genetic conditions such as Williams and Joubert syndromes provide a framework of understanding how atypical body features may impact socio-cognitive development.

Overall, the neuropsychological profile of BWS is uniform and shows abilities within the normative range across all domains. The absence of cognitive deficits and multiple epigenetic mechanisms involved in BWS limit the possibility of detecting a specific cognitive phenotype. Findings suggest that abnormal bodily features may be particularly relevant for socio-cognitive abilities in BWS. The relative strength in social perception skills hints at a developmental link between one’s own body perception, an apprehension towards judgement from others and to an enhanced ability to perceive and understand another’s feelings and mental states. It is important to stress that higher social perception abilities do not imply fewer problems in social relationships. In conditions of chronic illness such as BWS, it may be the opposite (Martinez et al., 2011). A child may understand another's emotions but appear as withdrawn and have fewer friendships. The survey-based study of Drust (2023) reported that adults with BWS had childhood and adolescence experiences of discrimination and social isolation which they connect with their perception of themselves in relation to others. Increased social perception may be the result of coping strategies with social stress (Compas et al., 2012), as it allows the anticipation of others' social and emotional reactions and the possibility of avoiding negative reactions.

A secondary developmental effect of atypical bodily features in BWS may be a relative slowness in cognitive tasks. Speech difficulties due to macroglossia may partially explain the weaknesses in word reading and timed verbal subtests. Participants with BWS in a study by Drust (2023) reported problematic childhood experiences in the educational system for people with speech difficulties. People with cleft lip/palate (Dardani et al., 2020) experience prejudice in the educational system; they report a negative bias towards people with speech difficulties and/or atypical facial features. This starts a vicious circle, ultimately leading to lower educational outcomes. Nevertheless, many participants of this study showed low performance also in calculation speed, so further research is needed to understand the nature of these learning difficulties in BWS.

Sotos and Malan syndromes present cognitive deficits that are similar to those observed in genetic diseases such as Williams syndrome. Interestingly, memory for faces was a relative strength for all groups. The same ability is considered to be strongly impaired in autism, manifesting a lack of interest towards socially relevant information – a core feature of this condition (Riby & Hancock, 2009; Weigelt et al., 2012). Social perception was not found to be a relative weakness of the profile in Sotos syndrome. Instead it was found as a relative strength in Williams syndrome, with a dissociation between low- and high-level socio-cognitive skills. These findings suggest that these conditions show specific socio-cognitive phenotypes that are distinct from autism, although there is a relatively frequent comorbidity observed in Sotos (Lane et al., 2017; Riccioni et al., 2024) and Williams syndromes (Vivanti et al., 2018).

It is important to note for the Sotos syndrome that the presence of a secondary neurodevelopmental disorder (mainly ASD and ADHD) did not result in a different neuropsychological profile. However, participants with average intellectual functioning showed a defective performance in at least one subtest. These results highlight that the genetic and epigenetic alterations associated with Sotos syndrome impact on neurocognitive development even in absence of evident intellectual disability (Harris & Fahrner, 2019). For Sotos and Malan syndromes the difficulties of visual-motor integration reported here and in sensory processing can affect proprioception (Mulder et al., 2020; Smith et al., 2023), thus influencing related dimensions of body perception, from the body schema to body awareness (see Chapter 4).

The study on the Joubert syndrome represents a third model to study cognitive development in rare genetic syndromes with neurological alterations. By comparing groups with distinct brain malformations, it is possible to advance speculations on the neural substrates of specific neuropsychological deficits. As both Sotos and Malan syndromes are associated with structural and functional brain abnormalities (Oishi et al., 2019; Priolo, 2019; G. B. Schaefer et al., 1997; Türkmen et al., 2015), this model can be applied in future research to shed light on the interaction between genes, the brain and observed phenotypes.

Limitations should be acknowledged in interpreting the findings of these studies. The small sample size and the high age variability within and between groups asks for caution in generalizing the results presented here, even though the number of participants recruited was in line with previous studies on cognitive development of these syndromes (Alfieri et al., 2022; Butti, Castagna, et al., 2022; Lane, Milne, et al., 2019). Moreover, all studies adopted a cross-sectional design; longitudinal data are needed to define the specific developmental trajectories of each syndrome. The small sample size also prevented the investigation of specific genotype-cognitive phenotype associations (Mussa, Russo, De Crescenzo, et al., 2016; Serrano-Juárez et al., 2023; Siracusano et al., 2023). Nevertheless, the multi-level analyses, from domains to subtests to intra-individual weaknesses, indicated consistent results for participants with the same syndrome. The adoption of a co-normed battery overcame the methodological limitations of previous studies, obtaining reliable measures of performance for each neuropsychological skill. However, the direct comparison with multiple patient populations might provide a more complex picture of socio-cognitive weaknesses and strengths with respect to specific neuropsychological profiles (Lane, Van Herwegen, et al., 2019b; Morel et al., 2018).

Limitations notwithstanding, these studies provide a first comprehensive description of the neuropsychological profiles of BWS, Sotos and Malan syndromes in developmental ages, and present new information on the reciprocal influence between body and cognition.

4. Body perception in adolescents with overgrowth syndromes: results from a multidimensional assessment

4.1 Introduction

More than half of the individuals with overgrowth syndromes show neonatal or postnatal macrosomia (Brioude et al., 2019). Children with overgrowth syndromes experience structural abnormalities of their bodies from birth. As well, they are often exposed to medical examinations and procedures that interfere with their bodily experience. As mentioned in Chapter 1, a coherent representation of the one's own body starts forming in the early stages of life through the integration of multiple sensory information and (embodied) interactions with the caregivers (De Klerk et al., 2021; Montirosso & McGlone, 2020). Literature has brought evidence of abnormal body perception in children with altered early motor, sensory and more general bodily experiences (Butti et al., 2019; Butti, Montirosso, et al., 2020; Gauduel et al., 2023; Marshall & Meltzoff, 2020). Accordingly, alterations of body experience due to overgrowth syndromes may affect the development of body representation, with effects on social and cognitive functioning (Meltzoff & Marshall, 2020). Adolescence is particularly critical for the perception and representation of one's own body, due to both the physiological changes of puberty and the importance of body in social interaction with peer groups (De Witte et al., 2016; Gatti et al., 2014), and thus might represent a critical window for studying body perception and its effects on social functioning in overgrowth syndromes.

The present study compares adolescents with overgrowth syndromes and healthy peers on a multidimensional, comprehensive assessment of body perception. One's own body image was evaluated through a standardized questionnaire. A stop-distance paradigm was used to assess changes in the extensions of PPS and IPD, which are representations of action and social spaces around the body strictly related to the body schema (Iachini et al., 2014). Interoceptive abilities were examined through a psychophysical task that measured sensitivity to cardiac signals (Schandry, 1981). This task has been used in paediatric populations to study the influence of interoceptive processing on emotion regulation and processing (Koch & Pollatos, 2014). Cardiac sensitivity has been associated with anxiety in healthy and clinical populations (Palser et al., 2018; Pollatos et al., 2009). Lastly, multisensory integration was investigated through a bodily illusion paradigm that assessed different components of body awareness such as self-identification, self-location, and perceived touch location (Cowie et al., 2018; Ionta et al., 2011).

4.2 Materials and methods

4.2.1Participants

Of the whole sample recruited in the project, 32 adolescents ages 11-18 years with overgrowth syndromes participated in the body perception assessment (16 females; age mean = 14.4, SD = 2.4). Of them, 10 had a diagnosis of BWS (8 females; age mean = 13.5, SD = 2.5), 19 of Sotos syndrome (7 females; age mean = 14.5, SD = 2.3) and 3 of Malan syndrome (1 female; age mean = 17.1, SD = 2.4). Inclusion criteria were: i) confirmed diagnosis of overgrowth syndrome, ii) age ranging from 11 to 18 years, iii) absence of severe motor and visual impairments that could interfere with task execution.

Healthy adolescents were recruited as control sample. Inclusion criteria were: i) age 11-18 years, ii) having normal or corrected-to-normal vision (with glasses/contact lenses), iii) having no history of or any form of neurological and psychiatric disorders. Twenty-six participants were included in this control group (19 females; age mean = 13.3, SD = 1.8). For the pc-based task assessing IPD and PPS, six male participants were further recruited in collaboration with master students of the University of Udine, for a total of 32 control participants. Age did not differ significantly between the control and overgrowth-syndromes groups ($t_{62} = 1.65$, $p = 0.104$).

4.2.2 General procedure

Participants completed the full-body illusion (FBI) paradigm in a virtual-reality (VR) laboratory of the Scientific Institute Medea. Next, they moved to a quiet room where they were administered the heartbeat counting task, the time estimation task and the pc-based stop-distance paradigm. This latter was administered on a 15.4-inch LCD monitor (resolution 1024 × 768 pixels; refresh frequency 60 Hz) and kept at eye distance of approximately 50 cm. The monitor was connected to a laptop PC running E-Prime 3® software, which checked for task administration, randomization and response collection. Participants were asked to fill out the Body Uneasiness Test (BUT), a self-report questionnaire about body image disturbances. According to their age, participants (> 15 years) or their parents compiled the Autism Quotient (AQ) questionnaire concerning the presence of autistic traits. All procedures required about 90 minutes to be completed.

For the group with overgrowth syndromes, other clinical measures were also taken into account. They include the presence of preserved vs. delayed cognitive functioning, the performance at social perception subtests assessing theory of mind and affect recognition skills (see Chapter 3 for details), the presence of anxiety problems assessed through a parent-report questionnaire (see Chapter 5 for details), and the body mass index (BMI).

4.2.3 Body Uneasiness Test

The BUT is a self-report questionnaire developed for the screening and assessment of abnormal body image attitudes in adolescents and adults (Cuzzolaro et al., 2006). The questionnaire consists of two separate sections, in which individuals are asked to rate a list of statements on a 6-point Likert scale from 0 = ‘never’ to 6 = ‘always’, with higher rates corresponding to greater body uneasiness. The 34-item BUT A assesses five dimensions of body uneasiness:

- Weight Phobia (WP), as fear of being or becoming fat;
- Body Image Concerns (BIC), evaluating worries related to physical appearance;
- Avoidance (A), concerning body image-related avoidance behaviour;
- Compulsive Self-Monitoring (CSM), testing the compulsive checking of physical appearance;
- Depersonalization (D), measuring feelings of detachment and estrangement towards the own body.

Each dimension is measured as the average score attributed to the corresponding items.

The 37-item BUT B asks to specify uneasiness level towards specific body parts (e.g., hair, teeth) or bodily signs (e.g., blushing, sweating). The BUT B provides a sum of total positive symptoms, namely the number of items rated higher than zero, and the positive symptom distress index, that is the average rating attributed to BUT B items.

Despite the fact it was originally designed for patients with ED, the BUT has shown to detect body image alterations in populations with other psychiatric disorders as well. (Carta et al., 2008).

As the BUT requires comprehension and reflection skills, eight adolescents (five with Sotos syndrome, three with Malan syndrome) were not able to fulfil the questionnaire. Hence, data from 24 adolescents with overgrowth syndromes (14 females; age mean = 14.2, SD = 2.5) and 26 control participants were collected. The two samples were similar in terms of age ($t_{48} = 1.55$, $p = 0.127$) and both had a prevalence of female vs. male participants.

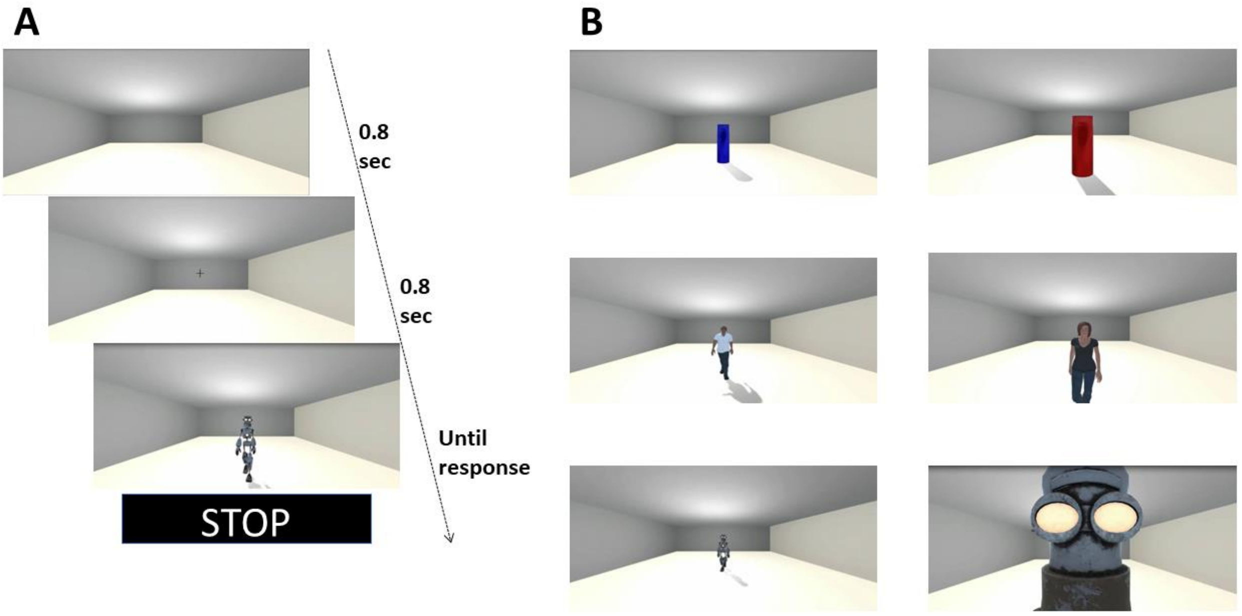
4.2.4 Virtual stop-distance paradigm

A computer-based stop-distance paradigm was developed in collaboration with the University of Lille (Prof. Yann Coello, Dr. Alice Cartaud). On the basis of previous research (Cartaud et al., 2020; Iachini et al., 2014), two tasks were administered to assess comfort- and reachability distance, which are considered as proxies of IPD and PPS, respectively.

The two tasks were presented as separate blocks of a single experiment, in which participants were shown the same videos but they received different instructions. For the comfort-distance block, they were asked to press the space bar when the virtual stimulus was at a comfortable distance for interaction (to interact with it without feeling discomfort). For reachability judgements, participants had to press the space bar when the stimulus was in the correct place to be reached with their hands without effort. The videos were shown in a first-person perspective and displayed an approaching stimulus in an empty room. The stimuli were a red or a blue cylinder, representing a non-social object, a male or a female human character, considered as social stimulus, and a light or a dark robot, a hybrid figure between the object and social stimuli. Each stimulus appeared at the end of the room, corresponding to a virtual distance of 404 cm from the participant's perspective, and then moved closer with a constant velocity of 40 cm/sec. The cylinder movement was created by means of a presentation of 47 pictures with an 8-cm step between each picture. Walking movements of the human and robot stimuli simulated the natural swing of biological motion.

Each trial started with a frame displaying the empty room for 0.8 sec, followed by a fixation cross of the same time length and placed in the same spot where the stimulus would appear. The stimulus would then appear and start moving towards the participants' perspective. When the participant pressed the space bar a next trial started. If the participant did not press the bar, the stimulus disappeared when it was 28 cm from the participant's perspective and the response was not recorded. Trial timelines and examples of the three categories of stimuli at various distances in the virtual room are reported in Figure 9.

Figure 9. Trial timeline and stimuli of the virtual stop-distance paradigm. Panel A represents the trial timeline; panel B represents the two stimuli for each category at different distances.



Ten trials were conducted for each virtual stimulus for a total of 60 trials in each block. Trial and block presentation were randomised. Each block lasted about 10 minutes, with a short break allowed in between.

4.2.5 Heartbeat counting task

In order to assess interoceptive accuracy (IAcc), a heartbeat counting task was proposed. This simple and classic psychophysical task requires participants to count their heartbeats in predetermined time intervals (Dirupo et al., 2020; Schandry, 1981). Specifically, participants were asked to track their heartbeat during three time intervals of 25, 35 and 45 seconds. The actual heartbeats were recorded through a CE-marked wearable device, the E4 wristband (Empatica inc., Cambridge, MA), which allowed the heart pulse to be determined in an unobtrusive way by photoplethysmography (Nelson et al., 2020). E4 reliability in assessing heartrate under non-movement conditions was reported to be comparable to the gold standard electrocardiography (Schuurmans et al., 2020). Offline analysis of interbeat interval and blood volume pulse provided the correct number of heartbeats for each time interval. Participants' responses were then compared to the recorded heartbeats in each interval to obtain an index of IAcc using the following formula:

IAcc = 1- |reported heartbeats - actual heartbeats| / ((actual heartbeats + reported heartbeats)/2)

As a control task, participants were required to count seconds in prespecified time intervals (19, 37, 49 seconds), and their responses were compared to the actual seconds. The total time length of the intervals was the same in the two tasks (105 seconds). An index of time estimation accuracy was calculated in a similar manner to that for the heartbeat (Desmedt et al., 2020; Koreki et al., 2021).

As a measure of awareness of their accuracy, participants were asked to indicate the confidence level of their responses on a VAS, from 0 = 'Not at all' to 10 = 'Very much'.

Before starting the heartbeat counting task, the mean beats per minute (BPM) were recorded in a 10-second interval at rest.

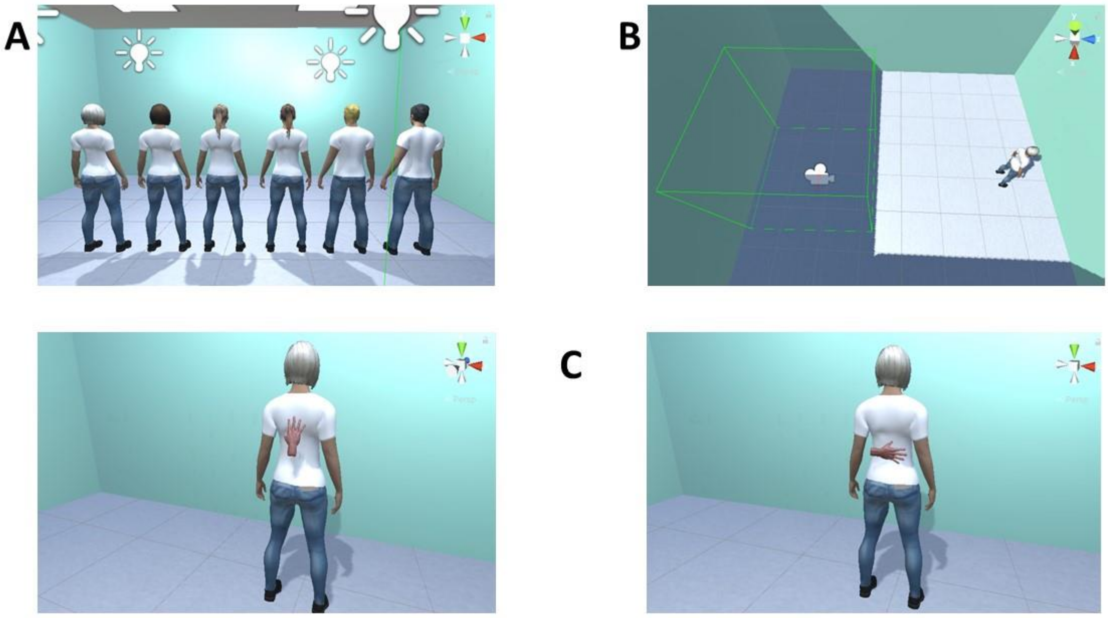
Two participants with moderate-to-severe cognitive disability were not able to carry out the task. As well, participants with an accuracy index < 0.50 in the time estimation task were excluded from the analysis. This criterion was chosen in order to ensure that participants were sufficiently able to count and track time, a prerequisite for executing also the heartbeat counting task (Desmedt et al., 2020). Four participants with overgrowth syndromes and two healthy controls were excluded (overgrowth syndromes N = 26, control participants N = 24).

4.2.6 Full-Body Illusion paradigm

An FBI paradigm already adopted in paediatric populations was adapted to be administered through VR viewers (Cowie et al., 2018). Similar to the rubber-hand illusion, this paradigm uses synchronous or asynchronous visual-tactile stimulation to elicit changes in ownership of the entire body (‘self-identification’), self-location, and perceived touch location (Ehrsson, 2007; Lenggenhager et al., 2007; Scarpina et al., 2019). As it involves the whole body and not only specific body parts, the FBI provides insights into how multisensory integration contributes to a sense of body awareness (Ehrsson, 2020; Zaidel & Salomon, 2023).

The task was created by means of the software Unity (Unity technologies Inc., San Francisco, CA) in collaboration with the bioengineering and robotics department of the Scientific Institute Medea (Silvia Bellazzecca, Dr Eng. Emilia Biffi). First, a virtual room identical to the laboratory where the test was carried out was reproduced. Then, the open-source MakeHuman application was used to create models of male and female avatars. These avatars could have blond or dark hair as well as short or long (only for female avatars) hair, for a total of six different models. All virtual characters wore a white t-shirt and blue jeans. The avatars were then modified through the Blender software to appear as different heights – from 150 to 190 cm. Each avatar was virtually placed 2 m ahead of the participant’s point of view. Lastly, a virtual hand was located on the back of the avatar, adjusting its position according to the avatar’s height. During the task, the virtual hand moved slowly (approximately 5 cm/sec) on the avatar’s back along the vertical or horizontal axis (Figure 10).

Figure 10. Virtual characters and scenarios of the full-body illusion paradigm. Six different models were created (A); avatars were located in the virtual room 2 m ahead of the participant’s point of view (B); two animations displayed a virtual hand stroking the avatar’s back (C), moving along the vertical (left) or the horizontal axis (right).



Each participant stood in the same position of the room and completed: (i) a baseline self-location proprioceptive drift measurement, (ii) one synchronous and one asynchronous test trial (order randomized), and (iii) another baseline self-location proprioceptive drift measurement. After each test trial the self-location drift measurement and a questionnaire were administered. In total, four drift measurements were taken.

The self-location measurement was taken according to the instructions of Cowie and colleagues (2018). Participants wore an eye mask that prevented them from seeing. Then the experimenter guided them 1.5 m backwards from the starting position. The participants were asked to make ‘small, penguin steps’ to prevent the possibility of counting the number of steps taken. With the eye mask still on, they were asked to return to the starting position using normal-sized steps. The proprioceptive drift was taken, measuring the distance in centimetres between the starting and finishing position in the direction of the virtual body. The difference in the proprioceptive drift between baseline and test trials provided an implicit measure of changes in bodily self-location after the illusion. The higher the positive drift, the stronger the illusion of embodiment over the avatar.

After measuring the drift, participants were moved back to the starting point, using a figure-of-eight walking path. As well, they received no feedback regarding their self-location estimation accuracy.

Participants were then asked to wear the Oculus Quest VR-viewers, a commercial headset already used in clinical paediatric populations (Malerba et al., 2023). Participants were informed that they would be stroked on the back by the experimenter while watching a virtual character in the viewer. They were also asked to stand still and to focus on the back of the avatar. The avatar was chosen to match as much as possible the height and hair of each participant.

In the synchronous trial, participants observed the animation with the hand moving along the horizontal axis on the avatar’s back for 2 minutes. The experimenter then stroked the participant’s back in the same way, simultaneously to what was on the screen. The experimenter could watch on a monitor the virtual hand movement in order to synchronize touch velocity. In the asynchronous trial, participants observed the animation with the hand moving along the vertical axis on the avatar’s back for 2 minutes. This time, however, the experimenter still stroked the participant’s back on the horizontal axis, thus creating a conflict between the tactile stimulation and the visual feedback.

After each test trial, participants were asked to keep their eyes closed while the experimenter put the mask on their eyes, and the proprioceptive drift procedure was repeated. When participants were back at the starting point, they were asked to answer questions about their experience on a Likert scale from 0 = ‘No, definitely not’ to 6 = ‘Yes, lots and lots’. The questionnaire was adapted from previous research with the FBI and other bodily illusion paradigms (Cowie et al., 2016, 2018; Lenggenhager et al., 2007). The questions were as follows:

1) While you were being stroked, did it sometimes seem as if you could feel the touch of the hand on the virtual body you saw over there?
2) While you were being stroked, did you sometimes feel like the virtual body you saw over there was your body?
3) While you were being stroked, did it feel like your nose was growing?

4) (only after the second trial) Did you notice any difference between the first and second times you were being stroked?

The two first questions assessed touch referral and sense of ownership over the virtual body respectively. Question 3 was a control question to assess differences in affirmative responding due to cognitive impairments. Question 4 provided a measure of explicit awareness of differences between synchronous and asynchronous stimulations.

One participant with overgrowth syndrome did not complete the procedure due to a cyber-sickness episode, and was thus excluded from the analysis.

4.2.7 Assessment of autistic traits

The Italian version of the AQ was administered to assess traits associated with the autistic spectrum (Auyeung et al., 2008; Baron-Cohen et al., 2006; Ruta et al., 2012). The AQ is a 50-item self- or parent-report questionnaire that evaluates five areas of autism-like behaviours: social skills, attention switching, attention to detail, communication and imagination. Answers are provided on a Likert scale from 0 = ‘Strongly agree’ to 3 = ‘Strongly disagree’, with some items reversely scored. The 10 items of each scale are summed up to obtain a score of autistic traits in that dimension. A total score – the autism quotient – is also calculated by summing all scale scores. The higher the score, the more the autistic traits. Here, as the main interest was on social functioning, only the social skills scale and the total autism-quotient were considered, with higher scores in these variables representing greater problems in social interaction and general autistic traits respectively.

4.2.8 Data handling and statistical analysis

For the body image questionnaire, independent-sample *t*-tests were used to compare the two groups across all scales. As differences between males and females were reported in previous research (Cuzzolaro et al., 2006), *t*-tests with biological sex as a categorical factor were also run across groups.

Regarding the IPD and PPS tasks, the comfort and reachability distances were inserted into a mixed-model ANOVA with group (overgrowth syndromes vs. control) as a between-subject factor, and task (IPD vs. PPS) and stimulus (cylinder, human, robot) as within-subject variables. To explore the influence of the cognitive level on the performance, adolescents with overgrowth syndromes were split into two groups, one with an average or above-average cognitive level, and one with cognitive impairments. These two cognitive-level groups were inserted as categorical factors in a mixed-model ANOVA with task and stimulus as within-subject variables. Spearman's *r* correlations were used to investigate associations between BMI and the comfort and reachability distances with various stimuli. A Buffer Space (BS) index was calculated by subtracting the reachability distance from the comfort distance for the human stimuli. This index represents the buffer zone around the action space that offers a sense of security and comfort during social interaction (Coello & Cartaud, 2021). A Social Sensitivity (SS) index was calculated as the mean difference between human and object stimuli for both PPS and IPD. This index represents the expected preference (i.e., shorter distances) towards social vs. non-social stimuli (Iachini et al., 2014). These indexes were correlated with the total autism-quotient and with problems in social skills assessed by the questionnaire. Only in the clinical group, the BS and SS indexes were also correlated with the performance at the theory of mind and affect recognition subtests.

