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A systematic review of physiological reactivity to stimuli in autism

Sinéad Lydon¹, Olive Healy¹, Phil Reed², Teresa Mulhern³, Brian M. Hughes³, & Matthew S. Goodwin⁴

¹*School of Psychology, Trinity College Dublin, Dublin, Ireland,* ²*Department of Psychology, Swansea University, Swansea, UK,* ³*School of Psychology, National University of Ireland, Galway, Ireland,* and ⁴*Department of Health Sciences, Northeastern University, Boston, MA, USA*

Abstract

Objective: The prevalence of abnormal behavioural responses to a variety of stimuli among individuals with autism has led researchers to examine whether physiological reactivity (PR) is typical in this population. This article reviewed studies assessing PR to sensory, social and emotional, and stressor stimuli in individuals with autism. **Methods:** Systematic searches of electronic databases identified 57 studies that met our inclusion criteria. Studies were analysed to determine: (a) participant characteristics; (b) physiological measures used; (c) PR to sensory, social and emotional or stressor stimuli; (d) the relation between PR and behavioural or psychological variables and (e) baseline physiological activity. A novel measure of methodological quality suitable for use with non-randomized, non-interventional, psychophysiological studies was also developed and applied. **Results:** Individuals with autism were found to respond differently than typically developing controls in 78.6%, 66.7% and 71.4% of sensory, social and emotional, and stressor stimulus classes, respectively. However, this extant literature is characterized by variable and inconsistent findings, which do not appear to be accounted for by varying methodological quality, making it difficult to determine what specific factors differentiate individuals with autism who present with atypical PR from those who do not. **Conclusions:** Despite this uncertainty, individual differences in PR are clearly present in autism, suggesting additional research is needed to determine the variables relating to PR among those with ASD and to examine the possible existence of physiological subtype responders in the population.

Keywords

Autonomic reactivity, autism, physiological reactivity, sensory, social and emotional, stressor stimuli

History

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Introduction

Behavioural hypo-reactivity (e.g. lack of reaction to human speech, loud noises and pain) and hyper-reactivity (e.g. heightened sensitivity, agitation or distress in response to particular clothing or food textures or to everyday noises) to stimuli have long been described in individuals with autism [1]. Abnormal behavioural reactions are considered characteristic of autism and oftentimes used as criteria that distinguish the condition from other developmental disorders, such as intellectual disability [2, 3]. Furthermore, abnormal behavioural reactivity has been linked to several negative outcomes in autism, including internalising and externalising behaviours that complicate participation in typical childhood leisure, social and educational activities [4, 5]. Several researchers have hypothesized that abnormalities in physiological reactivity (PR) may underlie behavioural issues in autism, wherein hyper-arousal is associated with experiences of fear, anxiety and avoidance [6–9] and hypo-arousal is associated with feelings of dullness, under-stimulation and sensory seeking [10, 11]. Moreover, researchers have postulated that challenging behaviours such as aggression, self-injury, tantrums, elopement and stereotypy are associated with

PR (for a review see [12]). Taken together, the existence of and diversity across these theories, increasing prevalence of autism, and behavioural problems associated with the condition all suggest a need for further examination of PR in this population and serves as the impetus for the present review.

PR has been defined as “the deviation of a physiologic response parameter from a comparison or control value that results from an individual’s response to a discrete, environmental stimulus” [13]. In this way, PR may be conceptualized as the difference between physiological activation in response to a stimuli or stressor as compared to resting or baseline levels. PR is most commonly measured by assessing autonomic nervous system (ANS) and limbic–hypothalamic–pituitary–adrenal axis (LHPA) activation. The ANS comprises sympathetic, parasympathetic and enteric branches. To our knowledge, little is known about the enteric system in autism; therefore, we include no further discussion of it in this review. The sympathetic nervous system (SNS) is responsible for activation and mobilization of the body to facilitate attention, fight and flight. The parasympathetic nervous system is responsible for recovery and restoration. The LHPA axis regulates bodily responses to stress and promotes restoration of homeostasis following a stressor. The role of the LHPA can be considered protective [14]; it ensures that the body returns to normal physiological functioning following a stressor to prevent damage to the body from its own physiological reaction to stress. Changes occur quickly in

Correspondence: Olive Healy, PhD, School of Psychology, Trinity College Dublin, College Green, Dublin 2, Ireland. Tel: 00353 1 896 1886. Fax: 00353 1 671 2006. E-mail: olive.healy@tcd.ie

the ANS in response to stimulation, while the LHPA response is significantly slower. Typically, the two systems are thought to co-activate in response to stress or stimulation. However, while correlations between LHPA and ANS responses have been recorded [15], other studies find little association between them [16].

Activation of the ANS in response to stimulation or stress is most commonly measured through heart rate (HR), heart rate variability (HRV), blood pressure (BP) and electrodermal activity (EDA), while LHPA system functioning is typically assessed through measurement of cortisol [17–19]. Although PR is highly individually variable, all of these measures have at least some degree of temporal stability [20–22]. Furthermore, a number of specific ANS and LHPA response patterns have been found to associate with an individual's perception of, response to and putative feelings about stimuli in the environment. Slowing of HR and a corresponding increase in EDA is associated with attention and interest [23–25]. Defensive reactivity, in the form of adaptive physiological mobilization allowing an individual to respond behaviourally, indicates the perception of a stimulus as threatening or harmful [26]. Perceptions and feelings of stress and anxiety are manifested through SNS and LHPA activation as reflected through increased HR, BP, EDA and production of cortisol, and concurrent decreases in HRV. Habituation is associated with attenuation of hormonal and physiological responses following repeated presentation of a stimulus or set of stimuli [27]. Habituation to stimuli perceived to be stressful is highly important, as long-term physiological activation in response to stress has been linked to changes in behaviour, disruption of normal physiological functioning and disease [27, 28].

PR has been shown to play an important role in a variety of areas relating to typical child development. For instance, Kagan et al. [29] identified a relationship between patterns of social interaction among children and their internal physiological activation such that behaviourally inhibited children, who were shy and fearful, could be differentiated from behaviourally uninhibited children, who were extraverted and fearless, on the basis of their respective LHPA or SNS activation. Fox [30] demonstrated that PR was associated with emotional reactivity and sociability among infants such that greater PR to positive or negative events at five months was associated with greater sociability at 14 months. Hart et al. [31] found that cortisol reactivity in maltreated and socially deprived children was positively correlated with social competence and negatively correlated with shyness and internalizing behaviour. Keenan et al. [32] have proposed that poor or faulty modulation of PR to stimuli in the early years may be a risk factor for later development of behavioural or emotional problems, with empirical findings suggesting that cortisol reactivity is related to maladaptive behaviour in typically developing infants.

Studies have also identified PR as a risk factor for a variety of atypical behaviours and psychiatric comorbidities relevant to autism. Bauer et al. [33] reviewed studies examining correlations between PR and behaviour and concluded that low levels of PR and baseline arousal are associated with externalising symptoms, such as aggression or disruptive behaviours, while high levels of PR and baseline arousal are

associated with internalizing symptoms, such as social withdrawal and anxiety. A meta-analysis by Lorber [34] concluded that high EDA reactivity, low baseline HR and high HR reactivity are associated with aggression and conduct problems. Other research has identified associations between PR and a variety of psychiatric disorders including anxiety, oppositional defiant disorder, depression and post-traumatic stress disorder [16, 35, 36]. High rates of co-morbid psychiatric disorders are commonly reported in individuals with autism [37] suggesting that PR may contribute to their development, emergence and/or expression.

Given the developmental, behavioural and psychiatric significance of PR, the purpose of this article was to systematically review, quantitatively synthesize and evaluate the methodological quality of extant research focusing on cardiovascular, electrodermal and hormonal measures of PR in individuals with autism in response to different types of stimulus presentations. We conclude with open questions, research challenges to be overcome and suggestions for future research.

Methods

Search procedures

We identified articles by conducting comprehensive searches on PsycInfo, Psychology and Behavioural Sciences Collection, Medline, Scopus and Web of Science. Searches were carried out by inputting *autism* in combination with the following key words: *stimuli, habituation, orientation, reactivity, responsivity, physiology, autonomic, psychophysiology, stress, arousal, hyperarousal, hypoarousal, heart, cardiac, blood pressure, skin conductance, galvanic skin response, electrodermal* and *cortisol*. Publication year was not restricted, but only papers published in the English language were considered for inclusion.

