



Review

Interoception in Autism Spectrum Disorder: A review



Denise DuBois^{a,b}, Stephanie H. Ameis^{c,d,e}, Meng-Chuan Lai^{e,f,g}, Manuel F. Casanova^h,
Pushpal Desarkar^{a,c,*}

^a Adult Neurodevelopmental Services, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

^b Rehabilitation Science Institute, University of Toronto, Toronto, Ontario, Canada

^c Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

^d Research Imaging Centre, Campbell Family Mental Health Research Institute, The Centre for Addiction and Mental Health, Toronto, Ontario, Canada

^e Child and Youth Mental Health Collaborative at the Centre for Addiction and Mental Health and The Hospital for Sick Children, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

^f Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

^g Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

^h Department of Psychiatry and Behavioral Sciences, University of Louisville, Louisville, KY, USA

ARTICLE INFO

Article history:

Received 12 April 2016

Received in revised form 10 May 2016

Accepted 11 May 2016

Available online 3 June 2016

Keywords:

Interoception

Autism Spectrum Disorder

Internal sensation processing

Homeostatic afferent pathway

Insula

ABSTRACT

Purpose: This review article summarizes original scientific research published to date on interoception in individuals with Autism Spectrum Disorder (ASD). Sensory processing has been shown to be atypical in ASD, yet physiological processing and subjective experience of internal sensation processing, namely interoception, has not been reported sufficiently in research or clinical settings.

Background: There is a small but growing body of scientific research on interoception in ASD, which is relevant to understanding the behavioral and cognitive characteristics inherent in this condition, and may provide a foundation for clinical interventions such as biofeedback, pain management, and brain stimulation techniques.

Methods: A literature review of original research was performed using major scientific databases.

Results: Interoception, which occurs due to multisensory connections and integration of internal afferents in cortical and subcortical areas, is atypical in ASD, but the degree and directionality of this abnormality is not yet clear due to the heterogeneity of the condition. Between-group interoceptive differences in individuals with and without ASD have been repeatedly demonstrated, with a slight tendency towards hyporeactivity in interoceptive awareness in individuals with ASD.

Significance: Multidimensional research combining neuroimaging with psychophysiological and self-report measures guided by a clear theoretical model is necessary to understand how interoceptive differences link to the behavioral and cognitive characteristics of ASD. Sensory processing models and autism theory should also be updated to incorporate these recent findings.

© 2016 ISDN. Published by Elsevier Ltd. All rights reserved.

Contents

1. Introduction	105
1.1. Interoception—theoretical underpinnings	105
1.2. Neurophysiological underpinnings of interoception	105
1.2.1. Typical interoceptive pathways and connections	105
1.2.2. Interoceptive pathways and connections in ASD	106
1.3. Clinical implications of interoceptive research in ASD	106
2. Methods	106
2.1. Literature search	106

* Corresponding author at: Department of Psychiatry, University of Toronto, Centre for Addiction and Mental Health, 1001 Queen Street West, Unit 4-4, Toronto, ON M6J 1H4, Canada.

E-mail address: pushpal.desarkar@camh.ca (P. Desarkar).

2.2.	Study selection	106
2.3.	Data extraction	107
3.	Results	107
3.1.	Measuring brain activity patterns during interoception	107
3.2.	Measuring interoceptive awareness	107
3.3.	Measuring interoceptive accuracy	108
3.4.	Measuring interoceptive sensibility	108
4.	Discussion	108
4.1.	Measuring interoceptive awareness—methodological limitations	108
4.2.	Future methodological considerations	109
5.	Conclusions	109
	Conflict of interest	110
	Acknowledgments	110
	References	110

1. Introduction

When Sherrington (1906) first described interoception in 1906, his definition reflected limited knowledge of basic reflexes and visceral sensations in the central nervous system. As knowledge of brain pathways has expanded over the past century, so has understanding of how interoception is consciously experienced in humans. Today, interoception represents a complex phenomenon of visceral afferent information reaching conscious awareness and the manner in which perception of these afferent signals may affect human behavior (Cameron, 2002).

The basic process of interoception encompasses how sensory signals related to internal body experiences such as pain, temperature, itch, sensual touch, muscular and visceral sensations, vasomotor activity, hunger, thirst, and ‘air hunger’ reach conscious awareness (Craig, 2003, 2015). By integrating bottom-up afferent signals from the body and top-down predictive signals from higher order cortical structures in the frontal and sensorimotor regions, the anterior insula plays a key role in interoceptive processes. It acts as an integration center for physiological and emotional perception. Neuroimaging studies of the insula have demonstrated functional connectivity during emotional and interoceptive awareness in humans (Calì et al., 2015; Cox et al., 2012; Geliebter, 2013; Gu et al., 2013, 2015; Stern, 2014). In addition, the size and volume of the right anterior insula has been shown to directly correlate with subjective awareness of internal sensation (Garfinkel et al., 2013; Craig, 2004).

Atypical sensory processing is now a diagnostic criterion of ASD but the well-known examples of sensory symptoms in ASD (e.g. hyper- or hypo sensitivity to touch, pain, etc) relate to external sensory inputs only. Thus, interoception and its potential relation with clinical symptoms remain a very important, yet poorly understood area of research.