For the heartbeat counting task, a preliminary *t*-test was conducted to detect potential differences of the BPM between groups. Then, the IAcc and time estimation indexes were inserted as dependent variables in a mixed-model ANCOVA, with group as a between-subject factor, task as a within-subject variable and BPM as covariate. Significant effects of the covariate were explored by means of Spearman's *r* correlations. Within each group, correlations were performed also between the VAS scores and the corresponding accuracy indexes to assess interoceptive awareness. The IAcc and time estimation indexes were correlated with anxiety problems and affect recognition abilities in the group with overgrowth syndromes.

For the FBI paradigm assessing body awareness, proprioceptive drifts of synchronous and asynchronous stimulations were inserted as a within-subject variable in a mixed-model ANOVA with group as a categorical factor. As the self-identification questionnaire scores represented ordinal responses to a single question, non-parametric tests were used to analyse them. Within each group, Wilcoxon paired-sample tests were used to verify differences between synchronous and asynchronous stimulations; Mann-Whitney *U* tests were adopted for between-group analyses.

All analyses were performed with Statistica 8.0 (Statsoft, Tulsa, OK), with the significance threshold set at $p < 0.05$ for all effects. Duncan's post-hoc test was used to explore significant interactions. Effect sizes were reported as partial eta squared (n^2_p) for ANOVA designs and as Cohen’s d for pairwise comparisons, adopting conventional cut-off of 0.01, 0.06, and 0.14, and of 0.2, 0.5, and 0.8 for small, medium, and large effect sizes, respectively, (Lakens, 2013).

4.3 Results

4.3.1 Body image disturbances

The scores obtained in the BUT A and B are presented in Table 13, divided by group and biological sex.

Table 13. Scores obtained at the Body Uneasiness Test. Scores are reported as mean (SD).

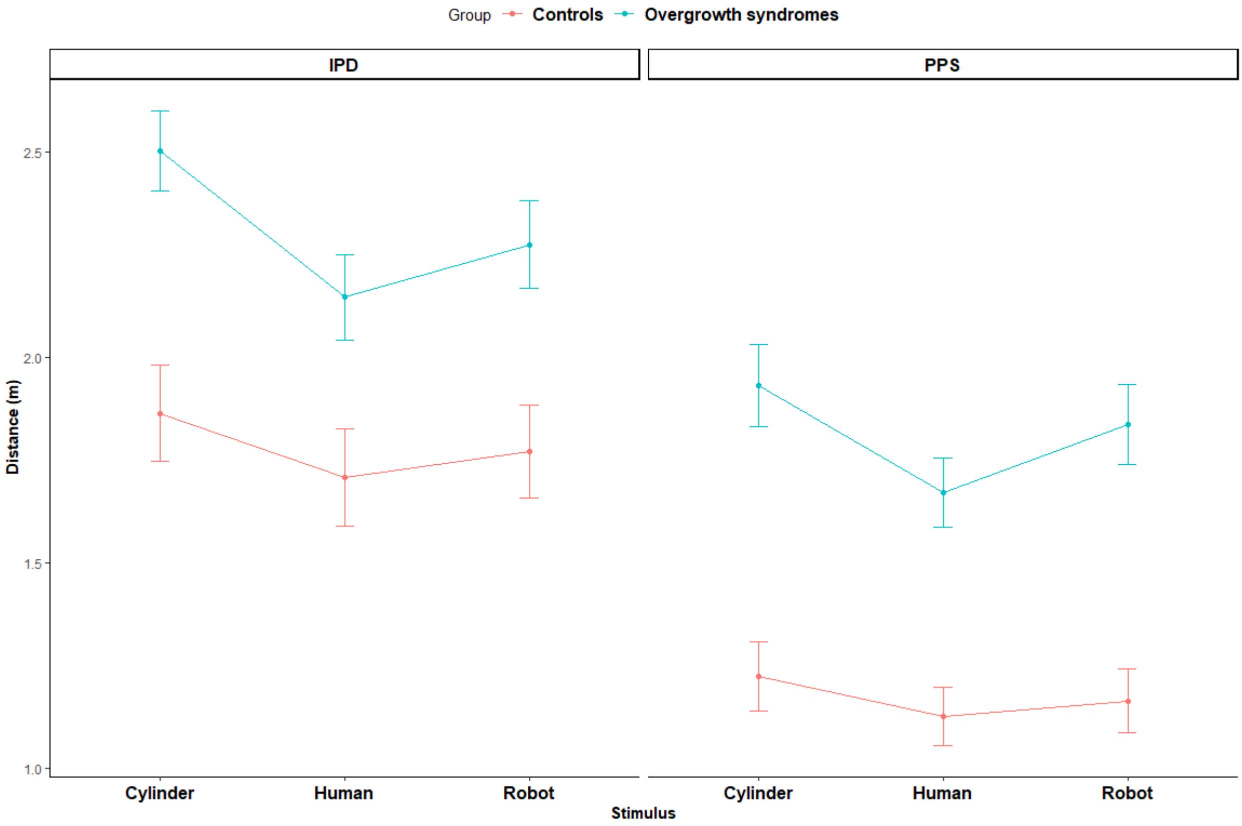
	Overgrowth syndromes			**Control participants**		
	Male	Female	Total	Male	Female	Total
N	10	14	24	7	19	26
BUT A						
Global severity index	0.3 (0.4)	1 (1.1)	0.7 (0.9)	1.1 (0.6)	1.5 (0.9)	1.4 (0.8)
Weight phobia	0.3 (0.4)	1.2 (1.4)	0.8 (1.2)	1.6 (0.7)	2 (1.2)	1.9 (1.1)
Body image concerns	0.4 (0.5)	1 (1.2)	0.7 (1)	1.4 (0.8)	1.8 (1)	1.7 (0.9)
Avoidance	0.3 (0.8)	0.6 (0.7)	0.5 (0.8)	0.6 (0.7)	0.6 (0.7)	0.6 (0.7)
Compulsive self-monitoring	0.3 (0.8)	1.1 (1.1)	0.8 (1)	1.2 (0.8)	1.8 (1)	1.6 (0.9)
Depersonalization	0.2 (0.3)	0.7 (1)	0.5 (0.8)	0.5 (0.3)	0.9 (1)	0.8 (0.9)
BUT B						
Positive symptom total	1.6 (2.5)	10 (10)	6.3 (8.9)	13.3 (10.6)	18 (8.4)	16.7 (9.1)
Positive symptom distress index	0.1 (0.2)	0.7 (0.8)	0.4 (0.7)	0.7 (0.6)	1.3 (0.8)	1.1 (0.8)

The independent-sample *t*-tests revealed that control participants obtained higher scores than adolescents with overgrowth syndromes across all scales (all $t > 2.87$, all $p < 0.007$, all Cohen's $d > 0.80$) with the exception of avoidance ($t_{48} = 0.45$, $p = 0.657$, Cohen's $d = 0.13$) and depersonalization ($t_{48} = 1.37$, $p = 0.176$, Cohen's $d = 0.39$). As well, female participants reported higher scores in all scales (all $t > 2.01$, all $p < 0.05$, all Cohen's $d > 0.67$) except for avoidance ($t_{48} = 0.70$, $p = 0.485$, Cohen's $d = 0.21$).

4.3.2 Peripersonal space and interpersonal distance

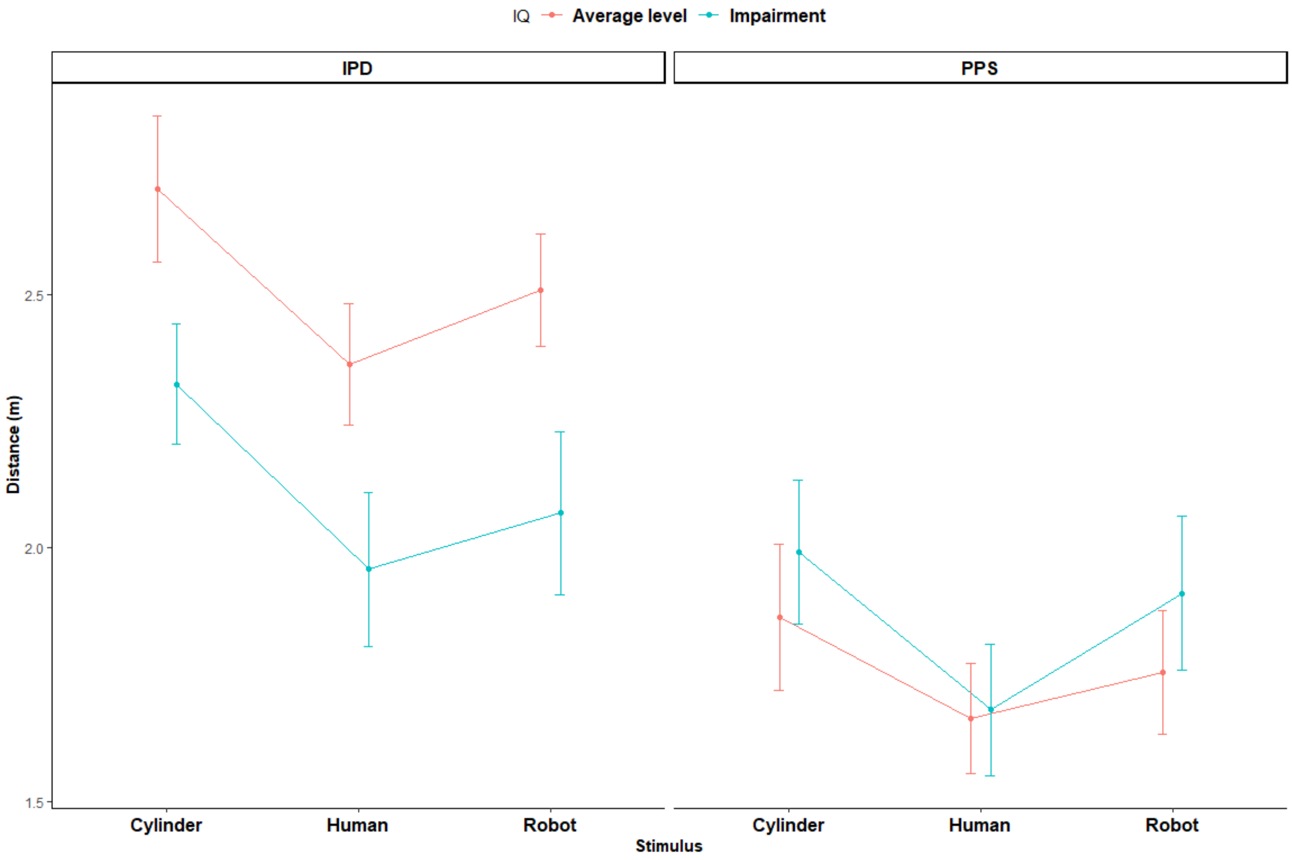
The mixed-model ANOVA revealed a significant main effect of group ($F_{1,62} = 25$, $p < 0.001$, $n^2_p = 0.29$), indicating that the group with overgrowth syndromes preferred larger distances than the control participants (2.06 ± 0.08 vs. 1.48 ± 0.08). The main effects of task ($F_{1,62} = 69.32$, $p < 0.001$, $n^2_p = 0.53$) and stimulus ($F_{2,124} = 31.48$, $p < 0.001$, $n^2_p = 0.34$) were also significant, further characterized by their significant interaction ($F_{2,124} = 3.59$, $p = 0.030$, $n^2_p = 0.05$). These findings confirm that reachability distances were shorter than comfort distances for all stimuli (1.49 ± 0.06 vs. 2.05 ± 0.07) and that larger distances were kept from cylinders (1.88 ± 0.06) across the two tasks, compared to robot (1.76 ± 0.06) and human (1.66 ± 0.06) stimuli. Distances for robots were larger than those for human stimuli (all $p < 0.001$). The stimuli x group interaction was also significant ($F_{2,124} = 5.54$, $p = 0.049$, $n^2_p = 0.08$), showing that in the control sample there was no difference between robot and human stimuli ($p = 0.202$). Importantly, the preference (i.e., shorter distance) for human compared to object stimuli was detected in both groups (all $p < 0.002$). The performance of adolescents with overgrowth syndromes and control participants at the stop-distance paradigm is reported in Figure 11.

Figure 11. Interpersonal distance (IPD) and peripersonal space (PPS) in overgrowth syndromes and control participants. Bars represent SEM.



When splitting the group with overgrowth syndromes according to cognitive level, the main effects of task ($F_{1,30} = 46.14$, $p < 0.001$, $n^2_p = 0.61$) and stimuli ($F_{2,60} = 21.51$, $p < 0.001$, $n^2_p = 0.42$) were still significant. Importantly, the main effect of cognitive level was non-significant ($F_{1,30} = 0.87$, $p = 0.359$, $n^2_p = 0.03$), but the task x cognitive level interaction was found as significant ($F_{1,30} = 11.50$, $p = 0.002$, $n^2_p = 0.27$). Duncan's post-hoc tests clarified that comfort distances were larger than reachability distances across participants with overgrowth syndromes (all $p < 0.023$). The group with average cognitive level showed larger comfort distances (2.53 ± 0.13) than the group with cognitive impairments (1.76 ± 0.13), while such a difference was not detected for reachability-distance judgements (2.12 ± 0.13 vs. 1.86 ± 0.12) (Figure 12).

Figure 12. Interpersonal distance (IPD) and peripersonal space (PPS) in adolescents with overgrowth syndromes with average cognitive level and with cognitive impairments. Bars represent SEM.



In the group with overgrowth syndromes, the BMI was significantly correlated with reachability distances regardless of the type of stimulus (all $r > 0.35$, $p < 0.047$), while no significant correlations emerged between BMI and comfort distances (all $r < 0.17$, $p > 0.380$). These results indicate that a larger BMI was associated with larger action (PPS) but not social (IPD) spaces in adolescents with overgrowth syndromes. Only in the control group, higher difficulties in social skills were significantly associated with larger BS ($r = 0.38$, $p = 0.030$), and with shorter SS ($r = -0.49$, $p = 0.005$). That is, control participants with higher problems in social interaction show enlarged comfort compared to reachability distances and fewer preferences towards human stimuli. Conversely, these correlations were non-significant in the sample with overgrowth syndromes (all $r < 0.16$, all $p > 0.393$). Also, significant correlations were found between the performance at the affect recognition subtest and both the BS ($r = 0.47$, $p = 0.006$) and SS ($r = -0.44$, $p = 0.013$). These correlations indicate that adolescents with overgrowth syndromes and with higher abilities of facial affect recognition prefer larger comfort distances and show fewer preferences towards human stimuli. No significant correlations emerged with the theory of mind subtest (all $r < 0.34$, all $p > 0.058$). A summary of correlation results for the BS and SS indexes is reported in Table 14.

Table 14. Correlation analysis between performance at the stop-distance paradigm and social functioning. Spearman's *r* values are reported for each correlation between BS and SS indexes and scales of social functioning in the two samples. Asterisks indicate significant correlations.

		Buffer space	**Social sensitivity**
Overgrowth syndromes	*Social skill problems*	0.02	-0.16
	Autism quotient	-0.1	0.01
	Theory of mind	0.34	-0.08
	Affect recognition	0.47*	-0.44*
Control participants	*Social skill problems*	0.38*	-0.49*
	Autism quotient	0.22	-0.32

4.3.3 Interoceptive accuracy

BPM, interoceptive and time estimation accuracy indexes are shown in Table 15.

Table 15. Results of the interoceptive accuracy task. Data are reported as mean (SD).

	Overgrowth syndromes	**Control participants**
BPM	82 (10)	79 (12)
Interoceptive accuracy	0.59 (0.23)	0.47 (0.24)
Time estimation accuracy	0.75 (0.15)	0.82 (0.12)

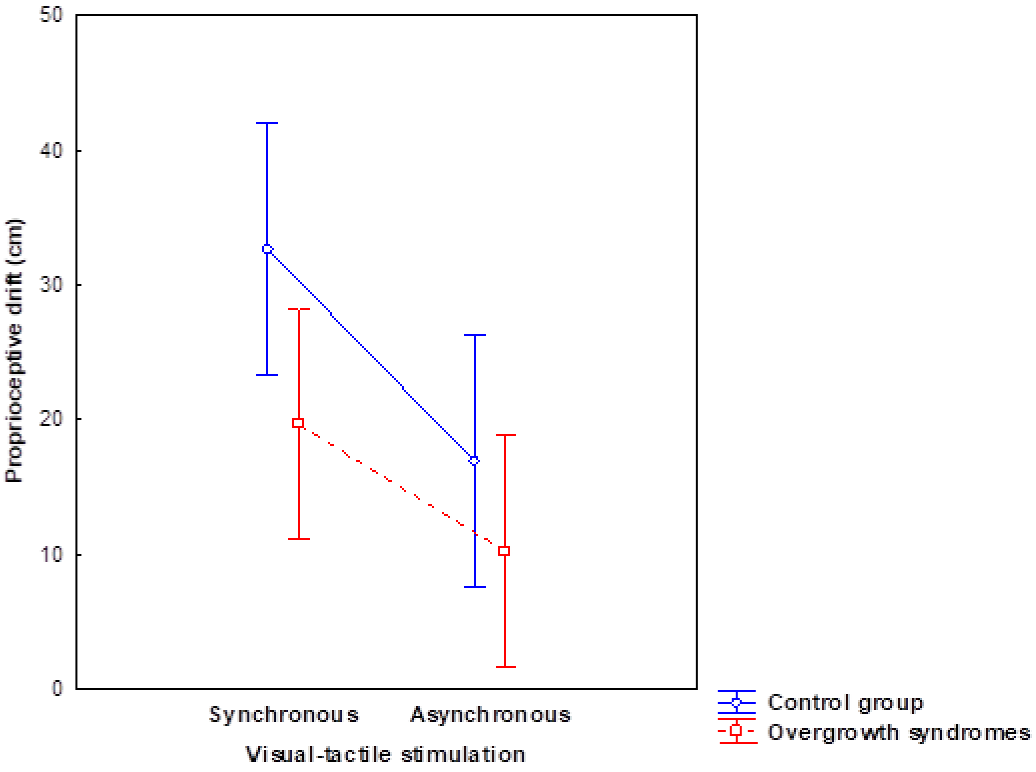
The preliminary t-test confirmed that the two groups had comparable BPM ($t_{48} = 0.73$, $p = 0.470$). The analysis revealed a significant effect of the covariate BPM ($F_{1,47} = 5.93$, $p = 0.019$, $n^2_p = 0.11$), with higher BPM associated with lower IAcc ($r = -0.31$, $p = 0.028$) but not with time estimation accuracy ($r = -0.05$, $p = 0.731$). Although the main effects of group and task were non-significant (all $F < 1.18$, all $p > 0.284$), their significant interaction pointed to a different performance of the two groups in the tasks ($F_{1,47} = 6.84$, $p = 0.012$, $n^2_p = 0.13$). Post-hoc tests clarified that both groups had lower IAcc than time estimation indexes (all $p < 0.006$). While both groups showed comparable ability to track time ($p = 0.171$), adolescents with overgrowth syndromes were better than control participants in counting their heartbeats ($p = 0.026$).

Concerning the estimation of accuracy awareness, a significant correlation between IAcc and the VAS scores emerged in the group with overgrowth syndromes ($r = 0.40$, $p = 0.043$), but the same relationship was not significant in the control group ($r = 0.20$, $p = 0.342$). Conversely, time estimation accuracy and the corresponding VAS score were not correlated in both groups (all $r < 0.21$, all $p > 0.325$). No significant correlations emerged between IAcc and anxiety symptoms nor abilities to recognise facial expressions (all $r < |0.21|$, all $p > 0.307$).

4.3.4 Body awareness

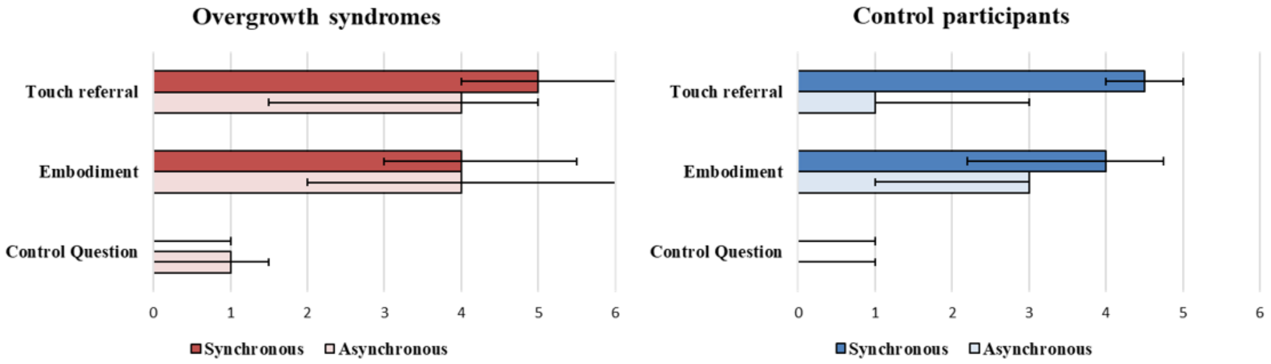
The analysis on the self-location drift yielded a significant main effect of stimulation ($F_{1,55} = 7.55$, $p = 0.008$, $n^2_p = 0.12$), indicating that synchronous visual-tactile stimulation resulted in larger proprioceptive drift compared to asynchronous stimulation (26 ± 6 vs. 14 ± 6). Neither the main effect of group nor its interaction with stimulation were significant (all $F < 0.69$, all $p > 0.409$). Thus, on an implicit level, the illusion was similarly elicited in both groups (Figure 13).

Figure 13. Proprioceptive drift in the full-body illusion paradigm in adolescents with overgrowth syndromes and control participants. Bars represent SEM.



The answers given by participants with overgrowth syndromes to the questions on touch referral, embodiment, and to the control question (i.e., nose length) were not significantly different between synchronous and asynchronous stimulations (all $Z < 1.82$, all $p > 0.068$). Control participants reported higher touch referral ($Z = 3.63$, $p < 0.001$) and embodiment ($Z = 2.65$, $p < 0.008$) feelings after synchronous compared to asynchronous stimulation, with the exception of the control question ($Z = 0.77$, $p = 0.441$). The between-group comparisons highlighted that the two groups attributed similar scores after synchronous stimulation (all $Z_{adjusted} < 1.74$, all $p > 0.080$). After asynchronous stimulation, adolescents with overgrowth syndromes expressed higher ratings than control participants on the touch-referral ($Z_{adjusted} = 3$, $p = 0.003$) and embodiment ($Z_{adjusted} = 2.71$, $p = 0.007$) questions, but not in the control question ($Z_{adjusted} = 1.56$, $p = 0.118$). No difference emerged for the awareness question ($Z_{adjusted} = 0.37$, $p = 0.712$). To summarize, on an explicit level, participants with overgrowth syndromes did not detect differences between synchronous and asynchronous visual-tactile stimulations in the sense of touch referral and embodiment (Figure 14).

Figure 14. Bar chart of the responses to the self-identification questionnaire after synchronous and asynchronous visual-tactile stimulations. For each question the median and interquartile range are reported, divided by group and stimulation.



4.4 Discussion

This study has investigated multiple dimensions of body perception in adolescents with overgrowth syndromes compared to healthy peers. Adolescents with overgrowth syndromes reported lower scores than the control group in the questionnaire assessing concerns towards the own body image. In the stop-distance paradigm assessing reachability and comfort distances, the group with overgrowth syndromes showed larger action and social spaces than control participants. Interestingly, participants with overgrowth syndromes and average cognitive abilities exhibited larger comfort but not reachability distances compared to adolescents presenting cognitive impairments. This result and the correlation analyses indicated enlarged social distances in adolescents with overgrowth syndromes. Also, the clinical sample showed an increased accuracy in detecting cardiac signals compared to the control group. The FBI paradigm elicited the illusion in both groups. However, for the self-identification questionnaire, adolescents with overgrowth syndromes reported greater touch referral and embodiment of the avatar after the asynchronous stimulation. Overall, the findings suggest differences in body perception between adolescents with overgrowth syndromes and healthy peers, which may affect their social functioning.

Adolescents with overgrowth syndromes reported less disturbances of the body image than their healthy peers. As expected, females tended to experience more concerns about their body image than male adolescents (Cuzzolaro et al., 2006). The high prevalence of female individuals in the control sample may at least partially explain the results about lesser body image concerns in adolescents with overgrowth syndromes. This issue should be addressed in future research with sex-matched groups. The BUT assesses mainly the affective dimensions of body image that are strictly related to ED-symptomatology, such as weight phobia and compulsive self-checking (McLean & Paxton, 2019). Interestingly, no between-group differences emerged in scales that describe behaviours not specific to ED (i.e., avoidance, depersonalization). While overgrowth syndromes appear to not be associated with ED-related body image disturbances, adolescents with these conditions may still have concerns or fears towards their physical appearance. As for other congenital diseases that involve atypical facial features, such as cleft palate/lip, their concerns may be related to specific body parts rather than affecting the whole body image (Crerand et al., 2020, 2023; Kelly & Shearer, 2020). For instance, BWS concerns may regard the tongue or the limb affected by hemihyperplasia. Accordingly, a recent survey-based study on adults with BWS documented that most participants had experienced differences with their mouth or teeth and suffered from the perception of being different from others (Drust et al., 2023). This evidence suggests that the perceived stigma due to atypical bodily features may play a role in the social functioning of adolescents with overgrowth syndromes.

The findings from the stop-distance paradigm support this perspective. Indeed, adolescents with overgrowth syndromes, especially without cognitive impairments, showed a specific enlargement of the preferred social distance. While this enlargement of social compared to action spaces and the index of sensitivity towards human stimuli were associated with problems in social skills in the control sample, these correlations were non-significant in the group with overgrowth syndromes. These results suggest that adolescents with these conditions and average cognitive functioning may choose to keep larger distances during social interactions, regardless of their social skills. But why would they prefer larger social distances? Previous studies have documented that IPD adjustments are particularly sensitive to perceived emotional states in others, as is primarily reflected in their facial expressions, and to the approach-avoidance tendencies related to morality judgements (Cartaud et al., 2020; Coello & Cartaud, 2021). Accordingly, in our sample with overgrowth syndromes, a greater ability to recognize facial affect expressions was associated with an enlargement of social distance and with fewer preferences towards the human stimuli. A dissociation between PPS and IPD was also found in keeping with previous studies in healthy and clinical populations (Candini et al., 2019; Patané et al., 2017). For overgrowth syndromes, action space may be enlarged due to the participant's (overgrown) body features, as suggested by the correlations between PPS and BMI. An expansion of PPS has been reported, for instance, in women during pregnancy, as the sensorimotor representation of action space adapts to the bodily change (Cardini et al., 2019). Nevertheless, adolescents with overgrowth syndromes tend to prefer larger social distances, an evidence suggesting an altered permeability of their interpersonal space (Candini et al., 2020, 2021). Overall, these findings sustain the hypothesis that is the perception of the other's judgement towards their appearance that mainly affects social distance regulation in adolescents with overgrowth syndromes, rather than alterations of the sensorimotor representation of their body. This is the case especially in individuals with higher cognitive and social perception abilities.