Inclusion and exclusion criteria. Searches were limited to peer-reviewed journals. We included studies if they (1) had at least one participant diagnosed with autism; (2) measured either HR, HRV, respiratory sinus arrhythmia (RSA), BP, EDA or cortisol; and (3) used research designs that exposed participant(s) to at least one stimulus condition different from baseline. We excluded studies if they (1) only measured baseline physiological activity; (2) were described as a case study; (3) investigated physiological activity during challenging behaviour; (4) utilized physiological measures to assess the effects of a treatment or pharmacological intervention; (5) grouped participants with autism with non-autistic participants for analysis; (6) compared the PR of those with autism to a control group comprised of individuals with other psychological diagnoses (e.g. intellectual disabilities and developmental delays) only and (7) examined PR to more than one type of stimulus and did not present findings to each stimulus type separately. In studies that utilized a typically developing control group along with one or multiple control groups with other diagnoses, only data on the autism and typically developing groups were extracted for the purposes of this review.

Our search produced 128 articles that utilized physiological measures with persons diagnosed with autism. After filtering them, using the process presented in Figure 1 that

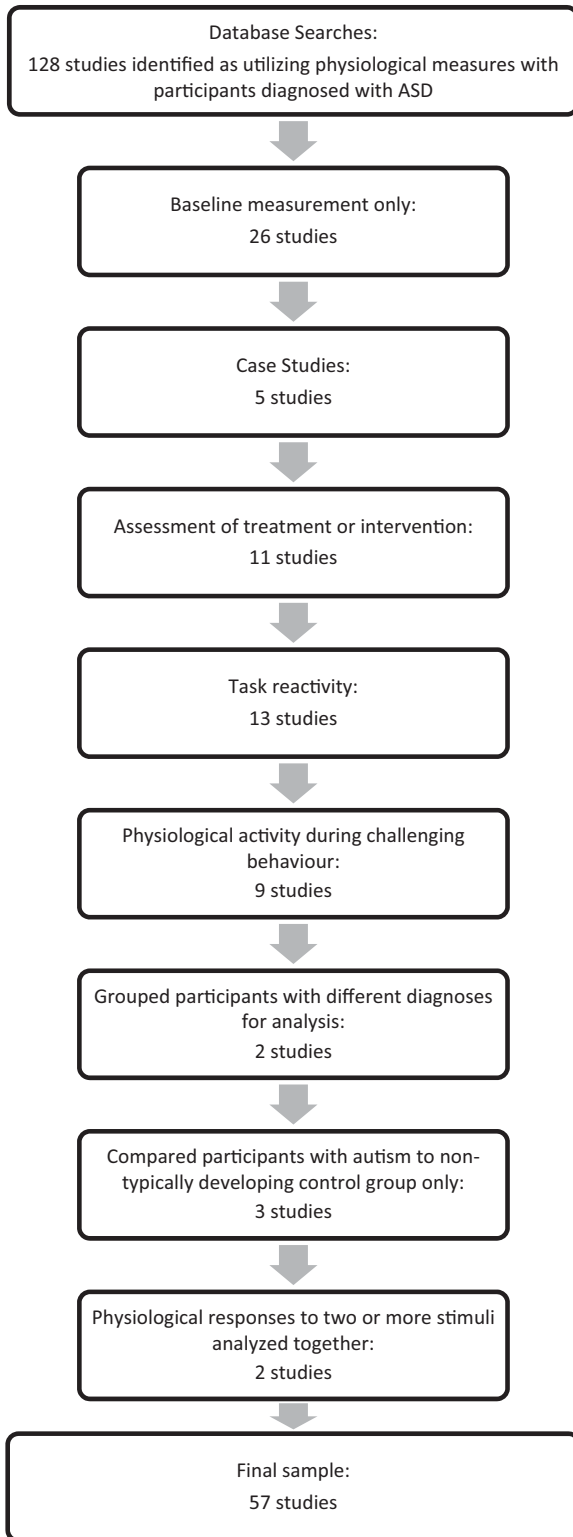


Figure 1. Flow diagram showing inclusion/exclusion of studies identified during database search process.

reflects our inclusion/exclusion criteria, 57 studies remained and were subsequently sorted into the following three stimulus classes: *sensory stimuli* were defined as any stimulus perceived by an individual's senses such as pictures, lights, sounds, tastes, movements, odors or textures. *Social and emotional stimuli* were defined as a stimulus involving other individuals, elements of social interaction (e.g. eye gaze or speech) or human affect or emotion. *Stressor stimuli* were

defined as any situation hypothesized or intended to cause participants stress. The accuracy of the data extracted was determined by having a second rater review all studies and calculating interrater reliability. Interrater reliability was found to be 94.73% (range 74.1–100%). In cases of non-agreement, consensus was achieved between raters through discussion.

Quality assessment

The importance of assessing the methodological quality of studies included in systematic reviews is widely recognized and plays a key role in the derivation of conclusions from existent research [38–40]. Extensive literature searches conducted during the preparation of the manuscript failed to identify any existing quality assessment instrument suitable for the application to non-randomized, non-interventional, psychophysiological research studies such as those included in the current review. For this reason, a quality assessment measure suitable for use with the included studies was devised in accordance with Farrington's [38] suggestions for the assessment of methodological quality standards and the deficits or faults of research in this area, which have been previously identified by Cohen et al. [12]. Table I. lists the measure that was applied to the included studies. It is comprised of 22 items, separated into four of the key categories of methodological quality identified by Farrington [38]. Three of the items are comprised of multiple related sub-items. In total, raters were required to make 33 judgements or evaluations for each study, marking each criterion as present or absent with the exception of the external validity criterion, which was scored as either 3 (very good), 2 (adequate), 1 (poor) or 0 (very poor). The measure was scored by calculating the number of items that were met per category. If 91% or more of the criteria in a category were met, then the study received a rating of three for that category indicating a "very good" outcome. A rating of two was assigned to studies that met 71–90% of the criteria indicating an "adequate" outcome on that category. A rating of one was assigned to studies that met 51–70% of the criteria in a category indicating a "poor" outcome on that category, and a rating of zero indicated studies which met 50% or less of the criteria within a category resulting in a "very poor" outcome on that category. In this way, the highest possible quality rating achievable was 12 points. Within each stimulus category, a median split was performed subsequent to scoring, whereby studies receiving a score equal to, or higher than, the median were classified as being of higher quality and studies receiving a rating below the median score were classified as being of lower quality. Interrater reliability was calculated to assess the agreement across all criteria of the quality assessment, for all included studies, between two independent raters. The mean interrater agreement for each study was 94.3% (range 84.8–100%). In cases of non-agreement, consensus was achieved between raters through discussion. The quality assessment provided a differentiation of studies within each of the three stimulus classes according to high and low methodological quality. The analysis of studies, identified as being of high methodological quality within each stimulus class, allowed us to examine whether methodological rigor

Table I. Criteria used to assess the methodological quality of the included studies.

Criteria	
Descriptive validity	<ul style="list-style-type: none"> • Experimental design is stated • Sample size is stated • The following participant characteristics are outlined: <ol style="list-style-type: none"> (a) Age (b) Gender (c) Co-morbid medical and psychological diagnoses (d) ASD severity (e) Intellectual functioning (f) Medication use • Background factors which affect physiological responses are measured: <ol style="list-style-type: none"> (a) General physical fitness (b) Affective state during the experimental procedures (c) Physical activity during the experimental procedures • The physiological response, and any behavioural responses being measured, are operationally defined • The stimulus/stimuli presented are described in detail including information on their intensity and duration • If standardized measures are used, the psychometric properties of these are described • Statistical methods employed are outlined
Internal validity	<ul style="list-style-type: none"> • A control group or control condition is utilized • If a control group is used, an attempt to match the experimental and control group on pertinent variables is made • Consideration of potential mediator or moderator variables within analyses is evident • Background factors that impact physiological responses are controlled for either through procedural consideration or analyses: <ol style="list-style-type: none"> (a) Psychological or medical conditions (b) Medication use (c) General physical fitness (d) Affective state (e) Physical activity during experimental session • Baseline physiological activity is considered during analyses • Experimental procedures are conducted in a natural or familiar setting or an effort to habituate participants to the experimental setting prior to data collection is documented • An attempt is made to habituate participants to the physiological recording device prior to data collection • Multiple measures of physiological activity are employed during experimental procedures
External validity	<ul style="list-style-type: none"> • Experimental stimuli are representative of those which may be encountered in everyday life
Statistical conclusion validity	<ul style="list-style-type: none"> • The statistical significance of findings is examined • Effect sizes are calculated for findings • Confidence intervals are calculated for findings • Analyses appropriate for the research question are utilized • If group analyses are employed, individual responding is also examined.

impacted upon experimental outcomes and to provide more robust conclusions on the existence of abnormalities in PR among those with ASD compared to typical developing controls.

