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Is autonomic function during resting-state atypical in Autism: A systematic review of evidence

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ABSTRACT

Background: Theories of differences in resting-state arousal in autistic individuals are influential. Differences in arousal during resting-state would impact engagement and adaptation to the environment, having a cascading effect on development of attentional and social skills.
Objectives: We systematically evaluated the evidence for differences in measures of autonomic arousal (heart rate, pupillometry or electrodermal activity) during resting-state in autistic individuals; to understand whether certain contextual or methodological factors impact reports of such differences.
Data sources: We searched PsycInfo, MEDLINE and EMBASE databases for papers published until 16th May 2019. Of 1207 titles initially identified, 60 met inclusion criteria.
Results and Conclusions: Of the 51 studies that investigated group differences between neurotypical and autistic participants, 60.8 % found evidence of group differences. While findings of hyperarousal were more common, particularly using indices of parasympathetic function, findings of hypo-arousal and autonomic dysregulation were also consistently present. Importantly, experimental context played a role in revealing such differences. The evidence is discussed with regard to important methodological factors and implications for future research are described.

1. Introduction

Autism Spectrum Disorder is a heterogeneous neurodevelopmental condition with prevalence estimated at 1% in the UK (Laurie and Border, 2020). The condition is well-characterized at the behavioural level by a variety of symptoms, including difficulties with social interaction and communication alongside repetitive and restricted behaviours (RRBs), from an early age (American Psychiatric Association, APA, 2013). The criteria used to diagnose autism spectrum disorder have evolved over the years and there has been a shift from using multiple sub-categories to refer to different presentations (Diagnostic and Statistical Manual (DSM)-3, APA, 1980) to the current diagnostic criteria which use one term (ASD) to refer to a broad spectrum of widely varying presentations that have in common differences in the above-mentioned domains (DSM-5, APA, 2013). For this reason, and due to reports of autistic individuals indicating a preference for the term "autism" and identity first language (Kenny et al., 2016), we have endeavoured to use this preferred terminology throughout.

An influential theory in the field of autism proposed that autistic individuals have atypical profiles of physiological arousal during resting-state (i.e., states of rest or relaxation). First put forward by Hutt et al. (1964), this theory suggested that autistic individuals may be in a "chronically high state of arousal" (Hutt et al., 1964, p.908); which may lead to sensory over-responsivity and prevent habituation to environmental stimuli. According to this theory, social avoidance and repetitive behaviours in autism may be a coping mechanism to regulate arousal. Indeed, if autistic individuals are in a chronic state of hyperarousal at rest, they might be hyper-reactive to different sensory stimuli in the environment and might feel overwhelmed. Avoiding rich sources of sensory stimulation, such as social situations, and engaging in repetitive

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behaviours to reduce the amount of sensory stimulation received, might therefore help to down-regulate arousal (Kinsbourne, 2011; McCormick et al., 2014). Theoretically then, these two core areas of differences (social avoidance and RRBs) in autistic individuals could be explained by a profile of resting hyperarousal.

On the other hand, it has also been proposed that states of hypoarousal at rest might underlie core features of autism (DesLauriers and Carlson, 1969). According to this theory, reduced responsiveness to social environments might be explained by chronic hypoarousal, while RRBs might serve the purpose of stimulating an under-aroused system (Lovaas et al., 1987). It is important to note that these two theories are not mutually exclusive; there might be subgroups of autistic individuals with profiles of resting-state hyper- or hypo-arousal; and the same individuals may present with one or the other profile in different contexts. However, both hyper- and hypo- aroused states at rest are likely to impact engagement with the environment and responsivity to cognitive tasks.

If present, differences in resting-state arousal may develop earlier than the first symptoms of autism typically appear. Evaluating the utility of theories of differences in resting-state profiles of arousal in autism thus has important implications for early detection, diagnostic practices and intervention routes in autism. Early differences in profiles of resting-state arousal may impact subsequent acquisition of adaptive, socialization and cognitive skills and may contribute to the heterogeneity in the autistic phenotype (Charman et al., 2005). Thus, proper examination of the evidence for these theories has importance towards understanding developmental pathways of autism and parsing the heterogeneity of the autistic spectrum.

This is the motivation behind the present review, which aims to evaluate the evidence for differences in profiles of resting-state arousal in autism. In experimental contexts, resting-state refers to an absence of sensory stimulation or the demands of a cognitive task. In studies that use cognitive tasks, evoked responses that are time-locked to stimuli or responses tend to be the focus, with any other spontaneous activity considered irrelevant and a source of noise. On the other hand, in resting-state studies of arousal, it is the spontaneous activity of the central or peripheral nervous system that is the focus. Even in studies that are specifically focussed on task-related measures, a baseline measure is typically taken of the index in question, to look at differences from baseline when task-evoked activity occurs. This is because it can be difficult to interpret task-related differences in any function, without first investigating differences at rest (Wang et al., 2013).

If the theories of atypicalities in resting-state arousal in autistic individuals are true, there should be differences between autistic and neurotypical controls in autonomic arousal during resting-state, which would influence how autistic individuals then respond to stimulation or task demands. In this review, we chose to focus on autonomic arousal because indices of autonomic arousal have been most commonly used to study profiles of arousal in autism. Further, autonomic indices of arousal are relatively easy and inexpensive to measure, and thus have high utility with regard to implementation in clinical practice. Before presenting the methods and results of the review, we describe the role of the autonomic nervous system in cognition and how this may be altered in autism.

1.1. What is autonomic arousal?

Arousal refers to one's state of alertness and vigilance towards internal and external stimuli. Arousal can be theoretically divided into tonic arousal, which refers to diurnal fluctuations in alertness and energy towards the external world, and phasic arousal, which refers to fluctuations in arousal that are spontaneous or in response to events or stimuli in the environment (Orekhova and Stroganova, 2014). Tonic and phasic arousal are interdependent, for instance, optimal phasic responsivity occurs at certain levels of tonic arousal (Aston-Jones and Cohen, 2005). An optimal state of arousal is crucial to regulate dynamic and flexible adaptation to different contexts and is governed by interactions between the central and peripheral nervous systems. The autonomic nervous system (ANS) refers to the branch of the peripheral nervous system that regulates involuntary functions of internal organs (such as breathing, heartbeats and digestion) to support the ongoing adaptation of the body to the demands of the environment. The ANS is typically divided into the sympathetic and parasympathetic nervous systems (SNS and PNS, respectively), although, recently, the enteric nervous system has been considered as another division of the ANS (Wood, 2008). Due to lack of articles directly measuring activity of the enteric system in autism, this will not be considered any further in this article. For those interested, Rao and Gershon (2016) and Yarandi et al. (2016) discuss evidence in autism in relation to enteric system function.

The SNS regulates what is traditionally called the 'flight or fight' response and it is crucial for responding to environmental stressors appropriately, by preparing the body for action in response to a threat. It does so by broadly upregulating the cardiovascular and endocrine systems with associated responses such as increases in heart rate and pupil dilations (Porges, 1992). In contrast, the PNS serves the complementary 'rest and digest' function. During times of rest, the PNS promotes a "calm, physiological state" (Klusek et al., 2015, p.3) by slowing down the heart and promoting bodily functions such as digestion and urination. At times of stress, reduced activity of the PNS allows increased activation of the SNS by releasing its brake and enabling physiological excitation (Porges, 1992). While the SNS and PNS serve complementary functions, which may be antagonistic in nature, they work in coordination to maintain homeostasis and regulate responsivity to the environment (Berntson et al., 1991).

The ANS is regulated by and provides input to the central nervous system (CNS). Specifically, the ANS sends signals to brainstem regions that directly influence systems involved in regulating consciousness and release of neurotransmitters (Thayer and Brosschot, 2005). The locus coeruleus (LC) in the brainstem, which is the primary source of norepinephrine (NE) in the cortex (Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005; Loughlin et al., 1986), receives autonomic signals through the nucleus tractus solitaris (NTS) and in turn has reciprocal connections with higher level regions in the prefrontal cortex, hypothalamus, insula and amygdala (Van Bockstaele and Aston-Jones, 1995, as reviewed by Sara and Bouret, 2012; Critchley and Garfinkel, 2018). Arousal regulation thus occurs through concurrent and coordinated involvement of ANS, the brainstem and cortical systems. Peripheral indices of arousal capture meaningful variation in arousal that results from this coordinated activity between CNS and ANS; this is evidenced by studies showing that indices of peripheral ANS such as pupil dilation correlate with arousal and responsivity in the CNS (Murphy et al., 2014, 2011).

The most common indices of peripheral ANS function are heart rate (HR) and heart rate variability (HRV), electrodermal activity (EDA) and pupil size (Wass et al., 2015). HR is a measure of the average number of beats of the heart per minute. HRV is an important index of adaptive autonomic function to the environment. HR is regulated by both SNS and PNS, with activation of the SNS being related to accelerations in HR and PNS activation being associated with HR decelerations. EDA measures electrical skin conductance and is affected by activity in the eccrine sweat glands, which have predominantly sympathetic cholinergic innervation and are thus widely interpreted to index SNS influence. Finally, both SNS and PNS are involved in constriction and dilation of the pupil, but pupil size also correlates with activity in the LC and thus has been found to be a valid peripheral index of ANS function (Wass et al., 2015). Another common peripheral index of ANS function is Blood Pressure (which measures the force of the circulating blood on the walls of arteries), although we do not focus on this measure in this review as it has rarely been utilized to measure ANS function in autism.

Differences in peripheral indices of ANS function, including HR, EDA and pupil size, are closely linked with differences in sensory responsivity (Schoen et al., 2009), cognition (Gilzenrat et al., 2010; Howells et al.,

2012), socialization (Porges, 2011), and emotion processing (Cuve et al., 2018); all of which are domains of functioning that are affected in autism (Kushki et al., 2014). Analysing these peripheral indices of ANS could thus prove useful to investigate mechanisms underlying stress and psychopathology in autism.

1.2. Autism and autonomic arousal

Specific evidence for differences in peripheral indices of autonomic arousal in autism is mixed. Autistic individuals present with a high prevalence of sleep disorders, suggesting differences in regulation of diurnal cycles (Tudor et al., 2012). There is also evidence to suggest that autistic people may struggle to respond effectively to stressful social contexts by upregulating their autonomic response as neurotypical individuals do (Edmiston et al., 2016). Further, autistic individuals may demonstrate atypical attention and behavioural responses to sensory stimuli in their environment, which might be indicative of difficulties maintaining a stable level of alertness and vigilance, and in regulating phasic responsivity to the environment (McCormick et al., 2014). Importantly, studies have reported significant differences between autistic and neurotypical groups in phasic autonomic activity when measured at baseline (prior to starting a cognitive task) which persist during the task. Task-based atypicalities in autonomic activity in autistic individuals might therefore be partly driven by differences in arousal during resting-state (Hubert et al., 2009; Mathersul et al., 2013b).

In light of recent evidence, recent theoretical models support a hyperarousal model of autism. These cite reduced parasympathetic activation as a mechanism driving atypical arousal in autism. Porges' Polyvagal Theory (Porges, 2003) cites an important role of the vagus nerve in social engagement, stating that cortical brain regions exert influence on the ANS through the myelinated vagus, via the brainstem, which supports social interaction with others. They propose that differences in this social engagement system in autism are paralleled by reduced vagal influence over the heart via the vagus nerve. Similarly, the neurovisceral integration theory (Thayer and Lane, 2000) draws links between parasympathetic activity and emotion dysregulation and anxiety, both of which are highly prevalent in autism (McVey, 2019). Specifically, this theory suggests that reduced HRV, reflecting reduced activation of PNS, is associated with hypervigilance to the environment, and reduced flexibility in adapting to the environment, leading to deficits in emotion regulation and increased anxiety (Friedman, 2007). Importantly, the neurovisceral integration theory implicates cortical structures (such as prefrontal cortex, anterior cingulate cortex, amygdala and insula) in regulating autonomic responsivity. Structural, functional and connectivity differences in these cortical structures are also implicated in the neurobiology of autism (Kushki et al., 2014).

There is additional evidence for differences in cortical arousal from resting-state electroencephalography (EEG) studies which have reported differences in power in high and low frequency oscillations, particularly in the left hemisphere, indicative of differences in arousal between autistic and control participants in the CNS (Wang et al., 2013). It is possible then, that findings of ANS differences in autistic individuals are related to differences in CNS function (Gu et al., 2015). In summary, theoretical models have implicated atypical interactions between central and peripheral nervous system function in autism and this has been linked to autistic symptoms such as sensory over-responsivity, hypervigilance, anxiety, and reduced socialization skills.

A number of recent reviews have attempted to bring together the vast body of research in autonomic function in autism. However, these have tended to focus on specific aspects of functioning in autism; such as physiological responsivity to sensory and socio-emotional stimuli (Lydon et al., 2016), emotion recognition (Cuve et al., 2018); or on specific indices of autonomic function such as cardiac function (Benevides and Lane, 2015) and cortisol (Taylor and Corbett, 2014). Evidence for differences in autonomic arousal at rest across autonomic measures has not been reviewed systematically and thoroughly.

This is the motivation behind the present review, which aims to systematically evaluate the evidence for differences in profiles of arousal during resting-state in autism. A careful evaluation of this evidence might shed light on whether there are such differences, but more importantly, on factors that may underlie such differences. Specifically, there might be certain contexts or specific measures that are more likely to reveal differences in autonomic arousal during resting-state in autistic individuals. This is the lens we will adopt in this review.

We will focus on any studies that have directly measured an index of peripheral autonomic arousal (such as heart rate, EDA or pupil size) at rest or baseline (i.e., before a task). We believe that this will not only shed light on the utility of resting-state theories of dysregulated autonomic arousal in autism; but more importantly, results from this review may guide understanding of where such differences lie and which methodological or sample characteristics might be important to understand heterogeneity in the findings.

Resting-state is typically measured in two ways: either participants are asked to relax, sit or lie down quietly or they are asked to passively look at something (a dot on a wall, a calm video that is age appropriate). There are pros and cons to measuring resting-state in these different ways. Resting-state could be considered a measure of inward-directed attention, when an individual is not asked to process, evaluate or respond to anything external. Therefore, traditionally, it is measured while participants are in contexts that induce rest such as lying down quietly, with eyes open or closed, not doing anything. However, such measurements can be quite demanding for children who struggle to sit still for extended periods of time. Thus, passive attention resting-states, where individuals are given something to look at such as an age-appropriate video are often used in these cases, particularly with younger children (Bazelmans et al., 2019). Further, resting-state measurements where individuals are asked to sit quietly with eyes open or closed might introduce a different type of noise to the data, since different participants might think of different things and there might be factors between clinical groups that impact such data systematically. Passive attention resting-state measurements (which provide participants something to look at) might control for this noise while not necessarily asking participants to perform a task. In our review, we included studies using both types of measurement and investigated whether these contextual factors influence the pattern of findings in any way.

1.3. Purpose of this review

We applied a systematic approach to gathering and evaluating evidence on differences in autonomic arousal during resting-state in autistic individuals. In this review, we focus on describing the findings and evaluating their implications for the field. Specifically, we reviewed studies that compare autistic and neurotypical groups on ANS measures of cardiac function (i.e. heart rate variability), electrodermal activity, and pupil size, both at rest and during pre-task baseline periods. We did not include evidence from studies measuring CNS arousal or cortisol/neurotransmitters, because indices of arousal at CNS are debated, and some of this evidence has been reviewed (Berman et al., 2015; Kleberg, 2015; Wang et al., 2013).

