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Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence

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ABSTRACT

Although arousal mechanisms have frequently been found to be atypical in ADHD, these findings usually emerged from indirect behavioural measures which give only a limited understanding of arousal dysregulation in this condition. To assess the hypothesis that functioning of the autonomic nervous system (ANS), one component of arousal, is atypical in ADHD, we carried out a systematic review of the literature on 55 studies investigating electro-dermal, heart rate and pupillometry measures under different experimental conditions (resting-state, cognitive tasks and in response to reinforcers or socio-emotional stimuli). Our literature review identified ANS dysfunction in individuals with ADHD, more often in the direction of hypo-arousal than hyper-arousal, particularly at rest and during tasks requiring response regulation and sustained attention. Almost half of the reported findings were null. Stimulant medications increased ANS activity and, in some studies, re-inforcers and rewards produced a similar effect, suggesting that ANS function can be modified in ADHD. Further research is needed to assess the influence of comorbid symptoms and to explore methodological parameters that may influence findings.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common and enduring neurodevelopmental disorder characterised by developmentally atypical inattention and/or hyperactivity and impulsiveness (American Psychiatric Association, 2013). The condition affects around 5 % of children (Polanczyk et al., 2014) and 3 % of adults (Fayyad et al., 2007) worldwide, resulting in lifelong impairments in most cases, including mental health problems, unemployment and criminality (Erskine et al., 2016). Compared to typically developing controls, individuals with ADHD are cognitively impaired (see Frazier et al., 2004, for a meta-analysis), with impairments most commonly found in sustained and selective attention (Mueller et al., 2017) and executive functions (EF) (Willcutt et al., 2005). However, when cognitive tasks require less effort (Borger and van der Meere, 2000), when stimulus event rate is optimal (Wiersema et al., 2006; 2014) or when rewards are given for performance (Groom et al., 2010, 2013; Liddle et al., 2011), children and adults with ADHD exhibit fewer cognitive impairments. To account for these features, it has been suggested that a decreased ability to regulate arousal may contribute to the higher-level cognitive deficits in ADHD, and this may be an important aspect of the pathology of the condition (Kuntsi and Klein, 2012; Sergeant, 2000; Van Der Meere, 2002; Van Der Meere et al., 2010). Specifically, manipulations such as optimising the event rate within a cognitive task or providing performance-based incentives may improve cognition in ADHD by stimulating arousal and thereby reducing the effort required to complete a cognitive task (Sergeant, 2000; 2005). To date, however, much of the research in this area has inferred impaired arousal regulation in ADHD from cognitive performance measures, such as reduced accuracy, slower response speed and increased reaction time variability (RTV) (Karalunas et al., 2014). Indirect measures, such as these, give only a limited understanding of arousal dysregulation in ADHD.

Arousal refers to the neural, behavioural and physiological mechanisms that regulate states of wakefulness and alertness, which are governed by interactions between the peripheral and central nervous systems (CNS). The autonomic nervous system (ANS) forms one part of the peripheral nervous system and regulates bodily functions (including heart rate, respiration, perspiration and pupil dilation) by controlling smooth muscle fibres, cardiac muscle fibres and glands. The two branches of the ANS, the Sympathetic (SNS) and Parasympathetic Nervous Systems (PNS), exert opposing forces on one another to facilitate constant and dynamic shifts in ANS activity, depending on the

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requirements of a given environment or task. The ANS is, therefore, a core component of the arousal system, but its role in the clinical and cognitive features of ADHD is not well understood. To advance knowledge of ANS function in ADHD, we conducted a systematic review of studies investigating ANS activity in ADHD in the context of a cognitive task or a defined resting-state period. Specifically, we predicted that if arousal dysregulation is a feature of ADHD, as suggested by previous research cited above, and if this is at least partly due to dysfunction in the ANS, measures of ANS activity will differ significantly between individuals with ADHD and typical control participants either at rest (when not engaged in a specific activity) and/or during a task. Reviewing the literature on ANS activity in ADHD will, therefore, provide useful information to help guide theories of arousal regulation in ADHD and may also prove useful in understanding how medications and other therapies exert their effects. Before presenting the methods and results of the review, we first describe relationships between ANS activity and cognition and, briefly, how these relationships might be impaired in ADHD.