Results

Sample characteristics

Sample sizes ranged from 3 to 188 participants with a mean of 45.3 participants per study among those studies reporting total sample size. A weighted mean age was calculated for the total sample of each study. We found 33 studies (57.9%) included children (1–11 years), 11 studies (19.3%) included adolescents (12–17 years) and 8 studies (14%) included adults (18+ years). Insufficient data were reported in five studies (8.8%) to calculate weighted mean age of all participants. Participants with autism as a primary diagnosis were included in all of the studies. Participants with asperger syndrome were included in 10 studies (17.5%). Participants with PDD-NOS were included in nine studies (15.8%). Five studies (8.8%) did not employ a control group, while the remaining 52 studies (91.2%) employed typically developing control groups.

Physiological measures

The majority of studies (59.6%) used only one physiological measure. EDA was used in 52.6% of studies, HR in 40.4% of studies and cortisol in 24.6% of studies. Measures of RSA, HRV and BP were less frequent, being employed in 12.3%, 5.3% and 1.8% of studies, respectively. Other physiological measures employed were respiration, heart period, pre-ejection period, interbeat interval, peripheral vasoconstriction, cephalic vasodilation, peripheral blood flow, vagal tone, evoked cardiac response, evoked cardiac deceleration, urinary mucoprotein excretion, temperature, neuroendocrine measures, EEG and plasma β -endorphin. The minority of studies (40.4%) employed more than one physiological measure. Combined use of HR and EDA was observed in seven studies (12.3%), and HR and cortisol was observed in four studies (7%). Participants with autism showed responses statistically significantly different from controls in 65.5% of studies employing EDA; 50% of studies employing HR; and in 53.8% of studies employing cortisol. All of these primary physiological measures thus seemed similarly sensitive to PR differences in participants with autism.

Sensory stimuli

Fifteen studies assessing PR to sensory stimuli are listed in Table II. Participants with autism could be distinguished from controls in 11 of 14 controlled studies (78.6%) [41–51]. Across physiological measures employed, participants with autism were similar to controls in EDA, HR and HRV (38.9%) when exposed to auditory stimuli, odorous stimuli and the sensory challenge protocol [44, 51–54]; showed increased PR in EDA and HR (22.2%) when exposed to visual, auditory, olfactory, kinesthetic, tactile and gustatory stimuli [41–43, 50]; decreased PR in EDA (11.1%) when exposed to visual stimuli and the sensory challenge protocol [46, 49]; and different patterns of PR among participants with autism in HR and EDA (27.8%) when exposed to various auditory stimuli and the sensory challenge protocol [44, 45, 47, 48, 51]. With respect to participants with autism only, one study demonstrated the absence of a physiological orienting response when exposed to auditory stimuli of varying social importance [44]; two studies found delays in stimulus registration when exposed to auditory stimuli [47, 48]; three studies observed slow or absent habituation when exposed to auditory or visual stimuli [41, 43, 47]; two studies reported faster habituation when exposed to auditory stimuli [48, 51]; and one study reported less physiological changes from one stimulus to another among participants with ASD than among controls [45].

An examination of the 10 studies examining PR to sensory stimuli, which were categorized as ‘‘high’’ quality [41, 45, 46, 49–55], revealed that the exclusion of studies of lower quality led to a reduced proportion of studies (66.7% from 78.6%) suggesting abnormalities in PR among those with ASD as compared to typically developing controls. In addition, many of the studies suggesting issues with orientation, stimulus registration or habituation were eliminated; only two remaining studies were suggestive of faulty habituation processes [41, 51], and one study suggestive of less physiological changes from one stimulus to another among participants with ASD [45]. A non-controlled study by Schoen et al. [55], which identified the presence of hypo- and hyper-aroused participants among their sample of individuals diagnosed with ASD, was also classified as ‘‘high quality’’.

Social and emotional stimuli

Twenty-six studies assessing PR to social (73.1%) and emotional (26.9%) stimuli, including social interaction, are listed in Table III. Of the controlled studies comparing reactivity to social stimuli, it was possible to distinguish participants with autism from controls in 12 of 17 studies (70.6%) [56–67]. Across 22 physiological measures employed, participants with autism showed similar PR to controls in RSA, EDA and HR (40.9%) when exposed to eye gaze stimuli, facial stimuli with neutral expressions, the strange situation procedure, conversation and child-directed speech [61, 62, 68–72]; increased PR in cortisol and EDA (9.1%) when exposed to play with peers or eye gaze stimuli [56, 58]; decreased PR in EDA and cortisol (13.6%) when exposed to human faces, eye gaze stimuli and the strange situation procedure [57, 62, 66]; different patterns of cortisol

reactivity by age (4.5%) when exposed to peer interaction [64]; and differential responding to stimuli (22.7%), or non-differential responding (4.5%), to stimuli observed among control participants in EDA, HR and RSA when exposed to various eye gaze stimuli, faces, a stranger approach procedure, and videos of familiar or unfamiliar persons [59, 60, 63, 65, 67]. One study (4.5%; [61]) identified abnormalities in physiological habituation to the stimuli among participants with ASD when exposed to facial stimuli. In one study reviewed [66], participants with autism only had weaker electrodermal reactivity to eye gaze stimuli if they had a co-morbid language delay, while participants with autism and no language delay were similar in PR to typically developing controls.

Fifteen of the studies [56, 59–67, 70–74] examining PR to social stimuli were classified as being of higher quality. The exclusion of the remaining studies did not greatly impact upon the percentage of controlled studies suggesting significant differences in PR between participants with ASD and controls (69.2% from 70.6%).

Of the seven controlled studies comparing reactivity to emotional stimuli, it was possible to distinguish participants with autism from controls (57.1% reporting significant differences) in four studies when exposed to threatening stimuli (e.g. a shark, a gun and a face with an angry expression), pictures from the International Affective Picture System, experimenter affect, emotionally evocative images and emotional facial expressions [75–78]. Across 12 physiological measures, participants with autism were similar to controls in HR, HRV and EDA (58.3%) when exposed to social and nonsocial pictures from the International Affective Picture System, emotional or neutral slides and videos, emotionally evocative images and nonsocial pictures [77, 79–81]; demonstrated decreased PR in EDA (8.3%) when exposed to emotional facial expressions [78]; a different pattern of PR in HR and BP (16.6%) when exposed to pictures from the International Affective Picture System and different HR and BP responses to certain stimuli [76]; differential responding to emotionally evocative images and nonsocial pictures in EDA (8.3%; [77]); and non-differential responding in EDA to stimuli (8.3%) than was observed among control participants, when exposed to distressing, threatening or neutral stimuli [75].

Of the three studies [75, 79, 80] examining PR to emotional stimuli, which were classified as being of higher quality, only one of these (33.3%, a reduction from 57.1%; [75]) reported differences between individuals with ASD and controls in the form of non-differential responding to stimuli among participants with ASD than was observed among control participants.

Stressor stimuli

Sixteen studies assessing PR in response to stressor stimuli are listed in Table IV. It was possible to distinguish participants with autism, and participants with autism and co-morbid anxiety, from controls in 10 of 14 studies (71.4%) [82–91]. Across 20 physiological measures, participants with autism responded similarly to controls in cortisol, HR, HRV and EDA (45%) when exposed to nonsocial environmental

Table II. Summary of studies utilising sensory stimuli.