The present review aims to answer the following questions:

1 What is the evidence for atypical ANS activity during resting-state in autistic individuals as compared with neurotypical controls?
2 Does it take the form of hypo- or hyper-arousal?
3 Are there any patterns in the findings that may indicate that particular indices of autonomic measurement or particular contexts of measurement are more reliable in revealing differences between autistic and neurotypical groups?

2. Methods

2.1. Search strategy

Ovid Advanced Search was used to simultaneously search three databases: Embase (1974 to 16.05.2019), Ovid Medline® All (1946 to 16.05.2019) and PsycINFO (1806 to May Week 2 2019). We used keywords in the fields of autism or autism spectrum disorder, arousal, and autonomic nervous system (see Fig. 1 for a PRISMA flowchart of the articles screened, adapted from Moher et al. (2009)). We supplemented these keywords with words that refer to the key measures typically used to assess ANS function, including 'electrodermal activity/galvanic skin response', 'pupil dilation', 'heart rate' and 'heart rate variability' (see Supplementary Materials for the search syntax).

The references identified in the above search were imported into Endnote Version 8.0 and the Endnote function "deduplicate" was used to remove duplicates. Subsequently, the references were screened in two stages to identify eligibility for inclusion in this review.

a) Initial abstract screening: One author reviewed all titles and abstracts against the inclusion/exclusion criteria and excluded those not pertinent (these criteria are provided in Supplementary materials)
b) Full-text review: For articles passing stage 1, full-texts were reviewed against the inclusion and exclusion criteria by one author. Where there was doubt, another author reviewed those articles to reach consensus. Investigators of primary studies were not contacted to confirm data.

Through the above process, we identified studies that compared ANS activity at rest between a group of individuals with Autism and a group of typical individuals at any age. We also included studies that investigated autonomic activity in a group of typical individuals if they investigated autistic traits in their samples. We also included studies that may not have included group comparisons but looked at continuous relationships between autonomic activity at rest and symptom severity of autism or function in different domains relevant to autism. Further inclusion/exclusion criteria are provided in Supplementary Materials.

Importantly, we excluded studies where the diagnostic criteria used to identify individuals in the autistic sample followed definitions of autism prior to DSM-III. This is because prior to DSM-III, definitions of autism were significantly different than our current understanding of autism, with autism being considered to be a childhood form of schizophrenia (APA, 1968). Even so, definitions and understandings of autism have changed since DSM-III and this might have an impact on the type of individuals included in the autistic sample over the years, which might in turn have an impact on the findings. This should be held in mind when interpreting the results.

One researcher performed data extraction (a full list of data extracted is provided in Supplementary Materials). The studies included in the review were assessed for risk of bias using a tool adapted from Hombrados and Waddington (2012). The studies were rated on the following items, where applicable: a) equivalence of autistic and control groups, b) representativeness of the autistic sample, c) sample size, d) selective outcome reporting, e) selective analysis reporting and f) reporting of missing data. The tool is provided in fuller detail in Supplementary Materials.

We decided not to conduct a meta-analysis since there was huge variability in study methods and measures used. We obtained full-text articles for all those that passed the initial screening (as summarized in Fig. 1), and these were reviewed against inclusion/exclusion criteria, by two reviewers. Thereafter, we extracted data on key features for each article included in the review. The reviewers involved in the screening process discussed any articles that were unclear before reaching a decision on their inclusion or exclusion. Finally, the papers were analysed

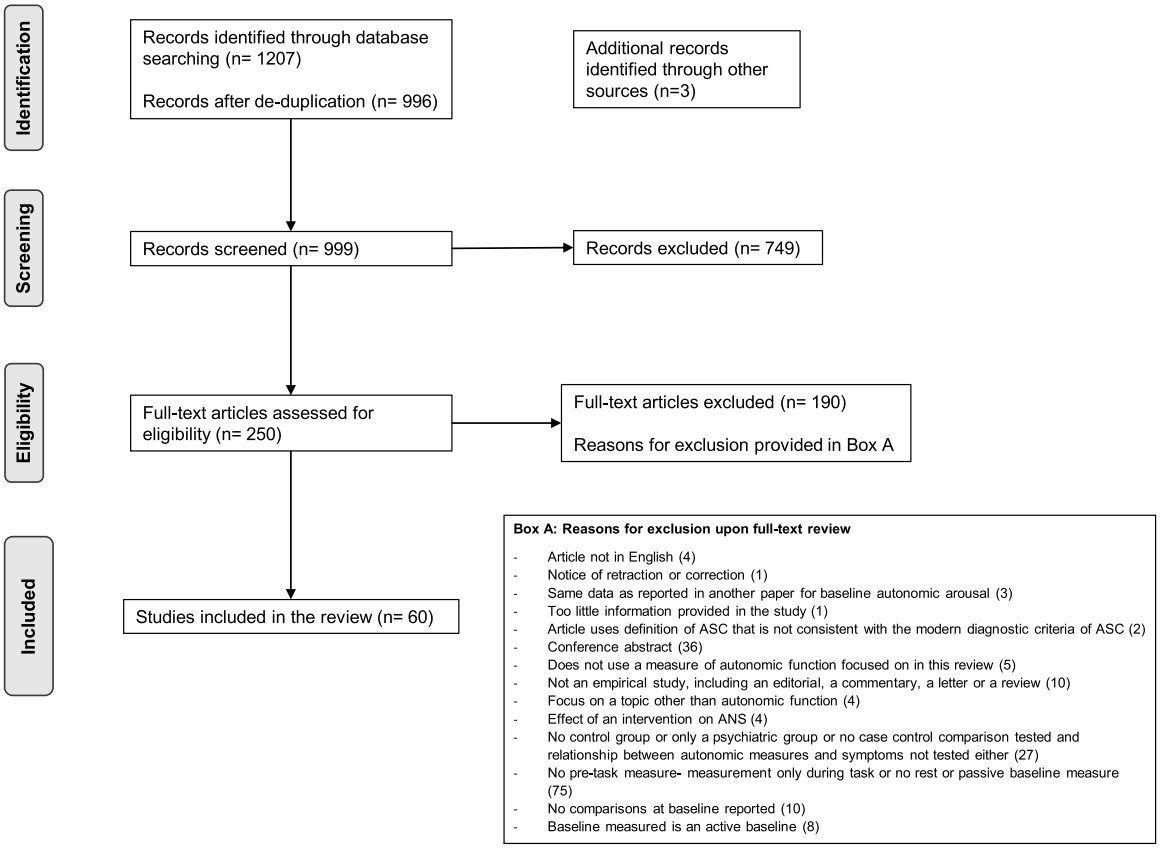

Fig. 1. PRISMA flowchart describing the numbers of studies identified, screened, excluded, and included in the systematic review process.

based on key factors relevant to the analysis, such as presence/absence of significant group differences, evidence of hyperarousal or hypoarousal in the patient group compared to the control group and other factors related to the methodology of the study.

3. Results

3.1. Studies included

After full-text review, a total of 60 studies were included in this review (see Fig. 1). One of these studies was a conference publication from a peer-reviewed journal (Tiinanen et al., 2011). A summary of the ANS measures used in these studies (including their acronyms and abbreviations, and their interpretation with regard to ANS function) can be found in Table 1. Of the 60 studies, 51 studies made 130 comparisons on 53 samples of autistic and neurotypical groups on various autonomic measures at rest/baseline (i.e. a defined period of inactivity immediately prior to a cognitive task). 17 studies measured linear associations between autonomic function during resting-state/baseline and clinical symptoms and/or behavioural functions associated with autism. 41 studies reported data from cardiac measures, either as the sole measure (n = 35) or in combination with other measures (n = 6). 19 studies reported data from EDA, either as the sole measure (n = 13) or in combination with others (n = 6). 7 studies reported data from pupil measures, either as the sole measure (n = 5) or in combination with others (n = 2). A description of all the studies included in the review (with key methodological factors and main findings summarized) can be found in Table 2.

3.1.1. Quality assessment

Of 355 individual ratings (6 criteria for 60 studies), 59.72 % (n = 212) were rated as good, 29.58 % (n = 105) were rated as moderate, and 10.7 % (n = 38) were rated as poor. Two studies included in the review were rated green in all areas of risk of bias assessment. 32 studies had no category rated as poor. 28 studies had at least one category rated as poor, of which six has two or more. Sample size and selective outcome reporting were the most common limitations. As can be seen in Fig. 2, most studies were deemed to be of low or medium risk of bias.

3.2. Spread of group differences

We categorized each study that compared neurotypical and autistic participants on an ANS measure based on whether or not they reported a significant group difference on at least one ANS measure. Some studies reported findings for different indices of the same ANS domain, such as multiple indices of heart-rate variability from cardiac data (for example, time- domain and spectral-domain measures of HRV), or multiple indices from different ANS domains, e.g., EDA and HRV measures. Studies have been categorized as finding a significant group difference if they found a significant difference between the neurotypical and autistic groups on at least one measure. Of the 51 studies on 53 samples, 20 studies (39.2 %) found null effects, while 31 studies (60.8 %) reported significant group differences (see Table 3). Two studies (Keith et al., 2019b; Kushki et al., 2013) reported marginally significant effects (p-values of the effect being 0.1 and 0.06 respectively) on their group comparison and have been included in the significant group differences category.

Of the 31 studies (33 samples) that found group differences, 21 studies (67.8 %) found evidence of hyperarousal, five studies (16.1 %) found evidence of hypoarousal and the remaining five studies (16.1 %) found other effects indicative either of overall autonomic dysregulation or differences in adaptation to the experimental context (Table 3). Here, autonomic dysregulation refers to findings that could not be categorized as hyperarousal or hypoarousal, e.g., evidence of both hyperarousal and hypoarousal on different measures, or evidence of higher or lower variability in the autonomic index (which would reflect overall readiness to adapt to the context, with higher variability at rest generally reflecting better readiness to adapt to different environmental contexts, although this is not always the case). Differences of reduced adaptation to the experimental context refer to studies wherein multiple measurements were taken during resting-state and change between time-points was measured; there were differences reported between groups in change in autonomic arousal over time.

Many studies compared autistic and neurotypical participants on several ANS measures. In order to represent this information, we analysed each group comparison made on a resting-state ANS measure across studies. When each group comparison was individually accounted for, it emerged that only 51 group comparisons were significant, out of the 130 comparisons in 53 samples (39.23 %); with the remainder (79 comparisons; 60.77 %) reporting no significant differences on indices of autonomic arousal between people with and without autism (See Table 3). It is possible that certain autonomic measures were more likely to reveal autonomic differences between groups, or other factors played a role in this. We will evaluate the role of various factors on the nature of results in Sections 3.3- 3.5.

3.3. Contextual factors

It is likely that the context of measurement influences states of arousal and thus, the likelihood of finding true effects. The studies included in this review (see Table 2) used a variety of measurement contexts, from sitting quietly with eyes closed to watching a calming video passively. We investigated whether these contextual factors had an impact on reports of group differences. In Table 4, we describe pertinent contextual factors we analysed, including duration of autonomic function measurement, what participants were asked to do during measurement, and whether activities (e.g cognitive tasks) were scheduled to take place after resting-state measurement. For studies that used ANS measures of different types (i.e. cardiac, electrodermal or pupil), we evaluated the effects of these factors on each type of measure separately. This led to 58 comparisons across 51 studies. These results are further described in Sections 3.3.1- 3.3.4 below.

3.3.1. Length of ANS measurement period

We categorized studies based on the length of time over which the ANS activity measure was calculated: a) very short (less than or up to 2 min), b) short (3−5 min) or c) long (more than 5 min) (see Table 5). Due to missing information on length of ANS measurement in four studies, we could make 54 out of 58 comparisons for this factor. When the measurement periods were very short (n = 18/54), the number of studies that found group differences (n = 8) was similar to the number of studies that did not (n = 10). On the other hand, in periods of measurement of 3−5 min (n = 27/54), the number of significant effects (n = 18) were double the number of null effects (n = 9). In longer periods of measurement (5−10 min) (n = 9/54), the number of significant group differences (n = 8) were much higher than the null findings (n = 1). It is possible that periods of measurement shorter than 2 min are not reliable at revealing differences in states of autonomic arousal in autism. It should be noted though that the majority of the studies fell in the 'short' category, with most studies reporting measurements between 3−5 min (See Table 5).

We analysed whether the type of differences found (hyperarousal or hypoarousal) was impacted by the length of measurement. As can be seen from Table 5, among the studies that found group differences, findings of hyperarousal were more likely regardless of the length of measurement. It should be noted though that across all studies, a small proportion of studies tended to find hypoarousal or other forms of autonomic atypicalities.

Only one study explicitly evaluated changes in arousal over time within the resting-state measurement period itself, to evaluate habituation of arousal to the experimental context. Zahn et al. (1987) measured skin conductance (SCL and NSSCRs) at baseline and found

Table 1
Description of measures which were used in the studies included in the review, including their relation with functioning of the autonomic nervous system and the methodology usually used to collect and extract these measures.