The results from the heartbeat counting task indicate that adolescents with overgrowth syndromes may be more accurate and aware than control peers in reading their own internal bodily signals. A comparable performance of the clinical and control groups at the control task of time estimation rules out that between-group differences in cognitive abilities may account for this result. These findings seem to suggest that adolescents with overgrowth syndromes may pay more attention to bodily internal signals, perhaps because they are often exposed to medical examinations and procedures. Even though interoception is thought to play a role in emotional regulation and social cognition (Gao et al., 2019; Herbert & Pollatos, 2012), the IAcc index was not associated with either anxiety problem, assessed through a parent-report questionnaire, nor affected emotion recognition abilities. This lack of a correlation may partially depend on the adopted measures. Previous studies have documented that interoception as indexed by the heartbeat counting task is not related to the direct rating of emotional pictures (Ferentzi et al., 2022), and that interoceptive abilities contribute to a more general, superficial appraisal of emotional features (e.g., unpleasantness) rather than characterizing specific states (Dirupo et al., 2020). It is notable that the IAcc index was low in both groups, a result that limits speculations on potential social and cognitive implication of (increased) interoceptive accuracy in overgrowth syndromes.

The findings from the last experiment characterise further body perception in adolescents with overgrowth syndromes. The results on the proprioceptive drift confirm that the bodily illusion was elicited in both groups. But adolescents with overgrowth syndromes reported similar levels of touch referral and embodiment after both stimulations. No difference was found in the control question, assessing the tendency to affirmative answers due to the cognitive impairments presented by many adolescents with overgrowth syndromes. These results suggest atypical multisensory integration of visual-tactile information in overgrowth syndromes, which may alter the bodily-Self boundaries. Recent clinical studies have started to document the presence of abnormal sensory processing in Sotos and Malan syndromes (Mulder et al., 2020; Smith et al., 2023). These abnormalities regard mainly proprioception and touch sensitivity, two sensorial dimensions that are strongly involved in the FBI paradigm. As well, the findings of the neuropsychological assessment document weaknesses in visual-motor integration in Sotos syndrome. The results reported here might thus provide first evidence of how these abnormalities in sensory processing and multisensory integration affect higher cognitive-affective processes underlying body awareness and representation.

The study has some limitations. First, the limited and unequal number of individuals for each syndrome prevented the analysis of likely differences in body perception between these conditions. While Malan and Sotos syndromes have similar phenotypes and cognitive impairments, BWS is not usually associated with cognitive disability (Brioude et al., 2019). The group with cognitive impairments included only one individual with BWS. These differences introduce a certain degree of distortion when considering the impact of cognitive level on the performance at the stop-distance paradigm. There was a different distribution of age and sex in the subgroups with BWS and Sotos syndrome as well. With the exception of the stop-distance paradigm, the control sample was smaller than the group with overgrowth syndromes. As well, the control group had a high prevalence of female participants. The findings reported here should thus be confirmed in age- and sex-matched samples with the same number of participants. Concerning the stop-distance paradigm, the administration of the tasks through a PC monitor limits the ecological validity of the results compared to lab-based and VR-based tasks (Candini et al., 2019; Simões et al., 2020). The tasks adopted here do not manipulate perspective (first- vs. third-person perspectives) and sense of agency (active vs. passive movements), conditions that affect PPS and IPD differently (Candini et al., 2017; Iachini et al., 2014). The heartbeat counting task has been questioned in its reliability as index of interoception (Körmendi et al., 2022; Zamariola et al., 2018) but see (Ainley et al., 2020). Interoception should be considered as a multidimensional construct (Garfinkel et al., 2015), while here only interoceptive accuracy and awareness were considered. For the FBI paradigm, despite the creations of different models to be matched with each participant's features, the stimuli did not represent the actual participant. As well, the participant's body was not represented in the virtual scenario, so that when looking at their own body the participant would not have seen anything. These conditions may have influenced the effectiveness of illusory ownership over the virtual body (Cowie et al., 2018; Scarpina et al., 2019). Despite these limitations, this study provides the first, multidimensional description of body perception in adolescents with overgrowth syndromes, which can pave the way for future investigations of body representation, social functioning and sensory processing in these genetic conditions.

5. Socio-emotional development in children and adolescents with overgrowth syndromes: emotional-behavioural problems and autistic traits in Beckwith-Wiedemann, Sotos and Malan syndromes

5.1 Introduction

Socio-emotional development results not only from age-appropriate social and emotional competences, but also from the adjustment to the environment (Bohlin & Hagekull, 2009). When assessing socio-emotional development, the presence of emotional problems is usually conceptualized as internalizing or externalizing behaviours (Achenbach et al., 2016). Internalization refers to anxious, depressed, fearful behaviours and psychosomatic complaints. Externalization refers to the expression of emotional distress through external, disruptive reactions such as aggressive and rule-breaking behaviours. Some research on socio-emotional development is related to the comorbidities with psychopathological disorders affecting social functioning, particularly with ASD. Accordingly, previous studies have mainly investigated socio-emotional development in overgrowth syndromes in terms of emotional-behavioural problems and frequency of autism-like behaviours.

Socio-emotional development has long been neglected in clinical practice and research on BWS. A first study in 2008 documented greater emotional problems and difficulties in interaction with peers in school-age children with BWS (Kent et al., 2008). The study also suggested an increased risk of ASD in BWS. Although the recommendations of the Italian scientific committee of AIBWS asked for a wider consideration of psychosocial adjustment in children with BWS (Mussa, Russo, Larizza, et al., 2016), this appeal went largely unheeded. Studies focusing on specific features of BWS, such as macroglossia, abdominal wall defects, and increased tumoral risk, have provided indirect evidence of emotional-behavioural problems and psychosocial risk in children with BWS (Burnett et al., 2018; Duffy et al., 2018; Shipster et al., 2012). A recent survey in an adult population with BWS documented that more than a third of the sample faced psychiatric issues in their lives, and that negative social experiences, such as bullyism, teasing and social isolation were frequently reported (Drust et al., 2023). These results call for a deeper understanding of emotional-behavioural problems and social functioning in children with BWS.

Abnormalities in social behaviour were previously reported in Sotos syndrome (Cole & Hughes, 1994; de Boer et al., 2006; Sarimski, 2003), but only in recent years have emotional-behavioural problems been systematically investigated (Lane et al., 2016; Sheth et al., 2015). Evidence has been brought forward of an association between Sotos syndrome and ASD, even though their behavioural phenotypes may not overlap (Riccioni et al., 2024). Other emotional-behavioural problems have been documented in Sotos syndrome, such as aggressive behaviours, attention problems, impulsivity, and anxiety (Lane et al., 2016; Sheth et al., 2015; Siracusano et al., 2023).

Characterisations of the behavioural profile of Malan syndrome have been proposed in recent studies. Evidence of comorbidity with ASD is conflicting, with studies suggesting an increased risk of ASD in Malan syndrome (Mulder et al., 2020) and others suggesting only minimal signs of this disorder (Alfieri et al., 2023). This literature also highlights comorbidities with anxiety, ADHD, social and attention problems.

Below is an investigation of socio-emotional development in overgrowth syndromes through standardized questionnaires. The first study reports data of preschool-age children with BWS collected before the start of the main project on overgrowth syndrome. In the first years of life psychomotor development and emotional-behavioural functioning are strictly intertwined (Di Rosa et al., 2016). Accordingly, developmental difficulties and emotional-behavioural problems are examined in this study. The second and third studies complete the project presented in Chapters 3 and 4. Here, the presence of emotional-behavioural problems and autistic traits in school-age children and adolescents with BWS, Sotos and Malan syndromes are investigated.

5.2 Psychosocial difficulties in preschool-age children with Beckwith–Wiedemann syndrome[3]

5.2.1 Materials and methods

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[3] This study is reported in a published paper (Butti, Castagna, et al., 2022).

5.2.1.1 Participants

Thirty participants were recruited in collaboration with AIBWS. Inclusion criteria were: i) confirmed clinical and/or genetic diagnosis of BWS, ii) age > 1 ½ year and < 6 years, iii) absence of documented neurological and psychiatric conditions (e.g. epilepsy, ASD). This latter criterion could verify whether preschool children with BWS were afflicted with psychosocial difficulties that were not secondary to the presence of neurodevelopmental disorders. Seven participants were excluded, corresponding to the 19% of the sample. This percentage is in line with recent literature documenting the prevalence of neurodevelopmental disorders in children younger than eight year-old in USA (Straub et al., 2022). A description of socio-demographic and clinical variables of the sample is reported in Table 16.

Table 16. Socio-demographic and clinical variables of the sample of preschool-age children with BWS.

	Mean (SD)/N (%)	Notes
Demographic variables		
Sex (male)	8 (27%)	
Age (years)	3.3 (1.4)	
Familiar variables		
Maternal age (years)	37.7 (4.6)	
Maternal education (years)	13.7 (3.3)	
Paternal age (years)	41.2 (5.8)	
Paternal education (years)	13.3 (3.2)	
Socio-economic status	57 (19)	Corresponding to a medium-high level according to Hollingshead (1975)
Siblings	0.9 (0.7)	
Perinatal variables		
Birth Weight (g)	3427 (643)	
Birth Length (cm)	51 (4)	

Prematurity	13 (43%)	13 moderate-to-late preterm (32 to 37 weeks)
Genetic diagnosis		
Altered expression of *IGF2*	2 (7%)	
Altered expression of *CDKN1C*	21 (70%)	
Paternal Uniparental Disomy	5 (16%)	
Other	2 (7%)	1 altered methylation of both IC1 and IC2, 1 unknown
Main clinical features		
Macroglossia	24 (80%)	
Omphalocele /abdominal wall defects	12 (40%)	
Birthweight > 2 ds above the mean	10 (33%)	
Neonatal hypoglycaemia	10 (33%)	
Lateralized overgrowth	13 (43%)	
Tumour onset	1 (3%)	1 haemangioendothelioma
Clinical index according to the Consensus statement (2018)	5.1 (1.8)	

5.2.1.2 General procedure

The families affiliated with AIBWS received a letter from the president of the Association informing them of the possibility of participating in the study. All interested families were then sent an envelope containing: a) an informed consent form; b) an ad-hoc information form to collect socio-demographic and clinical variables; c) the two questionnaires assessing emotional-behavioural problems and different developmental areas. Parents were asked to sign the informed consent form and fulfil all the documents before sending them back via mail. All procedures of the study were in accordance with the Declaration of Helsinki and were approved by the Ethical Committee of the Scientific Institute, IRCCS E. Medea. Please note that data collection was carried out before the COVID-19 pandemic.

5.2.1.3 Assessment of emotional-behavioural problems

Mothers filled out the Child Behavior Checklist (CBCL 1½-5), an internationally adopted, standardized questionnaire designed to assess various types of behavioural and emotional problems in children aged 1½-5 years (Rescorla, 2005). The CBCL 1½-5 provides the following seven scales: emotional reactivity; anxiety/depression; somatic complaints; withdrawal; sleep problems; attention problems; aggressive behaviours. Raw scores of each scale were summed up and then transformed into T-scores (mean = 50, SD = 10) according to the normative values, so as a higher score indicated higher behavioural problems in that scale. Moreover, the CBCL 1½-5 provides cut-off scores according to percentile distribution so as to determine children scoring in the borderline and in the clinical range. The term clinical is used here as being synonymous with clinically abnormal, thus referring to children who show consistent problems in their behaviour, without any psychopathological evaluation of these problems having been made.

5.2.1.4 Assessment of child's development

The child's development was assessed using the Child Development Inventory (CDI (Doig et al., 1999; Ireton & Glascoe, 1995)), a parent-report questionnaire that describes children's abilities from 15 months to 6 years of age. To obtain a profile of child's development, the items were summed up into the following scales: social development; self-help; gross-motor; fine-motor; expressive language; language comprehension; letters knowledge; numbers knowledge. Raw scores obtained by summing the items of each scale were converted into T-scores according to the mean expected for each age group reported in the original manual. Higher T-scores indicated higher developmental level in that scale. According to the normative manual, scores ≤ 1.5 SD and ≤ 2 SD were considered as falling within the borderline and the clinical range. Similar to the CBCL 1½-5, the clinical term adopted here does not reflect a diagnosis of developmental delay, rather it helps to identify those children whose development is questionable and who (could) show less expected age-related competences in each specific area.

5.2.1.5 Data handling and statistical analysis

Preliminarily, descriptive statistics and the percentage of children exceeding the borderline and clinical thresholds were calculated for each scale of the two questionnaires. For the scales in which the number of children exceeding the borderline threshold was > 20%, chi-squared tests were adopted among dummy variables of the two questionnaires to verify whether the same individuals had behavioural problems and difficulties in specific developmental domains.

Consecutively for the two questionnaires, Spearman's r correlations and Student's t-tests were run for each scale with selected, background continuous variables and categorical factors, respectively. To control for socio-demographic variables sex, age, and socio-economic status (SES) were inserted into the analyses. As previous literature (Brioude et al., 2019; Burnett et al., 2018; Shipster et al., 2012) points to clinical variables as risk-factors for psychosocial development, these analyses included prematurity, neonatal hypoglycaemia, abdominal wall defects and macroglossia, and the clinical score obtained by each child according to the Consensus statement (Brioude et al., 2018).

For each test, a false-discovery rate analysis (FDR) was conducted to control for multiple testing, thus correcting the accepted p-value according to the number of comparisons (Benjamini & Hochberg, 1995). Significant background variables were inserted as covariates into RM-ANCOVAs separately for the two questionnaires, with scale as within-subject variable. Significant interaction effects were further examined with Tukey HSD post-hoc tests. The α value was set at $p < 0.05$ for all statistical tests. Effect sizes for the ANCOVAs were reported as partial Eta squared (η^2_p), adopting conventional cut-offs of $\eta^2_p = .01, .06$; and .14 for small, medium, and large effect sizes, respectively. All analyses were performed by means of the Statistica software version 8 (Statsoft, Tulsa, USA).

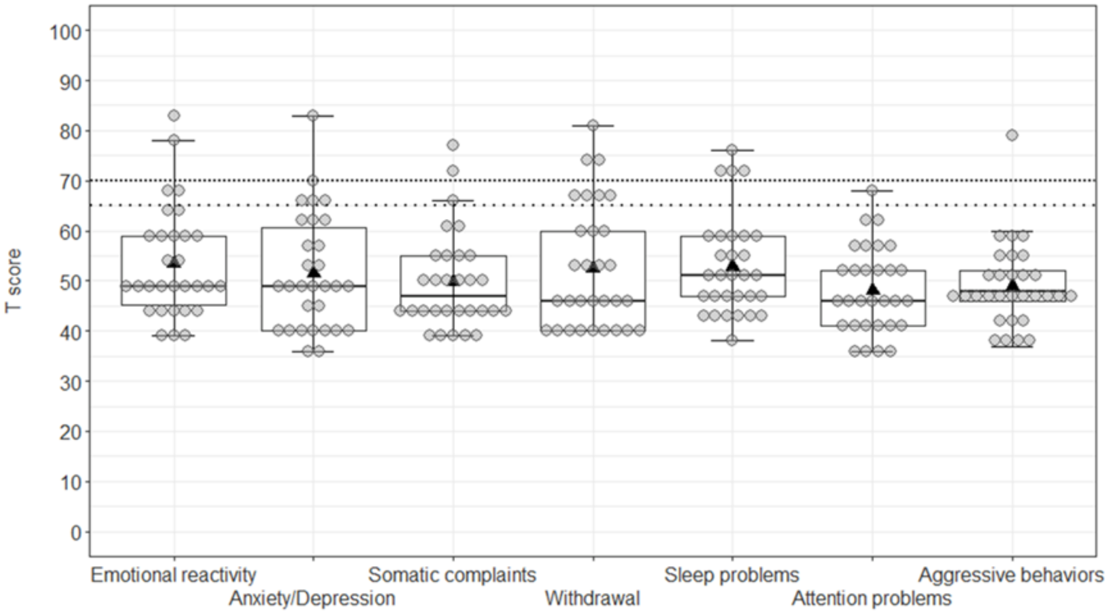
5.2.2 Results

For the CBCL 1½-5, significant correlations emerged between age, emotional reactivity ($r = 0.45$, $p = 0.012$) and anxiety/depression scales ($r = 0.61$, $p < .001$). All other findings for either continuous or categorical variables were non-significant (all $r < |0.39|$, all $t < 2.65$, all $p \geq 0.013$).

For The CDI, age was significantly correlated with social development (r = -0.79, $p < 0.001$), self-help (r = -0.45, p = 0.013), gross-motor (r = -0.45, p = 0.014), and letters knowledge scales (r = -0.47, p = 0.009). A significant association emerged between familiar SES and numbers knowledge scale (r = 0.53, p =.003), while all other correlations and *t*-test analyses were non-significant after controlling for multiple testing (all $r < |0.42|$, all $t < 2.26$, all p >.020).

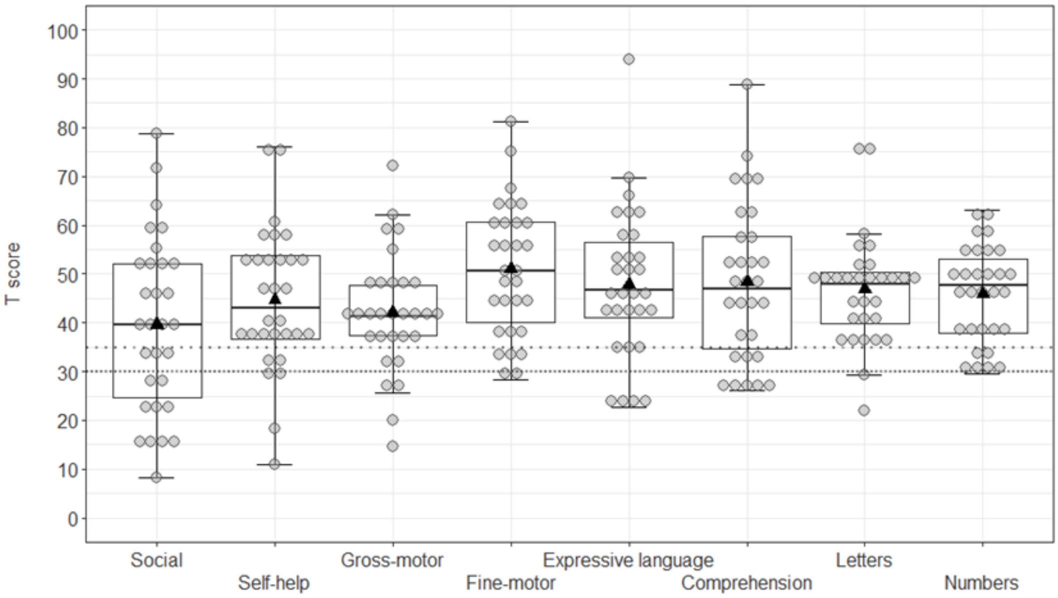
For the CBCL 1½-5, the ANCOVA confirmed a significant effect of the covariate age ($F_{1,28}$ = 9.98, $p < 0.001$, η^2_p =0.26), indicating that the more advanced the age, the higher the scores obtained at the CBCL/1½-5 (r = 0.51, p = 0.004). All other effects were non-significant (all $F < 1.62$, all $p >$ 0.144), thus highlighting no differences between the scales (Fig. 15).

Figure 15. Boxplot of T-scores at the CBCL 1½-5 of preschool-age children with BWS. Grey circles represent individual scores, black triangles indicate group mean scores; lines with wide and dense dots show, respectively, the borderline and clinical thresholds.



For the CDI, the ANCOVA confirmed a significant age effect ($F_{1,27}$ = 17.22, $p < 0.001$, η^2_p = 0.39), with a decrease in T-scores in older children across the scales (r = -0.64, $p < 0.001$). The interaction scale x age was significant ($F_{7,189}$ = 3.32, p = 0.002, η^2_p = 0.11). The Tukey HSD post-hoc comparisons indicated lower scores at the social development scale than at the fine-motor (p = 0.001) and language comprehension (*p* = 0.036) scales. Lower T-scores were detected at the gross-motor compared to the fine-motor scale (*p* = 0.026). All other effects were non-significant (all *F* < 1.20, all *p* > 0.178) (Fig. 16).

Figure 16. Boxplot of T-scores at the CDI of preschool-age children with BWS. Grey circles represent individual scores, black triangles indicate group mean scores; lines with wide and dense dots show, respectively, the borderline and clinical thresholds.



The chi-squared tests did not highlight significant results (all $\chi^2 < 0.72$, all *p* > 0.398) regarding the possible associations between behavioural problems and specific developmental difficulties.

5.2.3 Discussion

The presence of emotional-behavioural problems and difficulties in specific developmental domains was examined in preschool-age children with BWS through two standardized parent-report questionnaires.

In contrast with the study of Kent and colleagues (Kent et al., 2008), the results regarding the emotional-behavioural problems highlighted neither a group score lower than the expected mean nor significant differences between the scales. This inconsistency might depend on the age range of the samples, since here only preschool-age children were included, while Kent and colleagues recruited children from preschool age to adolescence. Higher behavioural problems may arise as age increases.

Almost 7% of the children in the study of Kent and colleagues had a diagnosis of ASD while here the presence of documented neuropsychiatric diagnosis was considered as an exclusion criterion. Nevertheless, when looking at the individual performance, seven out of thirty children exhibited problems of social withdrawal. Previous research has documented that children with chronic diseases show less prosocial behaviour and more emotional problems such as anxiety and depressive symptoms (Meijer et al., 2000; Pinquart & Shen, 2011). Interestingly, increasing age was associated with greater emotional reactivity and anxiety/depression problems. Overall, these results suggest that preschool-age children with BWS often display emotional problems that increase with age, even in absence of neurodevelopmental disorders.

The results highlighted developmental difficulties in the social domain, which became more pronounced in older children. 43% of children obtained scores exceeding the borderline threshold for social development, with even ten out of thirty children scoring within the clinical range. In keeping with previous findings on other chronic illness conditions (Martinez et al., 2011; Pinquart & Teubert, 2012), the present study corroborates that children with BWS at preschool ages can show problems in social interactions, which become more pronounced in older children (Kent et al., 2008).

It is worth noting that social withdrawal problems were independent from developmental difficulties in the social domain or in other scales. Both emotional-behavioural functioning and psychomotor development are aspects worthy of being monitored by caregivers, clinicians, and educational professionals.

For the CDI, a significant difference was detected between gross-motor and fine-motor skills, with lower scores obtained for the former. This result might depend on overgrowth conditions typical of the syndrome (Brioude et al., 2018), which would mainly affect gross-motor abilities, such as walking, running or climbing. This discrepancy, however, should be taken into account for screening and assessment of psychomotor development in the first years of life, even considering that seven out of thirty children scored beyond the borderline threshold in that scale.

With the exception of age, no other socio-demographic and clinical variables were associated with emotional-behavioural and developmental problems. These findings do not include risk factors such as prematurity and neonatal hypoglycaemia. To summarize, preschool-age children with BWS often exhibit psychosocial difficulties, which might may be influenced by their experience of living with a rare disorder that requires complex medical assistance since the first years of life.

5.3 Emotional-behavioural problems and autistic traits in school-age children and adolescents with Beckwith–Wiedemann syndrome

5.3.1 Materials and methods

5.3.1.1 Participants and general procedure

Of the 29 participants administered with the neuropsychological assessment, 24 participants aged 6-18 were included in this study (15 females; mean age = 10.2, SD = 3.3; see Chapter 3 for further demographic and clinical information). Parent-report and/or self-report standardized questionnaires were used to evaluate the presence of autistic traits and emotional-behavioural problems.

5.3.1.2 Assessment of autistic traits

The AQ questionnaire was administered to assess the presence of autistic traits (see Chapter 4 for a detailed description). Slightly different cut-offs predicting the presence of ASD have been proposed for children (4-11), adolescents (12-15) and adult versions of the AQ. Here, the cut-off of 76 on the total quotient was chosen as most of the sample was administered with the child-AQ. This cut-off has demonstrated high sensitivity (95%) and specificity (95%) in identifying children with ASD (Auyeung et al., 2008), however the AQ is a non-clinical instrument designed for research purposes and it cannot be used for clinical diagnosis of ASD.

5.3.1.3 Assessment of emotional-behavioural problems

Parents filled out the CBCL 6-18 (Achenbach, 2011). This questionnaire provides slightly different scales from the CBCL 1½-5, which represent the following emotional-behavioural problems: anxiety/depression, social withdrawal, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviours, aggressive behaviours. The scores of specific scales were clustered into two aggregated scales, internalization (anxiety/depression, social withdrawal, somatic complaints) and externalization (rule-breaking behaviours, aggressive behaviours), that indicate the tendency to problematise a situation as an internal problem and focus on oneself, or to react externally (Achenbach et al., 2016). All raw scores were converted into T-scores (mean = 50, SD = 10) according to the normative values, so as a higher score indicated higher behavioural problems in that scale. The borderline and clinical cut-offs were adopted to detect children with specific emotional-behavioural problems for each scale.

5.3.1.4 Data handling and statistical analysis

Descriptive statistics were calculated including the percentage of children exceeding the borderline, clinical thresholds for each CBCL scale, and the cut-off for the total AQ.

For the CBCL aggregated scales (i.e., internalization and externalization) and the total AQ, Spearman's *r* correlations and Student's *t*-tests were run with age and sex, respectively. To verify differences due to the presence of a secondary diagnosis of neurodevelopmental disorder (N = 6), this factor was inserted as a group factor in the Student's *t*-tests with internalization, externalization and total AQ as dependent variables. To further investigate into emotional-behavioural problems and whether they were associated with autism-like behaviours, Spearman's *r* correlations were run between the total AQ and the aggregated scales of the CBCL.

Next, differences in the CBCL aggregated scales were investigated by means of Student's *t*-tests, while the main scales were inserted as within-subject variable into a RM-ANOVA. Bonferroni post-hoc tests were used to analyse within-subject differences.

5.3.2 Results

The scores obtained at the AQ questionnaire are reported in Table 17.

Table 17. Autistic traits in school-age children with BWS.

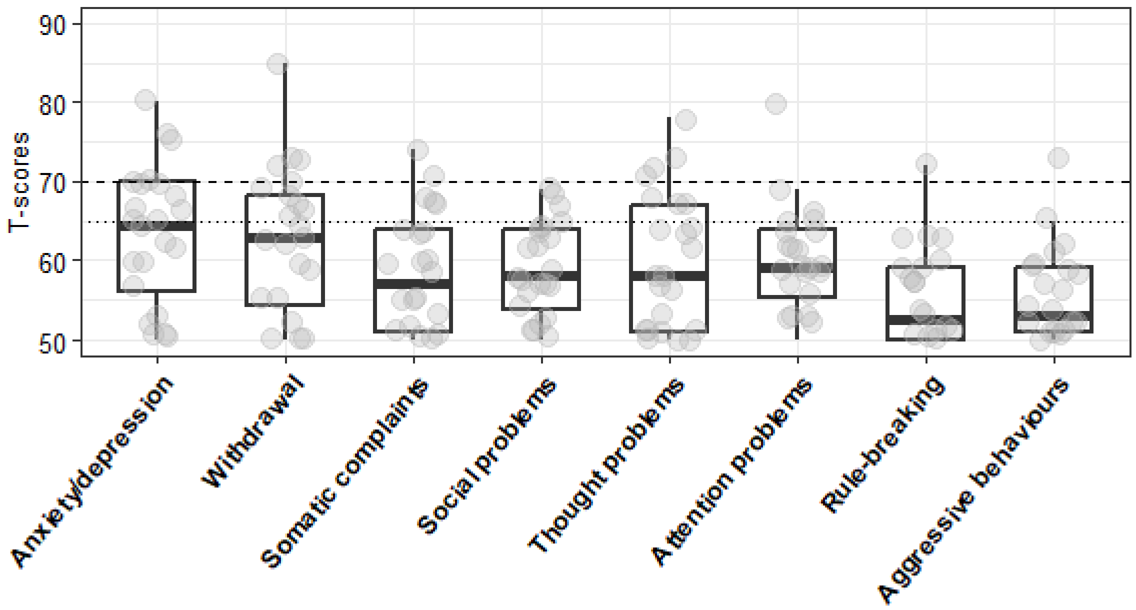
	Mean (SD)
Social skills	9.7 (3.7)
Attention switching	12.8 (4)
Attention to detail	12 (5.9)
Communication	10.2 (4.3)
Imagination	10.9 (4.5)
Total autism quotient	55.6 (11.7)

The mean autism quotient was well below that of the cut-off. Only one participant obtained a score above this cut-off.