Study	<i>n</i>	Age range (mean)	Experimental group diagnoses	Control group	Stimuli	Physiological measure(s)	Findings
Allen et al. [52]	47	– (34.7 years)	High-functioning autism	Typically developing	Auditory (musical stimuli)	<u>EDA</u>	Similar EDR to the stimuli in both groups.
Barry and James [41]	32*	4.9–17.2 years	Autism	Typically developing	Visual and auditory stimuli	<u>EDA</u> ; respiration; vasoconstrictive peripheral pulse amplitude response	Participants with autism demonstrated stronger PR to stimuli and did not show physiological habituation to the stimuli as control did.
Chang et al. [42]	50	5–12 years (8.2 years)	High-functioning autism	Typically developing	Auditory stimuli	<u>EDA</u>	The autism group was significantly more aroused at baseline. The autism group demonstrated significantly stronger PR to auditory tones (excepting sirens) than the control group. Physiological activity was significantly higher during the recovery period for participants with ASD. Auditory under- and over-responsiveness (Sensory Processing Measure-Home Form) were both positively correlated with PR to the auditory stimuli.
James and Barry [43]	80	4.5–16.9 years	Autism	Typically developing	Visual and auditory stimuli	<u>EDA</u> ; respiratory period; evoked cardiac response; vasoconstrictive peripheral pulse amplitude response	PR to the stimuli was significantly stronger among the autism group than among controls. A failure to habituate to repeated stimulus presentations was also noted among participants with ASD.
Legiša et al. [53]	16	8–14 years	High-functioning autism	Typically developing	Odoriferous stimuli	<u>HR</u> ; <u>EDA</u>	The groups did not differ on PR to the stimuli.
McCormick et al. [54]	87	2.4–4.7 years (3.3 years)	Autism Spectrum disorder	Typically developing	Sensory challenge protocol	<u>EDA</u>	The groups did not differ on baseline physiological activity. The groups did not differ on PR to any of the stimuli. Habituation to repeated stimulus presentation was evident in both groups. There was no correlation between behavioural measures (Short Sensory Profile; Repetitive Behavior Scale – Revised) and PR.
Palkovitz and Wiesenfeld [44]	20	5.8–10 years (7.6 years)	Autism	Typically developing	Auditory stimuli of varying social importance	<u>HR</u> ; <u>EDA</u>	Baseline EDA was significantly higher in the autism group while HR was similar in both groups. Control participants showed an orientation response in HR to all stimuli while children with autism did not. EDR to the stimuli was similar in both groups. Recovery of baseline HR was similar in both groups.
Schaaf et al. [45]	88	6–9 years (7.8 years)	Autism; Asperger syndrome; PDD-NOS	Typically developing	Sensory Challenge Protocol	<u>RSA</u> ; pre-ejection period	The ASD group was significantly more aroused at baseline; The ASD group showed less change in RSA from stimulus to stimulus than controls did; The ASD group were observed to demonstrate behavioural dysregulation in response to the stimuli which corresponded with their lack of flexibility in physiological responding.

Schoen et al. [46]	71	4–15 years (8.8 years)	High-functioning autism or Asperger Syndrome	Typically developing	Sensory challenge protocol	<u>EDA</u>	Baseline EDA was significantly lower in the autism group. The autism group showed consistently lower EDR to the sensory stimuli than the control group. There was no correlation between sensory behaviours and PR to stimuli (Short Sensory Profile).
Schoen et al. [55]	38	5–15 years (9 years)	High-functioning autism or Asperger syndrome	–	Sensory challenge protocol	<u>EDA</u>	Results suggest the presence of hypo-aroused participants (low baseline EDA, weak PR to stimuli, slow to respond to stimuli and quick to habituate) and hyper-aroused participants (high baseline EDA, short latency to respond, strong PR to stimuli and slow to habituate to stimuli).
Stevens and Gruzelier [47]	20*	7–17 years (10.9 years)	Autism	Typically developing	Auditory	<u>EDA</u>	Participants with ASD appeared to show delays in stimulus registration by responding more strongly to the second tone than the first. They were also slower to habituate to stimuli than controls.
van Engeland [48]	80	– (8.8 years)	Autism	Typically developing	Auditory	<u>EDA</u>	There were no differences in spontaneous electrodermal fluctuations pre-stimulation; The autism group showed delays in stimulus registration. The groups did not differ on habituation, EDR or recovery. There were significantly more non-responders in the ASD group than in the control group.
van Engeland et al. [49]	40	– (9.9 years)	Autism	Typically developing	Visual	<u>EDA</u>	The autism group showed significantly weaker EDR to stimuli. However, manipulation of stimulus subjective significance led to increased EDR. The groups did not differ on habituation to stimuli; No correlation between IQ and EDR was observed.
Woodard et al. [50]	16	2–3.2 years (2.7 years)	Autism	Typically developing	Visual; Auditory; Olfactory; Kinesthetic; Tactile; Gustatory	<u>HR</u>	Physiological measures indicated that children with autism were generally more hyper-reactive and less hypo-reactive than controls in response to sensory stimuli; There was a weak negative correlation between Low Registration (Infant/Toddler Sensory Profile) and PR.
Zahn et al. [51]	32	18–39 years (27.6 years)	High-functioning Autism	Typically developing	Auditory Stimuli	<u>EDA</u> ; <u>HR</u> ; <u>HRV</u> ; respiration; skin temperature	Groups were similarly aroused in EDA and HR at baseline but the autism group had higher HRV; Orientation and PR to the stimuli were similar among participants with autism and controls. However, participants with autism tended to habituate to the stimuli more quickly.

*Information relates to autism group only, data on control group not provided.

EDA, electrodermal activity; EDR, electrodermal reactivity; HR, heart rate; HRV, heart rate variability; PR, physiological reactivity; RSA, respiratory sinus arrhythmia.

Table III. Summary of studies utilising social or emotional stimuli.

Study	<i>n</i>	Age range (mean)	Experimental group diagnoses	Control group	Stimuli	Physiological measure(s)	Findings
Ben Shalom et al. [79]	20	9–18 years (12.4 years)	High-functioning autism; Asperger syndrome	Typically developing	Pictures from the International Affective Picture System	<u>EDA</u>	The groups did not differ significantly in EDR to stimuli.
Blair [75]	40	– (9.1 years)	Autism	Typically developing	Distress cue stimuli; Threatening stimuli; Neutral stimuli (International Affective Picture System)	<u>EDA</u>	There was no main effect of group on EDR. However, children with autism showed significantly weaker PR to threatening stimuli than control participants.
Bölte et al. [76]	20	– (27.2 years)	High-functioning autism	Typically developing	Pictures from the International Affective Picture System	<u>HR</u> ; <u>blood pressure</u>	The autism group presented with a stable to increasing pattern of PR to stimuli, while the opposite pattern was observed in the control group. Furthermore, the autism group differed from controls in their HR and blood pressure responses to several of the stimuli presented.
Cohen et al. [77]	40	10–17 years (12.8 years)	Autism; Autism and co-morbid Fragile X syndrome	Typically developing	Emotionally evocative images (NimStim facial affect set); nonsocial pictures	<u>EDA</u> ; <u>HR</u> ; <u>HRV</u> ; <u>interbeat interval</u> ; <u>vagal tone</u>	The ASD and Fragile X group had significantly higher EDA at baseline than the other groups; EDA and HR responses across stimuli differed very little between groups although within group analyses revealed differential responding according to picture type in electrodermal magnitude in the ASD group and in the number of electrodermal responses of the ASD and Fragile X group according to stimulus type.
Corbett et al. [56]	45	8–12.5 years (9.9 years)	High-functioning autism	Typically developing	Peer interaction playground paradigm	<u>Salivary cortisol</u>	Among participants with autism only, age mediated cortisol reactivity such that older children had significantly greater reactions to peer interaction than younger children. Significantly more children with autism showed heightened cortisol reactivity to play; Social functioning (Social Communication Questionnaire and Social Responsiveness Scale) was not predictive of cortisol reactivity. PR was positively correlated with peripheral play and negatively correlated with use of gestures.
Hirstein et al. [57]	50	3–13 years –	Autism	Typically developing	Human faces; objects	<u>EDA</u>	Controls showed greater EDR to faces while those with autism showed similar reactivity to faces and objects.
Hubert et al. [78]	32	– (26.4 years)	High-functioning autism; Asperger syndrome	Typically developing	Human faces expressing emotion and neutral faces; Objects	<u>EDA</u>	EDR of participants with autism was significantly weaker than that of controls in response to faces expressing emotion. EDR to neutral faces or objects was similar in both groups; EDR was not correlated with cognitive ability.