Domain	Measure	Acronym	methodology & Significance	Parameters	ANS indicator	Number of reviewed studies using the measure
Electro-Dermal Activity	Skin Conductance Level	SCL	SCL measures slow changes in electrical conductivity in the skin over time. It is measured by applying constant electrical voltage between two electrodes, typically placed on the palms of the hand. SCL is a measure of the electrical activity flowing between the electrodes. It is influenced by activity of the eccrine sweat glands, which is under SNS influence.	Mean SCL, Change in SCL over time (measured as a slope)	Higher SCL: increased sympathetic arousal	16 studies
	Non-Specific Skin Conductance Response	NS-SCR	NS-SCRs refer to phasic changes (difference from baseline) in the electrical conductivity of the skin that occur in absence of an identifiable external event/stimulus. They are measured using the same methodology as SCL.	Number/Rate of NS-SCRs Mean Amplitude of NS-SCRs	Higher NS-SCRs: increased phasic arousal/responsivity, not specific to any identifiable external event/stimulus	6 studies
PUPILLOMETRY	Pupil diameter		Typically measured using eye-tracking tools, for example, using image-based eye-trackers that use infra-red illumination. Highly sensitive to changes in luminance, pupil size is influenced by both SNS and PNS.	Mean pupil diameter	Higher mean pupil diameter: increased tonic arousal	7 studies
Heart rate	Heart rate	HR	Refers to the number of heart beats per minute, it is measured using an electrocardiogram, which measures the electrical activity of the heart.	Mean HR	Higher HR: hyper-arousal	23 studies
	Inter-beat interval, Heart Period	IBI, HP	The time interval between successive R-R waves (i.e. consecutive heart beats)	Mean IBI, Mean HP	Higher IBI, HP: hypo-arousal	6 studies
Heart rate variability (HRV)	Standard deviation of normal-to-normal intervals	SDNN	Average variability (indexed through standard deviation) of durations of inter-beat intervals over a period of time, SDNN is calculated after abnormal or ectopic beats have been removed from the data and therefore, it is specific to normal inter-beat intervals. In short-term resting recordings, parasympathetic influences are the main source of variation in HRV.	SDNN	Higher SDNN: increased HRV: higher parasympathetic function: hypo-arousal	4 studies
	Co-efficient of Variation	CV	Co-efficient of variation of the IBIs, calculated by dividing SDNN by the mean IBI: since HR is mathematically associated with HRV, this normalizes SDNN with respect to HR	CV	Higher CV: increased HRV: higher parasympathetic function: hypo-arousal	1 study
	Root Mean Square of Successive Differences	RMSSD	A measure of beat-to-beat variance in HR, measured by averaging the squared values of successive IBIs and then calculating a square root of the resulting value. It reflects vagally-mediated changes in HR.	RMSSD	Higher RMSSD: higher HRV: increased PNS function: hypo-arousal	6 studies
	Percentage of Normal-to-normal intervals >10 ms/ 50 ms	pNN10, pNN50	Calculated as the percentage of adjacent NN intervals (from all NN intervals) that differ from each other by more than 10 or 50 ms respectively. It is correlated to PNS activity.	pNN10, pNN50	Higher pNN10/ pNN50: higher HRV: higher PNS function: hypo-arousal	2 studies
	Pre-ejection period	PEP	PEP indexes the time-interval between the the beginning of electrical stimulation of the ventricles to the opening of the aortic valve to pump blood. It is a validated index of SNS influences on the heart.	PEP length	Higher PEP length: reduced SNS function: hypo-arousal	1 study
	Respiratory sinus arrhythmia	RSA	Represents the variability in IBIs in the high-frequency range of respiration; RSA indexes changes in HR associated with respiration. Changes in RSA are mediated via the vagus nerve and thus, is considered a valid index of PNS.	RSA	Increased RSA: increased PNS functioning: hypo-arousal	14 studies
	Low frequency	LF	A frequency domain measure of HRV, LF measures spectral power between 0.04−0.15 Hz on the fast fourier transform (FFT) spectrum of HRV. In resting conditions, LF reflects baroreflex activity.	Absolute LF power Relative LF power in normalized units Peak LF frequency Power spectrum density of LF frequency range	Increased LF: increased baroreflex effect: increased HRV	5 studies
	High frequency	HF				12 studies

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Table 1 (*continued*)

Domain	Measure	Acronym	methodology & Significance	Parameters	ANS indicator	Number of reviewed studies using the measure
Peak HF frequency Power spectrum density of HF frequency range			A frequency domain measure of HRV, it measures activity in the 0.15−0.40 Hz range on the fast fourier transform spectrum of HRV. It is linked with respiratory influences on HR and is an index of parasympathetic influences on HR.	Absolute HF power Relative HF power in normalized units	Increased HF: increased PNS functioning: hypo-arousal	
	Low/high frequency	LF/HF	The ratio between spectral power in the low and high frequency range (see above for specific ranges in Hz). Traditionally, it has been used to index the balance between SNS and PNS activity. However, this is challenged in the literature.	LF/HF ratio	Traditional interpretations (currently under debate): Increased LF/HF ratio: sympathetic dominance Reduced LF/HF ratio: parasympathetic dominance	7 studies
	Multi-Scale Entropy	MSE	An index of the regularity and complexity of the IBI time series at multiple timescales.	MSE	Higher MSE: higher complexity in heartbeat time series: better readiness to adapt to the environment	1 study
	Cardiac Sympathetic Index	CSI	This is a geometric analysis of a non-linear plot of RRIs (wherein each RRI is plotted against its consecutive RRI). CSI is calculated as the longitudinal component of the plot divided by the transverse component of the plot. CSI has been linked to sympathetic function.	CSI	Higher CSI: higher sympathetic function: hyperarousal	1 study
	Cardiac Vagal Index	CVI	This is a geometric analysis, similar to CSI but calculated as a multiplication of the longitudinal and transverse components of the plot. It has been linked to parasympathetic function.	CVI	Higher CVI: higher parasympathetic function: hypoarousal	1 study
	Cardiac Vagal Tone	CVT	It refers to pulse-synchronized phase shifts in consecutive cardiac cycles. It is calculated after phase demodulation to filter out sympathetic influences, and therefore is suggested to be specific to vagal tone.	CVT	Higher CVT: higher parasympathetic function: hypoarousal	2 studies

that, compared to neurotypical adults, autistic adults showed slower reduction in SCL over time during the resting state. They interpreted this to mean slower adaptation to the environment in autistic adults during the baseline period. This is an important finding, as it reflects that autistic individuals may be atypical in their ability to adapt to a given environmental context, which might then subsequently impact their response to a stimulus.

3.3.2. *Experimental context during measurement*

We also considered whether the experimental context could have affected findings, e.g., whether participants were asked to do something during the resting-state/baseline measurement. We divided the studies such that a study either asked participants not to do anything (No Activity Resting State, e.g., sit or lie down quietly and relax), or participants were asked to passively attend to something (Passive Attention Resting State, e.g., watching a video or looking at a screen). Due to missing information in eight studies (which compared groups on 10 ANS measures), we could make 48 of 58 comparisons. As can be seen in Table 6, in the passive attention condition, the frequency of finding significant group differences was fairly even (n = 13/23 studies found significant effects). However, this was markedly higher when a no activity resting-state measurement (without anything external to attend to) was used (n = 18/25 studies found significant effects). Interestingly, when looking at whether type of finding (i.e. hyper- or hypo- arousal) was impacted by context during measurement, it appears that studies using passive attention measurement were more likely to report hyperarousal in autistic participants (Table 6). In fact, 84.6 % of the studies with passive attention activity during resting-state, which reported significant group differences, found evidence of hyperarousal, while 15.4 % found evidence of hypoarousal. On the other hand, among the studies where no activity was carried out by participants during resting-state measurement, 61.1 % found hyperarousal, 22.2 % found hypoarousal and 16.7 % found evidence of autonomic dysregulation but not specifically hyper- or hypo-arousal.

3.3.3. *Experimental context after measurement*

Finally, we categorised studies according to whether they included an active cognitive task immediately after the resting-state period on the basis that when participants expect a task to follow, this might impact their ANS activity during the pre-task resting-state period. Therefore, we divided studies into whether they were followed by any tasks or not. Most studies (n = 47/58) included a task after resting-state. As can be seen in Table 7, when the resting-state measurement was followed by a task, the number of studies reporting a group difference (24/47) was similar to the number of studies reporting no group differences. In comparison, most studies that did not have a task following the resting-state period, reported a significant group difference (n = 10/11). A caveat to this analysis is that studies may not have reported that another task followed the resting state measurement.

We examined whether the direction of the effect (hypo- or hyper-

Table 2
Studies included in the review: key methodological characteristics and main findings are described.

First Author, Year	Age Groups[a]	Patient n (Autism[b])	Control n	ANS measure (s)	Paradigm	Length of measurement	Data duration	Main Finding
Anderson et al., 2013	Pre-school	Sample 1: 12 Sample 2: 18	Sample 1: 11 NT[c], 9 DS[d] Sample 2: 19 NT	Pupil	Looking at a blank grey slide	3 min	1 min	Sample 1: Autism > NT, DS (Hyper-arousal) Sample 2: Autism > NT (Hyper-arousal) Pupil size positively correlated with autism symptom severity in both samples
Bal et al., 2010	Children and Adolescents	17	36	Cardiac	Sitting quietly	2 min	2 min	Autism > NT on HR, Autism < NT on RSA (Hyper-arousal) Higher RSA related with better emotion recognition in Autism sample.
Billeci et al., 2018	Pre-school	20	20	Cardiac	Sitting quietly	5 min	5 min	Autism > NT on LF power, SDNN and CV (increased HRV, autonomic dysregulation) Increased CV associated with poor initiation of joint attention in autistic sample.
Bishop-Fitzpatrick et al., 2017	Adults	40	25	Cardiac	Sitting quietly	10 min	5 min	Autism > NT on HR (Hyper-arousal)
Bizzell et al., 2019	Children	12	12	Cardiac	Sitting quietly	3 min	3 min	No group differences
Bolte et al., 2008	Adults	10	10	Cardiac	Not described	Not reported	Not reported	No group differences
Bricout et al., 2018	Children	20	19	Cardiac	Rest in supine position	10 min	10 min	Autism > NT on LF power and total spectral power (increased HRV, autonomic dysregulation)
Bujnakova et al., 2017	Children and Adolescents	23	14	EDA	Lying down quietly	5 min	5 min	Autism < NT (Hypo-arousal)
Bujnakova et al., 2016	Children and Adolescents	15	15	Cardiac, EDA	Lying down quietly	5 min	5 min	EDA: Autism < NT (Hypo-arousal) Cardiac: Autism > NT on HR, Autism < NT on IBI, HF-HRV (Hyper-arousal)
Cai et al., 2019	Adults	24	20	Cardiac	Rest in supine position with eyes closed	10 min	5 min	Higher resting HRV associated with use of better emotion regulation strategies across autistic and NT participants
Chang et al., 2012	Children	25	25	EDA	Sitting quietly	3 min	3 min	Autism > NT (Hyper-arousal)
Corbett et al., 2019	Children	31	25	Cardiac	Not described	5 min	5 min	No group differences
Daluwatte et al., 2013	Children and Adolescents	152	107 NT, 36 NDD[e]	Pupil, Cardiac	Looking at a screen	5 min	5 min (for cardiac) Unclear (for pupil)	Cardiac: Autism > NT on HR (Hyper-arousal) Pupil: No group differences
Daluwatte et al., 2015	Children and Adolescents	152	107	Pupil	Looking at a screen	5 min	Unclear	Correlation between pupil diameter and sensory processing scores not significant in NT and autistic groups
DiCriscio and Troiani, 2017	Children and Adolescents	42 children of which 12 had a diagnosis of autism		Pupil	Looking at a grey screen	10 s	10 s	Correlation between pupil diameter and autistic traits was not significant
Dijkhuis et al., 2019	Adults	51	28	Cardiac	Looking at a silent video	5 min	1 min (HR) 5 min (RMSSD)	No group differences
Edmiston et al., 2016	Adolescents	21	13	Cardiac	Sitting quietly	5 min	5 min: Analysed in 1 min segments	Autism < NT on RSA Autism > NT on variability in RSA (Hyper-arousal) Higher RSA associated with reduced autism symptom severity and with less internalizing symptoms
Eilam-Stock et al., 2014	Adults	17	15	EDA	Looking at a crosshair during an fMRI scan	6 min	6 min	Autism < NT (Hypo-arousal)
Faja et al., 2013	Children	21	21	EDA	Looking at a picture	120 s	120 s	No group differences

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Table 2 (*continued*)

First Author, Year	Age Groups[a]	Patient n (Autism[b])	Control n	ANS measure (s)	Paradigm	Length of measurement	Data duration	Main Finding
Hollocks et al., 2014	Children and Adolescents	20 autism, 32 autism + Anxiety	23	Cardiac	Watching cartoons	20 min	15 min	Autism > NT, Autism + Anxiety on HR (Hyper-arousal)
Hu et al., 2018	Children	29	N/A	Cardiac	Sitting quietly	2 min	2 min (analysed as 4 30 s epochs)	Lower resting HF-HRV related to higher autistic traits. Higher self-reported parents' emotion regulation difficulties associated with higher parent-reported autistic traits in children only for children with relatively lower HF-HRV
Joseph et al., 2008	Children and Adolescents	20	20	EDA	Not described	2 min	2 min	No group differences
Keith et al., 2019a	Adolescents	25	21	Cardiac, EDA	Sitting quietly	5 min	5 min (analysed as average per minute)	EDA: No group differences Cardiac: Autism > NT (marginal significance) (Hyper-arousal)
Keith et al., 2019b	Adolescents	26	22	Cardiac	Sitting quietly	5 min	5 min	Higher mean HR associated with higher adolescent self-reported anxiety
Klusek et al., 2013	Children and Adolescents	40	28	Cardiac	Watching a movie	10 min	5.5 min	No group differences. Reduced RSA associated with higher autism symptom severity in NT group
Kootz et al., 1982	Children, Adolescents and Adults	16 (divided into high and low mental age)	N/A	Cardiac	Sitting quietly	15 min	Unclear	No group differences between higher and lower functioning autistic groups on mean HR
Kuiper et al., 2019	Adults	33	31	Cardiac, EDA	Sitting quietly	10 min	5 min	EDA: No group differences Cardiac: Autism > NT on HR (Hyper-arousal)
Kushki et al., 2014	Children and Adolescents	40	34	Cardiac	Watching a movie	15 min	3 min	Autism > NT on HR (Hyper-arousal)
Kushki et al., 2013	Children and Adolescents	12	17	Cardiac, EDA	Watching a movie	30 min	Middle 10 min	EDA: Autism > NT (Hyper-arousal) Cardiac: Autism > NT on HR (Marginally significant) (Hyper-arousal)
Mathersul et al., 2013a	Adults	30	31	EDA	Unclear, presumably looking at a screen	500 ms	500 ms	Autism < NT (Hypo-arousal)
Mathersul et al., 2013b	Adults	28	31	EDA	Sit quietly with eyes closed	2 min	2 min	No group differences, presence of a hypoaroused sub-group
Mathewson et al., 2011	Adults	15	16	Cardiac	Resting with eyes open and eyes closed	6 min	6 min (analysed as minute by minute average)	Autism > NT on HP, Autism < NT on RSA (Hyper-arousal) HP not correlated with symptoms of anxiety.
Matsushima et al., 2016	Children	37	32	Cardiac	Watching a timer on an IPAD	2 min	2 min	Autism < NT on HF-HRV (Hyper-arousal) Reduced HF-HRV associated with higher symptoms of RRBs and higher visual and auditory hyper-reactivity.
McCormick et al., 2014	Pre-school	54	33	EDA	Watching a video	2 min	2 min	No group differences
Ming et al., 2005	Children	28	17	Cardiac	Sitting on an inclined chair with music or videos if required	25 min	10 min	Autism > NT on HR, Autism < NT on CVT (Hyper-arousal)
Ming et al., 2016	Children	19	18	Cardiac	Sitting on an inclined chair with music or videos if required	25 min	10 min	Autism > NT on HR, Autism < NT on CVT (Hyper-arousal)
Neuhaus et al., 2014	Children and Adolescents	18	18	Cardiac	Sitting quietly	5 min	Last 2 min (analysed as 4 30 s epochs)	Autism < NT on RSA (Hyper-arousal) Higher RSA associated with better social functioning and fewer social problems.