1.1. Interoception—theoretical underpinnings

Recently, Craig (2015) summarized the theoretical and physiological underpinnings of interoception and how it pertains to emotions. Further advances in neuroimaging have led to updated theories of how consciousness is perceived in the human mind. Although there are varying models to explain how the brain integrates bottom up and top down information, generally most computational models of neuroscience suggest a predictive feedback system. For instance, Craig’s discovery of the Homeostatic Afferent Pathway substantiated the James-Lange Theory of Emotion and its predecessor Damasio’s Somatic Marker Hypothesis (Craig, 2009, 2015). These theorists suggest that previously experienced autonomic patterns lead to neural learning and predictive control of emotions, even precognitively (Craig, 2015).

The concept of interoception was further delineated by Seth et al. (2012), who have suggested that interoceptive awareness is reliant on the predictive coding of ascending interoceptive information based on top-down and lateral inhibitory signals from the sensorimotor and autonomic/motivational system. Within a predictive coding model, this hypothesis builds on a Bayesian model whereby prediction and error correction act as a basic method to understand how the brain operates. Top-down predictive signals continually operate to minimize discrepancy with incoming bottom-up perceptual signals. Seth (2013) applies a predictive coding framework to self-related experiences originating from both interoceptive and exteroceptive signals. The Experience of Body Ownership relies on predictive multisensory integration. The laws of free energy are to minimize top-down prediction error at each hierarchical level. Thus, anterior brain regions form prior (predictive) connections to lower level structures (i.e. anterior insula to posterior insula to multiple thalamocortical regions). As an example, Seth (2013) suggests that anxiety occurs when there is a mismatch between the incoming interoceptive information and the generative models sending top-down predictions.

A three-part neuropsychological model devised by Garfinkel et al. (2013, 2015) separates interoceptive processes into three measurable constructs, which can be distinguished from exteroception (external sensation) and proprioception (body position in space). The first process, *interoceptive accuracy*, includes measurable, discriminant processes such as heart rate, bladder fullness, or stomach distension. The second process, *interoceptive sensibility*, is the subjective experience of internal processes and to date has been measured by self-report questionnaires. The third process is termed *interoception awareness* and is a metacognitive measure of interoceptive accuracy, or to what extent one is aware of their ability to accurately perceive internal processes (Garfinkel et al., 2013).

1.2. Neurophysiological underpinnings of interoception

1.2.1. Typical interoceptive pathways and connections

In humans and primates, interoception occurs along the same central nervous system pathways as pain and other conscious and unconscious autonomic processes. In order to conceptualize how interoception occurs in higher-order brain areas, one must consider how internal sensation travels from a nerve ending (i.e. receptors in the internal organs) through the peripheral and central nervous systems.

Scientific work in rodents, primates, and humans over the past century has provided a detailed organizational map of the internal afferent pathways. Functional connections have been mapped to autonomic, homeostatic, pain, and internal sensations (Cortelli et al., 2013; Craig, 2003; Critchley, 2005). The homeostatic afferent pathway (HAP) conveys internal sensations to the insula and anterior cingulate cortex (ACC). Electro-chemical impulses

Table 1
PRISMA chart.

99 records identified from all sources (CINAHL, PubMed, Embase)		
63 titles & abstracts reviewed	49	34 duplicates excluded
	11	Titles & abstracts excluded
	38	Non-peer reviewed
16 full text records to be reviewed		Non-ASD population
		0 items not available for review
16 full text records reviewed	11	Titles & Abstracts Excluded
	3	Review/Theoretical articles
	2	Non-ASD population
	4	Empathic Definition
	2	No measurement of Interoception
Reporting on 5 original studies in review article		

from chemoreceptors, nociceptors and mechanoreceptors, such as Pacinian corpuscles and small C fibres, travel to lamina I in the trigeminal or spinal dorsal horn, while parasympathetic afferents ascend via the glossopharyngeal and vagal tracts (Roper, 2013). Lamina I is a hub for ascending somato-visceral-autonomic afferents and is also the only area that receives descending efferent tracts from the hypothalamus (Craig, 2003). Homeostatic and parasympathetic afferents also reach the nucleus of solitary tract (NTS), which provides reflexive control of circulation, respiration, gastrointestinal, and micturition functions (McGinnis et al., 2013).

The NTS and lamina I provide dense connections to the parabrachial nucleus (PBN), the main integration centre for all homeostatic afferent activity (Cortelli et al., 2013). These connections then transmit to both the periaqueductal gray area (PAG) and the hypothalamus. The lamina I, NTS and the PBN connect directly via spinothalamic tracts to the ventral medial nucleus (VMN) of the thalamus and the ventral posterior somatosensory nuclei. Thalamocortical afferent projections link to the limbic motor and sensory cortices, the ACC (motor), and the insula (sensory), respectively (Craig, 2003). Interoceptive activity ascends to the posterior insula and then is processed in the middle insula before proceeding to the anterior insula. The anterior insula is involved in all subjective feelings of self and other and is part of the Salience Network that is responsible for the integration of external and internal events (Craig, 2009).

1.2.2. Interoceptive pathways and connections in ASD

The use of resting state functional neuroimaging in individuals with ASD has repeatedly demonstrated group differences in functional connectivity in brain structures thought to be involved in interoception. These studies have focused on functional relationships between the insula and other primary sensory areas, as well as within the Salience Network and Default Mode Network (Bartfeld et al., 2012; Bernhardt et al., 2014; Ebisch et al., 2011; Uddin et al., 2013; Di Martino et al., 2014). For instance, a study published in 2011 found there was a reduced response or complete disconnection between the bilateral posterior insula to the anterior insula, and between corresponding somatosensory and limbic regions in adults with ASD (Ebisch et al., 2011). The posterior insula is considered the primary interoceptive cortex (Craig, 2004).