1.1. Relationships between the autonomic nervous system (ANS) and cognition

The well-known Yerkes-Dodson law (Yerkes and Dodson, 1908) describes an inverted U-shaped relationship between arousal and cognitive performance, with task-directed behaviour being negatively affected by too low or too high levels of arousal and requiring optimal regulation to achieve good performance. These links between arousal and cognition are governed by interactions between CNS and ANS (Aston-Jones et al., 2000; Aston-Jones and Cohen, 2005). In particular, the locus coeruleus (LC) in the brainstem pons region receives autonomic signals via the nucleus tractus solitarius (NTS) (Critchley and Garfinkel, 2018) and has widespread, reciprocal connections with prefrontal cortex (PFC) regions (including anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and ventromedial prefrontal cortex

(vmPFC)), insula, hypothalamus and amygdala (see Fig. 1). The LC is the sole source of norepinephrine (NE) in the cortex and NE availability in these regions influences a range of cognitive functions, including perception, memory, working memory, sustained attention and task switching (Sara and Bouret, 2012), partly by modulating the availability of dopamine (DA) and glutamate at task-relevant sites (Mather et al., 2016).

Animal (Aston-Jones and Cohen, 2005) and human (Gilzenrat et al., 2010; Murphy et al., 2014) studies have demonstrated the concurrent involvement of ANS, brainstem, and cortical systems in the dynamic regulation of behaviour and cognition. More specifically, in humans the correlations between activity in BOLD signals in ACC, vmPFC, and indices of ANS functioning such as heart rate (Critchley et al., 2003; Matthews et al., 2004) and electrodermal activity (EDA; Critchley et al., 2003; Nagai et al., 2004; Zhang et al., 2014) reflect the ongoing and dynamic integration of information about task demands (represented in cortex), the physiology required to meet those demands (signals between the ANS and brainstem) and the regulation of arousal to support specific behaviours (top-down control by cortical systems over LC). While in animals the direct measurement of ANS functioning is possible and it is widely used, investigating arousal in humans can be achieved by analysing peripheral indices of autonomic arousal, e.g., heart rate, pupil size and EDA (Wass et al., 2015).

While heart rate (HR) indicates the average number of beats per minute (BPM), heart rate variability (HRV) represents a measure of the fluctuations in heart rate over time. HRV has been shown to reflect the parallel activation of the SNS and the PNS. Specifically, acceleration of heart rate mirrors the activation of the SNS, while activity in the PNS is associated with heart rate decelerations (Wass et al., 2015). Moreover, studies have shown that activity in the LC-NE system is accompanied by excitatory effects on cardiac muscles resulting in activation of the SNS (Wang et al., 2014) and deactivation of the PNS (Samuels and Szabadi, 2008), demonstrating a direct relationship between HR and LC activity.