No differences between male and female participants emerged in internalization, externalization and the total AQ (all $t < 1.30$, all $p > 0.209$). The correlations with age were non-significant (all $r < 0.33$, all $p > 0.125$). The presence of a neurodevelopmental disorder diagnosis did not affect these variables (all $t < 1.25$, all $p > 0.224$). Neither internalization nor externalization were associated with the total AQ (all $r < 0.19$, all $p > 0.386$).

The significant *t*-test on the aggregated scales ($t_{46} = 3.70$, $p = 0.001$, Cohen's $d = 1.07$) indicated greater problems for internalization (mean = 62.5, SD = 9.6) than externalization (mean = 53.0, SD = 8.4). Accordingly, 16 participants (67%) had internalization problems, while only four (17%) obtained borderline or clinical scores in externalization. It is interesting to note that among these four children, three showed internalization problems. The standardized scores obtained at the CBCL 6-18 scales are represented in Figure 17.

Figure 17. Boxplot of T-scores at the CBCL 6-18 of school-age children with BWS. Grey circles represent individual scores; lines with wide and dense dots show, respectively, the borderline and clinical thresholds.



The RM-ANOVA indicated significant differences between scales ($F_{7,161} = 4.63$, $p < 0.001$, $\eta^2_p = 0.17$). That is, higher scores emerged in anxiety/depression and in social withdrawal than in rule-breaking and aggressive behaviours (all $p < 0.008$). The group mean scores fell within the normal range across all scales. Half of the sample (50%) exhibited problems in the anxiety/depression scale, with seven and five children showing scores beyond the borderline and clinical thresholds, respectively. Even in the social withdrawal scale almost half of participants (42%) were above the borderline threshold. A relatively high percentage of participants showed thought problems (29%). Conversely, only one child showed problems above the clinical threshold in both rule-breaking and aggressive behaviours, and another participant reached the borderline threshold in aggressive behaviours.

5.3.3 Discussion

The findings reported here integrate the results of the previous study on preschool-age children (see Section 5.2) regarding internalization problems in children with BWS. Internalization problems are mainly represented by anxiety symptoms and low-esteem feelings such as sadness, emotional stress, feeling lonely, and by social withdrawal behaviours like shyness and difficulty in adapting to new contexts.

An increased risk for internalization problems has been previously reported in research about paediatric chronic illness (Pinquart & Shen, 2011; van de Pavert et al., 2017). The presence of multiple physical problems may elevate children's risk of depression symptomatology, even in comparison to other children seeking mental health care (Wolock et al., 2020). As BWS involves a wide range of physical problems that require ongoing medical attention, there are various potential pathways through which children with these conditions may develop depressive and anxiety symptoms. Overall, the frequent hospitalizations, medical examinations and even surgical interventions are stressful experiences that can lead to increased anxiety and depression in school-age children (Mabe et al., 1991). The risk of embryonal tumours implies an important emotional burden for children with BWS and their families (Duffy et al., 2018). The macroglossia influences physical appearance as well as feeding, speech and drooling function (Shipster et al., 2012). Hemyhiperplasia may affect gross-motor skills and the possibility of participation in recreational and sport activities (Butti, Castagna, et al., 2022). These issues lead children with BWS to feel 'different', putting a strain on their self-esteem (Drust et al., 2023). The perception of being different may result also in increased shyness and social withdrawal.

A previous study of Kent and colleagues (2008) reported a high prevalence of emotional-behavioural problems in BWS, especially with regard to interaction with peers. These issues were related by authors to an increased incidence of ASD. The results of the current study strongly challenge this hypothesis, as only one participant showed above-threshold autistic traits and no association was found between internalization problems and autism-like behaviours. Even though social anxiety and withdrawal are core features of autistic behaviour (Kuusikko et al., 2008; Spain et al., 2018), the nature of these problems should be considered as not related to autism in BWS.

A longitudinal study across diverse childhood chronic conditions reported that externalization problems were higher in those conditions with an onset before the age of 7 years (Määttä et al., 2022). However, externalization problems are rare in the current study. The group mean score was close to the minimum value. A possible speculation for this inconsistency is that children with BWS tend to control their external reactions in order to cope with frequent medical examinations. Lesser aggressive and rule-breaking behaviours may be functional for these children and their families as access to hospitals is required several times a year (Compas et al., 2012). However, this coping strategy may lead to the development of phobias or to obsessive-like thoughts, as suggested by the relatively high incidence of thought problems.

Contrary to the first study on preschool-age children, here age was not associated with internalization problems. This result suggests that as early as six years of age, children with BWS may exhibit anxiety symptoms, depressive feelings and social withdrawal. School entry represents a critical event and exacerbates these emotional-behavioural problems, that should be carefully monitored by clinicians and educational professionals (Bell et al., 2016).

5.4 Emotional-behavioural problems and autistic traits in school-age children and adolescents with Sotos and Malan syndromes

5.4.1 Materials and methods

5.4.1.1 Participants and general procedure

Of the sample with Sotos syndrome administered with the neuropsychological assessment, all but one 5-year-old participant were included in this study (N = 28, 9 females; mean age = 12.5, SD = 3.7; see Chapter 3 for further demographic and clinical information). All six participants with Malan syndrome completed the procedures. As for BWS, the CBCL 6-18 and the AQ questionnaires were administered in order to evaluate emotional-behavioural problems and autistic traits, respectively.

5.4.1.2 Data handling and statistical analysis

The analyses within the Sotos syndrome group followed the same plan of analysis applied to the BWS group (see Section 5.3.1.4). In order to control differences in intellectual abilities, the sample was split into two subgroups: severe/moderate/mild intellectual disability (N = 15, 4 females; mean age = 11.4, SD = 3.9) or borderline/average cognitive functioning (N = 13, 5 females; mean age = 13.8, SD = 3.1). This group factor was inserted in Student’s *t*-tests with internalization/externalization problems and total AQ as dependent variables. The same tests were conducted considering the presence (N = 14, 2 females; mean age = 11.1, SD = 4.2) or absence (N = 14, 7 females; mean age = 13.9, SD = 2.5) of a neurodevelopmental disorder as categorical factor. As age and total AQ were found to be significantly associated with emotional-behavioural problems, these variables were inserted as covariates in a RM-ANCOVA with the CBCL scales as within-subject variable.

Due to the limited sample size, only descriptive statistics were calculated for Malan syndrome.

5.4.2 Results

For both syndromes, the scores obtained at the AQ questionnaire are reported in Table 18.

Table 18. Autistic traits in school-age children with Sotos and Malan syndromes.

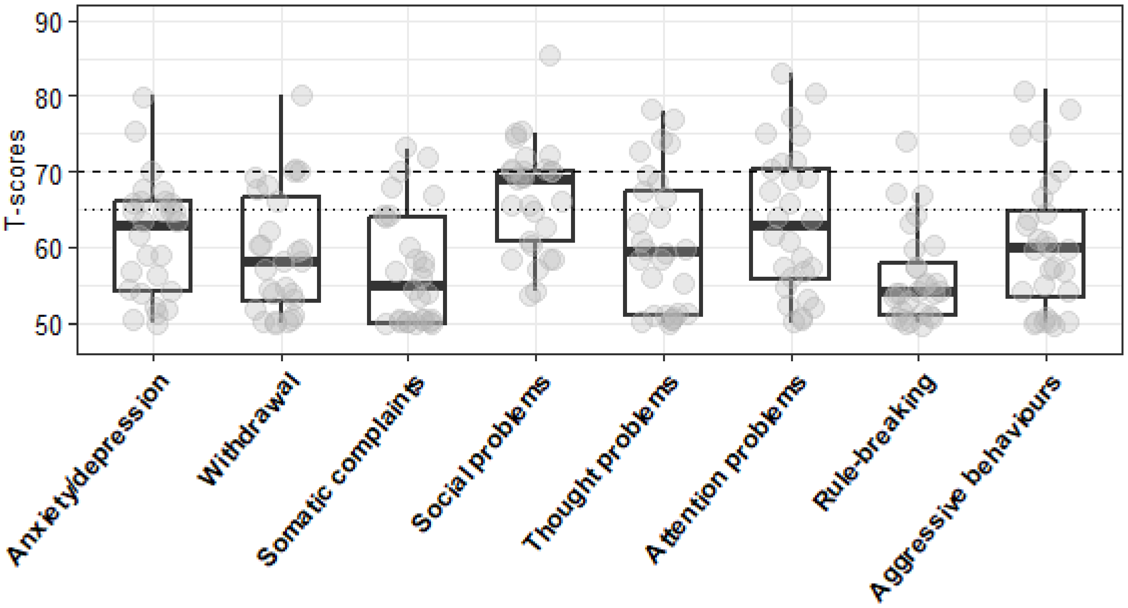
	Sotos syndrome Mean (SD)	**Malan syndrome** Mean (SD)
Social skills	12.8 (6)	13.2 (5.2)
Attention switching	17.4 (6.1)	17.7 (2.7)
Attention to detail	12.3 (4.5)	7.3 (6.4)
Communication	16.3 (6.2)	18.3 (5.1)
Imagination	17.8 (6.4)	19.8 (1.8)
Total autism quotient	76.6 (22.8)	76.3 (10.8)

Both syndromes obtained group mean scores at the cut-off. The total AQ was beyond this cut-off in more than half of the sample with Sotos syndrome (57%), and all but one participant with Malan syndrome. Lower scores were recorded in the attention-to-detail scale in both groups, especially in Malan syndrome, while higher scores were observed in communication and imagination.

Within the group with Sotos syndrome, no sex differences were found in internalization, externalization and total AQ (all $t < 1.53$, all $p > 0.139$). Conversely, children with neurodevelopmental disorders showed greater externalization problems ($t_{26} = 2.50$, $p = 0.019$, Cohen's $d = 0.95$) and autistic traits ($t_{26} = 2.15$, $p = 0.041$, Cohen's $d = 0.81$). There was no difference in internalization ($t_{26} = 1.69$, $p = 0.104$, Cohen's $d = 0.64$) between the groups with or without a secondary diagnosis. In a similar vein, children with intellectual disability exhibited higher autistic traits (t_{26} = 2.38, *p* = 0.025, Cohen's *d* = 0.90) than the subgroup with borderline or average intellectual functioning. Such a difference was not significant for internalization and externalization (all *t* < 1.38, all *p* > 0.179). A significant negative correlation emerged between age and externalization problems (*r* = -0.47, *p* = 0.012), indicating that there was a decrease of externalizing behaviours in older ages. The correlations between age and both internalization and total AQ were non-significant (all *r* < |0.20|, all *p* > 0.33). The total AQ was significantly associated with both internalization (*r* = 0.64, *p* < 0.001) and externalization problems (*r* = 0.57, *p* = 0.002).

For Sotos syndrome, the presence of internalization (mean = 60, SD = 9.6) and externalization problems (mean = 57.5, SD = 9.9) was comparable across the sample (t_{54} = 0.97, *p* = 0.336, Cohen's *d* = 0.26). Internalization problems were reported in more than half of the participants (64%), while 43% exhibited externalizing behaviours above the borderline threshold. The standardized scores obtained at the CBCL 6-18 scales are represented in Figure 18.

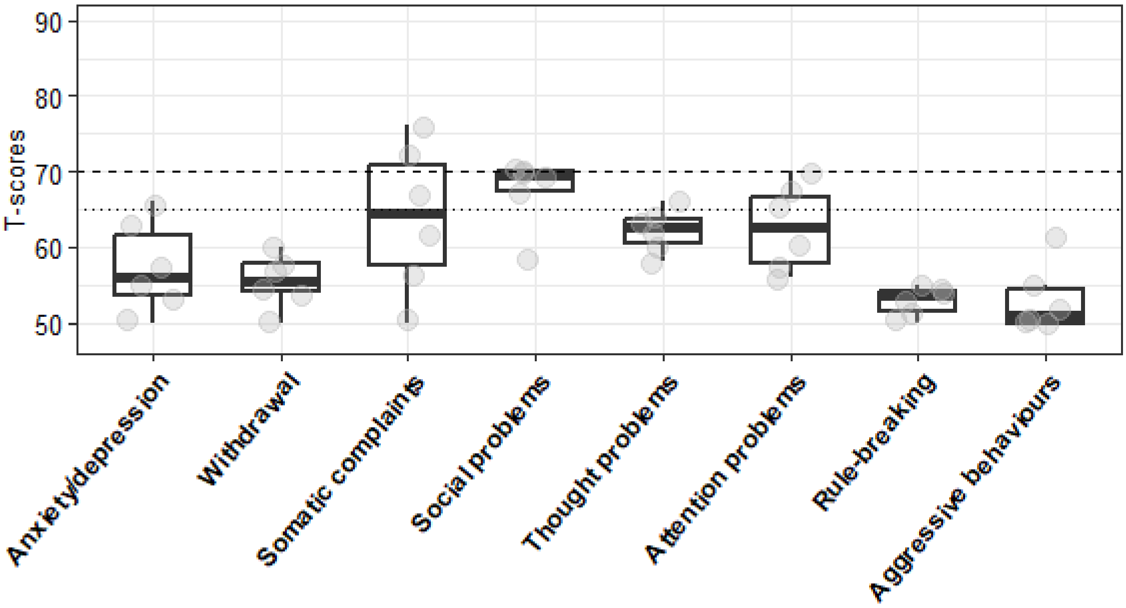
Figure 18. Boxplot of T-scores at the CBCL 6-18 of school-age children with Sotos syndrome. Grey circles represent individual scores; lines with wide and dense dots show, respectively, the borderline and clinical thresholds.



ANCOVA yielded significant main effects of the covariates age and total AQ. Age was negatively associated with attention problems (r = -0.54, p = 0.003) and aggressive behaviours (r = -0.44, p = 0.018), while other correlations were non-significant (all $r < |0.38|$, all $p > 0.05$). Higher autistic traits were associated with higher problems across all scales ($0.39 <$ all $r < 0.64$, all $p < 0.034$), with the exception of rule-breaking behaviours (r = 0.25, p = 0.193). The main effect of scale was non-significant ($F_{7,175}$ = 1.71, p = 0.108, η^2_p = 0.06). Its significant interaction with age allowed for the exploration of between-scale differences with post-hoc tests. The social problems scale was the only one with a group mean over the borderline threshold, and it obtained higher scores than all other scales (all $p < 0.010$), with the exception of attention problems (p = 0.596). This latter scale was reported as more problematic than somatic complaints (p = 0.001) and rule-breaking behaviours ($p < 0.001$). The scale with the lowest mean score was rule-breaking behaviours and was rated as less problematic than all other scales (all $p < 0.050$) except somatic complaints ($p > 0.999$) and social withdrawal (p = 0.596). On an individual level, the lowest percentage of children with scores above the borderline threshold were observed in rule-breaking behaviours (11%) and somatic complaints (18%). In all other scales, at least one quarter of the sample showed behavioural problems, with the highest percentage in social problems (67%). Aggressive behaviours were present in seven children (25%), while anxiety/depression was the most frequent problem (46%) among internalization behaviours.

For Malan syndrome, descriptive statistics showed greater internalization (mean = 59.5, SD = 8.4) than externalization (mean = 50.7, SD = 7.2) problems, with two participants falling above the clinical threshold and one above the borderline threshold in internalization. Conversely, only one participant obtained a score at the borderline threshold in externalization. The standardized scores obtained at the CBCL 6-18 scales are represented in Figure 19.

Figure 19. Boxplot of T-scores at the CBCL 6-18 of school-age children with Malan syndrome. Grey circles represent individual scores; lines with wide and dense dots show, respectively, the borderline and clinical thresholds.



Social problems had the highest mean score. Five out of six participants fell beyond the borderline threshold. Among internalization scales, somatic complaints received the highest mean score with three participants above the cut-off. A similar pattern was recorded for attention problems. Conversely, all participants were in the normal range in both externalizing behaviour scales (i.e., rule-breaking and aggressive behaviours).

5.4.3 Discussion

This study adds to previous literature that indicates increased risks of behavioural problems and autistic features in Sotos (Sheth et al., 2015; Siracusano et al., 2023) and Malan syndromes (Alfieri et al., 2023).

The findings clarify that in both syndromes autistic traits are often present, with greater autism-like behaviours in the communication and imagination scales. It is likely that these results depend on the striking language impairments and intellectual disability associated with these conditions, particularly with Malan syndrome (Alfieri et al., 2022; Priolo et al., 2018). Accordingly, the presence of intellectual disability in Sotos syndrome was associated with higher autistic traits. A similar result was reported in a recent study adopting the gold standard ADOS checklist to assess autistic symptoms (Riccioni et al., 2024). Again, autistic traits were associated with emotional-behavioural problems.

Internalization problems were observed in more than half of the sample with Sotos syndrome, while externalization problems were slightly below 50%. In line with previous literature (Lane et al., 2016; Sarimski, 2003), anxiety and depressive symptoms were relatively frequent among internalization behaviours. Regards externalization, aggressive behaviours reached the borderline threshold in a quarter of the sample. This is a relatively low frequency compared to previous studies that pointed to aggressive behaviours and tantrums as a common feature of Sotos syndrome (Mauceri et al., 2000; Sheth et al., 2015). As suggested by Lane and colleagues (2016), this discrepancy may depend on the overgrown size typical of this syndrome. Aggressive behaviours may be perceived as particularly problematic and draw the attention of families and clinicians, even if limited in frequency.

The highest score was observed in the social problems scale in both syndromes, as reported in previous studies adopting the same standardized questionnaire (i.e., CBCL) (de Boer et al., 2006; Finegan et al., 1994). Difficulties in social functioning have been consistently documented and associated with autism-like behaviours in Sotos syndrome (Lane et al., 2017; Lane, Van Herwegen, et al., 2019b; Sarimski, 2003). But it is notable that the CBCL social problems scale includes motor and language deficits. Clumsiness and language impairments are often present in Sotos syndrome (Ball et al., 2005; Baujat & Cormier-Daire, 2007; Lane, Van Herwegen, et al., 2019b). So too in the Malan syndrome (Alfieri et al., 2022, 2023). These features explain, at least partially, the higher scores observed in social problems.

Attention problems were detected in a wide part of the sample with Malan and Sotos syndromes, according to the frequent comorbidity with ADHD (Alfieri et al., 2023; Lane et al., 2016; Siracusano et al., 2023). This result is partially in line with the results of the neuropsychological assessment (Chapter 4), that revealed deficits in inhibitory control in more than half of the sample with Sotos syndrome. However, the relationship between behavioural impulsivity and inhibitory control is complex and heterogeneous among different neurodevelopmental disorders (Mirabella, 2021). Further studies are needed to elucidate whether difficulties in cognitive inhibition may account for the increased risk of ADHD observed in these syndromes.

Social and attention problems were roughly similar in both syndromes. But the somatic complaints scale was one of the least problematic scales in Sotos syndrome, one of the most affected in Malan syndrome. A hypothesis about this discrepancy is that intellectual disability and language impairments are more severe in Malan than in Sotos syndrome (Priolo et al., 2018). In the former condition emotional distress can be primarily expressed through somatic symptoms (e.g., headache, stomach ache, skin problems) (de Ruiter et al., 2007). For Malan syndrome, it is to note that only one participant obtained a score at the borderline threshold for anxiety/depressive symptoms. Previous literature has documented anxiety problems in this condition (Priolo et al., 2018). Notably, no problems were reported either in rule-breaking or aggressive behaviours, suggesting a low incidence of externalizing behaviours in Malan syndrome.

Older ages were associated with fewer attention problems and aggressive behaviours. These findings hint at a crucial role played by environmental factors such as school frequentation and rehabilitative interventions in limiting these behavioural problems as age increases (Bailey et al., 2019; Siracusano et al., 2024).

5.5 General discussion

As emerged in the neuropsychological assessment, BWS, Sotos and Malan syndromes represent quite different models of how living with an overgrown body may affect socio-emotional development.

For BWS, the assessment of emotional-behavioural difficulties in preschool- and school-age children indicates a prevalent phenotype characterized by increased anxiety, low self-esteem, social withdrawal and a tendency to control externalizing reactions. BWS involves a complex picture of physical symptoms that require frequent medical attention, thus increasing the emotional burden on the child and on the whole family system (Duffy et al., 2018; Pinquart, 2018). Hospitalization experiences as well as atypical facial and bodily features may increase the own perception of being 'different' from others (Drust et al., 2023). The significant associations between age and psychosocial difficulties emerging from the first study suggest that children with BWS might become more aware of their condition as age increases. They spend more time in social contexts outside the family so that they can experience more the sense of being different from peers (Pinquart & Teubert, 2012). In individuals with chronic pain it has been documented that perception or anticipation of negative social reactions may become internalized and affect self-esteem (Waugh et al., 2014). The perceived social stigma due to physical appearance and symptoms has been associated with increased preoccupation and considered as a challenging factor for identity development in conditions of chronic illness (O'Donnell & Habenicht, 2022). The observed phenotype of BWS may be the result of coping strategies to care-related emotional burdens, self-perception of being different from peers, and internalization of the perceived social stigma. The very low incidence of autism-like behaviours further corroborates this hypothesis, excluding the possibility that internalization problems depend on a presumed increased risk of ASD in this syndrome (Kent et al., 2008).

For Sotos and Malan syndromes, the frequent presence of autistic traits and neuropsychological features strongly affect the emotional-behavioural functioning. This includes intellectual disability, clumsiness and language impairments. Nevertheless, the interactions between autism-like behaviours, intellectual disability and emotional-behavioural problems make it difficult to disentangle the specific contribution of each of these factors to the observed phenotype.

It is important to stress that the AQ questionnaire provides measurements of autistic traits but cannot be considered as a diagnostic tool. Even in presence of autistic traits, a diagnosis of ASD should be assigned only after considering the impact of these autism-like behaviours on multiple life contexts (Auyeung et al., 2008). Despite the fact that internalization and social problems may overlap with the autistic phenotype, recent studies have reported low or minimal signs of ASD in Malan syndrome (Alfieri et al., 2023), and only mild symptoms of ASD in Sotos syndrome (Riccioni et al., 2024). Globally, these findings ask for caution when assessing psychopathological comorbidities in these syndromes. Further consideration is welcome regarding the impact of cognitive impairments on psychosocial functioning.

Regarding body and socio-emotional development, half of the participants with Malan syndrome exhibited somatic complaint problems. This finding suggests that, in the presence of moderate-to-severe intellectual disability and speech impairments, the body can be the most immediate way to express emotional distress.

There was a wide prevalence of emotional-behavioural problems in participants with Sotos syndrome. However, the observed between- and within-scale variability suggests there may be more than one behavioural profile which may depend on individual predisposition factors (e.g., autistic traits, intellectual delay) as well as environmental variables, as suggested by the negative association between age and behavioural problems. This evidence highlights the importance of rehabilitative interventions, school inclusion and comprehensive care involving the whole family for children with complex neurodevelopmental disabilities such as Sotos and Malan syndromes (Dykens, 2015).

Discussion of the above results should continue, keeping in mind several shortcomings. First, the sample size is relatively small. A selection bias cannot be excluded, as parents of children with more emotional-behavioural problems might be more inclined to participate in these studies. Despite the adoption of validated, standardized questionnaires that provide reliable results, the lack of an age-matched, and possibly mental-age matched control group requires caution in generalizing the findings. Some background demographics were considered, but the role of familiar psychological variables on psychosocial adjustment and emotional-behavioural functioning of overgrowth syndromes should be addressed by future research. As well, potential genotype-phenotype correlations should be explored in wider samples (Mussa, Russo, Larizza, et al., 2016; Siracusano et al., 2023). Lastly, these studies focused on the ‘negative’ side of socio-emotional functioning, that is emotional-behavioural problems and autism-like behaviours. Future research should consider socio-emotional resources and competences that can promote social adjustment in these syndromes.

Concluding remarks

The embodied cognition theories provide a valid framework to study how body perception influences cognition and emotion. When observing other people, we refer to our embodied, sensorimotor and visceral representations to understand another person’s feelings, thoughts and intentions. From womb to adult life, interpersonal tactile interactions are pervasive and play a primary role in conveying emotions and in forming social bonds. Starting from these assumptions, a project of this thesis investigated vicarious perception of the slow, caress-like stroking also called affective touch. Two consecutive experiments were conducted as part of the visiting experience at the Liverpool John Moores University. Above, behavioural and neurophysiological evidence of how we understand affective touch when we observe interpersonal tactile interactions was provided. According to embodied cognition accounts of touch, associations between vicarious perception of touch and interoceptive awareness were documented. These results contribute to a deeper understanding of the complex interplay between motor and somatosensory systems in social touch perception and emphasize the importance of affective touch in human social interactions. Future research should aim to explore these mechanisms further, particularly how these processes integrate with emotional and cognitive aspects of touch perception. These studies were conducted on healthy adult individuals yet the results and experience gained may allow affective touch perception and related topics, such as pain perception, to be investigated in future research with clinical populations.

We tend to consider the body as a whole but body perception is a multidimensional construct that reflects many representations of the body in the brain and the integration of multiple sensory channels, from touch to sight to interoceptive signals. On an explicit level, the image of one’s body visible in the mirror directly affects emotions, thoughts and behaviours. This body image is influenced by top-down mechanisms, such as cultural and social norms, that impact on what we think of how others perceive our physical appearance. On an implicit level, cognitive and affective processes are deeply rooted in the one’s own embodied experience. What happens when bodily experience is inherently biased with an overgrowth disorder? And how does this biased experience impact on cognitive and socio-emotional development of children and adolescents with overgrowth syndromes, specifically BWS, Malan and Sotos syndromes? The main project of this thesis addressed these questions by means of a series of experiments and assessments.