1.3. Clinical implications of interoceptive research in ASD

As previously stated, sensory symptoms are a defining characteristic of ASD, yet research to date has primarily focused on external sensory processing. Thus, interoception and its potential relation with clinical symptoms remain a very important, yet poorly understood area of research. Additionally, the co-morbid presence of physical conditions associated with a higher incidence of pain

or discomfort in people with ASD is remarkable. Autism has been associated with gastrointestinal symptoms (Mazurek et al., 2013), low muscle tone and joint hypermobility (Sinibaldi et al., 2015), migraines (Casanova, 2008), Chiari malformation (Jayarao et al., 2015), Ehlers Danlos syndrome (Baeza-Velasco et al., 2015), tuberous sclerosis (Curatolo et al., 2015; Millan, 2013; Seri et al., 1999), and even seizure disorders (Silver and Rapin, 2012). At this point the potential relationship between interoceptive disturbances and social-communication symptoms of ASD is poorly understood. Better understanding the interoceptive experiences in individuals with ASD and concurrent self-stimulatory behaviours could have significant treatment implications, specifically for pain and abnormal sensation management.

2. Methods

2.1. Literature search

A systematic search strategy was conducted to identify relevant literature from the following scientific databases: PubMed, CINAHL, and EMBASE. Searches were limited to English publications from January 1980 to December 2015. Search terms included: interoception, interoceptive, insula, Autism Spectrum Disorder, Autistic disorder, Asperger's, and Pervasive Developmental Disorder. Ninety-nine articles were found including 34 duplicates (Table 1). Only original empirical studies published in peer-reviewed journals were considered (Table 2).

2.2. Study selection

Inclusion and exclusion criteria for this review article were i) Study population: Individuals (aged 0–65 years) with Autism Spectrum Disorder. Studies were included as long as a subset of participants was identified as having a diagnosis of ASD (or previous DSM diagnoses included in the search terms), ii) Subject Matter: Due to the dearth in research papers specifically discussing interoception, related subject matter was also searched to ensure a comprehensive review. Thus, searches of the insular and pain pathways in ASD were also completed to ensure relevant studies had been included. Given that a review article of this topic has not been completed, and to provide a thorough critical analysis of interoception within the context of ASD, all empirical studies were included. Studies were included if their definition reflected Craig's description of interoception as the physiological awareness of internal sensation, and provided a clear method for measuring this process. Studies were excluded if they focused on socio-emotional constructs such as perspective-taking or affective empathy (e.g. Bernhardt et al., 2014; Cox et al., 2012). This exclusion criterion was determined in order to provide a clearer distinc-

Table 2
Studies included in the review.

Studies	Interoception Measures	Sample Size	Age Group	Gender	Population	Study Type	ASD Diagnosis
Bartfield et al. (2012)	fMRI – Resting, Oddball (Active), Interoceptive (focus on breathing)	hfASD = 12; TD = 12	ASD: m = 23.7; TD: m = 28.8	ASD: 9 men; 3 women	Adults, No ID	Neuroimaging	DSM-IV
Fiene and Brownlow (2015)	Online survey, Body/Thirst Awareness Questionnaire	hfASD = 74; Gen Pop = 228	17 to 67 years	ASD: 36 males, 38 females; Control: 53 males, 174 females, 1 unspecified	Adult; No ID	Cross-sectional; self-report questionnaire	Pre-diagnosed condition by an appropriately qualified professional ADOS, ADI-R, DSM-IV
Schauder et al. (2014)	Heart Rate Monitoring (Counting); Rubber Hand Illusion – Brushing Paradigm; CBCL; ADI-R, WASI, SCQ	ASD = 21; Controls = 24	8 to 17 years	ASD: 90.5% male; Control: 83.3% male	Children, No ID (ASD = IQ = 109.4; Control = 113.2)	Physiological; Quantitative testing	Recruited from ASD clinical service
Garfinkel et al. (2015)	Heart Rate Monitoring; Porges Body Perception Questionnaire; Discrepancy score between heart rate and VA score. Anxiety and Emotion scales: Spielberg Trait AI; Cambridge AQ; Cambridge Empathy Quotient	ASD = 18; Control = 18	Not provided	ASD: 16 male, 2 female; Control: 16 male, 2 female	Adults – IQ not provided	Physiological; Quantitative Testing; Self-Report Measure	
Elwin et al. (2012)	Content Analysis of 10 Published/Online Autobiographies	10 books	Adult	Not reported	Adults, No ID	Qualitative – Descriptive	Self-disclosed ASD

tion between empathic or socially-mediated internal sensations (i.e., pain experienced when watching another human experiencing pain) versus physiological processes related to self-mediated homeostatic internal sensations (i.e., stomach distension, temperature, sensual touch).

2.3. Data extraction

All titles and abstracts were independently extracted by the lead author (DD) and relevant articles were selected and reviewed by all authors (DD, PD, M-CL, SHA and MFC). Though references of retrieved articles were reviewed, no further articles were included. Five studies met inclusion criteria for consideration.

3. Results

Of the five studies that met inclusion criteria for the present review, one study measured interoception using functional magnetic resonance imaging (fMRI) during an interoceptive task, one study used self-report questionnaires, two studies used a physiological test of interoception (heart rate paradigm), and one study used qualitative analysis (Table 2).