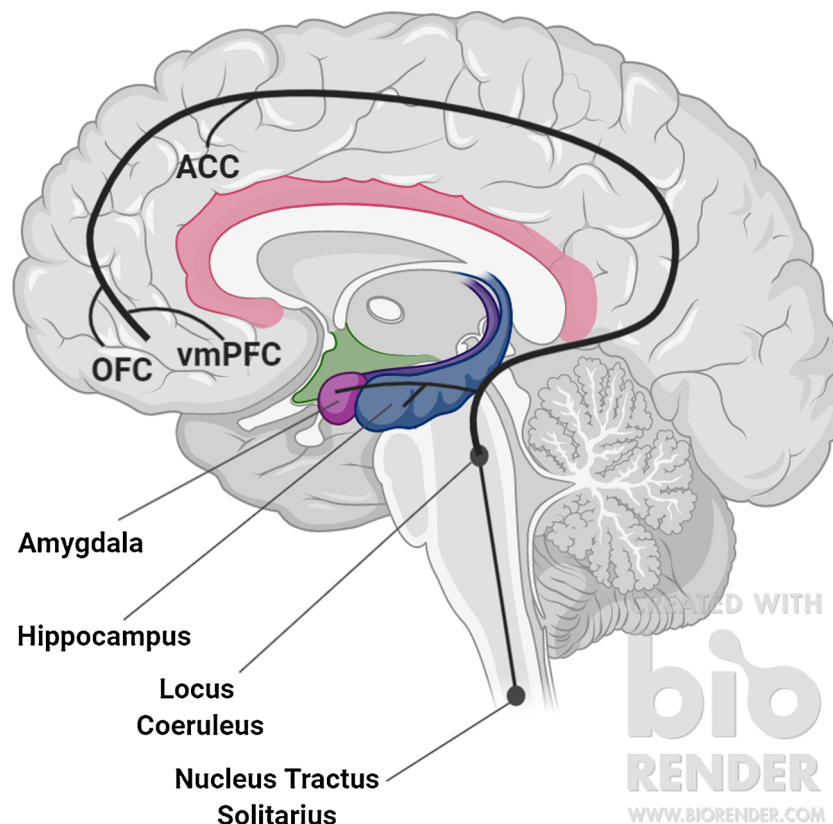Similarly, the constriction and dilation of the pupil are influenced

Fig. 1. Visual representation of the LC-NE system in the human brain (created on https://biorender.com/).

by activity in the SNS and the PNS (Bast et al., 2018) and studies have shown a direct correlation between slow fluctuations in LC activity and pupil size (Rajkowski, 1993; Murphy et al., 2014). Therefore, measuring pupil size during resting-state or cognitive tasks is likely to give an indication of ANS activity (Bast et al., 2018). Finally, electrodermal activity (EDA) is a measurement of changes in the constriction and dilation of blood vessels underneath the surface of the skin. Changes in skin conductance level (SCL) reflect changes in these veins and thus reflect changes in the activity of the ANS (Wass et al., 2015). Together, these indices of ANS activity represent useful measures of changes in autonomic arousal over time and under specific conditions.

1.2. The relation between autonomic arousal, cognition and behaviour in ADHD

Arousal dysregulation has frequently been described as an important feature of ADHD. Specifically, difficulties regulating arousal according to situational demands may contribute to the behavioural phenotype found in ADHD. For example, being unable to increase arousal during a monotonous or challenging cognitive task might undermine the type of attentive behaviour required to complete schoolwork. Similarly, an impairment in the ability to dampen heightened arousal may result in maladaptive behavioural strategies of arousal regulation, such as shouting or running. Geissler et al. (2014) suggest that reduced vigilance and allocation of attentional resources to the environment may be core to ADHD, reflecting a tonically hypo-aroused state, while hyperactivity and impulsive behaviours may be a consequent autoregulatory strategy to enhance arousal by creating a stimulating environment and so stabilize vigilance. Other features of ADHD which are suggestive of a disturbance in arousal regulation include emotional dysregulation (Faraone et al., 2019), sleep disorders (Hvolby, 2015), dysregulation of the Hypothalamus-Pituitary-Adrenal (HPA) axis (Isaksson et al., 2012) and problems regulating appetite (Hanc and Cortese, 2018).

It is noteworthy that medications for ADHD operate by altering the availability of NE and DA at cortical sites (Faraone and Buitelaar, 2010), and often have unwanted autonomic-related side effects, such as increases of heart rate and blood pressure, suggesting that part of their mechanism of action may be to alter ANS activity. Whether or not these ANS effects contribute to the clinical efficacy of these medications, needs to be established. Cognitive performance of children and adults with ADHD can also be improved following exercise interventions (Ng et al., 2017) and neurofeedback (Arns et al., 2014), both of which may influence arousal. This offers some promise for the development of new therapies for ADHD which, by targeting arousal, may improve the cognitive and behavioural features of the condition. To develop or refine interventions, however, a much fuller understanding of arousal in ADHD is needed.