Joseph et al. [58]	40	8.6–15.8 years (12.2 years)	Autism; PDD-NOS	Typically developing	Eye gaze stimuli (direct and averted)	<u>EDA</u>	Children with autism showed stronger EDR to both sets of stimuli; Facial recognition accuracy was negatively correlated with EDR to eye gaze.
Kaartinen et al. [68]	31	8.5–15.9 years (12.5 years)	Autism; Asperger Syndrome	Typically developing	Eye gaze stimuli (direct, averted and closed eyes)	<u>EDA</u>	There were no inter-group differences in EDR to any of the stimuli; EDR to direct eye gaze was correlated with social communication skills and the use of language, the use of gesture, and nonverbal play (Developmental, Dimensional, and Diagnostic Interview).
Klusek et al. [69]	68	4.1–14.6 years (9.6 years)	Autism	Typically developing	Conversation	<u>HR</u> ; <u>RSA</u> ; interbeat interval; vagal tone	Participants with ASD showed similar HR and RSA activity to typically developing controls in response to conversation; Neither autism severity nor anxiety (Child Behavior Checklist) were associated with any of the physiological responses of the ASD group; Neither HR nor interbeat interval change were significantly associated with pragmatic skills (Comprehensive Assessment of Spoken Language). RSA during conversation was a significant predictor of pragmatic skills on one measure (Pragmatic Rating Scale-School Age) but not another (Comprehensive Assessment of Spoken Language).
Kylliäinen and Hietanen [59]	24	6.1–16 years (9.4 years)	Autism	Typically developing	Eye gaze stimuli (direct and averted)	<u>EDA</u>	Participants with autism showed significantly greater EDR to direct eye gaze than averted eye gaze, while controls responded the same to both stimuli.
Kylliäinen et al. [60]	29	10.6–14.8 years (12.9 years)	Autism	Typically developing	Eye gaze stimuli (eyes shut, eyes normally open and eyes wide open)	<u>EDA</u> ; EEG	EDR to open eyes was significantly greater than to closed eyes among the autism group. Eyes wide open provoked significantly greater EDR than eyes normally open among participants with autism. EDR of control participants was similar for all stimuli.
Lopata et al. [73]	33	6–13 years (9.8 years)	Asperger syndrome; High-functioning autism; PDD- NOS	–	Interaction with familiar peer; Interaction with unfamiliar peer	<u>Salivary cortisol</u>	PR to unfamiliar peer interaction was significantly higher than PR to familiar peer interaction. Participants who experienced familiar peer interaction first showed significantly greater PR to the subsequent unfamiliar peer interaction than participants who experienced unfamiliar peer interaction first; self-reported distress was positively correlated with cortisol reactivity.

(continued)

Table III. Continued

Study	<i>n</i>	Age range (mean)	Experimental group diagnoses	Control group	Stimuli	Physiological measure(s)	Findings
Louwerse et al. [70]	65	12–21 years (16 years)	High-functioning autism	Typically developing	Eye gaze stimuli (direct, averted or closed eyes)	<u>HR</u> ; <u>EDA</u>	The groups did not differ on their HR or EDR to any of the stimuli; Neither HR reactivity nor EDR were correlated with social deficits (Children's Social Behavior Questionnaire). The groups did not differ in their electrodermal or HR response to either type of stimulus.
Louwerse et al. [80]	73	– (16.1 years)	High-functioning autism	Typically developing	Emotional stimuli with social content or non-social content (International Affective Pictures System)	<u>HR</u> ; <u>EDA</u>	
Maras et al. [81] (i)	38	– (36.5 years)	Autism	Typically developing	Emotional or neutral slide sequence	<u>EDA</u>	It was not possible to differentiate the groups on the basis of PR to either slide sequence. HR reactivity to the videos did not differ between the groups.
Maras et al. [81] (ii)	48	– (41.9 years)	Autism	Typically developing	Emotional or neutral video	<u>HR</u>	Cardiac responses to the stimuli were similar in both groups. The groups did not differ in initial EDR to the stimuli. However, abnormalities in habituation to the stimuli were evident in the electrodermal response of autism group.
Mathersul et al. [61]	61	18–73 years (39.9 years)	High-functioning autism	Typically developing	Facial stimuli with neutral expressions.	<u>EDA</u> ; <u>HR</u> ; evoked cardiac deceleration	Baseline cortisol levels and rhythms did not differ between the groups; Autism did not predict HR reactivity but autism symptoms did predict lower cortisol reactivity. While controls showed significantly greater EDR to the faces seen in person, participants with autism showed similar EDR to both types of stimuli. Children with ASD had higher average cortisol levels than typically developing children of the same age. For younger children these declined over time while older children with autism were more likely to show cortisol increases in response to the play paradigm.
Naber et al. [62]	52	– (2.4 years)	Autism; PDD-NOS	Typically developing	Strange situation procedure	<u>HR</u> ; <u>salivary cortisol</u>	The autism group was significantly more likely to respond physiologically to the proximal stranger than the distal stranger, a relationship which was not observed among controls; PR was associated with social functioning (Vineland Adaptive Behavior Scales) among participants with ASD.
Riby et al. [63]	24	12.6–17.6 years (14 years)	Autism	Typically developing	Human face seen on video; human face seen in person	<u>EDA</u>	
Schupp et al. [64]	52	8–12 years (10.1 years)	Autism; PDD-NOS	Typically developing	Peer interaction playground paradigm	<u>Salivary cortisol</u>	
Sheinkopf et al. [65]	23	2.5–6.6 years (4.1 years)	Autism	Typically developing	Stranger approach procedure (distal stranger and proximal stranger)	<u>HR</u> ; <u>RSA</u>	

Stagg et al. [66]	50	7–15 years (9.8 years)	High-functioning autism-language normal; High- functioning autism- language delay	Typically developing	Eye gaze stimuli (direct, averted and closed eyes)	<u>EDA</u>	Both typically developing participants and participants with high-functioning autism and normal language presented with significantly stronger PR to the stimuli than participants with high-functioning autism and a language delay. The groups did not differ in their patterns of PR to the different forms of eye gaze stimuli; A positive correlation between verbal mental age (The British Vocabulary Picture Scale-II) and PR to the presented stimuli was identified while neither the onset of first word nor the language and social communication subscale of the Developmental, Dimensional and Diagnostic Interview were correlated with EDR.
van Hecke et al. [67]	33	8–12 years (9.9 years)	High-functioning autism	Typically developing	Video of familiar person; video of unfamiliar person	<u>RSA</u> ; <u>EEG</u>	Children with autism showed significantly decreased HR regulation in response to the unfamiliar person while controls did not; Higher levels of HR regulation were correlated with better social behaviours and fewer problem behaviours (Social Skills Rating System - Elementary Parent Form; Social Responsiveness Scale-Parent Form).
Watson et al. [74]	22	2.3–3.5 years (2.9 years)	Autism	–	Child-directed speech; Non-social stimuli	<u>RSA</u>	PR to child-directed speech was positively correlated with receptive language skills at entry and expressive language and social communicative abilities at follow-up (MacArthur-Bates Communicative Developmental Inventory, Words and Gestures Form; The Preschool Language Scale, Fourth Edition; The Mullen Scales of Early Learning; The Vineland Adaptive Behaviour Scales).
Watson et al. [71]	51	0.5–3.5 years (2.4 years)	Autism	Typically developing	Child-directed speech; Non-social stimuli	<u>RSA</u> ; heart period/interbeat interval	Participants with autism had smaller inter-beat-intervals (indicative of faster HR) in response to both sets of stimuli but did not differ in their RSA response.
Willemssen-Swinkels et al. [72]	51	– (5.2 years)	Autism; PDD-NOS	Typically developing	Strange situation procedure	<u>HR</u>	Attachment style, rather than diagnosis, predicted HR responses to separation from, and reunion with, parents.

EDA, electrodermal activity; EDR, electrodermal reactivity; HR, heart rate; HRV, heart rate variability; PR, physiological reactivity; RSA, respiratory sinus arrhythmia.

Table IV. Summary of studies utilising stressor stimuli.

Study	<i>n</i>	Age range (mean)	Experimental group diagnoses	Control group	Stimuli	Physiological measure(s)	Findings
Corbett et al. [82]	22	6–11 years (8.8 years)	Autism	Typically developing	Nonsocial environmental stressor (mock MRI scan)	<u>Salivary cortisol</u>	Cortisol circadian rhythms were similar among both groups. However, there was greater variability in cortisol levels across the day in the autism group. The majority of participants with ASD showed cortisol increases in response to the stressor while the majority of controls showed no response or a decrease in cortisol. There was no relationship between scores on the Stress Survey Schedule or Short Sensory Profile and cortisol.
Corbett et al. [92]	44	6.5–12 years (9.1 years)	Autism	Typically developing	Nonsocial environmental stressor (mock MRI scan and real MRI scan)	<u>Salivary cortisol</u>	Both groups showed the expected cortisol rhythms although, over the course of sampling, morning cortisol levels decreased in the autism group and evening cortisol levels were consistently higher than in controls. Greater variability in cortisol levels was also observed in the autism group. The groups did not differ in PR to the initial stressor and both demonstrated increased PR prior to the second stressor presentation.
Corbett et al. [93]	44	6–12 years (9.1 years)	Autism	Typically developing	Nonsocial environmental stressor (mock MRI scan)	<u>Salivary cortisol</u>	There was greater variability, and dysregulation, in cortisol levels throughout the day in the autism group than in the control group. The groups did not differ in cortisol reactivity to the stressor. PR to the stressor was not significantly related to Stress Survey Schedule or Short Sensory Profile Score.
Corbett et al. [94]	59	8–12.6 years (10 years)	Autism; PDD-NOS	Typically developing	Trier Social Stress Test – Child version; The Peer Interaction Playground Paradigm	<u>Salivary cortisol</u>	PR to the stressors did not differ between the groups. However, significantly greater variability in cortisol levels across the stressor paradigms was noted in the autism group. Quick physiological recovery from stress was evident in the typically developing group while the physiological response in the autism group persisted for significantly longer.
Goodwin et al. [83]	10	8–18 years (13.8 years)	Autism	Typically developing	Stressors from the Stress Survey Schedule for Persons with Autism and other Developmental Disabilities	<u>HR</u>	Baseline HR was higher among participants with autism than among typically developing controls; The autism group demonstrated significant PR to stressors on 22% of occasions while the typically developing participants showed significant PR on 60% of occasions.
Groden et al. [96]	10	13–27 (24 years)	Autism; PDD-NOS	–	Stressors from the Stress Survey Schedule for Persons with Autism and other Developmental Disabilities	<u>HR</u>	Each of the stressor domains led to significant HR changes in some participants. However PR, and the stressors that evoked it, demonstrated a high degree of individual variability.