3.1. Measuring brain activity patterns during interoception

Bartfield et al. (2012) used fMRI to study interoception in adults ($n = 24$) with ASD compared to controls. While undergoing fMRI, participants underwent three tasks: an auditory oddball paradigm which represented an “exteroceptive” state, a “resting state” with eyes closed, and an interoceptive state where participants focused on breathing and heart rate. During the interoceptive state, connectivity patterns increased in those with ASD compared to controls. An opposite effect was found in the exteroceptive task, with controls having increased connectivity compared to those with ASD. In addition, while the control group’s functional connectivity was fairly stable across exteroception and interoception tasks, the ASD group’s connectivity fluctuated significantly across states. The functional networks in the ASD group also showed more compact connectivity during the interoceptive condition, particularly within the cingulo-opercular, fronto-parietal and Default Mode networks. The authors also found a positive correlation between increasing levels of hyperconnectivity in the interoceptive state and ASD symptom severity as measured by the Autism Diagnostic Observation Schedule (ADOS). They concluded that unlike controls, brain network connectivity in ASD increased when participants were asked to concentrate on internal processing, and decreased when attention was directed outwards to the environment (Bartfield et al., 2012).

3.2. Measuring interoceptive awareness

To measure interoceptive awareness in males with ASD ($n = 18$), Garfinkel et al. (2016) tested their three-part model of interoception. To measure interoceptive accuracy, authors utilized a heartbeat monitoring task. Subjects were also asked to rate if an auditory tone was synchronous with their heartbeat. Individuals with ASD had significantly impaired interoceptive accuracy based on tracking scores. A discrepancy score between actual heartbeat and perceived performance, reported as a heartbeat error score, was also calculated to measure interoceptive awareness. No statistical differences were found between the ASD and control groups on this measure. Interoceptive sensibility was measured through a subsection of Porges Body Perception Scale (PBPO), which included questions on sensitivity to internal sensations (e.g. stomach and gut pains). Individuals with ASD scored significantly higher on this measure than controls. Authors suggest this demonstrates an

increased belief in interoceptive aptitude, which did not predict accuracy on heartbeat monitoring.

The authors also included an interoceptive trait prediction error (ITPE) to test their hypothesis that individuals with ASD present with an impaired ability to objectively detect bodily signals and an over-inflated subjective perception of bodily sensations. Operationally defined as the difference between objective interoceptive accuracy and subjective interoceptive sensibility, the heartbeat tracking score, heartbeat detection score, and awareness subsection of the PBPQ were used to create two discrepancy scores for each participant. Positive scores indicated an over-estimation of interoceptive ability, and negative scores indicated an under-estimation. The ITPE values significantly differed between groups. While individuals with ASD demonstrated higher interoceptive sensibility and lower interoceptive accuracy, the opposite was found for control participants. Measures of anxiety, autism severity, and empathy were also collected. The ITPE scores in the ASD group predicted both state and trait anxiety scores and a significant relationship was found between empathy and the heart rate tasks.

3.3. Measuring interoceptive accuracy

An earlier study measured interoceptive accuracy in children with ASD ($n = 21$) and controls ($n = 24$). Schauder et al. (2014) used a heart rate detection task to test interoceptive awareness, defined in this study as the conscious perception of internal bodily cues such as heartbeat and breathing, which will be termed interoceptive accuracy based on Garfinkel and Critchley's model (Garfinkel et al., 2015). The participants were asked to monitor their heartbeat using a mental tracking method over four time durations. Actual heart rate was measured using a pulse oximeter and finger transducer. Only children who could detect their heartbeat were included in the study, which accounts for the differing sizes in groups. This study reported that children with ASD included in the trials did not differ significantly from typically-developing control children in their interoceptive ability to accurately detect and monitor heart rate, but were able to sustain attention to heart rate more accurately than controls in the longest trial (i.e., 100 s). That is, there was no effect between groups, but the performance of the ASD group across four time durations was more constant than controls. The authors suggest that this sustained mental tracking demonstrates a heightened ability in children with ASD to sustain attention to internal information. Since earlier research has revealed that sustained attention differences in ASD are related to motivation (Schauder et al., 2014), internal sensory stimuli may have a particular salience for children with ASD.

3.4. Measuring interoceptive sensibility

Two studies provided information about how interoceptive processes are subjectively experienced by individuals with ASD. First, an online survey attempted to directly assess differences in the subjective perception of body and thirst awareness in individuals with and without ASD (Fiene and Brownlow, 2015). Adults with ASD ($n = 74$) and neurotypical controls ($n = 228$) were asked to complete the Body Awareness Questionnaire (BAQ) (Shields et al., 1989). The BAQ measures one's beliefs about their ability to identify inner sensations and to discern subtle homeostatic, non-emotive bodily processes on a 7-point Likert scale. The BAQ has been used in previous research and has adequate psychometric properties (Mehling et al., 2009). On the other hand, the Thirst Awareness Questionnaire (TAQ) included in this study is still undergoing item refinement and factor analysis. On both measures, a higher total score denotes a greater subjective sensitivity to bodily processes, which would represent high interoceptive sensibility in Garfinkel and Critchley's

and model (Garfinkel et al., 2015). These results point to decreased interoceptive sensibility in ASD participants (Fiene and Brownlow, 2015). They had significantly decreased scores when compared to controls on both measures representing a large effect $d = -1.26$, $P < 0.001$; TAS; $d = -1.02$, $P < 0.001$. In addition, when results on the TAQ were compared to self-reported levels of fluid intake, those with ASD were just as likely to consume large amounts of fluid (more than 20 glasses per day) if they reported very low thirst awareness, or to consume very low amounts of fluid (1–3 glasses per day) if they reported higher awareness. The authors suggest that their results are in line with the theory that an underconnected anterior insula demonstrates a brain area unable to initiate higher order brain responses to salient interoceptive signals.