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Table 2 (*continued*)

First Author, Year	Age Groups[a]	Patient n (Autism[b])	Control n	ANS measure (s)	Paradigm	Length of measurement	Data duration	Main Finding
Neuhaus et al., 2015	Children	18	18	EDA	Sitting quietly	5 min	Last 2 min analysed as 4 30 s epochs	NT group showed higher variability in NS-SCRs during the resting-state than Autism (autonomic dysregulation) Higher variability in NS-SCRs associated with better social skills in NT group and with more problem behaviours in autistic group.
Nuske et al., 2014	Pre-school	25	21	Pupil	Looking at a grey slide	13 s	7 s	No group differences
Pace and Bricout, 2015	Children	10	10	Cardiac	Rest- not described	5 min	5 min	Autism < NT on HR (Hypo-arousal)
Patriquin et al., 2013a	Pre-school and Children	23	N/A	Cardiac	Watching a video	3 min	3 min	Reduced RSA associated with more parent-reported language and cognitive delays
Patriquin et al., 2013b	Pre-school and Children	23	N/A	Cardiac	Watching a video	3 min	3 min	Higher RSA associated with better social behaviour and receptive language abilities
Patriquin et al., 2014	Pre-school	106 NT		Cardiac	Watching a video	2 min	2 min	Atypical development of RSA (between 5−48 months) associated with more social responsiveness difficulties at 48 months of age
Porges et al., 2013	Children, Adolescents and Adults	78	68	Cardiac	Not described	2 min	2 min	Autism < NT on HP and RSA (Hyper-arousal)
Riby and Whittle, 2012	Adolescents	12	12	EDA	Relax in a silent room	5 min	5 min	No group differences
Saghir et al., 2017	Children and Adolescents	45	34	Cardiac	Watching a movie	5 min	5 min	No group differences
Schaaf et al., 2015	Children	59	29	Cardiac	Sitting quietly	3 min	3 min	No group differences
Schoen et al., 2009	Children and Adolescents	38	33 NT, 31 SMD[f]	EDA	Sitting quietly	3 min	3 min	Autism < NT, SMD (Hypo-arousal)
South et al., 2011	Children and Adolescents	30	30	EDA	Not described	Not reported	Not reported	No group differences
Tessier et al., 2018	Sample 1: Children and Adolescents Sample 2: Adults	Sample 1: 13 Sample 2: 16	Sample 1: 13 Sample 2: 17	Cardiac	15 min before and after sleep-no other description	5 min	5 min	Sample 1: No group differences Sample 2: Autism < NT on normalized HF power (Hyper-arousal)
Thapa et al., 2019	Adolescents and Adults	55	55	Cardiac	Sitting quietly	5 min	5 min	Autism > NT on HR, Autism < NT on HF-HRV, RMSSD (Hyper-arousal)
Tiinanen et al., 2011[h]	Children	20	21	Cardiac	Sitting quietly	40 s	40 s	No group differences
Toichi and Kamio, 2003	Adolescents and Adults	20	20	Cardiac	Looking at a blank white wall	3 min	50 s	No group differences on CSI or CVI (presence of a subgroup with reduced CVI and thus, hyper-arousal)
Top et al., 2018	Adults	31	36 NT, 28 NT + Anxiety[g]	Pupil	Looking at a fixation cross	3−4 min	20 s	Autism > NT, NT-Anx (Hyper-arousal)
Van Engeland, 1984	Children	35	45	EDA	Not described	5 min	5 min	No group differences
van Engeland et al., 1991	Children	20	20	Pupil, EDA	Not described	Unclear	1 min (for EDA) Unclear (for pupil)	Pupil: No group differences EDA: No group differences
Van Hecke et al., 2009	Children	19	14	Cardiac	Looking at a blank screen	3 min	3 min	Autism < NT on RSA (Hyper-arousal) Higher RSA associated with lower autism symptom severity
Zahn et al., 1987	Adults	13	20	Cardiac, EDA	Not described	5 min	EDA: 5 min (analysed as average per minute) Cardiac: 5 min (analysed as average per 10 s epochs)	EDA: Slope of SCL declined more rapidly during resting state in NT than autism (reduced adaptation to context in autistic sample) Cardiac: No group differences on HR, Autism > NT on Maxima's MSSD (higher HRV, autonomic dysregulation)

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Table 2 (*continued*)

First Author, Year	Age Groups[a]	Patient n (Autism[b])	Control n	ANS measure (s)	Paradigm	Length of measurement	Data duration	Main Finding
Zantinge et al., 2017	Pre-school	28	45	Cardiac	Watching a video	3 min	1 min	No group differences
Zantinge et al., 2019	Pre-school	21	45	Cardiac	Watching a video	3 min	1 min	No group differences

[a] Age groups: Pre-school children: < = 6 years, Children: 6–12 years, Adolescents: 12–18 years, Adults: >18 years.
[b] Autism: Autism Spectrum Disorder.
[c] NT = Neurotypical.
[d] DS = Down's Syndrome.
[e] NDD: neurodevelopmental disorders other than autism.
[f] SMD: Sensory Modulation Disorder.
[g] NT-Anx: neurotypical individuals presenting with symptoms of anxiety.
[h] One article is a conference publication from a peer-reviewed journal (Tiinanen et al., 2011).

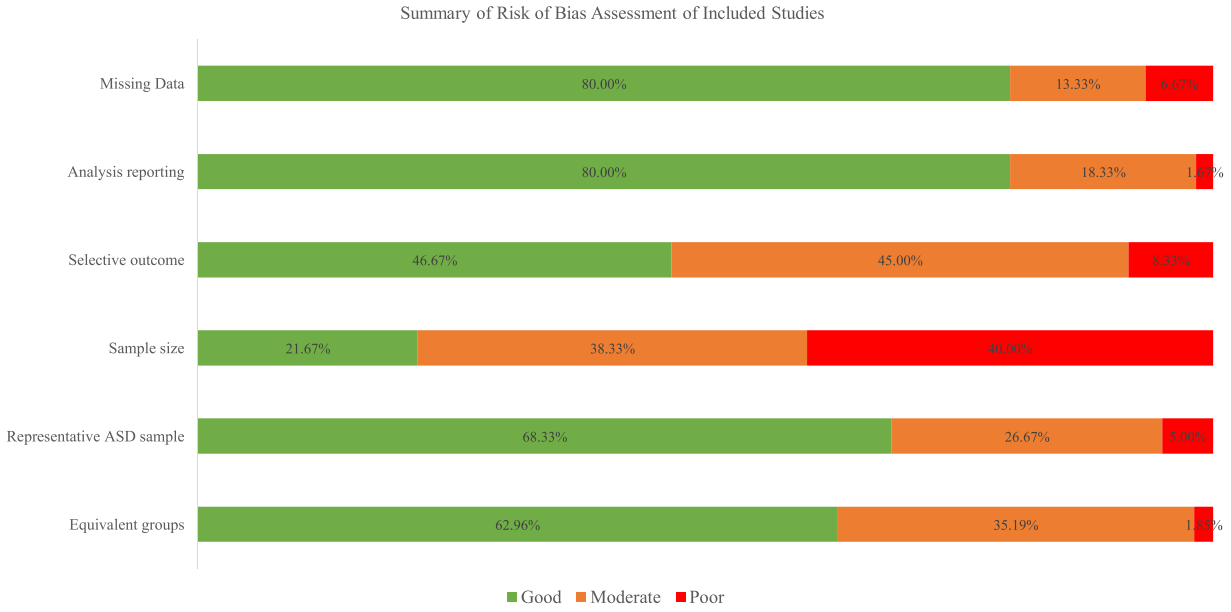

Fig. 2. Summary of risk of bias assessment of included studies.

Table 3
Spread of Group Differences in Studies included in the review.

	No group differences	Group differences Overall	Hyper-arousal	Hypo-arousal	Other
Number of Studies	20/51 (39.2 %)	31/51 (60.8 %)	21/31 (67.8 %)	5/31 (16.1 %)	5/31 (16.1 %)
Number of Group Comparisons	79/130 (60.77 %)	51/130 (39.23 %)			

Each study included in the review that compared neurotypical and autistic participants on an ANS measure is categorized based on whether or not they reported a significant group difference on at least one ANS measure. Studies that found group differences have been categorized based on whether they found evidence of hyperarousal, hypoarousal or other evidence of other autonomic arousal differences (such as evidence of both hyperarousal or hypoarousal on difference autonomic indices, increased variability on an autonomic index or differences in change in autonomic indices over time during resting state measurement). Since many studies reported on multiple measures of autonomic function, an additional categorization is presented of each group comparison carried out on an autonomic index and the proportion of group comparisons that observed a significant group difference between autistic and neurotypical participants.

arousal) was impacted by the expectation of a task to follow or not. As shown in Table 7, there was not a clear pattern. Of the studies that found group differences, findings of hyperarousal were more likely whether a task followed or did not follow the resting-state measurement. A small proportion of studies found evidence of hypoarousal or autonomic dysregulation as well.

We highlight the role of experimental context here since autonomic arousal should vary with contextual demands and differences found in studies may therefore be state-dependent rather than a stable difference attributable to autism. Often authors do not clearly describe this context or give sufficient credit to the possible role of experimental circumstances. Mathersul et al. (2013a, 2013b) reported contrasting findings from the same sample in two different studies. In one study (Mathersul et al., 2013b), SCL was recorded while participants spent two minutes with their eyes closed and found no significant overall group differences between adults with and without autism. Interestingly, in another paper with the same sample of adults with and without autism (Mathersul et al., 2013a), the authors measured SCL for the duration of 500 ms before stimulus onset in a social judgement task. In this study they reported hypoarousal in autistic adults compared to neurotypical adults. It is unclear why the two studies show differences in findings in the same group of participants, and any effect of changes in experimental context were not reported by the authors. It is likely that both length of measurement and change in experimental context (from a no-activity

Table 4
Description of experimental contextual factors in studies included in the review that compared groups of autistic and neurotypical participants.

First Author	Measure	Duration of measurement	Resting-State Paradigm	Experimental context during measurement	Followed by a task	SignificantGroup Differences present	Hyper/Hypo/ Other/N/A
Bujnakova et al., 2016	Cardiac	Short	Lie down quietly	No activity	No	Yes	Hyper
Neuhaus et al., 2014	Cardiac	Short	Sitting quietly	No activity	No	Yes	Hyper
Tessier et al., 2018	Cardiac	Short	15 min before and after sleep- no other description	No activity	No	Yes	Hyper
Thapa et al., 2019	Cardiac	Short	Sitting quietly	No activity	No	Yes	Hyper
Bal et al., 2010	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Edmiston et al., 2016	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Keith et al., 2019a,b	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Kuiper et al., 2019	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Mathewson et al., 2011	Cardiac	Short	Resting- eyes open, eyes closed	No activity	Yes	Yes	Hyper
Bishop-Fitzpatrick et al., 2017	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Chang et al., 2012	Skin Conductance	Short	No stimulation- inside a pretend spaceship	No activity	Yes	Yes	Hyper
Pace and Bricout, 2015	Cardiac	Short	Rest- not described	No activity	Yes	Yes	Hypo
Bujnakova et al., 2017	Skin Conductance	Short	Lie down quietly	No activity	No	Yes	Hypo
Bujnakova et al., 2016	Skin Conductance	Short	Lie down quietly	No activity	No	Yes	Hypo
Schoen et al., 2009	Skin Conductance	Short	Sitting quietly	No activity	Yes	Yes	Hypo
Billeci et al., 2018	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Overall autonomic dysregulation
Bricout et al., 2018	Cardiac	Short	Rest in supine position	No activity	Yes	Yes	Increased heart rate variability
Neuhaus et al., 2015	Skin Conductance	Short	Sitting quietly	No activity	Yes	Yes	Differences in adaptation
Tiinanen et al., 2011	Cardiac	Very short	Sitting quietly	No activity	Yes	No	N/A
Tessier et al., 2018	Cardiac	Short	15 min before and after sleep- no other description	No activity	No	No	N/A
Bizzell et al., 2019	Cardiac	Short	Sitting quietly	No activity	Yes	No	N/A
Schaaf et al., 2015	Cardiac	Short	Sitting quietly	No activity	Yes	No	N/A
Keith et al., 2019a,b	Skin Conductance	Short	Sitting quietly	No activity	Yes	No	N/A
Kuiper et al., 2019	Skin Conductance	Short	Sitting quietly	No activity	Yes	No	N/A
Mathersul et al., 2013b	Skin Conductance	Short	Sitting quietly with eyes closed	No activity	Yes	No	N/A
Riby and Whittle, 2012	Skin Conductance	Short	Relax in a silent room	No activity	Yes	No	N/A
Daluwatte et al., 2013	Cardiac	Short	Unclear- looking at a screen	Passive Attention	Yes	Yes	Hyper
Matsushima et al., 2016	Cardiac	Short	Watching a timer on an IPAD	Passive Attention	Yes	Yes	Hyper
Hollocks et al., 2014	Cardiac	Long	Watching cartoons	Passive Attention	Yes	Yes	Hyper
Kushki et al., 2014	Cardiac	Long	Watching an animated movie	Passive Attention	Yes	Yes	Hyper
Van Hecke et al., 2009	Cardiac	Short	Looking at a blank screen	Passive Attention	Yes	Yes	Hyper
Ming et al., 2005	Cardiac	Long	Rest on a chair inclined to 30 degrees with music or videos if required- subject dependent	Passive Attention	No	Yes	Hyper
Ming et al., 2016	Cardiac	Long	Rest on a chair inclined to 30 degrees with music or videos if required- subject dependent	Passive Attention	No	Yes	Hyper
Kushki et al., 2013	Skin Conductance	Long	Watching movie	Passive Attention	Yes	Yes	Hyper
Top et al., 2018	Pupil	Very short	Looking at a fixation cross	Passive Attention	Yes	Yes	Hyper
Anderson et al., 2013	Pupil	Short	Look at a blank grey slide	Passive Attention	Yes	Yes	Hyper
Anderson et al., 2013	Pupil	Short	Look at a blank grey slide	Passive Attention	Yes	Yes	Hyper
Mathersul et al., 2013a	Skin Conductance	Very short	Unclear- presumably looking at a screen	Passive Attention	Yes	Yes	Hypo
Eilam-Stock et al., 2014	Skin Conductance	Short	Looking at a crosshair inside fMRI	Passive Attention	No	Yes	Hypo
Dijkhuis et al., 2019	Cardiac	Short	Looking at a silent nature video	Passive Attention	Yes	No	N/A
Klusek et al., 2013	Cardiac	Short	Watching a movie	Passive Attention	Yes	No	N/A
Saghir et al., 2017	Cardiac	Short	Watching a movie	Passive Attention	Yes	No	N/A

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Table 4 (*continued*)

First Author	Measure	Duration of measurement	Resting-State Paradigm	Experimental context during measurement	Followed by a task	SignificantGroup Differences present	Hyper/Hypo/ Other/N/A
Toichi and Kamio, 2003	Cardiac	Short	Sit quietly looking at a blank white wall	Passive Attention	Yes	No	N/A
Zantinge et al., 2017	Cardiac	Short	3 min fish video	Passive Attention	Yes	No	N/A
Zantinge et al., 2019	Cardiac	Short	3 min fish video	Passive Attention	Yes	No	N/A
Kushki et al., 2013	Cardiac	Long	Watching movie	Passive Attention	Yes	No	N/A
McCormick et al., 2014	Skin Conductance	Short	Watching a video	Passive Attention	Yes	No	N/A
Faja et al., 2013	Skin Conductance	Very short	Sitting quietly, looking at a picture	Passive Attention	Yes	No	N/A
Nuske et al., 2014	Pupil	Very short	Looking at grey slides	Passive Attention	No	No	N/A
Daluwatte et al., 2013	Pupil	Short	Unclear- presumably looking at a screen	Passive Attention	Yes	No	N/A
Porges et al., 2013	Cardiac	Short	Baseline	Unclear	Yes	Yes	Hyper
Zahn et al., 1987	Cardiac	Short	5 min rest period- not described	Unclear	Yes	Yes	Increased heart rate variability
Zahn et al., 1987	Skin Conductance	Short	5 min rest period- not described	Unclear	Yes	Yes	Differences in adaptation
Corbett et al., 2019	Cardiac	Short	No description	Unclear	Yes	No	N/A
Bolte et al., 2008	Cardiac	Unclear	Not described	Unclear	Yes	No	N/A
Joseph et al., 2008	Skin Conductance	Very Short	Unclear- before visual stimulation	Unclear	Yes	No	N/A
van Engeland et al., 1991	Skin Conductance	Unclear	Not described	Unclear	Yes	No	N/A
van Engeland et al., 1991	Skin Conductance	Unclear	Not described	Unclear	Yes	No	N/A
South et al., 2011	Skin Conductance	Unclear	Not described, likely looking at a screen, possibly performing a preference task as they acclimate to the lab of which picture they prefer	Unclear	Yes	No	N/A
van Engeland et al., 1991	Pupil	Unclear	Not described	Unclear	Yes	No	N/A

Duration of measurement refers to the length of resting state measurement based on which the autonomic index in the study has been calculated. It is categorized as followed: Very short (less than two minutes), Short (3–5 min) and Long (more than 5 min). For studies that used multiple types of indices of autonomic function (pupil, cardiac and EDA), each type of index is represented separately. Experimental context during measurement refers to characterization of studies based on whether the experimental context during the resting state measurement involved a No Activity resting state (i.e., participants were asked not to do anything) or a Passive Attention Resting State (i.e. participants were asked to passively attend to something external).