The application of the cognitive energetic model (Sanders, 1983) to ADHD by Sergeant (2000; 2005) was the first notable attempt to link together cognition and arousal in ADHD, by describing the roles of effort (described as the energy needed to meet task demands), activation (conceptualised as tonic arousal) and energy (likened to phasic, stimulus-locked arousal) in supporting cognitive function. Although these components of the model have proven difficult to test empirically (Johnson et al., 2009), empirical studies designed to test more broadly the concept of state (dys)regulation have supported a potential role for arousal in ADHD (Strauß et al., 2018). In particular, evidence that cognitive functions improve in ADHD when tasks are combined with performance-based incentives (Liddle et al., 2011; Groom et al., 2010, 2013) or are delivered at an optimal pace (Metin et al., 2012; Wiersema et al., 2006), suggest that these factors help to offset impaired arousal regulation in ADHD. Further support for this comes from evidence of increased intra-individual reaction time variability (RTV) across a range of experimental paradigms (see Kofler et al., 2013, for a meta-analysis), particularly during monotonous cognitive tasks (Metin et al.,

2012). This has been interpreted as a potential marker of impaired arousal regulation in ADHD since it is thought to reflect fluctuations in performance due to difficulties in maintaining an optimal level of vigilance (Borger and van der Meere, 2000; Sergeant, 2005).

Although informative, these studies provide only an indirect assessment of arousal in ADHD because they are based on performance measures. The brainstem regions that mediate the link between ANS and the neural systems that support cognition and behaviour, such as the LC, have not been studied thoroughly in ADHD. Neither there is a clear picture of the degree of dysfunction of the ANS which is likely to play a crucial role in arousal regulation. It is therefore unclear which mechanisms or systems supporting the interface between autonomic arousal and cognition are affected in ADHD. A deeper understanding of the functioning of the ANS in ADHD may increase our knowledge about the mechanisms underpinning this neurodevelopmental condition and facilitate new therapies which would target the symptoms more effectively.

2. Review aims and methods

To assess the evidence of ANS dysfunction in ADHD, we conducted a systematic review of the literature, with the aim of identifying articles comparing ANS activity at rest or during a cognitive task between children, adolescents and adults with ADHD and typical individuals. The review aimed to answer the following questions: 1) Is there evidence of atypical ANS function in ADHD? 2) If so, does this take the form of hypo-arousal or hyper-arousal? 3) And is it only in the resting state (indicating deficient tonic, baseline arousal) or is it also evident in response to **a** cognitive and emotional stimulus of some sort (indicating deficient regulation of phasic arousal)?

We performed searches of PsycInfo, MEDLINE and EMBASE databases from 1975 to 18th December 2018 using keywords in the fields of ADHD, attention, autonomic nervous system, arousal and arousal regulation (see Fig. 2 for a PRISMA flowchart of the articles screened, from Moher et al., 2009). These terms were supplemented with words that describe the key measures used to assess ANS function, including pupil dilation, heart rate, heart rate variability and electrodermal activity/ galvanic skin response. Meta-analysis was not performed as there were too few similarities between study methods and measures. The full search strategy, including details of inclusion/exclusion criteria, are available in supplementary materials (SM1). Full-text articles were obtained for all those retained and were again reviewed against inclusion/exclusion criteria, before extracting data on key features of each included article. A discussion was held between reviewers involved in the screening process to reach a decision for any articles that were unclear. Finally, papers were broadly grouped into those presenting evidence of hyperarousal or hypoarousal in the patient group compared with a control group, or no group differences.