One qualitative study also focused on interoceptive sensibility by analyzing the autobiographies of individuals with ASD from excerpts related to sensory symptoms including interoceptive abnormalities (Elwin et al., 2012). The majority of the participants reported hyposensitivity to interoceptive cues and difficulty detecting internal sensations such as pain. Hyposensitivity was categorized into either no or indistinct registration of stimuli, decreased discrimination and recognition of stimuli, and strong cravings for specific stimuli. This interoceptive hyposensitivity was reported to be long-standing, or persistent throughout the lifespan.

4. Discussion

It is clear from this review that interoception is an aspect of a sensory processing abnormality found in ASD that has not yet received much clinical or neuroscientific attention. Between-group differences of individuals with and without ASD in interoceptive processing have been repeatedly demonstrated, yet whether the brain structures and functional connections responsible for interoception are either hypo- or hyperconnected in ASD has not been confirmed. In fMRI studies, hypoconnectivity in the insular cortices and related functional networks has generally been found in adults and across experimental designs targeting socioemotional processes, while evidence of hyperconnectivity has been noted in experimental designs focused on internal processing. In addition, other study designs using questionnaires and heart rate monitoring also reveal heterogeneity in results, with a slight bias towards hyporeactivity to internal sensation processing in individuals with ASD. It should be noted that most sample sizes were under 50 participants which limits generalizability. In addition, individuals with comorbidities of ASD and a developmental disability (DD) have been excluded from all studies to date, although in the general population possibly more than half of individuals with ASD also have an DD (Baio, 2012).

4.1. Measuring interoceptive awareness—methodological limitations

Based on the three-dimensional model of interoception proposed by Garfinkel et al. (2015, 2013), the studies highlighted in this review largely demonstrate a one-dimensional measure of interoceptive accuracy (i.e. Schauder et al., 2014; Bartfeld et al., 2012) or interoceptive sensibility (i.e. Fiene and Brownlow, 2015). Only one study attempted to analyze interoceptive awareness (Garfinkel et al., 2016). The authors did not provide age or IQ of the participants. In addition, it could be argued that the measures used for the ITPE discrepancy score should specifically reflect the physiological process being measured (i.e. heart rate), yet the self-report measure was a general measure of body awareness. In addition, it may be that the model as posited by these authors, should be theoretically expanded to incorporate the ITPE as a subconstruct of interoceptive awareness.

Schauder et al. (2014) also completed a heart rate monitoring task in children with ASD. However, children who could not detect their heartbeat (potentially demonstrating very low interoceptive sensibility) were excluded from participating in this study, which may limit the study findings. A control task was introduced part way through the study, which may have impacted results and also demonstrates a potential limitation to utilizing a heart rate counting task in an ASD population. If a heart rate task is to be used in the future, the following factors should be considered and reported in order to allow for the measurement of interoceptive awareness in ASD: hypo- or hyperresponsivity baseline sensory patterns, descriptive and quantitative measures of participants' perception of their heart rate, and recording of ECG data at baseline and during the task.

There are a handful of self-report questionnaires, such as the Body/Thirst Awareness Scale (BAQ) (Shields et al., 1989; Fiene and Brownlow, 2015), the Autonomic Perception Questionnaire (Mandler et al., 1958), and Porges Body Perception Questionnaire (Porges, 1993), all of which aim to measure interoceptive sensibility. Only one study attempted to measure body and thirst awareness in ASD using the Body/Thirst Awareness Scale (Fiene and Brownlow, 2015). The reliability and validity of the BAQ have only been reported twice in the scientific literature. Furthermore, in this online survey study, the ASD sample was defined based on a self-disclosed previous diagnosis of ASD and the authors did not clearly report how the sample was recruited. Other more recent questionnaires such as the Multidimensional Assessment of Interoceptive Awareness (Mehling et al., 2012) and the Self-Awareness Questionnaire (Longarzo et al., 2015) have not yet been tested in individuals with ASD. Moreover, to fully understand body awareness, interoception, and sensory processing, which likely represent overlapping constructs, the relationship between sensory processing assessment measures, such as the Sensory Processing Quotient (Tavassoli et al., 2014), the Sensory Processing Scale (Schoen et al., 2014), the Sensory Profile (Dunn, 2001) and body awareness questionnaires might also provide a more detailed understanding of an individual's perception of both exteroceptive and interoceptive sensory processes. In addition, similar to self-awareness in traumatic brain injury, a proxy-report measure may be useful to compare an individual's subjective experiences to that of a caregiver or significant other to measure discrepancy in awareness of experience.

The functional imaging study also presented some methodological challenges. Bartfeld et al. (2012) had a small sample size, and there was a seven-point group difference in IQ between the ASD and control groups. Authors also did not report on co-morbid conditions or medication history within their sample. That being said, this was the first study to implement a feasible method to measure interoception in real time while collecting functional connectivity data in individuals with ASD.

All studies to date have focused on mostly male populations with normal intelligence. For instance, those individuals in the Elwin et al. (2012) study likely have normal intelligence since they had written extensive autobiographies, but neuropsychological results were unavailable in this qualitative study. Due to the obvious difficulty in measuring internal processing in children and adults who are non-verbal or have comorbid developmental disability, it might seem reasonable that most research on interoception has focused on verbal ASD participants who do not have a developmental disability. Findings therefore cannot be easily generalized to a larger, heterogeneous ASD population.