Multiple dimensions of body perception were investigated in adolescents with overgrowth syndromes. Adolescence was the focus, as the body is particularly invested in affective and social meanings in this age range. Adolescence thus represents a critical window to study how atypical bodily experiences affect social functioning. When compared to healthy peers, the group with overgrowth disorders showed differences across all experiments. Regarding body image, adolescents with overgrowth syndromes reported fewer problems in symptoms and behaviours usually associated with eating disorders, such as weight phobia and compulsive self-checking. On this explicit level, living with an overgrown body apparently does not imply specific concerns towards the own physical appearance. This surprising finding may depend on limitations in thinking critically about oneself due to intellectual disability often associated with Sotos and Malan syndromes. But for spared cognitive abilities, that is most individuals with BWS, this result may reflect coping strategies with atypical facial and bodily features and with the perception of other people’s judgement towards physical appearance. This hypothesis is corroborated by the findings of the experiment assessing interpersonal distance (i.e., social space) and peripersonal space (i.e., motor space) towards social and non-social stimuli. Large body sizes typical of these syndromes accounted for enlarged action space, greater cognitive and affect-recognition abilities were associated with larger interpersonal distances. The more adolescents with overgrowth syndromes are able to understand others’ facial expressions, the larger is the distance they prefer to maintain during social interaction. Another difference with healthy peers regarded interoceptive abilities. Adolescents with overgrowth syndromes were found to be more sensitive to internal bodily signals than healthy peers, most likely a result of frequent physical examinations. Notably, this increased sensitivity was not found to be associated with emotional-behavioural functioning. The last experiment above adopted synchronous and asynchronous visual-tactile stimulation to elicit an illusionary sense of embodiment over a virtual body. The bodily illusion was induced in a similar way across participants, but adolescents with overgrowth syndromes reported high sense of touch referral and embodiment even after asynchronous stimulations. These results hint that altered sensory processing already documented in Sotos and Malan syndromes affects higher-order socio-cognitive processes underlying body awareness and representation.

Standardized neuropsychological and emotional-behavioural assessments were carried out to examine socio-cognitive and socio-emotional development in children and adolescents with BWS, Sotos and Malan syndromes. The results confirm that BWS is not associated with specific neuropsychological impairments and indicate that children with this syndrome show greater social perception skills. Given the expected reactions from others towards their atypical body features, these children are particularly able to understand emotions and mental states. Paradoxically, increased social perception abilities may contribute to distancing and withdrawal behaviours in social contexts. However, these socio-emotional problems do not appear to be related with an increased prevalence of autism-like behaviours in BWS. Besides social withdrawal, the presence of anxiety and depressive symptoms and the limited incidence of externalizing behaviours constitute the main features of a common social-behavioural phenotype. This is likely to emerge as a result of coping strategies with the many emotional stressors inherently linked with this syndrome, such as hospitalizations, medical procedures, and the expected reactions of social contexts towards ‘diversity’. The complex interplay between atypical body features, such as macroglossia, negative bias at school and socio-emotional problems may also affect educational outcomes. A presumed increase in learning difficulties in BWS is worth further investigation. Importantly, in the study of Drust (2023) about living with BWS for adults, most of the participants stated to have overcome their social and emotional difficulties, suggesting that protective and resilience factors can lead to a better quality of life. Nevertheless, many participants reported difficulties from social hardships, psychiatric disorders and learning issues. Overall, the findings reported in this thesis ask for a wider consideration of psychological functioning, in terms of both cognitive and socio-emotional outcomes for children and adolescents with BWS.

Many can benefit from a screening of cognitive and socio-emotional development and from psychological help. This is the case especially during life stages characterised by changes in social context, such as access to primary school and adolescence.

Similarly to genetic disorders like Williams and Joubert syndromes, Sotos and Malan syndromes present pervasive neuropsychological impairments, with an increased incidence of autism-like behaviours. Nevertheless, the absence of specific deficits in social perception as well as other neuropsychological and emotional-behavioural features indicate that social phenotypes of these syndromes do not exactly overlap with autism. The complex interaction of intellectual disability, autistic traits and emotional-behavioural problems requires caution in generalising to Sotos and Malan syndromes characteristics and indications that may also apply to autism or other neurodevelopmental disorders. Abnormalities in sensory processing and sensorimotor integration needs further investigation considering their impact on body perception. The results of this thesis represent a contribution to further delineate the specific neuropsychological and behavioural profiles of these syndromes, from general intellectual functioning to learning outcomes, pointing to tailored rehabilitative intervention and support.

In conclusion, this thesis highlights different pathways through which embodied experience influences cognition, emotion, and social behaviour. The project on vicarious touch sheds light on specific neurocognitive mechanisms that underlie how we understand the affective and social meanings of touch when we observe interpersonal interactions. The results not only advance our understanding of the neural basis of social touch but also open new avenues for investigating the role of affective touch in social cognition and emotional empathy. The main project on overgrowth syndromes highlights that BWS, Sotos and Malan syndromes can be seen as different models of how bodily experience, cognition and emotion influence each other throughout development. The cognitive and emotional-behavioural sequelae of BWS are more similar to those of other chronic paediatric diseases and craniofacial malformations, such as cleft lip/palate. The burden of care, the perception of being different and the reactions from the social context concur to determine the psychosocial functioning of children and adolescents with BWS. This interplay between body features and social context may occur also in individuals with Sotos syndrome and relatively preserved socio-cognitive abilities. However, for Sotos and Malan syndromes, the inherent alterations of neurodevelopment constrain the emergence of body awareness and of higher-order representations of the bodily Self. The findings of this thesis have thus important implications for research about body perception as well as for clinical management of BWS, Sotos and Malan syndromes.

References

Achenbach, T. M. (2011). Child Behavior Checklist. In *Encyclopedia of Clinical Neuropsychology* (pp. 546–552). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1529

Achenbach, T. M., Ivanova, M. Y., Rescorla, L. A., Turner, L. V., & Althoff, R. R. (2016). Internalizing/Externalizing Problems: Review and Recommendations for Clinical and Research Applications. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(8), 647–656. https://doi.org/10.1016/J.JAAC.2016.05.012

Ackerley, R. (2022). C-tactile (CT) afferents: evidence of their function from microneurography studies in humans. *Current Opinion in Behavioral Sciences*, *43*, 95–100. https://doi.org/10.1016/j.cobeha.2021.08.012

Ackerley, R., Backlund Wasling, H., Liljencrantz, J., Olausson, H., Johnson, R. D., & Wessberg, J. (2014). Human C-tactile afferents are tuned to the temperature of a skin-stroking caress. *Journal of Neuroscience*, *34*(8), 2879–2883. https://doi.org/10.1523/JNEUROSCI.2847-13.2014

Ackerley, R., Carlsson, I., Wester, H., Olausson, H., & Backlund Wasling, H. (2014). Touch perceptions across skin sites: Differences between sensitivity, direction discrimination and pleasantness. *Frontiers in Behavioral Neuroscience*, *8*(FEB), 74060. https://doi.org/10.3389/FNBEH.2014.00054/BIBTEX

Ackerley, R., Saar, K., McGlone, F., & Backlund Wasling, H. (2014). Quantifying the sensory and emotional perception of touch: Differences between glabrous and hairy skin. *Frontiers in Behavioral Neuroscience*, *8*(FEB), 66596. https://doi.org/10.3389/FNBEH.2014.00034/BIBTEX

Addabbo, M., Quadrelli, E., Bolognini, N., Nava, E., & Turati, C. (2020). Mirror-touch experiences in the infant brain. *Social Neuroscience*, *15*(6), 641–649.

https://doi.org/10.1080/17470919.2020.1840431

Adler, J., & Gillmeister, H. (2019). Bodily self-relatedness in vicarious touch is reflected at early cortical processing stages. *Psychophysiology, 56*(12), e13465. https://doi.org/10.1111/psyp.13465

Ainley, V., Tsakiris, M., Pollatos, O., Schulz, A., & Herbert, B. M. (2020). Comment on "Zamariola et al. (2018), Interoceptive Accuracy Scores are Problematic: Evidence from Simple Bivariate Correlations." *Biological Psychology, 152,* 107870. https://doi.org/10.1016/j.biopsycho.2020.107870

Alfieri, P., Macchiaiolo, M., Collotta, M., Montanaro, F. A. M., Caciolo, C., Cumbo, F., Galassi, P., Panfili, F. M., Cortellessa, F., Zollino, M., Accadia, M., Seri, M., Tartaglia, M., Bartuli, A., Mammì, C., Vicari, S., & Priolo, M. (2022). Characterization of Cognitive, Language and Adaptive Profiles of Children and Adolescents with Malan Syndrome. *Journal of Clinical Medicine, 11*(14), 4078. https://doi.org/10.3390/JCM11144078/S1

Alfieri, P., Menghini, D., Marotta, L., De Peppo, L., Ravà, L., Salvaguardia, F., Varuzza, C., & Vicari, S. (2017). A comparison between linguistic skills and socio-communicative abilities in Williams syndrome. *Journal of Intellectual Disability Research, 61*(9), 866–876. https://doi.org/10.1111/jir.12401

Alfieri, P., Montanaro, F. A. M., Macchiaiolo, M., Collotta, M., Caciolo, C., Galassi, P., Panfili, F. M., Cortellessa, F., Zollino, M., Chinali, M., Accadia, M., Seri, M., Bartuli, A., Mammì, C., Tartaglia, M., Vicari, S., & Priolo, M. (2023). Behavioral profiling in children and adolescents with Malan syndrome. *Frontiers in Child and Adolescent Psychiatry, 2,* 1106228. https://doi.org/10.3389/frcha.2023.1106228

Ali, S. H., Makdani, A. D., Cordero, M. I., Paltoglou, A. E., Marshall, A. G., McFarquhar, M. J., McGlone, F. P., Walker, S. C., & Trotter, P. D. (2023). Hold me or stroke me? Individual differences in static and dynamic affective touch. *PLOS ONE*, *18*(5), e0281253. https://doi.org/10.1371/JOURNAL.PONE.0281253

Allen, M., & Tsakiris, M. (2018). The body as first prior : Interoceptive predictive processing and the primacy of self- models. In M. Tsakiris & H. De Preester (Eds.), *The interoceptive mind: From homeostasis to awareness*. Oxford University Press. https://psycnet.apa.org/record/2019-12575-002

Amoruso, L., Finisguerra, A., & Urgesi, C. (2016). Tracking the Time Course of Top-Down Contextual Effects on Motor Responses during Action Comprehension. *Journal of Neuroscience*, *36*(46), 11590–11600. https://doi.org/10.1523/JNEUROSCI.4340-15.2016

Amoruso, L., & Urgesi, C. (2016). Contextual modulation of motor resonance during the observation of everyday actions. *NeuroImage*, *134*, 74–84. https://doi.org/10.1016/j.neuroimage.2016.03.060

Anema, H. A., van Zandvoort, M. J. E., de Haan, E. H. F., Kappelle, L. J., de Kort, P. L. M., Jansen, B. P. W., & Dijkerman, H. C. (2009). A double dissociation between somatosensory processing for perception and action. *Neuropsychologia*, *47*(6), 1615–1620. https://doi.org/10.1016/j.neuropsychologia.2008.11.001

Asada, K., & Itakura, S. (2012). Social phenotypes of autism spectrum disorders and williams syndrome: similarities and differences. *Frontiers in Psychology*, *3*(JUL), 247. https://doi.org/10.3389/fpsyg.2012.00247

Atkinson, J. (2022). Williams Syndrome. In *Oxford Research Encyclopedia of Psychology*. Oxford University Press. https://doi.org/10.1093/acrefore/9780190236557.013.118

Auyeung, B., Baron-Cohen, S., Wheelwright, S., & Allison, C. (2008). The autism spectrum quotient: Children’s version (AQ-Child). *Journal of Autism and Developmental Disorders*, *38*(7), 1230–1240. https://doi.org/10.1007/S10803-007-0504-Z/TABLES/4

Baier, B., Karnath, H. O., Dieterich, M., Birklein, F., Heinze, C., & Müller, N. G. (2010). Keeping Memory Clear and Stable—The Contribution of Human Basal Ganglia and Prefrontal Cortex to Working Memory. *Journal of Neuroscience*, *30*(29), 9788–9792. https://doi.org/10.1523/JNEUROSCI.1513-10.2010

Baier, B., Müller, N. G., & Dieterich, M. (2014). What part of the cerebellum contributes to a visuospatial working memory task? *Annals of Neurology*, *76*(5), 754–757. https://doi.org/10.1002/ANA.24272

Bailey, T., Totsika, V., Hastings, R. P., Hatton, C., & Emerson, E. (2019). Developmental trajectories of behaviour problems and prosocial behaviours of children with intellectual disabilities in a population-based cohort. *Journal of Child Psychology and Psychiatry*, *60*(11), 1210–1218. https://doi.org/10.1111/JCPP.13080

Ball, L. J., Sullivan, M. D., Dulany, S., Stading, K., & Schaefer, G. B. (2005). Speech-language characteristics of children with Sotos syndrome. *American Journal of Medical Genetics Part A*, *136A*(4), 363–367. https://doi.org/10.1002/ajmg.a.30799

Barbiero, C., Montico, M., Lonciari, I., Monasta, L., Penge, R., Vio, C., Tressoldi, P. E., Carrozzi, M., De Petris, A., De Cagno, A. G., Crescenzi, F., Tinarelli, G., Leccese, A., Pinton, A., Belacchi, C., Tucci, R., Musinu, M., Tossali, M. L., Antonucci, A. M., … Ronfani, L. (2019). The lost children: The underdiagnosis of dyslexia in Italy. A cross-sectional national study. *PLOS ONE*, *14*(1), e0210448. https://doi.org/10.1371/JOURNAL.PONE.0210448

Baron-Cohen, S., Hoekstra, R. A., Knickmeyer, R., & Wheelwright, S. (2006). The Autism-Spectrum Quotient (AQ) - Adolescent version. *Journal of Autism and Developmental Disorders*, *36*(3), 343–350. https://doi.org/10.1007/S10803-006-0073-6/TABLES/4

Baujat, G., & Cormier-Daire, V. (2007). Sotos syndrome. *Orphanet Journal of Rare Diseases*, *2*(1), 36. https://doi.org/10.1186/1750-1172-2-36

Bekkali, S., Youssef, G. J., Donaldson, P. H., He, J., Do, M., Hyde, C., Barhoun, P., & Enticott, P. G. (2022). Do gaze behaviours during action observation predict interpersonal motor resonance? *Social Cognitive and Affective Neuroscience*, *17*(1), 61–71. https://doi.org/10.1093/SCAN/NSAA106

Bell, M. F., Bayliss, D. M., Glauert, R., Harrison, A., & Ohan, J. L. (2016). Chronic illness and developmental vulnerability at school entry. *Pediatrics*, *137*(5), 20152475. https://doi.org/10.1542/peds.2015-2475

Bellard, A., Trotter, P. D., McGlone, F. L., & Cazzato, V. (2023). Role of medial prefrontal cortex and primary somatosensory cortex in self and other-directed vicarious social touch: a TMS study. *Social Cognitive and Affective Neuroscience*, *18*(1). https://doi.org/10.1093/SCAN/NSAD060

Bellard, A., Trotter, P., McGlone, F., & Cazzato, V. (2022). Vicarious ratings of self vs. other-directed social touch in women with and recovered from Anorexia Nervosa. *Scientific Reports 2022 12:1*, *12*(1), 1–15. https://doi.org/10.1038/s41598-022-17523-2

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Berlucchi, G., & Aglioti, S. M. (1997). The body in the brain: neural bases of corporeal awareness. *Trends in Neurosciences*, *20*(12), 560–564. https://doi.org/10.1016/S0166-2236(97)01136-3

Berlucchi, G., & Aglioti, S. M. (2010). The body in the brain revisited. *Experimental Brain Research*, *200*(1), 25–35. https://doi.org/10.1007/s00221-009-1970-7

Betti, S., Finisguerra, A., Amoruso, L., & Urgesi, C. (2022). Contextual Priors Guide Perception and Motor Responses to Observed Actions. *Cerebral Cortex, 32*(3), 608–625. https://doi.org/10.1093/CERCOR/BHAB241

Bhanpuri, N. H., Okamura, A. M., & Bastian, A. J. (2014). Predicting and correcting ataxia using a model of cerebellar function. *Brain*, *137*(7), 1931–1944. https://doi.org/10.1093/brain/awu115

Björnsdotter, M., Morrison, I., & Olausson, H. (2010). Feeling good: On the role of C fiber mediated touch in interoception. *Experimental Brain Research*, *207*(3–4), 149–155. https://doi.org/10.1007/S00221-010-2408-Y/FIGURES/4

Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. *Nature Neuroscience 1998 1:7*, *1*(7), 635–640. https://doi.org/10.1038/2870

Blanke, O., Slater, M., & Serino, A. (2015). Behavioral, Neural, and Computational Principles of Bodily Self-Consciousness. *Neuron*, *88*(1), 145–166. https://doi.org/10.1016/j.neuron.2015.09.029

Boehme, R., Hauser, S., Gerling, G. J., Heilig, M., & Olausson, H. (2019). Distinction of self-produced touch and social touch at cortical and spinal cord levels. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(6), 2290–2299. https://doi.org/10.1073/PNAS.1816278116/SUPPL_FILE/PNAS.1816278116.SAPP.PDF

Boehme, R., & Olausson, H. (2022). Differentiating self-touch from social touch. *Current Opinion in Behavioral Sciences*, *43*, 27–33. https://doi.org/10.1016/J.COBEHA.2021.06.012

Bohlin, G., & Hagekull, B. (2009). Socio-emotional development: From infancy to young adulthood. *Scandinavian Journal of Psychology*, *50*(6), 592–601. https://doi.org/10.1111/J.1467-9450.2009.00787.X

Bolognini, N., Olgiati, E., Xaiz, A., Posteraro, L., Ferraro, F., & Maravita, A. (2012). Touch to See:

Neuropsychological Evidence of a Sensory Mirror System for Touch. *Cerebral Cortex*, *22*(9), 2055–2064. https://doi.org/10.1093/CERCOR/BHR283

Bolognini, N., Rossetti, A., Maravita, A., & Miniussi, C. (2011). Seeing touch in the somatosensory cortex: A TMS study of the visual perception of touch. *Human Brain Mapping*, *32*(12), 2104–2114. https://doi.org/10.1002/HBM.21172

Borgomaneri, S., Gazzola, V., & Avenanti, A. (2012). Motor mapping of implied actions during perception of emotional body language. *Brain Stimulation*, *5*(2), 70–76. https://doi.org/10.1016/J.BRS.2012.03.011

Borgomaneri, S., Gazzola, V., & Avenanti, A. (2015). Transcranial magnetic stimulation reveals two functionally distinct stages of motor cortex involvement during perception of emotional body language. *Brain Structure and Function*, *220*(5), 2765–2781. https://doi.org/10.1007/s00429-014-0825-6

Brioude, F., Kalish, J. M., Mussa, A., Foster, A. C., Bliek, J., Ferrero, G. B., Boonen, S. E., Cole, T., Baker, R., Bertoletti, M., Cocchi, G., Coze, C., De Pellegrin, M., Hussain, K., Ibrahim, A., Kilby, M. D., Krajewska-Walasek, M., Kratz, C. P., Ladusans, E. J., … Maher, E. R. (2018). Clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement. *Nature Reviews Endocrinology*, *14*(4), 229–249. https://doi.org/10.1038/nrendo.2017.166

Brioude, F., Toutain, A., Giabicani, E., Cottereau, E., Cormier-Daire, V., & Netchine, I. (2019). Overgrowth syndromes — clinical and molecular aspects and tumour risk. *Nature Reviews Endocrinology*, *15*(5), 299–311. https://doi.org/10.1038/s41574-019-0180-z

Brissenden, J. A., & Somers, D. C. (2019). Cortico–cerebellar networks for visual attention and working memory. *Current Opinion in Psychology*, *29*, 239–247. https://doi.org/10.1016/J.COPSYC.2019.05.003

Brissenden, J. A., Tobyne, S. M., Halko, M. A., & Somers, D. C. (2021). Stimulus-Specific Visual Working Memory Representations in Human Cerebellar Lobule VIIb/VIIIa. *Journal of Neuroscience*, *41*(5), 1033–1045. https://doi.org/10.1523/JNEUROSCI.1253-20.2020

Brissenden, J. A., Tobyne, S. M., Osher, D. E., Levin, E. J., Halko, M. A., & Somers, D. C. (2018). Topographic Cortico-cerebellar Networks Revealed by Visual Attention and Working Memory. *Current Biology : CB*, *28*(21), 3364-3372.e5. https://doi.org/10.1016/J.CUB.2018.08.059

Brugger, P., & Lenggenhager, B. (2014). The bodily self and its disorders. *Current Opinion in Neurology*, *27*(6), 644–652. https://doi.org/10.1097/WCO.0000000000000151

Bulgheroni, S., D’Arrigo, S., Signorini, S., Briguglio, M., Di Sabato, M. L., Casarano, M., Mancini, F., Romani, M., Alfieri, P., Battini, R., Zoppello, M., Tortorella, G., Bertini, E., Leuzzi, V., Valente, E. M., & Riva, D. (2016). Cognitive, adaptive, and behavioral features in Joubert syndrome. *American Journal of Medical Genetics, Part A*, *170*(12), 3115–3124. https://doi.org/10.1002/ajmg.a.37938

Burnett, A. C., Gunn, J. K., Hutchinson, E. A., Moran, M. M., Kelly, L. M., Sevil, U. C., Anderson, P. J., & Hunt, R. W. (2018). Cognition and behaviour in children with congenital abdominal wall defects. *Early Human Development*, *116*, 47–52. https://doi.org/10.1016/j.earlhumdev.2017.11.002

Butti, N., Biffi, E., Genova, C., Romaniello, R., Redaelli, D. F., Reni, G., Borgatti, R., & Urgesi, C. (2020). Virtual Reality Social Prediction Improvement and Rehabilitation Intensive Training (VR-SPIRIT) for paediatric patients with congenital cerebellar diseases: study protocol of a randomised controlled trial. *Trials*, *21*(1), 82. https://doi.org/10.1186/s13063-019-4001-4

Butti, N., Castagna, A., & Montirosso, R. (2022). Psychosocial Difficulties in Preschool-Age Children with Beckwith–Wiedemann Syndrome: An Exploratory Study. *Children*, *9*(4).

https://doi.org/10.3390/children9040551

Butti, N., Finisguerra, A., & Urgesi, C. (2022). Holistic processing of body stimuli: Evidence of body composite illusion in adults and children. *Developmental Psychology*, *58*(7), 1286–1297. https://doi.org/10.1037/dev0001353

Butti, N., Montirosso, R., Giusti, L., Borgatti, R., & Urgesi, C. (2020). Premature birth affects visual body representation and body schema in preterm children. *Brain and Cognition*, *145*(August), 105612. https://doi.org/10.1016/j.bandc.2020.105612

Butti, N., Montirosso, R., Giusti, L., Piccinini, L., Borgatti, R., & Urgesi, C. (2019). Early Brain Damage Affects Body Schema and Person Perception Abilities in Children and Adolescents with Spastic Diplegia. *Neural Plasticity*, *2019*, 17. https://doi.org/10.1155/2019/1678984

Butti, N., Oldrati, V., Ferrari, E., Romaniello, R., Gagliardi, C., Borgatti, R., & Urgesi, C. (2023). New Insights into the Neuropsychological Profile and Intellectual Quotient Variability in Joubert Syndrome Compared to Other Congenital Cerebellar Malformations. *The Cerebellum*, *0123456789*. https://doi.org/10.1007/s12311-023-01580-y

Butti, N., Urgesi, C., McGlone, F. P., Oldrati, V., Montirosso, R., & Cazzato, V. (2023). To touch or to be touched? Comparing pleasantness of vicarious execution and reception of interpersonal touch. *BioRxiv*, 2023.10.08.561444. https://doi.org/10.1101/2023.10.08.561444

Bytomski, A., Ritschel, G., Bierling, A., Bendas, J., Weidner, K., & Croy, I. (2020). Maternal stroking is a fine-tuned mechanism relating to C-tactile afferent activation: An exploratory study. *Psychology and Neuroscience*, *13*(2), 149–157. https://doi.org/10.1037/pne0000184

Campos, R., Martínez-Castilla, P., & Sotillo, M. (2017). False belief attribution in children with Williams syndrome: the answer is in the emotion. *Journal of Intellectual Disability Research*, *61*(11), 1003–1010. https://doi.org/10.1111/JIR.12404

Candini, M., Battaglia, S., Benassi, M., di Pellegrino, G., & Frassinetti, F. (2021). The physiological correlates of interpersonal space. *Scientific Reports 2021 11:1*, *11*(1), 1–8. https://doi.org/10.1038/s41598-021-82223-2

Candini, M., di Pellegrino, G., & Frassinetti, F. (2020). The plasticity of the interpersonal space in autism spectrum disorder. *Neuropsychologia*, *147*, 107589. https://doi.org/10.1016/j.neuropsychologia.2020.107589

Candini, M., Giuberti, V., Manattini, A., Grittani, S., di Pellegrino, G., & Frassinetti, F. (2017). Personal space regulation in childhood autism: Effects of social interaction and person's perspective. *Autism Research*, *10*(1), 144–154. https://doi.org/10.1002/AUR.1637

Candini, M., Giuberti, V., Santelli, E., di Pellegrino, G., & Frassinetti, F. (2019). When social and action spaces diverge: A study in children with typical development and autism. *Autism*, *23*(7), 1687–1698. https://doi.org/10.1177/1362361318822504/ASSET/IMAGES/LARGE/10.1177_1362361318822504-FIG6.JPEG

Cardinali, L., Brozzoli, C., & Farnè, A. (2009). Peripersonal Space and Body Schema: Two Labels for the Same Concept? *Brain Topography*, *21*(3–4), 252–260. https://doi.org/10.1007/s10548-009-0092-7

Cardini, F., Fatemi-Ghomi, N., Gajewska-Knapik, K., Gooch, V., & Aspell, J. E. (2019). Enlarged representation of peripersonal space in pregnancy. *Scientific Reports 2019 9:1*, *9*(1), 1–7. https://doi.org/10.1038/s41598-019-45224-w

Carta, I., Zappa, L. E., Garghentini, G., & Caslini, M. (2008). Immagine corporea: Studio preliminare dell'applicazione del Body Uneasiness Test (BUT) per la ricerca delle specificità in disturbi del comportamento alimentare, ansia, depressione, obesità. *Giornale Italiano Di Psicopatologia*, *14*, 23–28.

Cartaud, A., Quesque, F., & Coello, Y. (2020). Wearing a face mask against Covid-19 results in a reduction of social distancing. *PLOS ONE, 15*(12), e0243023. https://doi.org/10.1371/JOURNAL.PONE.0243023

Cascio, C. J., Moore, D., & McGlone, F. (2019). Social touch and human development. *Developmental Cognitive Neuroscience*, *35*, 5–11. https://doi.org/10.1016/j.dcn.2018.04.009

Cazzato, V., Mian, E., Serino, A., Mele, S., & Urgesi, C. (2015). Distinct contributions of extrastriate body area and temporoparietal junction in perceiving one's own and others' body. *Cognitive, Affective, & Behavioral Neuroscience*, *15*(1), 211–228. https://doi.org/10.3758/s13415-014-0312-9

Cazzato, V., Sacchetti, S., Shin, S., Makdani, A., Trotter, P. D., & McGlone, F. (2021). Affective touch topography and body image. *PLOS ONE*, *16*(11), e0243680. https://doi.org/10.1371/JOURNAL.PONE.0243680

Choufani, S., Ko, J. M., Weksberg, R., Lou, Y., Shuman, C., & Fishman, L. (2021). Paternal Uniparental Disomy of the Entire Chromosome 20 in a Child with Beckwith-Wiedemann Syndrome. *Genes 2021, Vol. 12, Page 172*, *12*(2), 172. https://doi.org/10.3390/GENES12020172

Ciaunica, A. (2019). The 'Meeting of Bodies': Empathy and Basic Forms of Shared Experiences. *Topoi*, *38*(1), 185–195. https://doi.org/10.1007/s11245-017-9500-x

Ciaunica, A., & Crucianelli, L. (2019). Minimal self-awareness from within: A developmental perspective. *Journal of Consciousness Studies*, *26*(3–4), 207–226.