3. Results

Fifty-five studies were included after full-text review (see Fig. 2). A summary of the ANS measures used (including their abbreviations and acronyms), alongside a description of each measure and their relationship with ANS functioning, can be found in Table 1. Thirty-two studies reported data from electro-dermal activity (EDA) measures, either as the sole measure (n = 19) or in combination with others (n = 13); 35 reported data from heart rate (HR) (22: HR only; 13: HR alongside other measures); 4 studies reported measures of pupil dilation and only one of these measured pupil dilation in combination with other measures. In total, there were 91 findings (i.e. measurements of group effects) from these 55 studies.

3.1. Resting state

Resting-state refers to a defined period of time when participants

Identification

Records identified through database searching (n = 1400)

Additional records identified through other sources (n = 3)

Screening

Records screened (n = 1403)

Records excluded (n = 1283)

Eligibility

Full-text articles assessed for eligibility (n = 120)

Full-text excluded and reasons (n = 65)
-Absence of control group, or presence of psychiatric control group only (9)
-Conference abstract (4)
-Focus on sample different from ADHD (10)
-Focus on EEG only or other measures (not autonomic) (12)
-Focus on metabolites only (6)
-Main focus on sleep (2)
-Medication trial to assess cardiovascular health (10)
-Notice of retraction or correction (2)
-Review (6)
-Sample size < 10 (1)
-Focused on sensory challenge (3)

Included

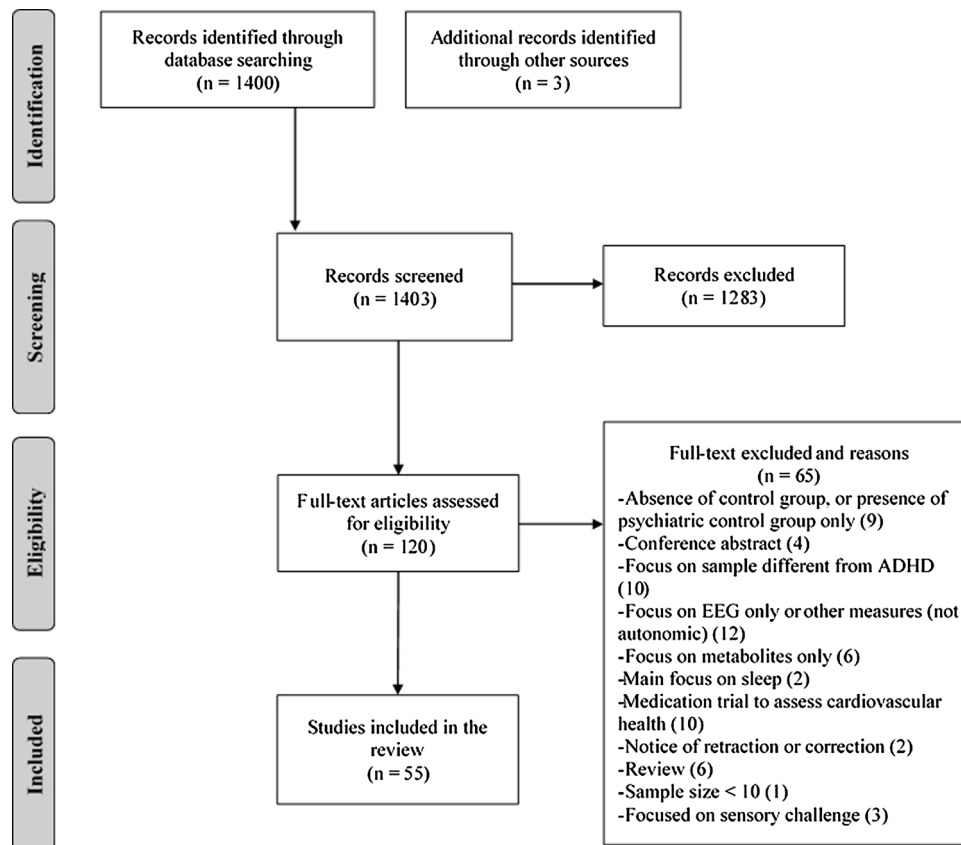Studies included in the review (n = 55)

Fig. 2. PRISMA flowchart describing the numbers of studies identified, screened, excluded and included in the systematic review process.

are not performing any task or activity. Atypical modulation of resting-state activity has been found in individuals with ADHD, who show increased power in slow- relative to fast-oscillations in EEG (Barry et al., 2003) and atypical activation of resting-state networks, such as the Default-Mode Network (DMN) (Rubia, 2018). It is not clear, however, whether these atypicalities are accompanied by ANS dysfunction.