4.2. Future methodological considerations

There is currently no appropriate methodology to test interoception, as the subjective experience of internal sensation

processing, in individuals with ASD who have low IQ and communication abilities. Garfinkel et al. (2013) have provided a sound model upon which to test interoception in many psychiatric conditions, however, the ability to provide self-report of internal experiences is central to their method. Their model may be appropriate for individuals with a mild developmental disability who can communicate. Advances in communication technology have demonstrated that many individuals with autism who are non-verbal may be able to provide feedback about physiological processes, if adapted to meet their communication and sensory needs (Arthur-Kelly et al., 2009). Incorporating the use of communication aids and providing adapted communication strategies such as pictures and visual scales should be included in future self-report paradigms. Yet, for those individuals who cannot participate in self-report due to moderate to severe developmental disabilities, other more complex study designs will be required.

Comparative studies of neurotypical and ASD participants using quantitative tests of biological processes (e.g. ECG halter monitor, ultrasonogram) while measuring behavioural responses (e.g. facial expression, motor stereotypies) is a feasible methodology appropriate for use across a greater spectrum of cognitive and communication abilities. Once established, these physiological-behavioral tasks can be combined with neuroimaging to further explore how interoceptive processing maps onto neural pathways. To date most designs have used heart rate tasks which represents only one specific type of interoceptive sensibility, which may be subthreshold much of the time. More clinically-relevant data may be garnered from interoceptive cues of evolutionary salient processes such as hunger, thirst, urgency to void, or internal discomfort.

For instance, a recent study published in a typical population demonstrates how to integrate functional neuroimaging, physiological data, and verbal report to measure interoceptive awareness of an evolutionarily salient process. Jarrahi et al. (2015) completed a real-time analysis of functional connections during viscerosensory stimulation of the bladder in seven female participants. The authors were able to map distinct functional connections when a participant had an empty bladder, at the moment of warm water injection (bladder fullness), and when participants consciously felt bladder urgency. Authors noted that at the moment participants were consciously aware of a full bladder, a 'connectional switch' occurred from Salience structures to motivational-arousal-affective systems in order to regulate and maintain homeostasis. Analyzing connectional 'switching' in an ASD population during an evolutionarily salient process described in this study may elucidate functional connectivity patterns that have a clear impact on everyday functioning.

Conducting well-designed multidimensional studies by simultaneously measuring brain patterns, physiological processes, and subjective experiences of interoceptive processes will aid us in understanding brain and body connections, which may allow for individualized, curative treatment such repetitive transcranial magnetic stimulation, deep brain stimulation, medication/hormone therapy, desensitization therapy, and biofeedback applications. In addition, devices that may be useful in a multidimensional experimental design, such as real time heart rate monitors may also hold clinical promise as a real time biofeedback device (Kushki et al., 2015; Anagnostou and Taylor, 2011). The evolution of wearable technology and smartphone applications could make this a feasible clinical treatment technique in the near future.

5. Conclusions

This review paper summarized the five papers to date, which have measured interoceptive differences in individuals with and

without ASD. The limited research available on this topic supports current neuroscientific theory that prediction errors in interoceptive processing systems may occur in ASD. The results of this review are limited in size and are not entirely generalizable to all individuals with ASD. Yet, they provide preliminary support that interoception in ASD may be abnormal, and could underlie other major symptoms inherent in this disorder. However, to become more clinically relevant, the extent of these internal sensation processing abnormalities and how they relate to clinical symptoms requires further study. Potential interventions may then be elucidated for a condition that still lacks effective treatment options.

Conflict of interest

The authors do not have conflicts of interest to declare.

Acknowledgments

The authors are grateful to Dr. Bud Craig for comments on the anatomical aspects of the manuscript. DD receives financial support from a fellowship at the University of Toronto. SHA receives financial support from the O'Brien Scholar's Program, the Ontario Mental Health Foundation New Investigator Fellowship, and the University of Toronto Dean's Fund New Staff Grant. M-CL receives research stipend support from the O'Brien Scholar's Program. PD is supported by the Innovation Fund from the Alternate Funding Plan of the Academic Health Sciences Centres of Ontario and Dean's Fund, Faculty of Medicine, University of Toronto.