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Study	<i>n</i>	Age range (mean)	Experimental group diagnoses	Control group	Stimuli	Physiological measure(s)	Findings
Hollocks et al. [84]	75	10–16 years (13.2 years)	Autism; Autism and co-morbid anxiety disorder	Typically developing	Trier Social Stress Test	HR; HRV; salivary cortisol	The ASD group had a higher resting HR than the ASD and anxiety group and controls while the groups did not differ on baseline measures of HRV or cortisol. The groups did not differ on HRV response to the stressor. The ASD group had higher HR during the stressor than the other groups while the ASD and anxiety group showed lower cortisol reactivity to the stressor than the other groups. Participants with ASD and controls did not differ significantly in cortisol and recovery slope while the HR of those with ASD and anxiety was slower to recover; HR reactivity and cortisol reactivity were negatively correlated with anxiety for the ASD and anxiety group only (The Child and Adolescent Psychiatric Assessment. The Spence Children's Anxiety Scale).
Jansen et al. [85]	22	– (9.4 years)	Autism	Typically developing	Psychosocial stressor	HR; salivary cortisol	Children with autism did not differ from controls in their cortisol response to the psychosocial stressor although they showed a different pattern of HR responses; There was no correlation PR and scores on the Child Behavior Checklist or IQ. Communication scores on the Autism Diagnostic Interview were correlated with cortisol during the stressor.
Jansen et al. [86]	24	– (21.3 years)	Autistic disorder; Asperger syndrome	Typically developing	Psychosocial Stressor	HR; salivary cortisol; adrenocorticotrophic hormone; oxytocin; vasopressin; nor-epinephrine; epinephrine	The autism group showed a decreased HR response to the stressor while their neuroendocrine response did not differ from that of controls; HR reactivity to the stressor was positively correlated with social interaction and communication (Autism Diagnostic Interview). The decreased HR reactivity was associated with less self-care and greater current social anxiety (Dutch Social Interaction Inventory).
Kushki et al. [87]	29	8–15 years (11.1 years)	Autism; Asperger syndrome	Typically developing	Anxiety-inducing task	HR; EDA; skin temperature	The autism group had significantly elevated HR and EDA during baseline. Participants with autism demonstrated higher HR in response to the stimulus than controls while participants with autism demonstrated a blunted electrodermal response to the stressor.
Lanni et al. [88]	30	8–12 years (9.7 years)	Autism	Typically developing	Trier Social Stress Test – Child Version	Salivary cortisol	There were no significant differences in resting cortisol levels between the groups. While control participants showed a greater cortisol response to the stressor, between group differences were not significant. Verbal ability (Verbal Fluency Test) was not related to cortisol responses. Self-reported anxiety (State-Trait Anxiety for Children) was also unrelated to cortisol responses.

(continued)

Table IV. Continued

Study	<i>n</i>	Age range (mean)	Experimental group diagnoses	Control group	Stimuli	Physiological measure(s)	Findings
Levine et al. [89]	30	8–12 years (9.7 years)	High-functioning autism; Asperger syndrome; PDD-NOS	Typically developing	Trier social stress test	<u>Salivary cortisol</u> ; <u>EDA</u> ; vagal tone	Neither cortisol, EDA, nor vagal tone differed between the groups at baseline; Individuals with autism were significantly more likely to show cortisol decreases in response to the stressor while controls typically showed cortisol increases. There were no differences in EDR in response to the stressor between the groups; The groups did not differ significantly on any of the physiological measures during the recovery period.
Moskowitz et al. [97]	3	6–9 years (7.7 years)	Autism spectrum disorder	–	Exposure to high anxiety context	<u>HR</u> ; <u>RSA</u>	For two participants, HR was significantly higher during the high anxiety context than during a low anxiety context while RSA was also lower during the high-anxiety context for two participants. All participants presented with more anxious behaviour and more challenging behaviour during the high anxiety condition.
Rattaz et al. [95]	71	–	Autism spectrum disorder	Typically developing	Blood draw stressor	<u>HR</u>	Children with autism had higher HR at baseline than controls. Participants with autism did not differ from controls in their HR reactivity to the stressor. The heart rate of children with autism remained higher during the recovery period than that of controls.
Spratt et al. [90]	48	3–12 years (6.1 years)	Autism	Typically developing	Blood draw stressor; novel environment	<u>Urinary, serum and salivary cortisol</u>	Children with ASD had significantly higher serum cortisol levels at baseline; Children with autism showed a significantly greater cortisol response to the stressor; Children with autism showed a prolonged cortisol response duration; There were no correlations between autism severity or symptoms (CARS score, DSM IV scores) or behaviour (The Child Behavior Checklist) and any of the cortisol measures.
Tordjman et al. [91]	188	– (12.3 years)	Autism	Typically developing	Blood draw stressor	<u>HR</u> ; plasma β -endorphin	The autism group had a significantly higher HR during baseline. The autism group showed greater HR reactivity to the stressor. The autism group had a significantly higher HR after the stressor.

EDA, electrodermal activity; EDR, electrodermal reactivity; HR, heart rate; HRV, heart rate variability; PR, physiological reactivity; RSA, respiratory sinus arrhythmia.

stressors (e.g. mock MRI scan), psychosocial stressors (e.g. public speaking task and Trier Social Stress test) and a blood draw stressor [84–86, 89, 92–95]; demonstrated increased PR in cortisol and HR (25%) when exposed to a nonsocial environmental stressor, a psychosocial stressor, an anxiety inducing task and blood draw stressors [82, 84, 87, 90, 91]; decreased PR in HR, cortisol and EDA (25%) when exposed to common stressors (derived from the Stress Survey Schedule for Individuals with Autism and other Developmental Disabilities), psychosocial stressors and an anxiety-inducing task [83, 86–89]; and different patterns of PR in HR (5%) when exposed to a psychosocial stressors [85]. Four studies [90, 91, 94, 95] noted a prolonged duration for physiological recovery, or higher physiological activity during the recovery period, among participants with autism, as compared to controls, following exposure to a nonsocial environmental stressor, psychosocial stressors or blood draw stressors. Hollocks et al. [84] exposed participants with autism, autism and a co-morbid anxiety disorder and typically developing controls to an adapted version of the Trier Social Stress Test. They found that participants with autism alone had the highest HR response to the stressor, while participants with autism and a co-morbid anxiety disorder were distinguishable from controls and participants with ASD alone on the basis of a blunted cortisol response to the stressor and slower HR recovery.

The examination of the 12 studies categorized as being of ‘‘high’’ quality [82–86, 88, 89, 91, 93, 94, 96, 97] revealed that the exclusion of studies of lower quality led to a somewhat increased percentage of studies (80% up from 71.4%) reporting discernible differences in physiological response between participants with autism and controls. This process also eliminated two of the four studies [90, 95] reporting a prolonged stress response among individuals with ASD.