Coello, Y., & Cartaud, A. (2021). The Interrelation Between Peripersonal Action Space and Interpersonal Social Space: Psychophysiological Evidence and Clinical Implications. *Frontiers in Human Neuroscience*, *15*, 92. https://doi.org/10.3389/fnhum.2021.636124

Cole, T. R. P., & Hughes, H. E. (1994). Sotos syndrome: a study of the diagnostic criteria and natural history. *Journal of Medical Genetics, 31*(1), 20. https://doi.org/10.1136/JMG.31.1.20

Compas, B. E., Jaser, S. S., Dunn, M. J., & Rodriguez, E. M. (2012). Coping with Chronic Illness in Childhood and Adolescence. *Annual Review of Clinical Psychology, 8*(1), 455–480. https://doi.org/10.1146/annurev-clinpsy-032511-143108

Cornoldi, C., & Carretti, B. (2016). *Prove MT-3-Clinica per la scuola primaria e secondaria di I grado*. Giunti Edu.

Cornoldi, C., Mammarella, I. C., & Caviola, S. (2020). *ACT-MT-3*. Centro Studi Erickson.

Cornoldi, C., Pra Baldi, A., & Giofrè, D. (2017). *Prove MT Avanzate-3-clinica per il biennio della scuola secondaria di II grado*. Giunti Edu.

Corti, C., Butti, N., Bardoni, A., Strazzer, S., & Urgesi, C. (2022). Body Processing in Children and Adolescents with Traumatic Brain Injury: An Exploratory Study. *Brain Sciences*, *12*(8), 962. https://doi.org/10.3390/brainsci12080962

Cowie, D., McKenna, A., Bremner, A. J., & Aspell, J. E. (2018). The development of bodily self-consciousness: changing responses to the Full Body Illusion in childhood. *Developmental Science*, *21*(3). https://doi.org/10.1111/desc.12557

Cowie, D., Sterling, S., & Bremner, A. J. (2016). The development of multisensory body representation and awareness continues to 10years of age: Evidence from the rubber hand illusion. *Journal of Experimental Child Psychology*. https://doi.org/10.1016/j.jecp.2015.10.003

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*, *13*(4), 500–505. https://doi.org/10.1016/S0959-4388(03)00090-4

Craighero, L., & Mele, S. (2018). Equal kinematics and visual context but different purposes:

Observer’s moral rules modulate motor resonance. *Cortex*, *104*, 1–11. https://doi.org/10.1016/J.CORTEX.2018.03.032

Crerand, C. E., Conrad, A. L., Bellucci, C. C., Albert, M., Heppner, C. E., Sheikh, F., Woodard, S., Udaipuria, S., & Kapp-Simon, K. A. (2023). Psychosocial Outcomes in Children with Cleft Lip and/or Palate: Associations of Demographic, Cleft Morphologic, and Treatment-Related Variables. *Cleft Palate Craniofacial Journal*, 10556656231181580. https://doi.org/10.1177/10556656231181581

Crerand, C. E., Rumsey, N., Kazak, A., Clarke, A., Rausch, J., & Sarwer, D. B. (2020). Sex differences in perceived stigmatization, body image disturbance, and satisfaction with facial appearance and speech among adolescents with craniofacial conditions. *Body Image*, *32*, 190–198. https://doi.org/10.1016/J.BODYIM.2020.01.005

Croy, I., Geide, H., Paulus, M., Weidner, K., & Olausson, H. (2016). Affective touch awareness in mental health and disease relates to autistic traits – An explorative neurophysiological investigation. *Psychiatry Research*, *245*, 491–496. https://doi.org/10.1016/J.PSYCHRES.2016.09.011

Croy, I., Luong, A., Triscoli, C., Hofmann, E., Olausson, H., & Sailer, U. (2016). Interpersonal stroking touch is targeted to C tactile afferent activation. *Behavioural Brain Research*, *297*, 37–40. https://doi.org/10.1016/j.bbr.2015.09.038

Crucianelli, L., Cardi, V., Treasure, J., Jenkinson, P. M., & Fotopoulou, A. (2016). The perception of affective touch in anorexia nervosa. *Psychiatry Research*, *239*, 72–78. https://doi.org/10.1016/J.PSYCHRES.2016.01.078

Crucianelli, L., & Filippetti, M. L. (2018). Developmental Perspectives on Interpersonal Affective Touch. *Topoi 2018 39:3*, *39*(3), 575–586. https://doi.org/10.1007/S11245-018-9565-1

Cruciani, G., Zanini, L., Russo, V., Boccardi, E., & Spitoni, G. F. (2021). Pleasantness ratings in response to affective touch across hairy and glabrous skin: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *131*, 88–95. https://doi.org/10.1016/J.NEUBIOREV.2021.09.026

Cuzzolaro, M., Vetrone, G., Marano, G., & Garfinkel, P. E. (2006). The Body Uneasiness Test (BUT): Development and validation of a new body image assessment scale. *Eating and Weight Disorders*, *11*(1), 1–13. https://doi.org/10.1007/BF03327738/METRICS

D'Angelo, M., di Pellegrino, G., Seriani, S., Gallina, P., & Frassinetti, F. (2018). The sense of agency shapes body schema and peripersonal space. *Scientific Reports*, *8*(1), 13847. https://doi.org/10.1038/s41598-018-32238-z

Damasio, A. (2003). Feelings of Emotion and the Self. *Annals of the New York Academy of Sciences*, *1001*(1), 253–261. https://doi.org/10.1196/annals.1279.014

Dardani, C., Howe, L. J., Mukhopadhyay, N., Stergiakouli, E., Wren, Y., Humphries, K., Davies, A., Ho, K., Weinberg, S. M., Marazita, M. L., Mangold, E., Ludwig, K. U., Relton, C. L., Davey Smith, G., Lewis, S. J., Sandy, J., Davies, N. M., & Sharp, G. C. (2020). Cleft lip/palate and educational attainment: cause, consequence or correlation? A Mendelian randomization study. *International Journal of Epidemiology*, *49*(4), 1282–1293. https://doi.org/10.1093/IJE/DYAA047

de Boer, L., Röder, I., & Wit, J. M. (2006). Psychosocial, cognitive, and motor functioning in patients with suspected Sotos syndrome: a comparison between patients with and without NSD1 gene alterations. *Developmental Medicine and Child Neurology*, *48*(7), 582–588. https://doi.org/10.1017/S0012162206001228

de Gelder, B., Van den Stock, J., Meeren, H. K. M., Sinke, C. B. A., Kret, M. E., & Tamietto, M. (2010). Standing up for the body. Recent progress in uncovering the networks involved in the perception of bodies and bodily expressions. *Neuroscience & Biobehavioral Reviews*, *34*(4), 513–527. https://doi.org/10.1016/j.neubiorev.2009.10.008

De Klerk, C. C. J. M., Filippetti, M. L., & Rigato, S. (2021). The development of body representations: an associative learning account. *Proceedings of the Royal Society B*, *288*(1949). https://doi.org/10.1098/RSPB.2021.0070

de Ruiter, K. P., Dekker, M. C., Verhulst, F. C., & Koot, H. M. (2007). Developmental course of psychopathology in youths with and without intellectual disabilities. *Journal of Child Psychology and Psychiatry*, *48*(5), 498–507. https://doi.org/10.1111/J.1469-7610.2006.01712.X

de Vignemont, F. (2010). Body schema and body image--pros and cons. *Neuropsychologia*, *48*(3), 669–680. https://doi.org/10.1016/j.neuropsychologia.2009.09.022

de Vignemont, F., & Iannetti, G. D. (2015). How many peripersonal spaces? *Neuropsychologia*, *70*, 327–334. https://doi.org/10.1016/j.neuropsychologia.2014.11.018

De Witte, N. A. J., Sütterlin, S., Braet, C., & Mueller, S. C. (2016). Getting to the Heart of Emotion Regulation in Youth: The Role of Interoceptive Sensitivity, Heart Rate Variability, and Parental Psychopathology. *PLOS ONE*, *11*(10), e0164615. https://doi.org/10.1371/journal.pone.0164615

Debrot, A., Stellar, J. E., MacDonald, G., Keltner, D., & Impett, E. A. (2021). Is Touch in Romantic Relationships Universally Beneficial for Psychological Well-Being? The Role of Attachment Avoidance. *Personality and Social Psychology Bulletin*, *47*(10), 1495–1509. https://doi.org/10.1177/0146167220977709/ASSET/IMAGES/LARGE/10.1177_0146167220977709-FIG1.JPEG

Della Longa, L., Valori, I., & Farroni, T. (2022). Interpersonal Affective Touch in a Virtual World: Feeling the Social Presence of Others to Overcome Loneliness. *Frontiers in Psychology*, *12*(January), 1–17. https://doi.org/10.3389/fpsyg.2021.795283

Desmedt, O., Corneille, O., Luminet, O., Murphy, J., Bird, G., & Maurage, P. (2020). Contribution of Time Estimation and Knowledge to Heartbeat Counting Task Performance under Original and Adapted Instructions. *Biological Psychology*, *154*, 107904. https://doi.org/10.1016/J.BIOPSYCHO.2020.107904

Devine, S. L., Walker, S. C., Makdani, A., Stockton, E. R., McFarquhar, M. J., McGlone, F. P., & Trotter, P. D. (2020). Childhood Adversity and Affective Touch Perception: A Comparison of United Kingdom Care Leavers and Non-care Leavers. *Frontiers in Psychology*, *11*, 2857. https://doi.org/10.3389/fpsyg.2020.557171

di Pellegrino, G., & Làdavas, E. (2015). Peripersonal space in the brain. *Neuropsychologia*, *66*, 126–133. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2014.11.011

Di Rosa, G., Cavallaro, T., Alibrandi, A., Marseglia, L., Lamberti, M., Giaimo, E., Nicotera, A., Bonsignore, M., & Gagliano, A. (2016). Predictive role of early milestones-related psychomotor profiles and long-term neurodevelopmental pitfalls in preterm infants. *Early Human Development*, *101*, 49–55. https://doi.org/10.1016/j.earlhumdev.2016.04.012

Dirupo, G., Corradi-Dell'Acqua, C., Kashef, M., Debbané, M., & Badoud, D. (2020). The role of interoception in understanding others' affect. Dissociation between superficial and detailed appraisal of facial expressions. *Cortex*, *130*, 16–31. https://doi.org/10.1016/j.cortex.2020.05.010

Doig, K. B., Macias, M. M., Saylor, C. F., Craver, J. R., & Ingram, P. E. (1999). The child development inventory: A developmental outcome measure for follow-up of the high-risk infant. *Journal of Pediatrics*, *135*(3), 358–362. https://doi.org/10.1016/S0022-3476(99)70134-4

Downing, P. E., & Peelen, M. V. (2011). The role of occipitotemporal body-selective regions in person perception. *Cognitive Neuroscience*, *2*(3–4), 186–203. https://doi.org/10.1080/17588928.2011.582945

Drust, W. A., Mussa, A., Gazzin, A., Lapunzina, P., Tenorio-Castaño, J., Nevado, J., Pascual, P., Arias, P., Parra, A., Getz, K. D., & Kalish, J. M. (2023). Adult experiences in Beckwith–Wiedemann syndrome. *American Journal of Medical Genetics, Part C: Seminars in Medical Genetics*, *193*(2), 116–127. https://doi.org/10.1002/ajmg.c.32046

Duffy, K. A., Grand, K. L., Zelley, K., & Kalish, J. M. (2018). Tumor Screening in Beckwith-Wiedemann Syndrome: Parental Perspectives. *Journal of Genetic Counseling*, *27*(4), 844–853. https://doi.org/10.1007/S10897-017-0182-8/TABLES/5

Duncan, D. (1955). Multiple range and multiple F tests. *Biometrics*, *11*(1), 1–42. https://doi.org/10.2307/3001478

Dunn, B. D., Galton, H. C., Morgan, R., Evans, D., Oliver, C., Meyer, M., Cusack, R., Lawrence, A. D., & Dalgleish, T. (2010). Listening to your heart: How interoception shapes emotion experience and intuitive decision making. *Psychological Science*, *21*(12), 1835–1844. https://doi.org/10.1177/0956797610389191/ASSET/IMAGES/LARGE/10.1177_0956797610389191-FIG5.JPEG

Durisko, C., & Fiez, J. A. (2010). Functional activation in the cerebellum during working memory and simple speech tasks. *Cortex*, *46*(7), 896–906. https://doi.org/10.1016/J.CORTEX.2009.09.009

Dykens, E. M. (2015). Family adjustment and interventions in neurodevelopmental disorders. *Current Opinion in Psychiatry*, *28*(2), 121–126. https://doi.org/10.1097/YCO.0000000000000129

Ebisch, S. J. H., Ferri, F., Salone, A., Perrucci, M. G., D'Amico, L., Ferro, F. M., Romani, G. L., & Gallese, V. (2011). Differential Involvement of Somatosensory and Interoceptive Cortices during the Observation of Affective Touch. *Journal of Cognitive Neuroscience*, *23*(7), 1808–1822. https://doi.org/10.1162/JOCN.2010.21551

Ebisch, S. J. H., Perrucci, M. G., Ferretti, A., Del Gratta, C., Romani, G. L., & Gallese, V. (2008). The Sense of Touch: Embodied Simulation in a Visuotactile Mirroring Mechanism for Observed Animate or Inanimate Touch. *Journal of Cognitive Neuroscience*, *20*(9), 1611–1623. https://doi.org/10.1162/JOCN.2008.20111

Ebisch, S. J. H., Salone, A., Ferri, F., De Berardis, D., Romani, G. L., Ferro, F. M., & Gallese, V. (2013). Out of touch with reality? Social perception in first-episode schizophrenia. *Social Cognitive and Affective Neuroscience*, *8*(4), 394–403. https://doi.org/10.1093/SCAN/NSS012

Ehrsson, H. H. (2007). The Experimental Induction of Out-of-Body Experiences. *Science*, *317*(5841), 1048–1048. https://doi.org/10.1126/science.1142175

Ehrsson, H. H. (2020). Multisensory processes in body ownership. In K. Sathian & V. S. Ramachandran (Eds.), *Multisensory Perception* (pp. 179–200). Elsevier. https://doi.org/10.1016/B978-0-12-812492-5.00008-5

Ellingsen, D. M., Leknes, S., Løseth, G., Wessberg, J., & Olausson, H. (2016). The neurobiology shaping affective touch: Expectation, motivation, and meaning in the multisensory context. *Frontiers in Psychology*, *6*(JAN), 1986. https://doi.org/10.3389/FPSYG.2015.01986/BIBTEX

Fadiga, L., Fogassi, L., Pavesi, G., & Rizzolatti, G. (1995). Motor facilitation during action observation: a magnetic stimulation study. *Journal of Neurophysiology*, *73*(6), 2608–2611. https://doi.org/10.1152/jn.1995.73.6.2608

Fairhurst, M. T., Löken, L., & Grossmann, T. (2014). Physiological and Behavioral Responses

Reveal 9-Month-Old Infants' Sensitivity to Pleasant Touch. *Psychological Science, 25*(5), 1124–1131. https://doi.org/10.1177/0956797614527114

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175–191. https://doi.org/10.3758/bf03193146

Ferentzi, E., Vig, L., Lindkjølen, M. J., Lien, M. E., & Köteles, F. (2022). Mental heartbeat tracking and rating of emotional pictures are not related. *Psychological Research, 86*(5), 1487–1494. https://doi.org/10.1007/S00426-021-01593-4/FIGURES/1

Ferrari, E., Butti, N., Gagliardi, C., Romaniello, R., Borgatti, R., & Urgesi, C. (2023). Cognitive predictors of Social processing in congenital atypical development. *Journal of Autism and Developmental Disorders*, *53*(9), 3343–3355. https://doi.org/10.1007/s10803-022-05630-y

Ferri, F., Frassinetti, F., Ardizzi, M., Costantini, M., & Gallese, V. (2012). A Sensorimotor Network for the Bodily Self. *Journal of Cognitive Neuroscience*, *24*(7), 1584–1595. https://doi.org/10.1162/jocn_a_00230

Field, T. (2010). Touch for socioemotional and physical well-being: A review. *Developmental Review, 30*(4), 367–383. https://doi.org/10.1016/J.DR.2011.01.001

Filippetti, M. L., Lloyd-Fox, S., Longo, M. R., Farroni, T., & Johnson, M. H. (2015). Neural Mechanisms of Body Awareness in Infants. *Cerebral Cortex, 25*(10), 3779–3787. https://doi.org/10.1093/cercor/bhu261

Finegan, J.-A. K., Cole, T. R. P., Kingwell, E., Smith, M. Lou, Smith, M., & Sitarenios, G. (1994). Language and Behavior in Children with Sotos Syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, *33*(9), 1307–1315. https://doi.org/10.1097/00004583-199411000-00013

Finisguerra, A., Ticini, L. F., Kirsch, L. P., Cross, E. S., Kotz, S. A., & Urgesi, C. (2021). Dissociating embodiment and emotional reactivity in motor responses to artworks. *Cognition*, *212*, 104663. https://doi.org/10.1016/J.COGNITION.2021.104663

Foglia, L., & Wilson, R. A. (2013). Embodied cognition. *Wiley Interdisciplinary Reviews: Cognitive Science*, *4*(3), 319–325. https://doi.org/10.1002/WCS.1226

Fotopoulou, A., von Mohr, M., & Krahé, C. (2022). Affective regulation through touch: homeostatic and allostatic mechanisms. *Current Opinion in Behavioral Sciences*, *43*, 80–87. https://doi.org/10.1016/J.COBEHA.2021.08.008

Frassinetti, F., Ferri, F., Maini, M., Benassi, M. G., & Gallese, V. (2011). Bodily self: An implicit knowledge of what is explicitly unknown. *Experimental Brain Research*, *212*(1), 153–160. https://doi.org/10.1007/s00221-011-2708-x

Friston, K. (2012). The history of the future of the Bayesian brain. *NeuroImage*, *62*(2), 1230–1233. https://doi.org/10.1016/j.neuroimage.2011.10.004

Friston, K., Mattout, J., & Kilner, J. (2011). Action understanding and active inference. *Biological Cybernetics*, *104*(1–2), 137–160. https://doi.org/10.1007/s00422-011-0424-z

Frost-Karlsson, M., Capusan, A. J., Perini, I., Olausson, H., Zetterqvist, M., Gustafsson, P. A., & Boehme, R. (2022). Neural processing of self-touch and other-touch in anorexia nervosa and autism spectrum condition. *NeuroImage: Clinical*, *36*, 103264. https://doi.org/10.1016/j.nicl.2022.103264

Fukushima, H., Terasawa, Y., & Umeda, S. (2011). Association between interoception and empathy: Evidence from heartbeat-evoked brain potential. *International Journal of Psychophysiology*, *79*(2), 259–265. https://doi.org/10.1016/J.IJPSYCHO.2010.10.015

Füstös, J., Gramann, K., Herbert, B. M., & Pollatos, O. (2013). On the embodiment of emotion regulation: Interoceptive awareness facilitates reappraisal. *Social Cognitive and Affective Neuroscience, 8*(8), 911–917. https://doi.org/10.1093/scan/nss089

Gagliardi, C., Brenna, V., Romaniello, R., Arrigoni, F., Tavano, A., Romani, M., Valente, E. M., & Borgatti, R. (2015). Cognitive rehabilitation in a child with Joubert Syndrome: Developmental trends and adaptive changes in a single case report. *Research in Developmental Disabilities, 47*, 375–384. https://doi.org/10.1016/j.ridd.2015.09.013

Gallagher, S. (2000). Philosophical conceptions of the self: implications for cognitive science. *Trends in Cognitive Sciences*, *4*(1), 14–21. https://doi.org/10.1016/S1364-6613(99)01417-5

Gallagher, S., & Cole, J. (1995). Body schema and body image in a deafferented subject. *Journal of Mind and Behavior, 16*(4), 369–390.

Gallese, V., & Ebisch, S. (2013). Embodied Simulation and Touch: the Sense of Touch in Social Cognition. *Phenomenology and Mind*, *4*, 196–210. https://doi.org/10.13128/PHE_MI-19602

Gallese, V., & Sinigaglia, C. (2010). The bodily self as power for action. *Neuropsychologia*, *48*(3), 746–755. https://doi.org/10.1016/j.neuropsychologia.2009.09.038

Gao, Q., Ping, X., & Chen, W. (2019). Body influences on social cognition through interoception. *Frontiers in Psychology*, *10*(SEP), 467171. https://doi.org/10.3389/FPSYG.2019.02066/BIBTEX

Gardiner, K., Chitayat, D., Choufani, S., Shuman, C., Blaser, S., Terespolsky, D., Farrell, S., Reiss, R., Wodak, S., Pu, S., Ray, P. N., Baskin, B., & Weksberg, R. (2012). Brain abnormalities in patients with Beckwith–Wiedemann syndrome. *American Journal of Medical Genetics Part A, 158A*(6), 1388–1394. https://doi.org/10.1002/ajmg.a.35358

Garfinkel, S. N., Barrett, A. B., Minati, L., Dolan, R. J., Seth, A. K., & Critchley, H. D. (2013). What the heart forgets: Cardiac timing influences memory for words and is modulated by metacognition and interoceptive sensitivity. *Psychophysiology*, *50*(6), 505–512. https://doi.org/10.1111/PSYP.12039

Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., & Critchley, H. D. (2015). Knowing your own heart: Distinguishing interoceptive accuracy from interoceptive awareness. *Biological Psychology*, *104*, 65–74. https://doi.org/10.1016/j.biopsycho.2014.11.004

Gatti, E., Ionio, C., Traficante, D., & Confalonieri, E. (2014). "I Like My Body; Therefore, I Like Myself": How Body Image Influences Self-Esteem—A Cross-Sectional Study on Italian Adolescents. *Europe's Journal of Psychology*, *10*(2), 301–317. https://doi.org/10.5964/ejop.v10i2.703

Gauduel, T., Blondet, C., Gonzalez-Monge, S., Bonaiuto, J., & Gomez, A. (2023). Alteration of body representation in typical and atypical motor development. *Developmental Science*, e13455. https://doi.org/10.1111/DESC.13455

Gazzola, V., & Keysers, C. (2009). The observation and execution of actions share motor and somatosensory voxels in all tested subjects: Single-subject analyses of unsmoothed fMRI data. *Cerebral Cortex*, *19*(6), 1239–1255. https://doi.org/10.1093/cercor/bhn181

Gentsch, A., Panagiotopoulou, E., & Fotopoulou, A. (2015). Active Interpersonal Touch Gives Rise to the Social Softness Illusion. *Current Biology*, *25*(18), 2392–2397. https://doi.org/10.1016/J.CUB.2015.07.049

Gomez, A., Costa, M., Lio, G., Sirigu, A., & Demily, C. (2020). Face first impression of trustworthiness in Williams Syndrome: Dissociating automatic vs decision based perception. *Cortex*, *132*, 99–112. https://doi.org/10.1016/J.CORTEX.2020.07.015

Grigorenko, E. L., Compton, D. L., Fuchs, L. S., Wagner, R. K., Willcutt, E. G., & Fletcher, J. M. (2020). Understanding, educating, and supporting children with specific learning disabilities:

50 years of science and practice. *American Psychologist*, *75*(1), 37–51. https://doi.org/10.1037/amp0000452

Guell, X., Gabrieli, J. D. E., & Schmahmann, J. D. (2018). Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *NeuroImage*, *172*, 437–449. https://doi.org/10.1016/j.neuroimage.2018.01.082

Gursul, D., Goksan, S., Hartley, C., Mellado, G. S., Moultrie, F., Hoskin, A., Adams, E., Hathway, G., Walker, S., McGlone, F., & Slater, R. (2018). Stroking modulates noxious-evoked brain activity in human infants. *Current Biology*, *28*(24), R1380–R1381. https://doi.org/10.1016/j.cub.2018.11.014

Habig, K., Schänzer, A., Schirner, W., Lautenschläger, G., Dassinger, B., Olausson, H., Birklein, F., Gizewski, E. R., & Krämer, H. H. (2017). Low threshold unmyelinated mechanoafferents can modulate pain. *BMC Neurology*, *17*(1), 1–11. https://doi.org/10.1186/S12883-017-0963-6/TABLES/1

Haggarty, C. J., Makdani, A., & McGlone, F. (2023). Affective Touch: Psychophysics, Physiology and Vicarious Touch Perception. *Neuromethods*, *196*, 109–128. https://doi.org/10.1007/978-1-0716-3068-6_6/COVER

Haggarty, C. J., Malinowski, P., McGlone, F. P., & Walker, S. C. (2020). Autistic traits modulate cortical responses to affective but not discriminative touch. *European Journal of Neuroscience*, *51*(8), 1844–1855. https://doi.org/10.1111/ejn.14637

Haggarty, C. J., Moore, D. J., Trotter, P. D., Hagan, R., McGlone, F. P., & Walker, S. C. (2021). Vicarious ratings of social touch the effect of age and autistic traits. *Scientific Reports 2021 11:1*, *11*(1), 1–13. https://doi.org/10.1038/s41598-021-98802-2

Hanley, M., Riby, D. M., Caswell, S., Rooney, S., & Back, E. (2013). Looking and thinking: How individuals with Williams syndrome make judgements about mental states. *Research in Developmental Disabilities*, *34*(12), 4466–4476. https://doi.org/10.1016/j.ridd.2013.09.026

Harris, J. R., & Fahrner, J. A. (2019). Disrupted epigenetics in the Sotos syndrome neurobehavioral phenotype. *Current Opinion in Psychiatry*, *32*(2), 55–59. https://doi.org/10.1097/YCO.0000000000000481

Head, H., & Holmes, G. (1911). Sensory disturbances from cerebral lesions. *Brain*, *34*(2–3), 102–254. https://doi.org/10.1093/brain/34.2-3.102

Herbert, B. M., & Pollatos, O. (2012). The Body in the Mind: On the Relationship Between Interoception and Embodiment. *Topics in Cognitive Science*, *4*(4), 692–704. https://doi.org/10.1111/j.1756-8765.2012.01189.x

Hétu, S., Grégoire, M., Saimpont, A., Coll, M.-P., Eugène, F., Michon, P.-E., & Jackson, P. L. (2013). The neural network of motor imagery: An ALE meta-analysis. *Neuroscience & Biobehavioral Reviews*, *37*(5), 930–949. https://doi.org/10.1016/j.neubiorev.2013.03.017

Heydrich, L., Aspell, J. E., Marillier, G., Lavanchy, T., Herbelin, B., & Blanke, O. (2018). Cardio-visual full body illusion alters bodily self-consciousness and tactile processing in somatosensory cortex. *Scientific Reports*, *8*(1), 9230. https://doi.org/10.1038/s41598-018-27698-2

Holroyd, S., Reiss, A. L., & Bryan, R. N. (1991). Autistic features in Joubert syndrome: A genetic disorder with agenesis of the cerebellar vermis. *Biological Psychiatry*, *29*(3), 287–294. https://doi.org/10.1016/0006-3223(91)91291-X

Iachini, T., Coello, Y., Frassinetti, F., & Ruggiero, G. (2014). Body space in social interactions: A comparison of reaching and comfort distance in immersive virtual reality. *PLoS ONE*, *9*(11), 25–27. https://doi.org/10.1371/journal.pone.0111511

Ibernon, L., Touchet, C., & Pochon, R. (2018). Emotion recognition as a real strength in Williams Syndrome: Evidence from a dynamic non-verbal task. *Frontiers in Psychology*, *9*(APR), 463. https://doi.org/10.3389/FPSYG.2018.00463/BIBTEX

Ionta, S., Gassert, R., & Blanke, O. (2011). Multi-Sensory and Sensorimotor Foundation of Bodily Self-Consciousness – An Interdisciplinary Approach. *Frontiers in Psychology*, *2*. https://doi.org/10.3389/fpsyg.2011.00383

Ireton, H., & Glascoe, F. P. (1995). Assessin Children's Development Using Parents' Reports: The Child Development Inventory. *Clinical Pediatrics*, *34*(5), 248–255. https://doi.org/10.1177/000992289503400504

Jablonski, N. G. (2021). Social and affective touch in primates and its role in the evolution of social cohesion. *Neuroscience*, *464*, 117–125. https://doi.org/10.1016/J.NEUROSCIENCE.2020.11.024

Jakubiak, B. K., & Feeney, B. C. (2017). Affectionate Touch to Promote Relational, Psychological, and Physical Well-Being in Adulthood: A Theoretical Model and Review of the Research. *Personality and Social Psychology Review*, *21*(3), 228–252. https://doi.org/10.1177/1088868316650307

James, W. (1890). The Principles Of Psychology. In *The Principles of Psychology*. H. Holt and Company.