References

- Anagnostou, E., Taylor, M.J., 2011. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. *Mol. Autism*, <http://dx.doi.org/10.1186/2040-2392-2-4>.
- Arthur-Kelly, M., Sigafoos, J., Green, V., Mathisen, B., Arthur-Kelly, R., 2009. Issues in the use of visual supports to promote communication in individuals with autism spectrum disorder. *Disabil. Rehabil.* 31, 1474–1486, <http://dx.doi.org/10.1080/09638280802590629>.
- Baeza-Velasco, C., Pailhez, G., Bulbena, A., Baghdadli, A., 2015. Joint hypermobility and the heritable disorders of connective tissue: clinical and empirical evidence of links with psychiatry. *Gen. Hosp. Psychiatry* 37, 24–30, <http://dx.doi.org/10.1016/j.genhosppsych.2014.10.002>.
- Baio, J., 2012. Prevalence of Autism Spectrum Disorders: Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. *Morbidity and Mortality Weekly Report. Surveillance Summaries. Volume 61, Number 3. Centers for Disease Control and Prevention*.
- Barttfeld, P., Wicker, B., Cukier, S., Navarta, S., Lew, S., Leiguarda, R., Sigman, M., 2012. State-dependent changes of connectivity patterns and functional brain network topology in autism spectrum disorder. *Neuropsychologia* 50, 3653–3662, <http://dx.doi.org/10.1016/j.neuropsychologia.2012.09.047>.
- Bernhardt, B., Valk, S., Silani, G., Bird, G., Frith, U., Singer, T., Bernhardt, B.C., Valk, S.L., Silani, G., Bird, G., Frith, U., Singer, T., 2014. Selective disruption of sociocognitive structural brain networks in autism and alexithymia. *Cereb. Cortex* 24, 3258–3267, <http://dx.doi.org/10.1093/cercor/bht182>.
- Calì, G., Ambrosini, E., Picconi, L., Mehling, W.E., Comitteri, G., 2015. Investigating the relationship between interoceptive accuracy, interoceptive awareness, and emotional susceptibility. *Front. Psychol.* 6, 1202, <http://dx.doi.org/10.3389/fpsyg.2015.01202>.
- Cameron, O.G., 2002. *Visceral Sensory Neuroscience: Interoception*. Oxford University Press, USA.
- Casanova, M.F., 2008. The minicolumnopathy of autism: a link between migraine and gastrointestinal symptoms. *Med. Hypotheses* 70, 73–80, <http://dx.doi.org/10.1016/j.mehy.2007.04.025>.
- Cortelli, P., Giannini, G., Favoni, V., Cevoli, S., Pierangeli, G., 2013. Nociception and autonomic nervous system. *Neurol. Sci.* 34 (1), 41–46.
- Cox, C.L., Uddin, L.Q., Di Martino, A., Castellanos, F.X., Milham, M.P., Kelly, C., 2012. The balance between feeling and knowing: affective and cognitive empathy are reflected in the brain's intrinsic functional dynamics. *Soc. Cogn. Affect. Neurosci.* 7, 727–737, <http://dx.doi.org/10.1093/scan/nsr051>.
- Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* 13, 500–505, [http://dx.doi.org/10.1016/S0959-4388\(03\)00090-4](http://dx.doi.org/10.1016/S0959-4388(03)00090-4).
- Craig, A.D., 2004. Human feelings: why are some more aware than others? *Trends Cogn. Sci.* 8, 239–241, <http://dx.doi.org/10.1016/j.tics.2004.04.004>.
- Craig, A.D., 2009. How do you feel—now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70, <http://dx.doi.org/10.1038/nrn2555>.
- Craig, A.D., 2015. *How Do You Feel?: An Interoceptive Moment with Your Neurobiological Self*. Princeton University Press, New York.
- Critchley, H.D., 2005. Neural mechanisms of autonomic, affective, and cognitive integration. *J. Comp. Neurol.* 493 (1), 154–166.
- Curatolo, P., Moavero, R., de Vries, P.J., 2015. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol.* 14, 733–745, [http://dx.doi.org/10.1016/S1474-4422\(15\)00069-1](http://dx.doi.org/10.1016/S1474-4422(15)00069-1).
- Di Martino, A., Yan, C.G., Li, Q., Denio, E., Castellanos, F.X., Alaerts, K., Deen, B., 2014. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol. Psychiatry* 19 (6), 659–667.
- Dunn, W., 2001. *The sensations of everyday life: empirical, theoretical, and pragmatic considerations*. *Am. J. Occup. Ther.* 55, 608–620.
- Ebisch, S.J.H., Gallese, V., Willems, R.M., Mantini, D., Groen, W.B., Romani, G.L., Buitelaar, J.K., Bekkering, H., 2011. Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum. Brain Mapp.* 32, 1013–1028, <http://dx.doi.org/10.1002/hbm.21085>.
- Elwin, M., Ek, L., Schröder, A., Kjellin, L., 2012. *Autobiographical accounts of sensing in Asperger syndrome and high-functioning autism*. *Arch. Psychiatric Nurs.* 26 (5), 420–429.
- Fiene, L., Brownlow, C., 2015. Investigating interoception and body awareness in adults with and without autism spectrum disorder. *Autism Res.*, <http://dx.doi.org/10.1002/aur.1486>, n/a–n/a.
- Garfinkele, S.N., Tiley, C., O'Keefe, S., Critchley, H.D., 2013. *Disassociating interoceptive focus and interoceptive accuracy in asperger's syndrome*. *Psychosomatic Medicine*, 75. Lippincott Williams & Wilkins, Philadelphia, PA USA, pp. A161.
- Garfinkele, S.N., Seth, A.K., Barrett, A.B., Suzuki, K., Critchley, H.D., 2015. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol. Psychol.* 104, 65–74, <http://dx.doi.org/10.1016/j.biopsycho.2014.11.004>.
- Garfinkele, S.N., Tiley, C., O'Keefe, S., Harrison, N.A., Seth, A.K., Critchley, H.D., 2016. Discrepancies between dimensions of interoception in autism: implications for emotion and anxiety. *Biol. Psychol.* 114, 117–126, <http://dx.doi.org/10.1016/j.biopsycho.2015.12.003>.
- Geliebter, A., 2013. Neuroimaging of gastric distension and gastric bypass surgery. *Appetite* 71, 459–465, <http://dx.doi.org/10.1016/j.appet.2013.07.002>.
- Gu, X., Hof, P.R., Friston, K.J., Fan, J., Gu, X., Hof, P.R., Friston, K.J., Fan, J., 2013. *Anterior insular cortex and emotional awareness*. *J. Comp. Neurol.*, 3371–3388, 10.1002/cne.23....
- Gu, X., Eilam-Stock, T., Zhou, T., Anagnostou, E., Kolevzon, A., Soorya, L., Hof, P.R., Friston, K.J., Fan, J., 2015. Autonomic and brain responses associated with empathy deficits in autism spectrum disorder. *Hum. Brain Mapp.*, <http://dx.doi.org/10.1002/hbm.22840>.
- Jarrah, B., Mantini, D., Balsters, J.H., Michels, L., Kessler, T.M., Mehnert, U., Kollias, S.S., 2015. Differential functional brain network connectivity during visceral interoception as revealed by independent component analysis of fMRI time-series. *Hum. Brain Mapp.* 36 (11), 4438–4468.
- Jayaram, M., Sohl, K., Tanaka, T., 2015. Chiari malformation I and autism spectrum disorder: an underrecognized coexistence. *J. Neurosurg. Pediatr.* 15, 96–100, <http://dx.doi.org/10.3171/2014.10.PEDS13562>.
- Kushki, A., Khan, A., Brian, J., Anagnostou, E., 2015. A Kalman filtering framework for physiological detection of anxiety-related arousal in children with Autism Spectrum Disorder biomedical engineering. *Trans. Biomed. Eng.* 62 (3), 990–1000.
- Longarzo, M., D'Olimpio, F., Chiavazzo, A., Santangelo, G., Trojano, L., Grossi, D., 2015. *The relationships between interoception and alexithymic trait. The Self-Awareness Questionnaire in healthy subjects*. *Front. Psychol.*, 6.
- McGinnis, W.R., Audhya, T., Edelson, S.M., 2013. Proposed toxic and hypoxic impairment of a brainstem locus in autism. *Int. J. Environ. Res. Public Health* 10 (12), 6955–7000.
- Mandler, G., Mandler, J.M., Uviller, E.T., 1958. *Autonomic feedback: the perception of autonomic activity*. *J. Abnorm. Soc. Psychol.* 56 (3), 367.
- Mazurek, M.O., Vasa, R.A., Kalb, L.G., Kanne, S.M., Rosenberg, D., Keefer, A., Murray, D.S., Freedman, B., Lowery, L.A., 2013. Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. *J. Abnorm. Child Psychol.* 41, 165–176, <http://dx.doi.org/10.1007/s10802-012-9668-x>.
- Mehling, W.E., Gopisetty, V., Daubenmier, J., Price, C.J., Hecht, F.M., Stewart, A., 2009. Body awareness: construct and self-report measures. *PLoS One* 4, <http://dx.doi.org/10.1371/journal.pone.0005614>.
- 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.
- Millan, M.J., 2013. An epigenetic framework for neurodevelopmental disorders: from pathogenesis to potential therapy. *Neuropharmacology* 68, 2–82, <http://dx.doi.org/10.1016/j.neuropharm.2012.11.015>.
- Porges, S., 1993. *Body perception questionnaire*. In: *Laboratory of Developmental Assessment*. University of Maryland.
- Schauder, K.B., Mash, L.E., Bryant, L.K., Cascio, C.J., 2014. Interoceptive ability and body awareness in autism spectrum disorder. *J. Exp. Child Psychol.* 131, 193–200.