Table 5
Spread of group differences and nature of differences based on length of autonomic measurement.

Length of autonomic data	No Group Differences	Group Differences Overall	Hyper-arousal	Hypo-arousal	Other
Very Short	10/18 (55.56 %)	8/18 (44.44 %)	6/8 (75 %)	1/8 (12.5 %)	1/8 (12.5 %)
Short	9/27 (33.33 %)	18/27 (66.67 %)	11/18 (61.1 %)	4/18 (22.2 %)	3/18 (16.7 %)
Long	1/9 (11.11 %)	8/9 (88.89 %)	6/8 (75 %)	1/8 (12.5 %)	1/8 (12.5 %)

Each study that compared autistic and neurotypical groups on an ANS index is categorized based on the length of data that the autonomic index is based on and proportion of significant group differences is presented. For studies that used ANS measures of different types (i.e. cardiac, electrodermal or pupil), each index is represented separately. Length of autonomic data has been categorized as follows: Very Short (upto 2 min), Short (3–5 min), Long (more than 5 min). For studies that found group differences, the proportion of studies that found evidence of hyperarousal, hypoarousal or other indications of differences in autonomic arousal (increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

Table 6
Spread of group differences depending upon experimental context during measurement of autonomic function.

Experimental Context	No group differences	Group differences Overall	Hyper-arousal	Hypo-arousal	Other
No Activity	7/25 (28 %)	18/25 (72 %)	11/18 (61.1 %)	4/18 (22.2 %)	3/18 (16.7 %)
Passive Attention	10/23 (43.48 %)	13/23 (56.52 %)	11/13 (84.6 %)	2/13 (15.4 %)	0/13 (0%)

Each study is categorized based on whether the experimental context during the resting state measurement involved a No Activity resting state (i.e., participants were asked not to do anything) or a Passive Attention Resting State (i.e. participants were asked to passively attend to something). Proportion of significant group differences is presented. For studies that found evidence of group differences, proportion of studies that found evidence of hyperarousal, hypoarousal or other differences in autonomic function (e.g., increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

resting-state to a pre-task baseline) influenced the measurement and arousal state in controls and autistic individuals differently. This highlights the importance of considering contextual factors in studies of autonomic arousal.

Table 7
Spread of group differences based on whether a task followed the resting measurement or not.

Resting State followed by a Task	No group differences	Group differences Overall	Hyper-arousal	Hypo-arousal	Other
No Task	1/11 (9.1 %)	10/11 (90.9 %)	7/10 (70 %)	3/10 (30 %)	0/10 (0%)
Task	23/47 (48.9 %)	24/47 (51.1 %)	16/24 (66.7 %)	3/24 (12.5 %)	5/24 (20.8 %)

Each study is categorized based on whether the resting state measurement was followed by a task or not. Proportion of significant group differences is presented. For studies that found evidence of group differences, proportion of studies that found evidence of hyperarousal, hypoarousal or other differences in autonomic function (e.g., increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

3.3.4. Summary of contextual factors

Overall, longer periods of autonomic measurement (3 min or longer) were more likely to yield significant group effects. Further, contexts of pure resting-state measurements (where no activity was reportedly given to the participants during or after the resting-state measurement) appeared to be more likely to discriminate autistic from neurotypical groups. Regardless of these contextual factors, findings of hyperarousal appeared to be more likely when group differences were found. However, a small proportion of studies across contexts yielded findings of hypoarousal or autonomic dysregulation that should not be disregarded. Interestingly, resting-state measurements where some sort of stimulation (typically age-appropriate neutral videos) was provided to the participants seemed to be more likely to yield findings of hyperarousal than not, suggesting that in presence of stimulation, autistic participants might find it difficult to regulate their arousal.

3.4. Type of autonomic measure used

We analysed whether specific ANS measures were more likely to capture significant differences between autistic and neurotypical groups. As can be seen in Table 8, studies using cardiac measures tended to find group differences more often than not (n = 23/34) as compared to pupil studies (n = 2/5) and studies using skin conductance (n = 9/19) which were as likely to find group differences as not. It should be noted though that many more studies in this review used cardiac measures, which seem to be the most often used to investigate autonomic arousal in autism.

Table 8
Spread of group differences based on the measure of autonomic function used.

Autonomic Measure	No group differences	Group differences Overall	Hyper-arousal	Hypo-arousal	Other
Cardiac	11/34 (32.4 %)	23/34 (67.6 %)	19/23 (82.6 %)	1/23 (4.4 %)	3/23 (13 %)
EDA	10/19 (52.6 %)	9/19 (47.4 %)	2/9 (22.2 %)	5/9 (55.6 %)	2/9 (22.2 %)
Pupil	3/5 (60 %)	2/5 (40 %)	2/2 (100 %)	0/3 (0%)	0/3 (0%)

Each study that compared autistic and neurotypical groups on an ANS index is categorized based on the type of autonomic index used (cardiac, EDA or pupil) and proportion of significant group differences is presented. For studies that used ANS measures of different types (i.e. cardiac, electrodermal or pupil), each index is represented separately. For studies that found group differences, the proportion of studies that found evidence of hyperarousal, hypoarousal or other indications of differences in autonomic arousal (increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

We next consider the direction of group differences (hypo- or hyperarousal) based on the measure used among the studies that found significant group differences. As can be seen from Table 8, cardiac and pupil measures tended to find hyperarousal while the skin conductance measures were more likely to find hypoarousal. These measures all capture different things at different levels of autonomic function and the difference in findings might be informative.

3.4.1. Pupil studies

Very few studies included in this review used Pupillometry to compare autistic and neurotypical groups on autonomic arousal (n = 5), of which three found null effects and two found evidence of hyperarousal (See Table 9). All used an average pupil diameter size measure as their measure of autonomic arousal. Overall, evidence from pupillometry was inconclusive, with some evidence for hyperarousal in preschool children and in adults, and no significant differences between autistic and neurotypical populations captured during childhood and adolescence. Notably, studies that used pupillometry in childhood and adolescence tended to include wide varying age ranges in their studies, which might impact sensitivity of this measure to differences between groups. It is noteworthy that due to the nature of measurement, pupillometry studies always involve directed looking at a screen. This means that in the context of resting-state, these studies are reflective of arousal during an outward-directed attention paradigm in the sense that participants were always asked to fixate on a central point on the screen.

3.4.2. Cardiac indices

Heart Rate and RSA were the most commonly used indices to measure cardiac autonomic function in autism. Both these indices were not highly reliable at picking up differences in autonomic function, with 14 out of 23 studies using HR finding group differences (See Table 10) and six out of 11 using RSA finding group differences (See Table 11). However, when they found group differences, they were both more likely to find evidence of hyperarousal (n = 13/14 studies using HR and n = 6/6 studies using RSA) than hypoarousal.

Similarly, 10 studies used spectral measures of heart rate variability (including power and peak frequencies in LF and HF HRV, and LF/HF ratio, See Table 12 for a summary of these studies and Table 1 for a description of the measures). Of these, six studies found evidence of group differences on a spectral measure, all in the direction of hyperarousal. Only seven studies used time-domain measures of heart rate

Table 9
Summary of results from studies comparing autistic and neurotypical groups on pupil size.

First Author	Age Range	Patient n	Control n	Arousal measure	Hyper/ Hypo/ None
Anderson et al., 2013	Pre-school children	Sample 1: 12 Sample 2: 18	Sample 1: 11 NT, 9 DS Sample 2: 19	Pupil size	Hyper
Top et al., 2018	Adults	31	28, 36	Pupil size	Hyper
Nuske et al., 2014	Pre-school children	25	21	Pupil size	None
Daluwatte et al., 2013	Children and Adolescents	152	107 NT, 36 NDD	Pupil size	None
van Engeland et al., 1991	Children and Adolescents	20	20	Pupil Size	None
					Count: 2 : 0 : 3

Table 10
Summary of results from studies comparing autistic and neurotypical groups on Heart Rate.

First Author	Age Range	Patient n	Control n	Arousal measure	Hyper/ Hypo/ None
Ming et al., 2016	Children	19	18	HR	Hyper
Ming et al., 2005	Children	28	17	HR	Hyper
Bal et al., 2010	Children and Adolescents	17	36	HR	Hyper
Daluwatte et al., 2013	Children and Adolescents	152	107 TD, 36 NDD	HR	Hyper
Bujnakova et al., 2016	Children and Adolescents	15	15	HR	Hyper
Hollocks et al., 2014	Children and Adolescents	52	23	HR	Hyper
Kushki et al., 2014	Children and Adolescents	40	34	HR	Hyper
Keith et al., 2019a, b	Adolescents	25	21	HR	Hyper
Porges et al., 2013	Children, adolescents and young adults	78	68	HR	Hyper
Kuiper et al., 2019	Adults	33	31	HR	Hyper
Mathewson et al., 2011	Adults	15	16	HR	Hyper
Thapa et al., 2019	Adults	55	55	HR	Hyper
Bishop-Fitzpatrick et al., 2017	Adults	40	25	HP	Hyper
Pace and Bricout, 2015	Children	10	10	HR	Hypo
Zantinge et al., 2017	Pre-school children	28	45	HR	None
Zantinge et al., 2019	Pre-school children	21	45	HR	None
Billeci et al., 2018	Pre-school children	20	20	HR	None
Tiinanen et al., 2011	Children	20	21	HR	None
Klusek et al., 2013	Children and Adolescents	40	28	HR	None
Kushki et al., 2013	Children and Adolescents	12	17	HR	None
Bolte et al., 2008	Adults	10	10	HR	None
Dijkhuis et al., 2019	Adults	51	28	HR	None
Zahn et al., 1987	Adults	13	19	HR	None Count: 13:1:9

Table 11
Summary of results from studies comparing autistic and neurotypical groups on Respiratory Sinus Arrhythmia.

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/ Hypo/ None
Van Hecke et al., 2009	Children	19	14	RSA	Hyper
Neuhaus et al., 2014	Children and Adolescents	18	18	RSA	Hyper
Bal et al., 2010	Children and Adolescents	17 (1 F)	36 (13 F)	RSA	Hyper
Edmiston et al., 2016	Adolescents	21	13	RSA	Hyper
Porges et al., 2013	Children, adolescents and young adults	78	68	RSA	Hyper
Mathewson et al., 2011	Adults	15	16	RSA	Hyper
Corbett et al., 2019	Children	31	25	RSA	None
Klusek et al., 2013	Children and Adolescents	40	28	RSA	None
Schaaf et al., 2015	Children	59	29	RSA	None
Kushki et al., 2014	Children and Adolescents	40	34	RSA	None
Kuiper et al., 2019	Adults	33	31	RSA	None
					Count: 6:0:5

variability (such as RMSSD, SDNN, CV, etc., see Table 13 for a summary of these studies and Table 1 for a description of the measures). Of these, four studies found group differences, either in the direction of hyperarousal (50 %) or evidence of some form of autonomic dysregulation (50 %).

The pattern of results from RSA and spectral measures is indicative of reduced parasympathetic activation in autism, given that RSA is a validated measure of vagal tone and the spectral measures that found differences tended to be in the direction of reduced HF-HRV or increased LF-HRV. Schaaf et al. (2015) were the only ones in this review that measured cardiac Pre-Ejection Period at baseline, which is a validated measure of sympathetic arousal using cardiac indices. They did not find any differences on this measure between autistic and neurotypical groups.

A few studies found evidence from spectral or time-domain measures of overall autonomic dysregulation, as indexed by higher overall variance in HRV in autistic than neurotypical participants (Billeci et al., 2018; Bricout et al., 2018; Zahn et al., 1987). One study found evidence for reduced autonomic adaptation between eyes-open and eyes-closed resting-state in autistic participants; reporting that while neurotypical participants demonstrated increased parasympathetic activation (as measured by RSA) during eyes closed as compared to eyes open conditions, the autistic participants did not exhibit this adaptation to changing context (Mathewson et al., 2011). Saghir et al. (2017) measured differences in multi-scale entropy which quantifies the complexity of the heartbeat time series and reported no group differences. According to the authors, this measure represents the ability of the organism to adapt to different environments. Therefore, it might be a useful way of quantifying readiness of the ANS to adapt in autistic individuals in future studies.

A few studies used different indices of cardiac autonomic function other than the commonly used spectral or time-domain measures (See Table 14). Ming et al. (2005) measured indices of cardiac vagal tone using a device that has been validated to be an index of brainstem function in real-time. They reported that Cardiac Vagal Tone (measured as pulse interval variability) was significantly lower in autistic children. This finding was then replicated in an independent sample by the authors (Ming et al., 2016).

Toichi and Kamio (2003) used measures of cardiac vagal index (CVI) and cardiac sympathetic index (CSI), which are calculated from the time-series of consecutive heartbeats. This is a non-linear method of quantifying variance in HRV. They found no differences in either measure in adolescents with or without autism. While there was no overall group difference, they categorized their participants based on responsivity to a subsequent task and discovered that a subgroup of autistic participants who did not show activation of parasympathetic system to the subsequent task had significantly reduced CVI at rest as compared to controls. This might indicate that a subgroup of those with autism have reduced parasympathetic activation and they might show different functional abilities.

3.4.3. *Skin conductance indices*

Two types of skin conductance measures were used (See Table 15). 16 studies compared groups on SCL, of which only six found group differences. Of these, five studies (83 %) found evidence of hypoarousal while just one study (16 %) found evidence of hyperarousal. Six studies used spontaneous fluctuations in skin conductance (NS-SCRs). Of these, three studies found no group differences while three found evidence of either hyperarousal in the form of higher variability in NS-SCRs (n = 2),

Table 12
Summary of results from studies comparing autistic and neurotypical groups on Spectral measures of HRV.