Keizer, A., Heijman, J. O., & Dijkerman, H. C. (2022). Do transdiagnostic factors influence affective touch perception in psychiatric populations? *Current Opinion in Behavioral Sciences*, *43*, 125–130. https://doi.org/10.1016/J.COBEHA.2021.09.006

Keizer, A., Van Elburg, A., Helms, R., & Dijkerman, H. C. (2016). A Virtual Reality Full Body

Illusion Improves Body Image Disturbance in Anorexia Nervosa. *PLOS ONE*, *11*(10), e0163921. https://doi.org/10.1371/JOURNAL.PONE.0163921

Kelly, S. N., & Shearer, J. (2020). Appearance and Speech Satisfaction and Their Associations With Psychosocial Difficulties Among Young People With Cleft Lip and/or Palate. *The Cleft Palate-Craniofacial Journal*, *57*(8), 1008–1017. https://doi.org/10.1177/1055665620926083

Kent, L., Bowdin, S., Kirby, G. A., Cooper, W. N., & Maher, E. R. (2008). Beckwith Weidemann syndrome: A behavioral phenotype–genotype study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147B*(7), 1295–1297. https://doi.org/10.1002/ajmg.b.30729

Kessler, K., & Thomson, L. A. (2010). The embodied nature of spatial perspective taking: Embodied transformation versus sensorimotor interference. *Cognition*, *114*(1), 72–88. https://doi.org/10.1016/j.cognition.2009.08.015

Keysers, C., Kaas, J. H., & Gazzola, V. (2010). Somatosensation in social perception. *Nature Reviews Neuroscience*, *11*(6), 417–428. https://doi.org/10.1038/nrn2833

Keysers, C., Wicker, B., Gazzola, V., Anton, J. L., Fogassi, L., & Gallese, V. (2004). A Touching Sight: SII/PV Activation during the Observation and Experience of Touch. *Neuron*, *42*(2), 335–346. https://doi.org/10.1016/S0896-6273(04)00156-4

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. *Cognitive Processing*, *8*(3), 159–166. https://doi.org/10.1007/s10339-007-0170-2

Kirsch, L. P., Besharati, S., Papadaki, C., Crucianelli, L., Bertagnoli, S., Ward, N., Moro, V., Jenkinson, P. M., & Fotopoulou, A. (2020). Damage to the right insula disrupts the perception of affective touch. *ELife*, *9*. https://doi.org/10.7554/ELIFE.47895

Kirsch, L. P., Krahé, C., Blom, N., Crucianelli, L., Moro, V., Jenkinson, P. M., & Fotopoulou, A.

(2018). Reading the mind in the touch: Neurophysiological specificity in the communication of emotions by touch. *Neuropsychologia*, *116*, 136–149. https://doi.org/10.1016/j.neuropsychologia.2017.05.024

Koch, A., & Pollatos, O. (2014). Cardiac sensitivity in children: Sex differences and its relationship to parameters of emotional processing. *Psychophysiology*, *51*(9), 932–941. https://doi.org/10.1111/psyp.12233

Koreki, A., Funayama, M., Terasawa, Y., Onaya, M., & Mimura, M. (2021). Aberrant Interoceptive Accuracy in Patients With Schizophrenia Performing a Heartbeat Counting Task. *Schizophrenia Bulletin Open*, *2*(1). https://doi.org/10.1093/SCHIZBULLOPEN/SGAA067

Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY—Second Edition (NEPSY-II)*. Harcourt Assessment.

Körmendi, J., Ferentzi, E., & Köteles, F. (2022). A heartbeat away from a valid tracking task. An empirical comparison of the mental and the motor tracking task. *Biological Psychology*, *171*, 108328. https://doi.org/10.1016/J.BIOPSYCHO.2022.108328

Kuusikko, S., Pollock-Wurman, R., Jussila, K., Carter, A. S., Mattila, M. L., Ebeling, H., Pauls, D. L., & Moilanen, I. (2008). Social anxiety in high-functioning children and adolescents with autism and Asperger syndrome. *Journal of Autism and Developmental Disorders*, *38*(9), 1697–1709. https://doi.org/10.1007/S10803-008-0555-9/TABLES/3

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00863

Lamm, C., Silani, G., & Singer, T. (2015). Distinct neural networks underlying empathy for pleasant and unpleasant touch. *Cortex*, *70*, 79–89.

https://doi.org/10.1016/J.CORTEX.2015.01.021

Landau, B., & Zukowski, A. (2003). Objects, motions, and paths: spatial language in children with Williams syndrome. *Developmental Neuropsychology*, *23*(1–2), 105–137. https://doi.org/10.1080/87565641.2003.9651889

Lane, C., Milne, E., & Freeth, M. (2016). Cognition and Behaviour in Sotos Syndrome: A Systematic Review. *PLOS ONE*, *11*(2), e0149189. https://doi.org/10.1371/journal.pone.0149189

Lane, C., Milne, E., & Freeth, M. (2017). Characteristics of Autism Spectrum Disorder in Sotos Syndrome. *Journal of Autism and Developmental Disorders*, *47*(1), 135–143. https://doi.org/10.1007/s10803-016-2941-z

Lane, C., Milne, E., & Freeth, M. (2019). The cognitive profile of Sotos syndrome. *Journal of Neuropsychology*, *13*(2), 240–252. https://doi.org/10.1111/jnp.12146

Lane, C., Van Herwegen, J., & Freeth, M. (2019a). Exploring the approximate number system in Sotos syndrome: insights from a dot comparison task. *Journal of Intellectual Disability Research*, *63*(8), 917–925. https://doi.org/10.1111/jir.12604

Lane, C., Van Herwegen, J., & Freeth, M. (2019b). Parent-Reported Communication Abilities of Children with Sotos Syndrome: Evidence from the Children's Communication Checklist-2. *Journal of Autism and Developmental Disorders*, *49*(4), 1475–1483. https://doi.org/10.1007/s10803-018-3842-0

Lee Masson, H., Pillet, I., Amelynck, S., Van De Plas, S., Hendriks, M., Op De Beeck, H., & Boets, B. (2019). Intact neural representations of affective meaning of touch but lack of embodied resonance in autism: a multi-voxel pattern analysis study. *Molecular Autism*, *10*(1). https://doi.org/10.1186/s13229-019-0294-0

Lee Masson, H., Van De Plas, S., Daniels, N., & Op de Beeck, H. (2018). The multidimensional representational space of observed socio-affective touch experiences. *NeuroImage*, *175*, 297–314. https://doi.org/10.1016/j.neuroimage.2018.04.007

Legrand, D. (2006). The Bodily Self: The Sensori-Motor Roots of Pre-Reflective Self-Consciousness. *Phenomenology and the Cognitive Sciences*, *5*(1), 89–118. https://doi.org/10.1007/s11097-005-9015-6

Lenggenhager, B., Tadi, T., Metzinger, T., & Blanke, O. (2007). Video ergo sum: Manipulating bodily self-consciousness. *Science*, *317*(5841), 1096–1099. https://doi.org/10.1126/SCIENCE.1143439/SUPPL_FILE/LENGGENHAGER.SOM.PDF

Lepage, J. F., Tremblay, S., & Théoret, H. (2010). Early non-specific modulation of corticospinal excitability during action observation. *European Journal of Neuroscience*, *31*(5), 931–937. https://doi.org/10.1111/J.1460-9568.2010.07121.X

Liljencrantz, J., Strigo, I., Ellingsen, D. M., Krämer, H. H., Lundblad, L. C., Nagi, S. S., Leknes, S., & Olausson, H. (2017). Slow brushing reduces heat pain in humans. *European Journal of Pain*, *21*(7), 1173–1185. https://doi.org/10.1002/EJP.1018

Liuzza, M. T., Candidi, M., Sforza, A. L., & Aglioti, S. M. (2015). Harm avoiders suppress motor resonance to observed immoral actions. *Social Cognitive and Affective Neuroscience*, *10*(1), 72–77. https://doi.org/10.1093/scan/nsu025

Löken, L. S., Evert, M., & Wessberg, J. (2011). Pleasantness of touch in human glabrous and hairy skin: Order effects on affective ratings. *Brain Research*, *1417*, 9–15. https://doi.org/10.1016/J.BRAINRES.2011.08.011

Löken, L. S., Wessberg, J., Morrison, I., McGlone, F., & Olausson, H. (2009). Coding of pleasant touch by unmyelinated afferents in humans. *Nature Neuroscience 2009 12:5*, *12*(5), 547–548.

https://doi.org/10.1038/nn.2312

Lorusso, M. L., Galli, R., Libera, L., Gagliardi, C., Borgatti, R., & Hollebrandse, B. (2007). Indicators of theory of mind in narrative production: A comparison between individuals with genetic syndromes and typically developing children. *Clinical Linguistics and Phonetics, 21*(1), 37–53. https://doi.org/10.1080/02699200600565871

Lough, E., Flynn, E., & Riby, D. M. (2016). Personal Space Regulation in Williams Syndrome: The Effect of Familiarity. *Journal of Autism and Developmental Disorders, 46*(10), 3207–3215. https://doi.org/10.1007/s10803-016-2864-8

Lough, E., Hanley, M., Rodgers, J., South, M., Kirk, H., Kennedy, D. P., & Riby, D. M. (2015). Violations of Personal Space in Young People with Autism Spectrum Disorders and Williams Syndrome: Insights from the Social Responsiveness Scale. *Journal of Autism and Developmental Disorders*, *45*(12), 4101–4108. https://doi.org/10.1007/S10803-015-2536-0/METRICS

Määttä, H., Honkanen, M., Hurtig, T., Taanila, A., Ebeling, H., & Koivumaa-Honkanen, H. (2022). Childhood chronic condition and subsequent self-reported internalizing and externalizing problems in adolescence: a birth cohort study. *European Journal of Pediatrics*, *181*(9), 3377–3387. https://doi.org/10.1007/S00431-022-04505-9/TABLES/4

Mabe, P. A., Treiber, F. A., & Riley, W. T. (1991). Examining Emotional Distress During Pediatric Hospitalization for School-Aged Children. *Children's Health Care, 20*(3), 162–169. https://doi.org/10.1207/s15326888chc2003_5

Macchiaiolo, M., Panfili, F. M., Vecchio, D., Gonfiantini, M. V., Cortellessa, F., Caciolo, C., Zollino, M., Accadia, M., Seri, M., Chinali, M., Mammì, C., Tartaglia, M., Bartuli, A., Alfieri, P., & Priolo, M. (2022). A deep phenotyping experience: up to date in management and diagnosis of Malan syndrome in a single center surveillance report. *Orphanet Journal of Rare*

Diseases, *17*(1), 1–16. https://doi.org/10.1186/S13023-022-02384-9/TABLES/4

Malan, V., Rajan, D., Thomas, S., Shaw, A. C., Louis Dit Picard, H., Layet, V., Till, M., Van Haeringen, A., Mortier, G., Nampoothiri, S., Pušeljić, S., Legeai-Mallet, L., Carter, N. P., Vekemans, M., Munnich, A., Hennekam, R. C., Colleaux, L., & Cormier-Daire, V. (2010). Distinct Effects of Allelic NFIX Mutations on Nonsense-Mediated mRNA Decay Engender Either a Sotos-like or a Marshall-Smith Syndrome. *The American Journal of Human Genetics*, *87*(2), 189–198. https://doi.org/10.1016/J.AJHG.2010.07.001

Malerba, G., Bellazzecca, S., Urgesi, C., Butti, N., D'Angelo, M. G., Diella, E., & Biffi, E. (2023). Is Social Training Delivered with a Head-Mounted Display Suitable for Patients with Hereditary Ataxia? *Brain Sciences*, *13*(7), 1017. https://doi.org/10.3390/brainsci13071017

Marini, A., Martelli, S., Gagliardi, C., Fabbro, F., & Borgatti, R. (2010). Narrative language in Williams Syndrome and its neuropsychological correlates. *Journal of Neurolinguistics*, *23*(2), 97–111. https://doi.org/10.1016/J.JNEUROLING.2009.10.002

Marshall, P. J., & Meltzoff, A. N. (2020). Body maps in the infant brain: implications for neurodevelopmental disabilities. *Developmental Medicine & Child Neurology*, *62*(7), 778–783. https://doi.org/10.1111/DMCN.14540

Martens, M. A., Wilson, S. J., & Reutens, D. C. (2008). Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry*, *49*(6), 576–608. https://doi.org/10.1111/J.1469-7610.2008.01887.X

Martínez-Castilla, P., Burt, M., Borgatti, R., & Gagliardi, C. (2015). Facial emotion recognition in Williams syndrome and Down syndrome: A matching and developmental study. *Child Neuropsychology*, *21*(5), 668–692. https://doi.org/10.1080/09297049.2014.945408

Martinez, W., Carter, J. S., & Legato, L. J. (2011). Social Competence in Children with Chronic Illness: A Meta-analytic Review. *Journal of Pediatric Psychology*, *36*(8), 878–890. https://doi.org/10.1093/jpepsy/jsr035

Marzoli, D., Menditto, S., Lucafò, C., & Tommasi, L. (2013). Imagining others' handedness: Visual and motor processes in the attribution of the dominant hand to an imagined agent. *Experimental Brain Research*, *229*(1), 37–46. https://doi.org/10.1007/S00221-013-3587-0/TABLES/2

Mauceri, L., Sorge, G., Baieli, S., Rizzo, R., Pavone, L., & Coleman, M. (2000). Aggressive behavior in patients with sotos syndrome. *Pediatric Neurology*, *22*(1), 64–67. https://doi.org/10.1016/S0887-8994(99)00105-8

McElroy, T. D., Duffy, K. A., Hathaway, E. R., Byrne, M. E., & Kalish, J. M. (2023). Investigation of a pervasive immune, cardiac, and behavioral phenotype in Beckwith-Wiedemann syndrome: A case report. *American Journal of Medical Genetics Part A*, *191*(4), 1107–1110. https://doi.org/10.1002/AJMG.A.63114

McGlone, F., Wessberg, J., & Olausson, H. (2014). Discriminative and Affective Touch: Sensing and Feeling. *Neuron*, *82*(4), 737–755. https://doi.org/10.1016/j.neuron.2014.05.001

McHugh, M. L. (2011). Multiple comparison analysis testing in ANOVA. *Biochemia Medica*, *21*(2), 203–209. https://doi.org/10.11613/BM.2011.029

McLean, S. A., & Paxton, S. J. (2019). Body Image in the Context of Eating Disorders. *Psychiatric Clinics of North America*, *42*(1), 145–156. https://doi.org/10.1016/j.psc.2018.10.006

Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E., & Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS ONE*, *7*(11), e48230. https://doi.org/10.1371/journal.pone.0048230

Meijer, S. A., Sinnema, G., Bijstra, J. O., Mellenbergh, G. J., & Wolters, W. H. G. (2000). Social functioning in children with a chronic illness. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *41*(3), 309–317. https://doi.org/10.1111/1469-7610.00615

Meltzoff, A. N., & Marshall, P. J. (2020). Importance of body representations in social-cognitive development: New insights from infant brain science. *Progress in Brain Research*, *254*, 25–48. https://doi.org/10.1016/BS.PBR.2020.07.009

Menghini, D., Addona, F., Costanzo, F., & Vicari, S. (2010). Executive functions in individuals with Williams syndrome. *Journal of Intellectual Disability Research*, *54*(5), 418–432. https://doi.org/10.1111/J.1365-2788.2010.01287.X

Mervis, C. B., & Becerra, A. M. (2007). Language and communicative development in Williams syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*, *13*(1), 3–15. https://doi.org/10.1002/MRDD.20140

Mervis, C. B., Robinson, B. F., Bertrand, J., Morris, C. A., Klein-Tasman, B. P., & Armstrong, S. C. (2000). The Williams Syndrome Cognitive Profile. *Brain and Cognition*, *44*(3), 604–628. https://doi.org/10.1006/BRCG.2000.1232

Miezah, D., Porter, M., Batchelor, J., Boulton, K., & Campos Veloso, G. (2020). Cognitive abilities in Williams syndrome. *Research in Developmental Disabilities*, *104*, 103701. https://doi.org/10.1016/J.RIDD.2020.103701

Minnebusch, D. A., & Daum, I. (2009). Neuropsychological mechanisms of visual face and body perception. *Neuroscience & Biobehavioral Reviews*, *33*(7), 1133–1144. https://doi.org/10.1016/j.neubiorev.2009.05.008

Mirabella, G. (2021). Inhibitory control and impulsive responses in neurodevelopmental disorders. *Developmental Medicine and Child Neurology*, *63*(5), 520–526.

https://doi.org/10.1111/DMCN.14778/ABSTRACT

Montirosso, R., & McGlone, F. (2020). The body comes first. Embodied reparation and the co-creation of infant bodily-self. *Neuroscience & Biobehavioral Reviews*, *113*, 77–87. https://doi.org/10.1016/j.neubiorev.2020.03.003

Morel, A., Peyroux, E., Leleu, A., Favre, E., Franck, N., & Demily, C. (2018). Overview of social cognitive dysfunctions in rare developmental syndromes with psychiatric phenotype. *Frontiers in Pediatrics*, *6*, 102. https://doi.org/10.3389/FPED.2018.00102/BIBTEX

Morrison, I. (2016). ALE meta-analysis reveals dissociable networks for affective and discriminative aspects of touch. *Human Brain Mapping*, *37*(4), 1308–1320. https://doi.org/10.1002/HBM.23103

Morrison, I., Björnsdotter, M., & Olausson, H. (2011). Vicarious Responses to Social Touch in Posterior Insular Cortex Are Tuned to Pleasant Caressing Speeds. *Journal of Neuroscience*, *31*(26), 9554–9562. https://doi.org/10.1523/JNEUROSCI.0397-11.2011

Morrison, I., Löken, L. S., & Olausson, H. (2010). The skin as a social organ. *Experimental Brain Research*, *204*(3), 305–314. https://doi.org/10.1007/S00221-009-2007-Y/FIGURES/2

Mulder, P. A., van Balkom, I. D. C., Landlust, A. M., Priolo, M., Menke, L. A., Acero, I. H., Alkuraya, F. S., Arias, P., Bernardini, L., Bijlsma, E. K., Cole, T., Coubes, C., Dapia, I., Davies, S., Di Donato, N., Elcioglu, N. H., Fahrner, J. A., Foster, A., González, N. G., … Hennekam, R. C. (2020). Development, behaviour and sensory processing in Marshall–Smith syndrome and Malan syndrome: phenotype comparison in two related syndromes. *Journal of Intellectual Disability Research*, *64*(12), 956–969. https://doi.org/10.1111/JIR.12787

Mungkhetklang, C., Crewther, S. G., Bavin, E. L., Goharpey, N., & Parsons, C. (2016). Comparison of Measures of Ability in Adolescents with Intellectual Disability. *Frontiers in Psychology*, *7*.

https://doi.org/10.3389/fpsyg.2016.00683

Mussa, A., Di Candia, S., Russo, S., Catania, S., De Pellegrin, M., Di Luzio, L., Ferrari, M., Tortora, C., Meazzini, M. C., Brusati, R., Milani, D., Zampino, G., Montirosso, R., Riccio, A., Selicorni, A., Cocchi, G., & Ferrero, G. B. (2016). Recommendations of the Scientific Committee of the Italian Beckwith–Wiedemann Syndrome Association on the diagnosis, management and follow-up of the syndrome. *European Journal of Medical Genetics*, *59*(1), 52–64. https://doi.org/10.1016/j.ejmg.2015.11.008

Mussa, A., Russo, S., De Crescenzo, A., Freschi, A., Calzari, L., Maitz, S., Macchiaiolo, M., Molinatto, C., Baldassarre, G., Mariani, M., Tarani, L., Bedeschi, M. F., Milani, D., Melis, D., Bartuli, A., Cubellis, M. V., Selicorni, A., Cirillo Silengo, M., Larizza, L., … Ferrero, G. B. (2016). (Epi)genotype–phenotype correlations in Beckwith–Wiedemann syndrome. *European Journal of Human Genetics*, *24*(2), 183–190. https://doi.org/10.1038/ejhg.2015.88

Mussa, A., Russo, S., Larizza, L., Riccio, A., & Ferrero, G. B. (2016). (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome: a paradigm for genomic medicine. *Clinical Genetics*, *89*(4), 403–415. https://doi.org/10.1111/cge.12635

Naish, K. R., Houston-Price, C., Bremner, A. J., & Holmes, N. P. (2014). Effects of action observation on corticospinal excitability: Muscle specificity, direction, and timing of the mirror response. *Neuropsychologia*, *64*, 331–348. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2014.09.034

Nelson, B. W., Low, C. A., Jacobson, N., Areán, P., Torous, J., & Allen, N. B. (2020). Guidelines for wrist-worn consumer wearable assessment of heart rate in biobehavioral research. *Npj Digital Medicine*, *3*(1), 90. https://doi.org/10.1038/s41746-020-0297-4

Noel, J., Blanke, O., & Serino, A. (2018). From multisensory integration in peripersonal space to bodily self-consciousness: from statistical regularities to statistical inference. *Annals of the*

New York Academy of Sciences, *1426*(1), 146–165. https://doi.org/10.1111/nyas.13867

O’Donnell, A. T., & Habenicht, A. E. (2022). Stigma is associated with illness self-concept in individuals with concealable chronic illnesses. *British Journal of Health Psychology*, *27*(1), 136–158. https://doi.org/10.1111/BJHP.12534

Oishi, S., Harkins, D., Kurniawan, N. D., Kasherman, M., Harris, L., Zalucki, O., Gronostajski, R. M., Burne, T. H. J., & Piper, M. (2019). Heterozygosity for Nuclear Factor One X in mice models features of Malan syndrome. *EBioMedicine*, *39*, 388–400. https://doi.org/10.1016/j.ebiom.2018.11.044

Olausson, H., Wessberg, J., Morrison, I., McGlone, F., & Vallbo, Å. (2010). The neurophysiology of unmyelinated tactile afferents. *Neuroscience & Biobehavioral Reviews*, *34*(2), 185–191. https://doi.org/10.1016/j.neubiorev.2008.09.011

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Palser, E. R., Fotopoulou, A., Pellicano, E., & Kilner, J. M. (2018). The link between interoceptive processing and anxiety in children diagnosed with autism spectrum disorder: Extending adult findings into a developmental sample. *Biological Psychology*, *136*, 13–21. https://doi.org/10.1016/j.biopsycho.2018.05.003

Passolunghi, M. C. (2011). Cognitive and Emotional Factors in Children with Mathematical Learning Disabilities. *International Journal of Disability, Development and Education*, *58*(1), 61–73. https://doi.org/10.1080/1034912X.2011.547351

Patané, I., Farnè, A., & Frassinetti, F. (2017). Cooperative tool-use reveals peripersonal and interpersonal spaces are dissociable. *Cognition*, *166*, 13–22. https://doi.org/10.1016/j.cognition.2017.04.013

Pawling, R., Trotter, P. D., McGlone, F. P., & Walker, S. C. (2017). A positive touch: C-tactile afferent targeted skin stimulation carries an appetitive motivational value. *Biological Psychology*, *129*, 186–194. https://doi.org/10.1016/J.BIOPSYCHO.2017.08.057

Peled-Avron, L., Glasner, L., Gvirts, H. Z., & Shamay-Tsoory, S. G. (2019). The role of the inferior frontal gyrus in vicarious social touch: A transcranial direct current stimulation (tDCS) study. *Developmental Cognitive Neuroscience*, *35*, 115–121. https://doi.org/10.1016/J.DCN.2018.04.010

Peled-Avron, L., Goldstein, P., Yellinek, S., Weissman-Fogel, I., & Shamay-Tsoory, S. G. (2018). Empathy during consoling touch is modulated by mu-rhythm: An EEG study. *Neuropsychologia*, *116*, 68–74. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2017.04.026

Peled-Avron, L., Levy-Gigi, E., Richter-Levin, G., Korem, N., & Shamay-Tsoory, S. G. (2016). The role of empathy in the neural responses to observed human social touch. *Cognitive, Affective and Behavioral Neuroscience*, *16*(5), 802–813. https://doi.org/10.3758/s13415-016-0432-5

Peled-Avron, L., & Shamay-Tsoory, S. G. (2017). Don't touch me! autistic traits modulate early and late ERP components during visual perception of social touch. *Autism Research*, *10*(6), 1141–1154. https://doi.org/10.1002/AUR.1762

Peled-Avron, L., & Woolley, J. D. (2022). Understanding others through observed touch: neural correlates, developmental aspects, and psychopathology. *Current Opinion in Behavioral Sciences*, *43*, 152–158. https://doi.org/10.1016/J.COBEHA.2021.10.002

Petzschner, F. H., Garfinkel, S. N., Paulus, M. P., Koch, C., & Khalsa, S. S. (2021). Computational Models of Interoception and Body Regulation. *Trends in Neurosciences*, *44*(1), 63–76. https://doi.org/10.1016/J.TINS.2020.09.012

Pinquart, M. (2018). Parenting stress in caregivers of children with chronic physical condition—A meta-analysis. *Stress and Health*, *34*(2), 197–207. https://doi.org/10.1002/smi.2780

Pinquart, M., & Shen, Y. (2011). Behavior Problems in Children and Adolescents With Chronic Physical Illness: A Meta-Analysis. *Journal of Pediatric Psychology*, *36*(9), 1003–1016. https://doi.org/10.1093/jpepsy/jsr042

Pinquart, M., & Teubert, D. (2012). Academic, Physical, and Social Functioning of Children and Adolescents With Chronic Physical Illness: A Meta-analysis. *Journal of Pediatric Psychology*, *37*(4), 376–389. https://doi.org/10.1093/jpepsy/jsr106

Pollatos, O., Traut-Mattausch, E., & Schandry, R. (2009). Differential effects of anxiety and depression on interoceptive accuracy. *Depression and Anxiety*, *26*(2), 167–173. https://doi.org/10.1002/da.20504

Porciello, G., Bufalari, I., Minio-Paluello, I., Di Pace, E., & Aglioti, S. M. (2018). The 'Enfacement' illusion: A window on the plasticity of the self. *Cortex*, *104*, 261–275. https://doi.org/10.1016/j.cortex.2018.01.007

Poretti, A., Boltshauser, E., & Valente, E. M. (2014). The Molar Tooth Sign Is Pathognomonic for Joubert Syndrome! *Pediatric Neurology*, *50*(6), e15–e16. https://doi.org/10.1016/J.PEDIATRNEUROL.2013.11.003

Priolo, M. (2019). Nuclear Factor One X Mice model for Malan syndrome: the less the better. *EBioMedicine*, *39*, 15–16. https://doi.org/10.1016/j.ebiom.2018.11.065

Priolo, M., Schanze, D., Tatton-Brown, K., Mulder, P. A., Tenorio, J., Kooblall, K., Acero, I. H., Alkuraya, F. S., Arias, P., Bernardini, L., Bijlsma, E. K., Cole, T., Coubes, C., Dapia, I., Davies, S., Di Donato, N., Elcioglu, N. H., Fahrner, J. A., Foster, A., … Hennekam, R. C. (2018). Further delineation of Malan syndrome. *Human Mutation*, *39*(9), 1226–1237.

https://doi.org/10.1002/HUMU.23563

Raven, J. C. (1982). Revised manual for Raven's Progressive Matrices and Vocabulary Scale. In *Revised manual for Raven's Progressive Matrices and Vocabulary Scale*. NFER Nelson.