- Schoen, S.A., Miller, L.J., Sullivan, J.C., 2014. Measurement in sensory modulation: the sensory processing scale assessment. *Am. J. Occup. Ther.* 68, 522–530, <http://dx.doi.org/10.5014/ajot.2014.012377>.
- Seri, S., Cerquiglioni, A., Pisani, F., Curatolo, P., 1999. Autism in tuberous sclerosis: evoked potential evidence for a deficit in auditory sensory processing. *Clin. Neurophysiol.* 110, 1825–1830.
- Seth, A.K., Suzuki, K., Critchley, H.D., 2012. An interoceptive predictive coding model of conscious presence. *Front. Psychol.*, <http://dx.doi.org/10.3389/fpsyg.2011.00395>.
- Seth, A.K., 2013. Interoceptive inference, emotion, and the embodied self. *Trends Cogn. Sci.* 17 (11), 565–573.
- Sherrington, C.S., 1906. *The Integrative Action of the Nervous System*. Scribners, New York.
- Shields, S.A., Mallory, M.E., Simon, A., 1989. The body awareness questionnaire: reliability and validity. *J. Pers. Assess.* 53 (4), 802–815.
- Silver, W.G., Rapin, I., 2012. Neurobiological basis of autism. *Pediatr. Clin. North Am.* 59, 45–61, <http://dx.doi.org/10.1016/j.pcl.2011.10.010>.
- Sinibaldi, L., Ursini, G., Castori, M., 2015. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: the link between connective tissue and psychological distress revised. *Am. J. Med. Genet. C. Semin. Med. Genet.* 169, 97–106, <http://dx.doi.org/10.1002/ajmg.c.31430>.
- Stern, E.R., 2014. Neural circuitry of interoception: new insights into anxiety and obsessive-compulsive disorders. *Curr. Treat. Opt. Psychiatry* 1, 235–247, <http://dx.doi.org/10.1007/s40501-014-0019-0>.
- Tavassoli, T., Hoekstra, R.A., Baron-Cohen, S., 2014. The Sensory Perception Quotient (SPQ): development and validation of a new sensory questionnaire for adults with and without autism. *Mol. Autism* 5 (1), 1.
- Uddin, L.Q., Supekar, K., Lynch, C.J., Khouzam, A., Phillips, J., Feinstein, C., Ryali, S., Menon, V., 2013. Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry* 70, 869–879, <http://dx.doi.org/10.1001/jamapsychiatry.2013.104>.