Relation between behavioural or psychological variables and PR

The reviewed studies were also examined for evidence of consideration of behavioural or psychological variables, which may be associated with PR. In total, 26 of the studies reviewed (45.6%; [42, 45, 46, 49, 50, 54, 56, 58, 62, 65–70, 73, 74, 78, 82, 84–86, 88, 90, 93, 97]) examined the association between PR and psychological or behavioural variables. The findings of individual studies with regards the correlation between PR and such variables are outlined in Tables II–IV. It was most common for studies to assess the association between PR and measures of social and communication abilities such as the Autism Diagnostic Inventory, Developmental, Dimensional and Diagnostic Interview, Children’s Social Behavior Questionnaire, Vineland Adaptive Behavior Scale, Social Communication Questionnaire, Social Responsiveness Scale, Social Skills Rating System, MacArthur-Bates Communicative Developmental Inventory, Words and Gestures Form and behavioural observations of play or use of gestures (34.6%; [56, 65–68, 70, 74, 85, 86]). With the exception of Louwse et al. [70] and Stagg et al. [66], all other studies reported significant correlations between PR to stimuli and at least one

measure relating to social or communicative abilities. The relation between PR and sensory behaviours was examined in six studies (23.1%; [42, 46, 50, 53, 82, 93]). Findings regarding the correlation of PR with measures of sensory behaviours including the Short Sensory Profile, the Sensory Processing Measure, and the Infant/Toddler Sensory Profile, were mixed with two studies (33.3%) reporting some correlation and four studies reporting no discernable correlation between these variables. The correlation between PR and indirect measures of stress or anxiety, such as the Stress Survey Schedule for Persons with Autism and other Developmental Disabilities, The Child and Adolescent Psychiatric Assessment, The Child Behavior Checklist, The Spence Children’s Anxiety Scale, The Dutch Social Interaction Inventory, State-Trait Anxiety for Children and self-reported distress, was examined by seven studies (26.9%; [69, 73, 82, 84, 86, 88, 93]) with only two (28.6%) of these reporting the identification of a correlation between these variables. Seven studies (26.9%; [49, 66, 69, 74, 78, 85, 88]) examined the correlation between PR and measures of intellectual or verbal functioning, such as the Comprehensive Assessment of Spoken Language, the Expressive Vocabulary Test, Pragmatic Rating Scale, Verbal Fluency Test, the Mullen Scales of Early Learning, MacArthur-Bates Communicative Developmental Inventory, Words and Gestures Form, The Preschool Language Scale, verbal mental age as per the British Vocabulary Picture Scale and IQ, with only three of these studies (42.9%; [66, 69, 74]) suggesting any correlation between PR and intellectual functioning or verbal ability. Four studies (16%; [54, 85, 90]) examined the correlation between PR and indirect measures of behaviour, including the Child Behavior Checklist, the Repetitive Behavior Scale-Revised, Social Skills Rating System, with only one of these studies (25%; [67]) suggesting a relation between PR and behaviour. Two studies (7.7%) examined the relation between PR and observations of challenging behaviour [97] and behavioural reactivity to stimuli [45], with both suggesting a relation between overt behaviour and physiological responses. Finally, three studies (11.5%; [62, 69, 90]) assessed the association between autism symptoms or severity, as measured by the CARS, DSM IV Scores and Autism Diagnostic Observation Schedule, with only one of these [62] suggesting any relation between PR and autism severity. In addition, three studies [66, 77, 84] examined the impact of a co-morbid diagnosis or additional impairment, fragile X syndrome, a language delay and an anxiety disorder respectively, on PR among those with ASD. In each of these studies, physiological activity differed between those with a sole diagnosis of autism and those with a co-morbid diagnoses or additional delay. Finally, Jansen et al. [86] reported a correlation between PR to a stressor and self-care, and Joseph et al. [58] reported a correlation between PR and facial recognition accuracy.

The exclusion of studies found to be of lower quality led to the removal of five studies [42, 58, 69, 78, 90]. This resulted in a reduction in the body of evidence suggestive of a relationship between PR and sensory behaviours, of an association between PR and facial recognition accuracy, PR and verbal or intellectual ability. The one remaining study examining autism symptoms suggested a positive association

with PR. The exclusion of these studies did not reduce the evidence suggestive of the association between PR and indirect or direct measures of behaviour, indirect measures of anxiety or stress, social and communication ability or the impact of various co-morbid diagnoses on PR among those with ASD.

Baseline physiological arousal

Previously mentioned theories of chronic hyper- and hypo-arousal among individuals with autism also prompted us to examine baseline levels of physiological arousal reported by the studies reviewed. Of the 22 studies reporting baseline physiological activity across 30 physiological measures, participants with autism and controls did not differ on 50% of these baseline measures, including cortisol, HR, HRV, RSA and EDA [44, 48, 51, 54, 62, 65, 77, 82, 84, 88, 89]; participants with ASD were more physiologically aroused on 40% of measures, including cortisol, EDA, HR, HRV and RSA [42, 44, 45, 51, 64, 83, 84, 87, 90, 91, 95]; lower on one (3.3%) measure of EDA [46]; and showing differences in cortisol secretion across the day in two studies (6.7% of measures; [92, 93]). One non-controlled study employing a measure of EDA when exposed to the sensory challenge protocol [55] identified both patterns of basal hypo-arousal and hyper-arousal among participants with autism. Furthermore, one study [77] noted differences in the baseline physiological arousal of those with ASD and co-morbid Fragile X syndrome as compared to participants with ASD alone and typically developing controls.

The exclusion of lower quality studies upon findings regarding baseline physiological activity appeared to have minimal impact on the overall pattern of results obtained. Of the 14 remaining studies of higher quality, which employed 18 physiological measures [45, 46, 51, 54, 62, 64, 65, 83, 84, 88, 89, 91–93], there were no significant differences in baseline physiological arousal on 10 measures (55.6%; [51, 54, 62, 65, 82, 84, 88, 89]), higher arousal among participants with ASD on five measures (27.8%; [45, 64, 83, 84, 91]), lower arousal among participants with ASD on two measures (11.1%; [46, 51]) and one study suggested differences in the daily patterns of cortisol secretion of those with ASD (5.6%; [93]).

Discussion

This systematic review examined PR to sensory, social and emotional and stressor stimuli among individuals with autism across 57 studies published between the years of 1978 and 2014. Findings suggest abnormalities in PR exist for at least some individuals with autism. Differences in PR on at least one physiological measure were observed in 78.6% of studies employing sensory stimuli; 66.7% of studies employing social or emotional stimuli; and 71.4% of studies employing stressor stimuli. Notably, however, findings were not uniform, even when the same or very similar physiological measures, test stimuli, methodological protocols and sample characteristics were used. Inconsistencies in results across these studies are an important finding of this review, and raise questions about whether atypical PR observed in individuals with autism is a valid marker for the existence of clinical subtypes,

relate to clinically relevant behaviours or arise from methodological artifacts.

Given the highly heterogeneous presentation of autism [66], it is perhaps unsurprising that PR varies widely across individuals who share the same diagnosis. The outcomes of the quality assessment included in this study suggest that the differences in PR, and inconsistent outcomes, persist even among the studies that were classified as being of higher quality. The purpose of the assessment of the methodological rigor of the included studies was to determine whether the methodological quality of the studies included impacted upon the outcomes of these studies. To achieve this, we assessed each study on a number of indicators of methodological strength and computed scores that allowed us to assign studies to a “low” or “high” quality category. The exclusion of the “low” quality studies resulted in limited impact on the overall outcomes of each category, or the great degree of inconsistency observed in each stimulus category. Therefore, the results allow us to conclude, with a greater degree of certainty, that PR to the various stimuli examined was variable among persons with autism.

A potential explanation for the high degree of variability in PR observed is the possible existence of subtypes of ASD characterized by different physiological profiles. The putative existence of subtypes within the autism spectrum is not new [98] and may account for the high degree of variability in PR observed among participants with autism in a number of the studies reviewed [52, 82, 92, 94, 96]. Arguably, the best current evidence for this hypothesis comes from the studies by Hirstein et al. [57] and Schoen et al. [55] who found distinct subtypes of physiological responders in their sample (i.e. hypo-aroused, normally aroused and hyper-aroused), while exposed to the same within-study stimuli sets. Future research is needed to further examine the prevalence of PR subtypes among individuals with autism to determine whether such patterns of responding are stable over time, constitute meaningful differences and have predictive validity.