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/HypoNone
Billeci et al., 2018	Pre-school children	20	20	LF, HF, LF/HF ratio	Higher LF (hyper), no other differences
Matsushima et al., 2016	Children	37	32	HF-HRV	Reduced HF-HRV (Hyper)
Bricout et al., 2018	Children	20	19	LF, HF, LF/HF ratio, Total power	Higher power in LF and higher total power (Hyper)
Bujnakova et al., 2016	Children and Adolescents	15	15	Power and peak frequency in LF and HF bands	Reduced power in HF (Hyper)
Tessier et al., 2018	Children and Adults	16 adults, 13 children	17 adults, 13 children	LF, HF, LF/HF ratio	Lower HF (n.u.) in adult autistic as compared to adult NT (Hyper)
Thapa et al., 2019	Adolescents and Adults	55	55	LF, HF	Reduced HF-HRV (Hyper), no other differences
Tiinanen et al., 2011	Children	20	21	LF, HF, LF/HF ratio	None
Bizzell et al., 2019	Children	12	12	HF-HRV	None
Daluwatte et al., 2013	Children and Adolescents	152	107 TD, 36 NDD	Normalized HF, LF/HF ratio	None
Hollocks et al., 2014	Children and Adolescents	52	23	HF, LF/HF ratio	None
					Count: 6:0:4

Table 13
Summary of results from studies comparing autistic and neurotypical groups on time-domain measures of HRV.

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/ Hypo/ Other[a]/ None
Bujnakova et al., 2016	Children and Adolescents	15	15	RR Intervals	Shorter RR intervals (Hyper)
Thapa et al., 2019	Adolescents and Adults	55	55	RMSSD, SDNN	Lower RMSSD (Hyper)
Billeci et al., 2018	Pre-school children	20	20	SDNN, CV, pNN10	Increased SDNN and CV (Other)
Zahn et al., 1987	Adults	13	19	HR Maxima's MSSD	Maxima's MSSD higher in autistic group (Other)
Bricout et al., 2018	Children	20	19	RMSSD, pNN50	None
Daluwatte et al., 2013	Children and Adolescents	152	107 TD, 36 NDD	SDNN, RMSSD	None
Dijkhuis et al., 2019	Adults	51	28	RMSSD	None
					Count: 2:0:2:3

[a] Other refers to findings of differences in autonomic function that cannot be categorized as evidence of hyper or hypo-arousal, for example, evidence of differences between groups of change in autonomic function over time during resting state measurement or evidence of differences in variability in the autonomic index.

or hypo-arousal, i.e., lower variability in NS-SCRs (n = 1).

As mentioned in Section 3.3.1, Zahn et al. (1987) measured skin conductance (SCL and NSSCRs) and reported slower reduction in SCL over time during the resting state, suggesting slower adaptation to the experimental context in autistic individuals as compared to neurotypical individuals. This is similar to a finding of higher variability in NS-SCRs during resting state in neurotypical than autistic participants (Neuhaus et al., 2015) and appears to index less readiness to respond to or adapt to changes in the experimental context. In neurotypical participants, a positive relationship was found between the number and amplitude of EDRs during baseline and social skills, indicating that those with higher social skills had more frequent and increased spontaneous electro-dermal responsivity at baseline, while this relationship was not present in the autistic group. It is possible that the integration of functioning of the ANS and higher-level brain systems that are associated with social skills, does not develop in the same manner in autistic individuals.

Mathersul et al. (2013b) measured SCL while participants spent 2 min with their eyes closed and found no significant overall group differences between adults with and without autism. However, they found more variability in the autistic group's SCL compared to the control group. Using cluster analysis, they found subgroups within the autistic sample with high and low SCL. While the high SCL subgroup did not differ statistically on SCL from controls, the low SCL subgroup was statistically significantly different from both controls and the high SCL autistic subgroup, demonstrating hypoarousal. Further, the authors reported differences in social abilities between the two subgroups. While all autistic adults showed low perspective taking skills, only the hypo-aroused subgroup showed poorer emotion recognition, a tendency to judge faces more negatively and reduced affective empathy.

3.4.4. Studies using multiple autonomic indices

Few studies measured autonomic arousal at rest using multiple indices. Bujnakova et al. (2016) reported shorter RR intervals and reduced HF-HRV in the autistic children as compared to neurotypical children but no differences in LF-HRV; suggesting that the autistic participants demonstrated a hyperaroused profile, possibly driven by reduced parasympathetic activation. Importantly, they concurrently measured skin conductance and found reduced skin conductance in autistic than neurotypical participants, suggesting that autistic participants showed reduced sympathetic activity as well. Similarly, Neuhaus et al. (2014, 2015) measured RSA and NSSCRs at baseline before a reward task, as children with and without autism sat quietly for 5 min. They found reduced RSA (suggesting parasympathetic hyperarousal), but also reduced variability in number of NSSCRs over time during the rest period in autistic children, compared to typically developing controls (suggesting sympathetic hypoarousal). These two studies highlight the importance of measuring ANS using multiple indices together. Both studies demonstrated evidence of hyperarousal using cardiac indices (which are impacted by both sympathetic and parasympathetic differences) and hypoarousal using electrodermal indices (which specifically measures SNS). Together, they suggest a profile of dysregulation in autonomic function in autistic individuals wherein possibly flexible adaptation to the context is impaired.

3.4.5. Summary of evidence based on type of autonomic measures used

In summary, cardiac indices were the most used measures of

Table 14
Summary of results from studies comparing autistic and neurotypical groups on other cardiac measures.

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/Hypo/None
Ming et al., 2016	Children	19	18	CVT, CSB	Reduced CVT and CSB in autistic compared to neurotypical (Hyper)
Ming et al., 2005	Children	28	17	CVT, CSB	Reduced CVT and CSB in autistic compared to neurotypical (Hyper)
Schaaf et al., 2015	Children	59	29	PEP	No differences
Saghir et al., 2017	Children and Adolescents	45	34	Multi-Scale Entropy	No differences
Toichi and Kamio, 2003	Adolescents and Adults	20	20	CVI, CSI	No overall group differences- a subgroup of autistic participants with reduced CVI compared to NT Count: 2:0:3

Table 15
Summary of results from studies comparing autistic and neurotypical groups on electrodermal activity.

First Author	Age Range	Patient n	Control n	Arousal measure	Hyper/Hypo/Other[a]/No differences
Chang et al., 2012	Children	25	25	SCL	Hyper
Kushki et al., 2013	Children and Adolescents	12	17	SCL and NS-SCR	Hyper
Bujnakova et al., 2017	Children and Adolescents	23	14	SCL	Hypo
Bujnakova et al., 2016	Children and Adolescents	15	15	SCL	Hypo
Schoen et al., 2009	Children and Adolescents	38	33, 31	SCL	Hypo
Eilam-Stock et al., 2014	Adults	17	15	SCL and NSSCRs	Hypo
Mathersul et al., 2013a	Adults	30	31	SCL	Hypo
Neuhaus et al., 2015	Children	18	18	Amplitude and frequency of NS-SCR	Other- Differences in Adaptation
Zahn et al., 1987	Adults	13	20	SCL, NSSCRs	Other- Differences in Adaptation
McCormick et al., 2014	Pre-school children	54	33	SCL	None
van Engeland, 1984	Children	35	45	NSSCRs	None
Faja et al., 2013	Children	21	21	NS-SCR	None
Joseph et al., 2008	Children and Adolescents	20	20	SCL	None
van Engeland et al., 1991	Children and Adolescents	20	20	SCL	None
South et al., 2011	Children and Adolescents	30	30	SCL	None
Keith et al., 2019a,b	Adolescents	25	21	SCL	None
Riby and Whittle, 2012	Adolescents	12	12	SCL	None
Mathersul et al., 2013b	Adults	28	31	SCL	None overall, presence of hypoaroused sub-group
Kuiper et al., 2019	Adults	33	31	SCL	None Count: 2:5:2:10

[a] Other refers to findings of differences in autonomic function that cannot be categorized as evidence of hyper or hypo-arousal, for example, evidence of differences between groups of change in autonomic function over time during resting state measurement (i.e., differences in adaptation of autonomic arousal during resting state) or evidence of differences in variability in the autonomic index.

autonomic arousal among the studies included in this review. Studies using these measures were more likely to identify group differences between those with and without autism than studies using EDA or pupillometry. Importantly, the pattern of findings was impacted by the specific indices used. Cardiac indices more frequently detected autonomic hyperarousal, specifically when using measures such as RSA or HF-HRV. Pupil measures, also detected hyperarousal more often. On the other hand, indices of electrodermal activity were the most likely to find evidence of hypoarousal. Importantly, measuring change in skin conductance over time or variability on the measure of skin conductance within the measurement duration appeared to be a critical factor in revealing differences in arousal between autistic and neurotypical individuals (Zahn et al., 1987; Mathersul et al., 2013b; Neuhaus et al., 2015). Future studies should evaluate habituation of arousal during the resting state measurement to investigate this further.

Bringing these findings together, it appears that there is evidence for co-occurring underactivation of both the parasympathetic system (from cardiac indices) and sympathetic system (from SCL) which might be why a few studies also found evidence of reduced adaptation of arousal to changes in context. Importantly, some studies found evidence of subgroups with different profiles of autonomic arousal in those with autism such that only a subgroup of autistic participants showed hyper- or hypo- arousal. Thus, it is possible that contradictory findings from cardiac and electrodermal indices reflect subgroups with opposing profiles, although given the findings of Bujnakova et al. (2016), Neuhaus et al. (2014, 2015), it appears possible that these two profiles co-exist among the same individuals.

3.5. Impact of other factors on study findings

Next, we will consider factors such as sample size, differences in age, IQ, exposure to medication, co-occurring conditions in Sections 3.5.1−3.5.6. Data on IQ, exposure to medication and co-occuring conditions is described for each study in Supplementary materials. In order to analyse these factors, we collapsed across measures and analysed data for each of the 51 studies included in the review that compared groups on an ANS measure.

3.5.1. Sample size

We considered whether studies with larger sample sizes were more likely to find significant effects, which might suggest that a number of studies have simply been unable to capture true effects due to reduced power. We categorized studies (based on number of clinical participants) as having either small sample sizes (clinical n $<$ 20), medium

Table 16
Spread of group differences based on sample size.

Sample Size	No group differences	Group differences
Small	7/22 (31.8 %)	15/22 (68.2 %)
Medium	10/23 (43.5 %)	13/23 (56.5 %)
Large	3/6 (50 %)	3/6 (50 %)

Each study that compared autistic and neurotypical groups on an ANS index is categorized based on the sample size of the autistic sample included in the study and proportion of significant group differences is presented. Sample sizes are characterized as followed: Small (N $\leq$ 20), Medium (N = 21–50) and Large (N $>$ 50).

sample sizes (clinical 20 < n < 50) or large sample sizes (clinical n > 50). This did not change the pattern of findings in any way (See Table 16). Studies with large sample sizes were as likely to find null effects as significant effects, similarly to studies with small or medium sample sizes.

3.5.2. Age

Most studies (n = 45/51, 88.2 %) controlled for age in some form, either by ensuring age-matched groups, or statistically controlling for age in their analyses. When studies were excluded for not doing so, pattern of results did not change. Studies reported significant group differences slightly more frequently after age was controlled for (n = 28/45, 62.2 %) as compared to when it was not controlled for (n = 17/45, 37.8 %). There was still a higher likelihood of finding hyperarousal, but findings of hypoarousal and autonomic dysregulation were present as well.

We analysed whether autonomic differences were more likely to emerge in particular age ranges or not. Across different age groups, there were no such patterns. At all age groups, some studies showed group differences with pre-school children (Anderson et al., 2013; Billeci et al., 2018), children and adolescents (Bal et al., 2010; Bricout et al., 2018) and adults (Eilam-Stock et al., 2014; Kuiper et al., 2019) while other studies did not find group differences with pre-school children (McCormick et al., 2014; Nuske et al., 2014), children and adolescents (Schaaf et al., 2015; Tessier et al., 2018), and adults (Bolte et al., 2008; Dijkhuis et al., 2019). Similarly, the findings of hyperarousal came equally from studies of children and adolescents (Bal et al., 2010; Matsushima et al., 2016) and adults (Mathewson et al., 2011; Top et al., 2018) and findings of hypoarousal were also equally likely from studies of children and adolescents (Bujnakova et al., 2017; Pace and Bricout, 2015) and adults (Eilam-Stock et al., 2014; Mathersul et al., 2013a). It should be noted though that age ranges tend to be quite large, and autonomic function itself undergoes developmental changes fairly quickly particularly during childhood.

One study that aimed to test age effects specifically (Tessier et al., 2018) examined spectral HRV in children (6–13 years) and adults (16–27 years) before and after sleep at rest. Interestingly, they reported a group effect in adults but not in children such that only autistic adults presented with reduced HF-HRV (and hence reduced parasympathetic activation) as compared to neurotypical adults.

Some studies examined relationships between age and arousal. The findings may be useful because they provide information about typical ANS function at different ages, and can therefore help pinpoint at which points in development, autistic individuals show atypical ANS function. A number of studies reported no significant relationships between age and arousal variables in pre-school aged children (Nuske et al., 2014); in children and adolescents (Chang et al., 2012; Hu et al., 2018); in adolescents and adults (Dijkhuis et al., 2019; Thapa et al., 2019). However, these studies tended to include participants from a limited age range thus potentially reducing the power to find developmental or maturational effects.

Studies that included a broader age range of participants reported evidence of changes in autonomic indices with age. For instance, DiCriscio and Troiani (2017) who included a broad age range of participants from 5 to 16 years of age reported a negative relationship between age and baseline pupil size such that older children had smaller baseline pupil sizes. Similarly, studies found evidence of reducing HR with age in samples of children and adolescents (Daluwatte et al., 2013; Kushki et al., 2014; Porges et al., 2013). Interestingly, this finding did not apply to all measures of cardiac autonomic function. For instance, Porges et al. (2013) did not find an association between age and RSA in children and adolescents. Cai et al. (2019) who included adults over a large age range, did not find any association between age and various indices of HRV (HF, SDNN and RMSSD). These relationships between age and autonomic function were not reported to vary based on clinical group, it therefore appears that those with autism might show a similar maturation of autonomic function as those without autism, at least from childhood onwards.

Only one study evaluated the effect of age on autonomic function in younger children. Patriquin et al. (2014) measured RSA at multiple time points from 5 to 48 months of age in a group of 106 typically-developing children. Using developmental trajectory modelling, they found evidence of two subgroups in their sample with a 'typical' and an 'atypical' trajectory of RSA development. In the 'typical' group, RSA gradually increased from 5 to 48 months of age. On the other hand, the 'atypical' group showed an increase in RSA from 5 to 24 months and thereafter a plateau in RSA development until 48 months of age. This 'atypical' group also showed difficulties with social responsiveness at 48 months of age. Studies that evaluate trajectory of development of autonomic function such as this might be more able to pick up on subtle differences in autonomic regulation in autism.

Overall, while it appears that during childhood and adolescence those with autism show similar maturation in autonomic function, there is preliminary evidence of atypical maturation of these functions during early childhood, which might affect later development of lower- and higher-level functions.