Rescorla, L. A. (2005). Assessment of young children using the Achenbach System of Empirically Based Assessment (ASEBA). *Mental Retardation and Developmental Disabilities Research Reviews*, *11*(3), 226–237. https://doi.org/10.1002/mrdd.20071

Rhodes, S. M., Riby, D. M., Park, J., Fraser, E., & Campbell, L. E. (2010). Executive neuropsychological functioning in individuals with Williams syndrome. *Neuropsychologia*, *48*(5), 1216–1226. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2009.12.021

Riby, D. M., & Hancock, P. J. B. (2009). Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. *Journal of Autism and Developmental Disorders*, *39*(3), 421–431. https://doi.org/10.1007/S10803-008-0641-Z

Riccioni, A., Siracusano, M., Arturi, L., Scoppola, C., Ferrara, M., Frattale, I., Galasso, C., Gialloreti, L. E., & Mazzone, L. (2024). Short report: Autistic symptoms in Sotos syndrome, preliminary results from a case-control study. *Research in Developmental Disabilities*, *145*(October 2023), 104655. https://doi.org/10.1016/j.ridd.2023.104655

Rigato, S., Banissy, M. J., Romanska, A., Thomas, R., van Velzen, J., & Bremner, A. J. (2019). Cortical signatures of vicarious tactile experience in four-month-old infants. *Developmental Cognitive Neuroscience*, *35*, 75–80. https://doi.org/10.1016/J.DCN.2017.09.003

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu Rev Neurosci*, *27*, 169–192. https://doi.org/10.1146/annurev.neuro.27.070203.144230

Rizzolatti, G., Scandolara, C., Matelli, M., & Gentilucci, M. (1981a). Afferent properties of periarcuate neurons in macaque monkeys. I. Somatosensory responses. *Behavioural Brain*

Research, *2*(2), 125–146. https://doi.org/10.1016/0166-4328(81)90052-8

Rizzolatti, G., Scandolara, C., Matelli, M., & Gentilucci, M. (1981b). Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses. *Behavioural Brain Research*, *2*(2), 147–163. https://doi.org/10.1016/0166-4328(81)90053-X

Romani, M., Micalizzi, A., & Valente, E. M. (2013). Joubert syndrome: congenital cerebellar ataxia with the molar tooth. *The Lancet Neurology*, *12*(9), 894–905. https://doi.org/10.1016/S1474-4422(13)70136-4

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., Di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Lefaucheur, J. P., Leocani, L., … Hallett, M. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology*, *132*(1), 269–306. https://doi.org/https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039. https://doi.org/https://doi.org/10.1016/j.clinph.2009.08.016

Royston, R., Waite, J., & Howlin, P. (2019). Williams syndrome: Recent advances in our understanding of cognitive, social and psychological functioning. *Current Opinion in Psychiatry*, *32*(2), 60–66. https://doi.org/10.1097/YCO.0000000000000477

Ruta, L., Mazzone, D., Mazzone, L., Wheelwright, S., & Baron-Cohen, S. (2012). The Autism-Spectrum Quotient—Italian Version: A Cross-Cultural Confirmation of the Broader Autism Phenotype. *Journal of Autism and Developmental Disorders*, *42*(4), 625–633. https://doi.org/10.1007/s10803-011-1290-1

Sacks, O. (1985). *The Man Who Mistook His Wife for a Hat and Other Clinical Tale*. Summit Books.

Sailer, U., & Leknes, S. (2022). Meaning makes touch affective. *Current Opinion in Behavioral Sciences*, *44*, 101099. https://doi.org/10.1016/J.COBEHA.2021.101099

Sarimski, K. (2003). Behavioural and emotional characteristics in children with Sotos syndrome and learning disabilities. *Developmental Medicine and Child Neurology*, *45*(3), 172–178. https://doi.org/10.1017/S0012162203000331

Scarpina, Serino, Keizer, Chirico, Scacchi, Castelnuovo, Mauro, & Riva. (2019). The Effect of a Virtual-Reality Full-Body Illusion on Body Representation in Obesity. *Journal of Clinical Medicine*, *8*(9), 1330. https://doi.org/10.3390/jcm8091330

Schaefer, G. B., Bodensteiner, J. B., Buehler, B. A., Lin, A., & Cole, T. R. P. (1997). The neuroimaging findings in Sotos syndrome. *American Journal of Medical Genetics*, *68*(4), 462–465. https://doi.org/10.1002/(SICI)1096-8628(19970211)68:4<462::AID-AJMG18>3.0.CO;2-Q

Schaefer, M., Heinze, H. J., & Rotte, M. (2012). Embodied empathy for tactile events: Interindividual differences and vicarious somatosensory responses during touch observation. *NeuroImage*, *60*(2), 952–957. https://doi.org/10.1016/J.NEUROIMAGE.2012.01.112

Schaefer, M., Kühn, E., Schweitzer, F., & Muehlhan, M. (2023). The neural networks of touch observation. *Imaging Neuroscience*, *2*, 1–16. https://doi.org/10.1162/imag_a_00065

Schaefer, M., Rotte, M., Heinze, H. J., & Denke, C. (2013). Mirror-like brain responses to observed touch and personality dimensions. *Frontiers in Human Neuroscience*, *7*(MAY), 44655. https://doi.org/10.3389/fnhum.2013.00227

Schandry, R. (1981). Heart Beat Perception and Emotional Experience. *Psychophysiology*, *18*(4), 483–488. https://doi.org/10.1111/J.1469-8986.1981.TB02486.X

Schauder, K. B., Mash, L. E., Bryant, L. K., & Cascio, C. J. (2015). Interoceptive ability and body awareness in autism spectrum disorder. *Journal of Experimental Child Psychology*, *131*, 193–200. https://doi.org/10.1016/j.jecp.2014.11.002

Schieppati, M., Trompetto, C., & Abbruzzese, G. (1996). Selective facilitation of responses to cortical stimulation of proximal and distal arm muscles by precision tasks in man. *The Journal of Physiology*, *491*(2), 551–562. https://doi.org/10.1113/JPHYSIOL.1996.SP021239

Schirmer, A., Cham, C., Zhao, Z., & Croy, I. (2023). What Makes Touch Comfortable? An Examination of Touch Giving and Receiving in Two Cultures. *Personality and Social Psychology Bulletin*, *49*(9), 1392–1407. https://doi.org/10.1177/01461672221105966

Schirmer, A., Chiu, M. H., & Croy, I. (2021). More than one kind: Different sensory signatures and functions divide affectionate touch. *Emotion*, *21*(6), 1268–1280. https://doi.org/10.1037/emo0000966

Schirmer, A., Lai, O., McGlone, F., Cham, C., & Lau, D. (2022). Gentle stroking elicits somatosensory ERP that differentiates between hairy and glabrous skin. *Social Cognitive and Affective Neuroscience*, *17*(9), 864–875. https://doi.org/10.1093/scan/nsac012

Schirmer, A., & McGlone, F. (2019). A touching Sight: EEG/ERP correlates for the vicarious processing of affectionate touch. *Cortex*, *111*, 1–15. https://doi.org/10.1016/J.CORTEX.2018.10.005

Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain*. https://doi.org/10.1093/brain/121.4.561

Schmidt, S. N. L., Hass, J., Kirsch, P., & Mier, D. (2021). The human mirror neuron system—A common neural basis for social cognition? *Psychophysiology*, *58*(5), e13781.

https://doi.org/10.1111/psyp.13781

Schuurmans, A. A. T., de Looff, P., Nijhof, K. S., Rosada, C., Scholte, R. H. J., Popma, A., & Otten, R. (2020). Validity of the Empatica E4 Wristband to Measure Heart Rate Variability (HRV) Parameters: a Comparison to Electrocardiography (ECG). *Journal of Medical Systems*, *44*(11), 1–11. https://doi.org/10.1007/S10916-020-01648-W/TABLES/3

Schwoebel, J., & Coslett, H. B. (2005). Evidence for Multiple, Distinct Representations of the Human Body. *Journal of Cognitive Neuroscience*, *17*(4), 543–553. https://doi.org/10.1162/0898929053467587

Serino, A. (2019). Peripersonal space (PPS) as a multisensory interface between the individual and the environment, defining the space of the self. *Neuroscience & Biobehavioral Reviews*, *99*, 138–159. https://doi.org/10.1016/j.neubiorev.2019.01.016

Serino, A., Alsmith, A., Costantini, M., Mandrigin, A., Tajadura-Jimenez, A., & Lopez, C. (2013). Bodily ownership and self-location: Components of bodily self-consciousness. *Consciousness and Cognition*, *22*(4), 1239–1252. https://doi.org/10.1016/j.concog.2013.08.013

Serrano-Juárez, C. A., Prieto-Corona, B., Rodríguez-Camacho, M., Sandoval-Lira, L., Villalva-Sánchez, Á. F., Yáñez-Téllez, M. G., & López, M. F. R. (2023). Neuropsychological Genotype–Phenotype in Patients with Williams Syndrome with Atypical Deletions: A Systematic Review. *Neuropsychology Review*, *33*(4), 891–911. https://doi.org/10.1007/s11065-022-09571-2

Seth, A. K. (2013). Interoceptive inference, emotion, and the embodied self. *Trends in Cognitive Sciences*, *17*(11), 565–573. https://doi.org/10.1016/j.tics.2013.09.007

Seth, A. K., & Friston, K. J. (2016). Active interoceptive inference and the emotional brain. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *371*(1708), 20160007.

https://doi.org/10.1098/rstb.2016.0007

Sheth, K., Moss, J., Hyland, S., Stinton, C., Cole, T., & Oliver, C. (2015). The behavioral characteristics of Sotos syndrome. *American Journal of Medical Genetics Part A*, *167*(12), 2945–2956. https://doi.org/10.1002/ajmg.a.37373

Shipster, C., Morgan, A., & Dunaway, D. (2012). Psychosocial, Feeding, and Drooling Outcomes in Children with Beckwith Wiedemann Syndrome following Tongue Reduction Surgery. *The Cleft Palate-Craniofacial Journal*, *49*(4), 25–34. https://doi.org/10.1597/10-232

Simões, M., Mouga, S., Pereira, A. C., de Carvalho, P., Oliveira, G., & Castelo-Branco, M. (2020). Virtual Reality Immersion Rescales Regulation of Interpersonal Distance in Controls but not in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *50*(12), 4317–4328. https://doi.org/10.1007/s10803-020-04484-6

Siracusano, M., Dante, C., Sarnataro, R., Arturi, L., Riccioni, A., Carloni, E., Cicala, M., Gialloreti, L. E., Galasso, C., Conteduca, G., Coviello, D., & Mazzone, L. (2024). A longitudinal characterization of the adaptive and behavioral profile in Sotos syndrome. *American Journal of Medical Genetics Part A*, *January*, 1–9. https://doi.org/10.1002/ajmg.a.63553

Siracusano, M., Riccioni, A., Frattale, I., Arturi, L., Dante, C., Galasso, C., Gialloreti, L. E., Conteduca, G., Testa, B., Malacarne, M., Coviello, D., & Mazzone, L. (2023). Cognitive, adaptive and behavioral profile in Sotos syndrome children with 5q35 microdeletion or intragenic variants. *American Journal of Medical Genetics Part A*, *191*(7), 1836–1848. https://doi.org/10.1002/ajmg.a.63211

Sirigu, A., Grafman, J., Bressler, K., & Sunderland, T. (1991). Multiple representations contribute to body knowledge processing. *Brain*, *114*(1), 629–642. https://doi.org/10.1093/brain/114.1.629

Slade, P. D. (1994). What is body image? *Behaviour Research and Therapy*, *32*(5), 497–502. https://doi.org/10.1016/0005-7967(94)90136-8

Slaughter, V., Heron, M., & Sim, S. (2002). Development of preferences for the human body shape in infancy. *Cognition*, *85*(3). https://doi.org/10.1016/S0010-0277(02)00111-7

Slavotinek, A., Gaunt, L., & Donnai, D. (1997). Paternally inherited duplications of 11p15.5 and Beckwith-Wiedemann syndrome. *Journal of Medical Genetics*, *34*(10), 819–826. https://doi.org/10.1136/JMG.34.10.819

Smit, S., Moerel, D., Zopf, R., & Rich, A. N. (2023). Vicarious touch: Overlapping neural patterns between seeing and feeling touch. *NeuroImage*, *278*, 120269. https://doi.org/10.1016/J.NEUROIMAGE.2023.120269

Smith, H., Lane, C., Al-Jawahiri, R., & Freeth, M. (2023). Sensory processing in Sotos syndrome and Tatton-Brown–Rahman Syndrome. *Journal of Psychopathology and Clinical Science*, *132*(6), 768–778. https://doi.org/10.1037/abn0000837

Spain, D., Sin, J., Linder, K. B., McMahon, J., & Happé, F. (2018). Social anxiety in autism spectrum disorder: A systematic review. *Research in Autism Spectrum Disorders*, *52*, 51–68. https://doi.org/10.1016/J.RASD.2018.04.007

Spence, C. (2022). Multisensory contributions to affective touch. *Current Opinion in Behavioral Sciences*, *43*, 40–45. https://doi.org/10.1016/J.COBEHA.2021.08.003

Stein, H. (2021). Why Does the Neocortex Need the Cerebellum for Working Memory? *The Journal of Neuroscience*, *41*(30), 6368–6370. https://doi.org/10.1523/JNEUROSCI.0701-21.2021

Stern, D. N. (1985). Exploring the Infant’s Subjective Experience: A Central Role for the Sense of Self. In *The Interpersonal World of the Infant*. Routledge.

https://doi.org/10.4324/9780429482137

Stern, D. N. (2009). Pre-reflexive experience and its passage to reflexive experience: A developmental view. *Journal of Consciousness Studies*, *16*(10–12), 307–331.

Straub, L., Bateman, B. T., Hernandez-Diaz, S., York, C., Lester, B., Wisner, K. L., McDougle, C. J., Pennell, P. B., Gray, K. J., Zhu, Y., Suarez, E. A., Mogun, H., & Huybrechts, K. F. (2022). Neurodevelopmental Disorders Among Publicly or Privately Insured Children in the United States. *JAMA Psychiatry*, *79*(3), 232–242. https://doi.org/10.1001/JAMAPSYCHIATRY.2021.3815

Suvilehto, J. T., Glerean, E., Dunbar, R. I. M., Hari, R., & Nummenmaa, L. (2015). Topography of social touching depends on emotional bonds between humans. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(45), 13811–13816. https://doi.org/10.1073/PNAS.1519231112/SUPPL_FILE/PNAS.1519231112.SAPP.PDF

Tager-Flusberg, H. (2000). A componential view of theory of mind: evidence from Williams syndrome. *Cognition*, *76*(1), 59–90. https://doi.org/10.1016/S0010-0277(00)00069-X

Tavano, A., & Borgatti, R. (2010). Evidence for a link among cognition, language and emotion in cerebellar malformations. *Cortex*, *46*(7), 907–918. https://doi.org/10.1016/j.cortex.2009.07.017

Tavano, A., Grasso, R., Gagliardi, C., Triulzi, F., Bresolin, N., Fabbro, F., & Borgatti, R. (2007). Disorders of cognitive and affective development in cerebellar malformations. *Brain*, *130*(10), 2646–2660. https://doi.org/10.1093/brain/awm201

Thomas, R., Press, C., & Haggard, P. (2006). Shared representations in body perception. *Acta Psychologica*, *121*(3), 317–330. https://doi.org/10.1016/j.actpsy.2005.08.002

Tran, D. M. D., McNair, N. A., Harris, J. A., & Livesey, E. J. (2021). Expected TMS excites the motor system less effectively than unexpected stimulation. *NeuroImage*, *226*, 117541.

https://doi.org/10.1016/J.NEUROIMAGE.2020.117541

Triscoli, C., Croy, I., Olausson, H., & Sailer, U. (2017). Touch between romantic partners: Being stroked is more pleasant than stroking and decelerates heart rate. *Physiology and Behavior*, *177*, 169–175. https://doi.org/10.1016/j.physbeh.2017.05.006

Trotter, P., Belovol, E., McGlone, F., & Varlamov, A. (2018). Validation and psychometric properties of the Russian version of the Touch Experiences and Attitudes Questionnaire (TEAQ-37 Rus). *PLOS ONE*, *13*(12), e0206905. https://doi.org/10.1371/journal.pone.0206905

Trotter, P. D., McGlone, F., Reniers, R. L. E. P., & Deakin, J. F. W. (2018). Construction and Validation of the Touch Experiences and Attitudes Questionnaire (TEAQ): A Self-report Measure to Determine Attitudes Toward and Experiences of Positive Touch. *Journal of Nonverbal Behavior*, *42*(4), 379–416. https://doi.org/10.1007/s10919-018-0281-8

Tsakiris, M. (2017). The multisensory basis of the self: From body to identity to others. *Quarterly Journal of Experimental Psychology*, *70*(4), 597–609. https://doi.org/10.1080/17470218.2016.1181768

Türkmen, S., Şahin, S., Koçer, N., Peters, H., Mundlos, S., & Tüysüz, B. (2015). Neuroimaging and clinical characterization of Sotos syndrome. *Genetic Counseling*, *26*(1), 1–12. https://europepmc.org/article/med/26043501

Urgesi, C., Alaerts, K., & Craighero, L. (2020). Editorial: How Do Motivational States Influence Motor Resonance? *Frontiers in Human Neuroscience*, *14*, 520702. https://doi.org/10.3389/FNHUM.2020.00027/BIBTEX

Urgesi, C., Berlucchi, G., & Aglioti, S. M. (2004). Magnetic stimulation of extrastriate body area impairs visual processing of nonfacial body parts. *Current Biology*, *14*(23), 2130–2134. https://doi.org/10.1016/j.cub.2004.11.031

Urgesi, C., Butti, N., Finisguerra, A., Biffi, E., Valente, E. M., Romaniello, R., & Borgatti, R. (2021). Social prediction in pediatric patients with congenital, non-progressive malformations of the cerebellum: From deficits in predicting movements to rehabilitation in virtual reality. *Cortex*, *144*, 82–98. https://doi.org/10.1016/j.cortex.2021.08.008

Urgesi, C., Calvo-Merino, B., Haggard, P., & Aglioti, S. M. (2007). Transcranial Magnetic Stimulation Reveals Two Cortical Pathways for Visual Body Processing. *Journal of Neuroscience*, *27*(30), 8023–8030. https://doi.org/10.1523/JNEUROSCI.0789-07.2007

Urgesi, C., Campanella, F., & Fabbro, F. (2011). *NEPSY-II, Contributo alla Taratura Italiana.* (2nd ed.). Giunti OS.

Urgesi, C., Candidi, M., & Avenanti, A. (2014). Neuroanatomical substrates of action perception and understanding: an anatomic likelihood estimation meta-analysis of lesion-symptom mapping studies in brain injured patients. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00344

Valenzuela-Moguillansky, C., & Reyes-Reyes, A. (2015). Psychometric properties of the multidimensional assessment of interoceptive awareness (MAIA) in a Chilean population. *Frontiers in Psychology*, *6*(FEB), 132945. https://doi.org/10.3389/FPSYG.2015.00120/BIBTEX

Vallbo, Å., Olausson, H., & Wessberg, J. (1999). Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. *Journal of Neurophysiology*, *81*(6), 2753–2763. https://doi.org/10.1152/jn.1999.81.6.2753

van de Pavert, I., Sunderland, M., Luijten, M., Slade, T., & Teesson, M. (2017). The general relationship between internalizing psychopathology and chronic physical health conditions: a population-based study. *Social Psychiatry and Psychiatric Epidemiology*, *52*(10), 1257–1265. https://doi.org/10.1007/S00127-017-1422-9/METRICS

Van Den Heuvel, E., Manders, E., Swillen, A., & Zink, I. (2016). Developmental trajectories of structural and pragmatic language skills in school-aged children with Williams syndrome. *Journal of Intellectual Disability Research, 60*(10), 903–919. https://doi.org/10.1111/JIR.12329

van Kuijk, A. A., Anker, L. C., Pasman, J. W., Hendriks, J. C. M., van Elswijk, G., & Geurts, A. C. H. (2009). Stimulus–response characteristics of motor evoked potentials and silent periods in proximal and distal upper-extremity muscles. *Journal of Electromyography and Kinesiology, 19*(4), 574–583. https://doi.org/10.1016/J.JELEKIN.2008.02.006

Van Puyvelde, M., Gorissen, A. S., Pattyn, N., & McGlone, F. (2019). Does touch matter? The impact of stroking versus non-stroking maternal touch on cardio-respiratory processes in mothers and infants. *Physiology & Behavior, 207*, 55–63. https://doi.org/10.1016/J.PHYSBEH.2019.04.024

Vicari, S., Brizzolara, D., Carlesimo, G. A., Pezzini, G., & Volterra, V. (1996). Memory Abilities in Children with Williams Syndrome. *Cortex, 32*(3), 503–514. https://doi.org/10.1016/S0010-9452(96)80007-4

Vicario, C. M., Kuran, K. A., & Urgesi, C. (2019). Does hunger sharpen senses? A psychophysics investigation on the effects of appetite in the timing of reinforcement-oriented actions. *Psychological Research, 83*(3), 395–405. https://doi.org/10.1007/S00426-017-0934-Y/FIGURES/3

Vivanti, G., Fanning, P. A. J., Hocking, D. R., Sievers, S., & Dissanayake, C. (2017). Social Attention, Joint Attention and Sustained Attention in Autism Spectrum Disorder and Williams Syndrome: Convergences and Divergences. *Journal of Autism and Developmental Disorders, 47*(6), 1866–1877. https://doi.org/10.1007/s10803-017-3106-4

Vivanti, G., Hamner, T., & Lee, N. R. (2018). Neurodevelopmental Disorders Affecting Sociability:

Recent Research Advances and Future Directions in Autism Spectrum Disorder and Williams Syndrome. *Current Neurology and Neuroscience Reports*, *18*(12), 94. https://doi.org/10.1007/s11910-018-0902-y

Von Mohr, M., Kirsch, L. P., & Fotopoulou, A. (2017). The soothing function of touch: affective touch reduces feelings of social exclusion. *Scientific Reports 2017 7:1*, *7*(1), 1–9. https://doi.org/10.1038/s41598-017-13355-7

Walker, S. C., Trotter, P. D., Woods, A., & McGlone, F. (2017). Vicarious ratings of social touch reflect the anatomical distribution & velocity tuning of C-tactile afferents: A hedonic homunculus? *Behavioural Brain Research*, *320*, 91–96. https://doi.org/10.1016/J.BBR.2016.11.046

Wang, K. H., Kupa, J., Duffy, K. A., & Kalish, J. M. (2020). Diagnosis and Management of Beckwith-Wiedemann Syndrome. *Frontiers in Pediatrics*, *7*, 562. https://doi.org/10.3389/FPED.2019.00562/BIBTEX

Watkins, R. H., Dione, M., Ackerley, R., Backlund Wasling, H., Wessberg, J., & Löken, L. S. (2021). Evidence for sparse C-tactile afferent innervation of glabrous human hand skin. *Journal of Neurophysiology*, *125*(1), 232–237. https://doi.org/10.1152/jn.00587.2020

Waugh, O. C., Byrne, D. G., & Nicholas, M. K. (2014). Internalized Stigma in People Living With Chronic Pain. *The Journal of Pain*, *15*(5), 550.e1-550.e10. https://doi.org/10.1016/J.JPAIN.2014.02.001

Wechsler, D. (2003). WISC-IV Administration Manual. In *Wechsler intelligence scale for children – Fourth edition (WISC-IV) administration and scoring manual*. The Psychological Corporation.

Weigelt, S., Koldewyn, K., & Kanwisher, N. (2012). Face identity recognition in autism spectrum disorders: A review of behavioral studies. *Neuroscience & Biobehavioral Reviews*, *36*(3), 1060–1084. https://doi.org/10.1016/j.neubiorev.2011.12.008

Weisman, O., Feldman, R., Burg-Malki, M., Keren, M., Geva, R., Diesendruck, G., & Gothelf, D. (2017). Comparing the broad socio-cognitive profile of youth with Williams syndrome and 22q11.2 deletion syndrome. *Journal of Intellectual Disability Research*, *61*(12), 1083–1093. https://doi.org/10.1111/JIR.12424

Wolock, E. R., Queen, A. H., Rodríguez, G. M., & Weisz, J. R. (2020). Chronic Illness and Internalizing Symptomatology in a Transdiagnostic Clinical Sample of Youth. *Journal of Pediatric Psychology*, *45*(6), 633–642. https://doi.org/10.1093/JPEPSY/JSAA028

Zaidel, A., & Salomon, R. (2023). Multisensory decisions from self to world. *Philosophical Transactions of the Royal Society B*, *378*(1886), 20220335. https://doi.org/10.1098/RSTB.2022.0335

Zamariola, G., Maurage, P., Luminet, O., & Corneille, O. (2018). Interoceptive accuracy scores from the heartbeat counting task are problematic: Evidence from simple bivariate correlations. *Biological Psychology*, *137*, 12–17. https://doi.org/10.1016/J.BIOPSYCHO.2018.06.006

Zebrowitz, L. a. (2006). Finally, Faces Find Favor. *Social Cognition*, *24*(5), 657–701. https://doi.org/10.1521/soco.2006.24.5.657