A number of the studies reviewed also suggest that an association may exist between PR and a number of behaviours and psychological variables highly relevant to individuals with autism, including social and communication abilities, intellectual or verbal functioning, autism symptoms or severity, overt behaviours including both challenging and sensory behaviours, co-morbid diagnoses or delays and indirect measures of stress or anxiety. Further research is needed to determine the nature of this relationship given its potential clinical significance. For instance, van Hecke et al. [67] found that participants with autism responded to social interactions with substantial increases in physiological arousal, suggesting that the experience was highly stressful for them. The authors suggest that physiological activation in the form of a nervous system primed to fight or flee during such encounters would directly hamper and impede the ability to engage in appropriate social interactions. In other cases, however, the association may not be causal and may be mediated by other variables. For example, Watson et al.’s [74] finding that increased PR to child-directed speech was positively associated with current and future language and communication skills might be explained by attentional processes. Furthermore, several of the studies reviewed [42,

83, 91] suggest that the observable behaviour of an individual with autism may not be indicative of his or her internal physiological arousal state. Baron et al. [99] emphasized the importance of further investigating this phenomenon systematically, especially in individuals with autism who have communication deficits and/or limited emotional expressivity. Future research examining the association between PR and overt behaviour, and the association between PR and important behavioural outcomes, among individuals with autism is warranted. For instance, research on the Yerkes–Dodson law [100] has led scholars [101, 102] to suggest a curvilinear relationship between physiological arousal and performance, wherein performance decreases when arousal is appreciably lower (i.e. an inert effect) or higher (i.e. an anxious effect) than an individual's homeostatic set point. In this way, a certain level of PR to stimuli, or the elevation of physiological arousal in response to stimuli, is necessary for appropriate interactions with a given stimulus. Correspondingly, weak or excessively strong PR may compromise performance or lead to inappropriate reactions to stimuli.

The association between PR and a variety of important health outcomes also suggests value in assessing ANS and LHPA functioning in individuals with autism. Negative health outcomes have been linked to both increased and reduced PR [103]. Much research has evidenced a connection between increased PR to stressors, and an increased risk of hypertension and coronary heart disease [104, 105]. Although the relationship has received less research attention, Lovallo [103] described how reduced PR to stressors is likely related to increased risk for autoimmune or metabolic disorders, obesity and engagement in behaviours with negative health consequences. Individuals with autism were observed to produce statistically significantly greater and weaker PR than controls to a wide variety of stimuli in this review. Assuming PR in an experimental context reflects PR in the natural environment, it is possible that these individuals are at risk for a variety of negative health outcomes due to their physiological over- or under-reactions. Furthermore, the findings of elevated baseline levels of physiological arousal in many of the studies [42, 44, 45, 64, 83, 84, 87, 90, 91, 95] also suggest that individuals with autism may be at increased risk for negative health outcomes associated with chronic stress, including reduced immune system responsivity, cardiovascular problems, stunted growth and diabetes [106]. Given the serious nature of these health outcomes, longitudinal investigations are needed to determine if abnormal PR evidenced among individuals with autism can predispose them to ill-health.

Finally, studies within this review suggest areas of potential physiological dysregulation in autism that merit future investigations. For instance, the LHPA and vagal system were both identified by recent research studies [86, 88, 93] as being possibly impaired in this population. The LHPA plays an important role in stress responses and was previously implicated as a potential underlying cause of autism for some individuals with the disorder [107]. Findings of greater cortisol variability and atypical cortisol circadian rhythms or levels among individuals with autism [82, 92–94] in the studies reviewed support the possibility that LHPA axis functioning may be impaired in this population. Jansen et al.

[86] implicated the vagal system as potentially dysfunctional, as participants with autism presented with abnormal HR responses to psychosocial stressors. The vagal system is thought to play a key role in social engagement and communication, and has been posited to relate to diagnostic features associated with autism [86, 108]. Such suggestions of physiological dysregulation highlight avenues for further research that may contribute to our understanding of the development or the presentation of autism.

This systematic review was limited in a number of ways. The decision to include all studies that examined PR among individuals with autism, regardless of experimental design, sample size or year of publication, may be criticized. However, given the breadth and span of research studies published on the topic and lack of a useful quantitative synthesis or overview of these to date, this review sought to be inclusive and to provide a comprehensive summary and discussion of the current state of research in this area. Furthermore, many of the included studies that utilized small sample sizes were considered to provide important findings, such as the presence of both hypo- and hyper-arousal among participants with autism [55]. Such a study may, for example, contribute to our understanding of discrepant findings observed in many of the other controlled studies and also have important implications for future research including the need to analyse variability in responding among participants with autism and greater consideration of participant's baseline physiological activity. Our division of stimuli into the categories of sensory, social and emotional and stressor may also be faulted given the overlap between these classes and our reliance on authors' description of stimuli and their intent of employment for categorization. However, it was considered necessary to subdivide the articles to better represent the findings with regards PR to the various stimuli and division by stimulus employed was deemed the most meaningful manner of doing this by our research team. Finally, our use of a self-developed, subjective, measure of quality to assess the included studies may also be criticized. However, extensive literature searches did not produce an already existing quality assessment measure suitable for use with the included studies. Given the inconsistent findings of the studies reviewed, it was considered important to assess within the current review whether methodological artifacts may have accounted for the variability in outcomes. Future research could further examine these limitations by utilising more stringent inclusion criteria than those reported in this study and assessing methodological quality of studies in an alternative manner.

In spite of these limitations, we believe the current review provides an important foundation for future research in this area. First, it is hoped that the provision of explicit indicators of methodological quality will have a positive impact upon future research studies in this area. Outcomes on the quality measured developed for this review were generally quite poor with scores ranging from 1 to 7 ($M = 3.8$) of a possible 12 points. Studies were most frequently faulted for the poor consideration of extraneous factors (e.g. co-morbid psychological or medical diagnoses, medication usage, affect, physical fitness, physical activity, exposure to novel settings and exposure to novel physiological recording devices) that may impact upon physiological outcomes (i.e. internal

validity). Furthermore, less than half of the studies employed more than one physiological measure. The use of multiple indices of PR obtained simultaneously is typically advised, as certain measures can be more sensitive to stimulus perception than others. This phenomenon, referred to as directional fractionation, indicates that autonomic responses may differ in their direction of change in response to external stimulation [109]. For example, in response to external arousal or unanticipated stimulation, increases in EDA have been frequently accompanied by HR decreases, although covariance of both responses is expected [110]. The possibility of such “fractionated” responding underlines the importance of measuring the activation of multiple physiological systems in response to stimulation. For instance, Lovallo [111] describes a series of experiments in which typically developing individuals engage in tasks that produce either aversive consequences or rewards. Cardiovascular reactivity to both tasks was similar; however, cortisol reactivity differed such that aversive tasks led to cortisol increases and reward tasks did not. Relying on only cardiovascular or cortisol measures in these studies may have failed to appreciate the complex relationship observed. The included studies performed better in the descriptive validity, external validity and statistical conclusion validity categories of the quality assessment. However, in studies that analysed group responding, the consideration of individual responding was infrequent. This is problematic given the findings of Hirstein et al. [57] and Schoen et al. [46] concerning potential subtypes of physiological responders among those with ASD and the possible impact of individuals presenting with hyper- or hypo-arousal on the outcomes of studies employing solely group analyses. Future research should seek to improve upon the methodological quality of past studies as a potential means of elucidating the nature of any differences in PR in autism.

The included studies can also be critiqued on a number of additional factors including the absence of screening for maltreatment, a suggested determinant of PR [112], in all but one study [90], the prevailing focus on higher-functioning individuals with ASD or those with no co-occurring cognitive impairment (although research suggests up to 70% of those with ASD have a co-morbid intellectual disability; [113]), and the infrequent examination of the impact of co-morbid psychological diagnoses, prevalent among those with ASD [37], on PR. The role of such factors in PR and autism could be further analysed in future research. This review also highlights the need for a quantitative analysis of findings in this literature and the examination of potential moderator variables, such as age, level of functioning, co-morbid diagnoses, type of stimulus presented, medication status or physiological measures used. It also suggests numerous avenues for future research including: studies exploring potential subtypes in autism distinguishable by physiological arousal or reactivity and associated profiles or behavioural presentations within these subtypes; examination of cortisol variability or dysregularity among individuals with autism and its impact on overt behaviours; correspondence between PR and overt behaviour or self-reported arousal or stress in autism; and examination of the relationship between PR and health issues in autism. These findings also highlight the need

for greater consideration of participant and stimulus characteristics in future studies of this kind.

Allen et al. [52] conclude that “within-group variability is much larger than any effect of autism, if it exists” and perhaps this can be considered a succinct summary of the findings of the present review. While the majority of studies indicate some abnormalities in PR to sensory, social and emotional and stressor stimuli among individuals with autism, other studies have evidenced normal PR to these stimuli. Such discrepant findings indicate that some atypicality exists in PR for some individuals with autism, but not for all. This review thus underscores the need for future research to investigate such discrepancies. It is likely that further investigation of PR among individuals with autism will further our understanding of the disorder, potential subtypes within it, associated behaviours and health outcomes.

Declaration of interest

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