3.5.3. IQ

We categorized studies included in the review according to how IQ was treated in their study. Of the 51 studies, 22 studies either did not report IQ characteristics at all, or reported an exclusion criterion (such as IQ < 70) and then did not report group IQ characteristics subsequently, or reported that their autistic and neurotypical groups were significantly different on IQ but then did not subsequently examine whether this related with differences in ANS measures and did not control for IQ in the analysis. These studies were categorized as 'Not Reliable' with regard to control for any influences of IQ, since any effects of differences in IQ between groups on ANS function cannot be examined within these studies. The remaining 29 studies either reported no group differences on IQ or statistically controlled for IQ in their analyses when groups were different or examined how IQ related with ANS measures and thus, with regard to IQ, they were categorised as 'Reliable' because in these studies, we can identify if findings are influenced by IQ. When studies categorized as 'Not reliable' were removed from the analysis, this did not affect frequency of group differences. Of the 29 'Reliable' studies, 17 (58.6 %) found group differences on ANS measures while 12 (41.4 %) did not; thus within these higher quality studies, proportion of studies that reported significant group differences was similar to the all the studies included in the review. Of the studies that did find group differences, 14 found evidence of hyperarousal, two found evidence of hypoarousal and one study found evidence of some form of autonomic dysregulation.

Only a few studies evaluated effects of IQ. Typically, studies included only participants above a certain level of intellectual ability (IQ > 75 or 80). In many studies, participants with and without autism did not differ from each other on IQ. While this controls for variance in IQ and thus provides potentially autism specific effects, autism is a spectrum with a wide range of intellectual ability. By not including those who have co-occurring intellectual disability, any effects that intellectual ability may bring in interaction with autism cannot be discovered.

One cross-sectional study (Porges et al., 2013) which included individuals from 6 to 21 years found a trend towards a relationship between IQ and RSA at baseline such that higher IQ was associated with higher parasympathetic activation, within the autistic group. This study indicates a potentially protective role of IQ in autistic children. Kootz et al. (1982) also divided their sample of autistic participants into two groups, based on whether they were able to learn how to do an active cognitive task. Participants who did not meet criterion on this active cognitive task also were more severely impaired with regard to development and had lower mental age. In this study, HR was measured during resting-state in three separate sessions. The higher and lower functioning groups were not different from each other on HR, but the

lower functioning group showed a significant decrease in resting HR over the course of the three sessions, which might reflect habituation to the context. Another cross-sectional study (Daluwatte et al., 2013) divided their large sample of children and adolescents into those with high or low IQ. They found that children with autism and higher-IQ showed a profile of hyper-arousal (as measured by heart rate) compared to typically developing children, and they did not differ from the lower-IQ autistic group. The implications of these latter two studies are less clear, given that they are reliant on null effects between groups of autistic children with higher and lower IQ. These studies do highlight though, the importance of looking at the role IQ might play in autonomic function in autistic individuals.

3.5.4. Presence of co-occurring symptoms

34 of 51 studies did not report on presence or absence of co-occurring conditions in their samples of those with autism. In nine (out of 51) studies, participants with co-occurring conditions were excluded. Typically, this meant that participants with a cardiac or respiratory disease which might affect autonomic response and/or participants with co-morbid mental or psychiatric conditions (undefined) were excluded. Seven out of these nine studies found group differences in autonomic function. In five (out of 51) studies, participants' co-occurring symptoms were reported but there was not enough power to control for this factor in analysis. Typically, these studies reported that some of their participants had co-occurring ADHD, anxiety disorders or externalizing disorders. Only three (out of 51) studies both reported and investigated the influence of co-occurring conditions on autonomic function.

Hollocks et al. (2014) divided their autistic sample into two, those with and without clinically significant symptoms of anxiety disorder. They reported that the autistic group without anxiety demonstrated significantly higher heart rate at baseline (before the start of a psychosocial stress task) as compared to the autistic group with anxiety and controls; and the difference between the autistic group with anxiety and controls reached only borderline significance. Thapa et al. (2019) found effects of comorbidities on LF-HRV but the direction of this effect was not specified. Bujnakova et al. (2017) divided their sample of autistic participants into those that had comorbidities (ADHD, anxiety disorders, disruptive disorders) and were treated with medication (different participants were on different medications for ADHD, depression, epilepsy, bipolar disorder etc.) and those who did not have any comorbidities and did not take any medications. The results are reported below in Section 3.5.5 since the study focused on effect of medication. Overall, within these three studies, different types of co-occurring symptoms were investigated and therefore, it is difficult to draw any conclusions on how these might impact autonomic function in autism.

Nine studies tested linear relationships between co-occurring symptoms and heart rate variability. Of these, five investigated the relationship between HRV and anxiety based on the suggestion that hyperarousal in autism is linked to presence of anxiety in autistic individuals (Cuve et al., 2018). One study reported that higher heart rate was associated with higher symptoms of anxiety (Keith et al., 2019a); importantly, this relationship was significant only when adolescents self-reported their symptoms of anxiety, but not with parental report. This is important to consider in a population where autistic individuals' emotional experiences can sometimes be hard for parents to observe.

On the other hand, four studies did not find any links between symptoms of anxiety and HRV (Cai et al., 2019; Edmiston et al., 2016; Klusek et al., 2013; Mathewson et al., 2011). Edmiston et al. (2016) reported that reduced RSA was associated with higher symptoms of depression in their autistic group; and similarly, Neuhaus et al. (2014) found a relationship between higher baseline RSA and lower internalizing symptoms.

Only two studies included in this review examined the relationship between sensory processing and arousal. Matsushima et al. (2016) reported that reduced vagal activity, which differentiated children with and without autism, was associated with higher visual and auditory hyperreactivity (as measured by a brief parent-report scale) within those with autism. On the other hand, Daluwatte et al. (2015) reported that resting pupil diameter was not associated with sensory processing scores in autistic and neurotypical participants.

Overall, results were quite variable with regard to whether co-occurring symptoms are associated with autonomic function or not. Most studies used different measures of co-occurring symptoms in relation to different measures of autonomic function. There is preliminary evidence to suggest that autonomic arousal might be linked with internalizing symptoms in autistic individuals. However, this evidence is not yet robust. It should be noted that conditions commonly comorbid with autism such as sleep disorders, seizures, tic disorders etc. that are themselves indicative of ANS dysfunction are important to consider, however, these were beyond the scope of this review. Further work is needed to understand their relevance to ANS atypicalities in autism.

3.5.5. Exposure to medication

Individuals with autism often take medications to manage symptoms of co-occurring conditions, such as medications for depression and anxiety, ADHD, tics, sleep disturbances, challenging behaviours and epilepsy. Exposure to such medications might directly impact autonomic function and measures of arousal. For instance, medications for ADHD (such as methylphenidate, dexamfetamine and atomoxetine) have pressor effects on noradrenergic transmission in the SNS resulting in increase in heart rate and blood pressure (Faraone, 2018; Bellato et al., 2020). In contrast, noradrenergic agnostic medications (including guanfacine and clonidine) to treat ADHD and/or tics can produce inhibition of the SNS resulting in bradycardia and hypotension (Osland et al., 2018). Given the high co-occurrence of ADHD in autism, it is important to understand whether these direct medication effects on the ANS are controlled for in the literature.

Many studies in this review did not report (n = 16/51) possible exposure to medication. Some studies excluded participants if exposed to medication (13/51) or asked them to withdraw medication during the study (7/51). These latter studies were more likely than not to report group differences (14 such studies found group differences while six did not). There was heterogeneity in their findings such that findings of hyperarousal were more likely, but evidence of hypoarousal or autonomic dysregulation or differences in adaptation were also found. Thus, control of exposure to medication did not impact the heterogeneity of the results but did appear to make it more likely to find group differences.

Eight of 51 studies reported medication use in their sample but did not have enough power to investigate whether this influenced their findings. Only seven studies examined impact of exposure to medication on autonomic function findings. Of these, one study (Dijkhuis et al., 2019) reported that baseline HR and HRV were not associated with medication use; one study reported that controlling for medication use did not influence group differences on autonomic measures (Saghir et al., 2017); and one study controlled for medication use by using this as a factorial covariate in their models but did not report whether it influenced results (Van Hecke et al., 2009).

Bujnakova et al. (2017) reported that exposure to medication (ADHD medications, antidepressants and epilepsy medications) had an ameliorating effect on SCL in autistic participants, such that only the non-treated group of autistic participants showed hypoarousal, while the treated group showed similar arousal to neurotypical participants. Notably, the majority of the participants in this study in the treated group had comorbid ADHD, which is a population known to have a hypoarousal profile (Bellato et al., 2020), which might have driven these effects.

In contrast, three studies (using measures of HR or HRV) reported that autistic individuals who were exposed to medications demonstrated profiles of hyperarousal, and those who were untreated showed arousal levels similar to neurotypical participants (Cai et al., 2019; Daluwatte

et al., 2013; Mathewson et al., 2011). Daluwatte et al. (2013) also found similar effects in a comparison group with other neurodevelopmental conditions, such that exposure to medication was linked with hyperarousal. While this might suggest that findings of hyperarousal might be driven by exposure to medications, it is important to point out that medication use is often associated with higher symptom severity of autism. For instance, Cai et al. (2019) found that use of medication was linked with lower HRV and more severe autistic symptoms. However, use of medication did not predict significant variance in HRV after autism symptom severity and emotion regulation strategies were accounted for. Finally, Thapa et al. (2019) found that medication as a factor only appeared to be linked with LF-HRV, but not with HR, HF-HRV or other measures. They found reduced LF-HRV in the medicated autism group (majority of the sample was using antidepressants or antipsychotics), but overall, their autistic sample had reduced HF-HRV. This would imply that while the autistic sample in their study overall demonstrated a profile of reduced parasympathetic activity (and hence hyperarousal) as compared to neurotypical participants, within the autistic group, participants who were medicated showed a profile also of reduced sympathetic arousal as compared to autistic participants who were not medicated. Thapa et al. (2019) did not compare their medicated and unmedicated autistic participants separately with neurotypical participants. Given that these findings of medication are on a different measure (LF-HRV) than the overall group differences (HF-HRV), it is difficult to interpret them. However, in this sample, when they re-categorized people based on presence of comorbidities, a factor that highly overlapped with exposure to medication, LF-HRV was implicated in this result as well (although the direction of the effect was not clearly described). It is thus difficult to tease apart whether exposure to medication impacts profiles of arousal or whether this might reflect presence of other co-occurring conditions, particularly since medication use and comorbidities are related to one another. Thus, exposure to medication may in itself, be an indicator of a subgroup of individuals with autism who present with more severe social-emotional challenges, which might be accompanied by differences in autonomic function.

3.5.6. Summary of other factors

Overall, we did not find any evidence that sample size or age were associated with the pattern of group differences across studies. While there was evidence of maturation of autonomic arousal indices with age, this did not appear to be different for the autistic groups from childhood onwards. There is preliminary evidence for different trajectories of autonomic arousal maturation in toddlerhood which may have cascading effects on autonomic function later. Similarly, there is unclear evidence for any variance in autonomic function as influenced by intellectual ability, mainly due to the lack of studies explicitly investigating this. It is also hard to draw any conclusions with regard to whether co-occurring symptoms or exposure to medications influences autonomic arousal in autistic individuals. This is primarily due to underreporting and lack of control of these factors in the literature. However, there is some evidence to suggest that there might be autonomic arousal differences in autistic individuals related to the presence of co-occurring symptoms of other conditions (such as ADHD, anxiety or internalizing symptoms) wherein autonomic function is known to also be affected. Further, exposure to medications for such conditions does seem to impact autonomic arousal profiles in autistic individuals, and this is important to control for in future studies.

3.6. Symptom associations

17 studies investigated associations between measures of autonomic function at rest and measures of either symptoms of autism or other behavioural measures relevant to autism.

3.6.1. Autonomic function and Autism symptom severity

There is some evidence that reduced parasympathetic activation (and thus, hyperarousal) is associated with higher autism symptom severity, although this is not robust. Eight studies examined the relationship between HF-HRV or RSA and autism symptom severity (measured using either parent-report scales such as the Social Responsiveness Scale (SRS) or Autism Spectrum Quotient (AQ) or through direct-observation based assessments such as the Autism Diagnostic Observation Schedule (ADOS)). Of these, six studies found significant negative associations between measures of heart rate variability and autism symptom severity; across autistic and neurotypical participants (Cai et al., 2019; Van Hecke et al., 2009); only in the autistic sample (Edmiston et al., 2016; Hu et al., 2018; Matsushima et al., 2016); or only in the neurotypical sample (Klusek et al., 2013). These studies suggest that higher symptom severity of autism is associated with reduced parasympathetic activation, and thus, profiles of hyperarousal. Further, Edmiston et al. (2016) found relationships between higher RSA and reduced symptom severity as measured by SRS, but not with the Social Communication Questionnaire (SCQ). Interestingly, two studies evaluated relationships between autonomic indices and specific items on measures of autism that tap into specific symptoms. Matsushima et al. (2016) found a relationship between reduced power in HF-HRV and higher symptoms of RRBs, but not overall symptoms of autism, as measured by the SRS. Similarly, Billeci et al. (2018) reported an association between increased heart rate variability with poor initiation of join attention (a specific item on the ADOS).

Two studies using the same sample did not find significant associations between cardiac function and autism symptom severity using SRS (Patriquin et al., 2013a, 2013b) in young children 4–7 years old. These were the only studies that measured dimensional relationships in such young children, all the other studies measured these in children 6 years of age and above.

Two studies measured the association between baseline pupil size and traits or symptoms of autism. Anderson et al. (2013) found that higher tonic pupil sizes were correlated with higher scores on the ADOS in two separate samples of participants. In contrast, DiCriscio and Troiani (2017) did not find a significant relationship between baseline pupil size traits of autism as measured by the SRS. No studies looked at dimensional relationships between skin conductance measures and autism symptomatology.

Overall, there was variance both in measures used for autism symptom severity and the measure of parasympathetic function, which might be the reason for the variation in findings. The same measures of symptom severity sometimes were related to autonomic function and at other times not, suggesting that possibly, these measures are not sensitive enough to the specific aspects of function that autonomic function impacts. It might be that differences in autonomic function are associated with differences in specific skills within autistic symptoms such as social interaction or restricted, repetitive behaviours. Further, many symptom measures (other than ADOS) were questionnaire based (self or parent report) which may be less reliable than assessing symptoms directly using behavioural tasks. Finally, the heterogeneous findings may be indicative of heterogeneous samples wherein certain associations apply only to a subset of participants and therefore a subtyping approach might be crucial to identify reliable patterns.

3.6.2. Autonomic function and social-emotional skills

Six studies measured associations between autonomic arousal and various social skills.

Of these, two examined associations between arousal and language and communication skills and reported consistent results such that higher cardiac arousal was associated with worse language and communication skills (Klusek et al., 2013; Patriquin et al., 2013a). Klusek et al. (2013) tested whether IBI and RSA could serve as predictors of pragmatic language skills, but their regression models proved non-significant once receptive/expressive vocabulary were accounted for.

Five studies reported consistent findings that reduced RSA was

linked to worse social-emotional skills (Bal et al., 2010; Cai et al., 2019; Neuhaus et al., 2014; Patriquin et al., 2013b; Van Hecke et al., 2009). This is in line with Porges' polyvagal theory which links vagal activity with development of socialization skills. Interestingly, Van Hecke et al. (2009) only found these relationships to be true across neurotypical and autistic groups; within each group, these relationships became non-significant possibly due to reduced variance. Bal et al. (2010) reported that children with higher amplitude RSA at baseline recognized emotions faster. Cai et al. (2019) examined emotion regulation strategies in adults with and without autism and found that those with higher resting HRV demonstrated use of better emotion regulation strategies across samples of autistic and neurotypical participants. Together these studies suggest that higher parasympathetic activation is linked with better social-emotional skills across autistic and neurotypical individuals.

Finally, two studies (Neuhaus et al., 2014, 2015) measured RSA and NSSCRs at baseline before a reward task in children with and without autism as they sat quietly for 5 min. They found reduced RSA (suggesting hyperarousal) in autistic than neurotypical individuals and higher variability in number of NSSCRs (suggesting hypoarousal) in the baseline period over time in neurotypical than in autistic participants. Thus, their sample of autistic participants demonstrated hyperarousal on one measure and hypoarousal on the other, suggesting profiles of both parasympathetic and sympathetic underactivation. The authors reported that higher frequency and amplitude of NSSCRs (and therefore, more variability in SNS function) was associated with better social skills (as measured by the Social Skills Improvement System, tapping into higher level skills such as cooperation, empathy, self-control) in the neurotypical group; and with more problem behaviours (measured by the same scale, comprising of internalizing, externalizing and hyperactivity behaviours) in the autistic group (Neuhaus et al., 2015). This was not interpreted by the authors since this was not the focus of the article but suggests that autonomic function is not integrated with higher order functions in the same way in autistic and neurotypical participants. Further, higher baseline RSA was associated with better social functioning (measured by Social Skills Improvement System and VABS), fewer social problems (measured by CBCL), and with internalizing subscales of CBCL (but not the externalizing subscales). The authors then used a regression model to examine whether social skills, internalizing and externalizing symptoms predicted variance in RSA and found independent and significant effects of all 3 in predicting variance in RSA; notably, higher externalizing symptoms were associated with higher RSA. Therefore, while higher RSA was associated with better social skills and lower internalizing symptoms, it was associated in this study with higher externalizing symptoms. The findings from skin conductance and RSA were reported in separate articles and thus, the authors did not integrate the findings from the two measures together.

Overall, again, heterogeneity in the measured constructs, the choice of scale or instrument, and the autonomic measure used, makes it difficult to draw out any consistent patterns. Despite this, there is some evidence that reduced parasympathetic function might be related to worse social-emotional skills. Further, there is preliminary evidence that parasympathetic and sympathetic activity are differentially associated with internalizing and externalizing behaviours, within autistic and neurotypical participants.

4. Discussion

This review aimed to systematically evaluate the evidence for differences in profiles of arousal during resting-state in autism. Of the 51 studies that investigated group differences between those with and without autism, 61 % of the studies found evidence of group differences. However, when counting each group comparison from each study (yielding 130 comparisons), findings of null effects were more prevalent with 61 % of the group comparisons yielding null effects. Further, within significant findings, while evidence of hyperarousal was more common, findings of hypoarousal were also consistently present in a small proportion of studies. Thus, overarching theories that suggest either hyper- or hypo-arousal as a dominant state in autistic individuals (DesLauriers and Carlson, 1969; Hutt et al., 1964) are not consistently supported by evidence in this review. Rather, the profile seems more mixed than this and may vary between settings and individuals. This is in line with findings from other reviews of ANS in autism, which have also typically tended to conclude that evidence for autonomic dysfunction in autism is at best variable and inconsistent, with between-group findings of hyperarousal, hypoarousal or null effects (Cuve et al., 2018; Lydon et al., 2016). We also highlighted methodological inconsistencies, such as use of different measures, poor control of extraneous factors such as co-occurring symptoms, IQ and exposure to medications impacting ANS functions, use of small sample sizes and hence reduced power to find true effects; all of which might have contributed to some of the heterogeneity in the findings.

An important finding of our review is that the experimental setting might have influenced findings. Reports of group differences in arousal were in fact more common in studies where resting-state was measured without any stimulation given to participants, as compared to studies where participants were asked to passively attend to some sort of stimulation. Not providing specific stimulation is likely to facilitate focus on internal states as compared to passive attention measurements where attention is focused on something external such as a silent movie or a fixation cross. Possibly, not being given a specific task to do is more demanding for autistic individuals, since it lacks the structure of a specific task or activity (Brodzeller et al., 2017). Importantly, it is possible that asking autistic participants to sit quietly and still or lie down with their eyes closed (or without the expectation of a task) influences their autonomic state (or they adapt to this differently) as compared to when participants' attention is directed to something fixed and external. This finding indicates that tasks that require inward-directed attention, or a lack of external focus, might be particularly important in identifying sources of difference in autism. In line with this, there is some evidence for differences in functional and structural organization of the Default Mode Network in autistic individuals (Padmanabhan et al., 2017) which is an interconnected network of brain structures involved in self-referential processing, and which becomes more active during states of inward-directed attention (Buckner et al., 2008). Methodologically, it is also important to note here that pure resting-state studies more often reported that participants were given some time to adapt to the laboratory context before autonomic measurement began. This might have influenced the findings as autistic participants are known to struggle with new environments (Lau et al., 2019). Similarly, studies that reportedly focused on solely resting-state measurement, as compared to those in which the resting-state measurement was followed by a task (cognitive or physical), were more likely to report group differences. If a task immediately follows a resting state measurement, this is likely to induce preparatory states in participants, or anxiety, which would vary depending upon the nature of the task that follows, thus introducing noise which might vary systematically between groups. Interestingly, with regard to the direction of significant findings, studies where participants were asked to passively attend to something external were more likely to report findings of hyperarousal (when they found group differences) than studies where participants were asked not to do anything and simply relax. Possibly, autistic participants might find it harder to down-regulate arousal in the presence of stimulation, which supports evidence of hyper-responsivity to sensory stimulation in autism (Green et al., 2015).

Across the studies that found significant differences between groups, findings of hyperarousal in the autistic group were the most frequent, particularly from indices of cardiac function and pupillometry. Using indices of RSA (which measures vagal tone) and spectral measures of HRV, there is some evidence in support of theories of reduced parasympathetic activation in autistic individuals. Some studies also reported associations between reduced parasympathetic function and

worse autism symptom severity (although this varied depending upon the arousal measure and the autism symptom severity scale used). However, given the high number of null findings using cardiac measures, it appears unlikely that resting-state cardiac indices of autonomic arousal could serve as an autism-specific index for diagnostic or treatment monitoring purposes. Indeed, it should be noted that reduced parasympathetic activation appears to be a trans-diagnostic factor that relates with socialization and communication skills in individuals in many other conditions such as anxiety disorders, and externalizing disorders such as oppositional-defiant disorder, both of which are noted as co-occurring with autism (Simonoff et al., 2008). In line with this, we found some evidence for reduced parasympathetic activation being associated with worse social-emotional skills, internalizing and externalizing symptoms (Neuhaus et al., 2014). These findings support suggestions of reduced vagal tone playing a role in atypicalities in socialization and emotional regulation (Porges, 2003; Thayer and Lane, 2000). Therefore, it appears that profiles of reduced parasympathetic function in autism might index a trans-diagnostic risk factor that relates with severity of impairment in specific domains of socialization and emotional regulation (and possibly, also index co-occuring symptoms of other conditions such as internalizing and externalizing disorders), rather than relating with autistic symptoms as a whole.

As compared to cardiac indices, studies using electrodermal activity provided more evidence for presence of hypoarousal in autistic individuals. EDA is under the control of the sympathetic branch of the ANS (Wass et al., 2015). It is difficult to interpret such contradictory findings of hyperarousal (driven by parasympathetic system) and hypoarousal (driven by the sympathetic system), particularly since most studies used only one of the two measures. Studies in our review which used multiple indices together were more informative and provided evidence of co-existence of hyper- and hypoarousal within the same individuals (Bujnakova et al., 2016; Neuhaus et al., 2014, 2015). This provides evidence of overall autonomic dysregulation or generally reduced responsivity of the ANS to the environment in autism. Indeed, a few studies provided specific evidence for reduced adaptation to the context in autistic groups (Mathewson et al., 2011; Neuhaus et al., 2015; Zahn et al., 1987) which is in line with findings of reduced responsivity to socially stressful contexts in autism (Edmiston et al., 2016). These studies indicate the importance of measuring variability of autonomic arousal within the measurement duration over time and this simple manipulation in analysis could reveal important differences in arousal regulation between neurotypical and autistic individuals. Only one study in our review combined measurement of ANS function with measurement of CNS function. Eilam-Stock et al. (2014) reported hypoarousal using EDA in the autistic group and NSSCRs in the autistic participants were less strongly correlated to activation in frontal brain regions (as measured by fMRI) that are involved in regulating peripheral autonomic function. Importantly, they also reported that in those with autism, reduced NSSCRs were correlated with more activation in sensory regions, suggesting that possibly during the task, their attention was more outwardly directed than internally directed during the measurement. It might therefore be that people with autism struggled to 'switch off' (inside a loud scanner), so that those without autism were more able to enter a 'resting mode' in this potentially stressful context. These studies highlight the importance of both experimental context but also of using multiple indices of ANS and CNS in order to understand where differences specific to autism lie.

Very few studies using pupillometry met our inclusion criteria for this review. While only half the studies using pupillometry found group differences, all the ones that found group differences found evidence of hyperarousal. Pupil dilation/constriction reflects a balance between sympathetic and parasympathetic influences and is mediated by the brainstem regions of LC—NE. It is possible that findings of hyperarousal using pupillometry are indicative of atypicalities in brainstem function or top-down regulation of brainstem which influences both parasympathetic activation and pupil constriction/dilation (Bast et al., 2018). This is partly corroborated by the studies (Ming et al., 2005, 2016) who found reduced vagal tone using a measure which is correlated with brainstem function. It is interesting to note that studies using pupillometry also found linear associations between tonic arousal (as indexed by pupil diameter) and autism symptom severity (Anderson et al., 2013). Other pupillometry parameters have been reported to have high specificity for autism, such as the pupillary light reflex (PLR) (Daluwatte et al., 2015; Dinalankara et al., 2017; Wagner et al., 2016), which has been found to be predictively associated with a later diagnosis of autism in 10 month old infants at elevated risk of autism (Nystrom et al., 2018). PLR indexes an automatic process of sensory responsivity, which is a core symptom of autism (American Psychiatric Association, 2013). Further research is needed using pupillometry to index states of rest and responsivity to stimuli in autistic individuals.

Finally, a suggestion has been made that resting-state physiology might not be homogeneous in autism and that there might be subgroups of autonomic responders linked with resting state physiology of hyper- or hypo-arousal (Hirstein et al., 2001; Schoen et al., 2008), however, very few studies consider using subtyping in the literature. Our review found some support for this suggestion (Bujnakova et al., 2017; Mathersul et al., 2013b; Toichi and Kamio, 2003; van Engeland, 1984). These studies divided their group of participants based on autonomic response on a subsequent task (for example higher or lower responsivity to sensory stimuli) and found that when divided in this way, a subgroup of hypo- or hyperaroused participants emerged. It is possible that a number of null findings are due to averaging over different profiles of arousal between subjects in a group and it would be important to consider sub-groups in the future. However, it is important to note that these subgroups emerged when their responsivity to sensory stimulation was investigated. Therefore, just a measurement of resting state, without evaluating adaptation to different contexts, may be less effective in finding subgroups if they exist. Importantly, in future studies, it will be important to investigate whether these subgroups relate with differential profiles of co-occurring symptoms of ADHD, anxiety etc.

We also considered whether factors such as age, exposure to medication, length of autonomic measurement, co-occurring symptoms and intellectual ability influenced findings. Studies that analysed autonomic function from at least 3 min of data or more tended to more frequently report significant differences between groups. Studies that used shorter measurements might not be able to reliably establish autonomic function profiles, although this likely depends on the measure used. Exposure to medication and co-occurring symptoms of other conditions appear to be important confounding factors. However, it is difficult to tease apart how these interact with autonomic function in autism since medication is linked both with higher symptom severity and particularly with presence of co-occurring difficulties. Further, some of the medications typically taken by autistic individuals for co-occurring difficulties directly influence arousal networks. There was some evidence that IQ might be somehow associated with measures of autonomic arousal. For example, one study reported that higher IQ was associated with higher parasympathetic activation, suggesting the possibility that IQ acts as a protective factor and facilitates responsivity to the environment in those with autism (Porges et al., 2013). Future studies should explore how presence of co-occurring conditions and individual differences in IQ are related with autonomic function in autism. We were unable to look at any differences in ANS profiles based on gender since most studies included either only male participants or predominantly male participants.

We did not find any evidence for atypical maturation of ANS indices from childhood onwards in autism. However, there is preliminary evidence for atypical maturation of ANS indices from infancy to early childhood, specifically as measured by RSA (Patriquin et al., 2014) in those with autism. This is corroborated by a recent study by Sheinkopf et al. (2019) who reported reduced maturation of RSA and hence atypical development of vagal tone in early childhood in those with autism as compared to those without autism. Notably, in this study,

there were no group differences between those with and those without autism at any time point from 1 to 6 years. However, the trajectory of change in RSA was atypical in those with autism. Possibly, early differences in development of ANS in interaction with the environment might lead to later differences in autonomic arousal and responsivity to the environment. This requires further investigation.

In summary, evidence included in this review did not consistently support theories of hyper- or hypo-arousal as a dominant state during rest in autistic individuals. Experimental context of measurement and index of autonomic arousal used impacted the nature of findings. There was some evidence for profiles of both parasympathetic and sympathetic underactivation, as well as possibly, presence of subgroups of autistic individuals with different autonomic profiles. There was an indication that autistic individuals might show differences in autonomic responsivity and adaptation to changing environmental contexts.

Recommendations for future research:

- It appears that experimental context plays an important role: those with autism might struggle to effectively regulate arousal to adapt to different contexts. More research is needed to understand whether differences in responsivity to different contexts are present in all individuals with autism or in a subgroup, and whether this is related to difficulties in maintaining an optimal state of physiological arousal. Importantly, systematic manipulation of the measurement context, manipulating inward and outward direction of attention is crucial in understanding where differences emerge.
- Future studies in the area should use multiple indices of ANS and CNS simultaneously in order to identify at which level the differences lie and what they are due to. Measurement of resting-state arousal can still be informative towards understanding mechanisms in the development of autism.
- Future studies should also investigate presence of subgroups of autistic individuals with different autonomic profiles. This might help stratify autistic individuals into subtypes that are clinically meaningful and help predict or inform the treatment strategies different subgroups would benefit from.
- Further investigation is also required in infancy and toddlerhood, particularly longitudinal research, for example, by longitudinally following infants at higher familial risk of autism. This might help us evaluate whether there are early differences in maturation of ANS indices which have cascading effects on development of socialization skills later.
- We found some evidence that social symptom severity in autism is related to increased pupil size and reduced parasympathetic activation. These findings merit further investigation, specifically with regard to vagal tone, brainstem function and the activity and integrity of the LC-NE in autism.
- An emerging area of research that is promising is the role of remote measurement technologies, such as sensing wearables and smartphones that would move measurement out of the lab into the real-world and into real-time contexts. These technologies can help evaluate the impact of environmental stimuli such as noise, crowds, different types of natural social interactions, that appear core to the autism symptomology. Evaluating the role and impact of arousal on attention and information processing in such real-world contexts is of further utility since atypical arousal regulation may impair attentional processing in a context-dependent manner, which is difficult to capture in controlled lab settings.
- Finally, neural or peripheral markers of dysfunction in the LC-NE system in autism could potentially help identify new targets for treatment, but further research is needed.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.02.041.

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