3.1.1. Electrodermal activity (EDA)

Reduced EDA has been reported by nine studies (out of 16) during resting-state periods (Table 2) in children/adolescents (Barry et al., 2009, 2012; Beauchaine et al., 2001; Clarke et al., 2013; Crowell et al., 2006; Dupuy et al., 2014; Herpertz et al., 2001; Lazzaro et al., 1999) and adults with ADHD (Hermens et al., 2004), while two reported hyper-arousal (Hermens et al., 2005a; Mukhopadhyay et al., 1997).

Barry et al. (2009; 2012) found signs of hypo-arousal during resting in ADHD, reflected in reduced mean skin conductance level (SCL; see Table 1 for a description of EDA measures and abbreviations), similarly to Clarke et al. (2013); Dupuy et al. (2014); Hermens et al. (2004) and Lazzaro et al. (1999). Using non-specific skin conductance responses (NS-SCRs), Beauchaine et al. (2001) and Lazzaro et al. (1999) found signs of hypo-arousal in children and adolescents with ADHD (reduced NS-SCRs), as did Crowell et al. (2006). However, in this last study, it was not possible to determine whether these effects were driven by symptoms of ADHD or symptoms of oppositional defiant disorder (ODD). Herpertz et al. (2001), instead, found reduced NS-SCRs in children with ADHD and conduct disorder (CD), compared to controls, but no significant difference between ADHD and controls, and they did not replicate these results on a larger sample (Herpertz et al., 2003)

Among the studies reporting hyper-arousal, the method of measuring skin conductance was not described in detail by Mukhopadhyay et al. (1997), while Hermens et al. (2005a) found signs of hyper-arousal in female adolescents with ADHD, using the difference of SCL from the beginning of the resting period (instead of mean SCL) as a measure of

autonomic arousal. It is therefore possible that these finding of hyper-arousal reflect the way EDA measures were collected or analysed. Among the five studies which reported no significant group differences, Herpertz et al. (2003); Iaboni et al. (1997); McQuade and Breaux (2017), and McQuade et al. (2017) found no group effect when analysing mean SCL, while Hermens et al. (2005b) did not find any difference when calculating the slope of SCL throughout the entire resting period.

3.1.2. Heart rate

Of the twenty studies that analysed heart rate (HR) during resting (Table 3), the majority (n = 12) found no group differences on this measure, while six reported hypo-arousal in ADHD (Beauchaine et al., 2001; Crowell et al., 2006; de Carvalho et al., 2014; Griffiths et al., 2017; Herpertz et al., 2003; Wang et al., 2013) and two reported evidence of hyper-arousal (Leikauf et al., 2017; Rukmani et al., 2016).

Some studies suggested that hypo-arousal at rest, in ADHD, may be mainly associated with increased activation of the PNS. For example, Wang et al. (2013) found that typically-developing male pre-schoolers with more inattentive/hyperactive traits showed lower sympathetic and higher parasympathetic activity, by analysing Heart Rate Variability (HRV) frequency measures. Similarly, de Carvalho et al. (2014) found signs of hyper-activation of the PNS branch in ADHD (i.e., increased NN50 and increased Poincarre T/L, see Table 1 for a description of these measures). Other studies, instead, argued that hypo-arousal at rest, in ADHD, may be due to reduced activation of the SNS. For example, Crowell et al. (2006) found that pre-schoolers with ADHD showed increased baseline pre-ejection period (PEP) length, and the same interpretation was proposed by Beauchaine et al. (2001), who found signs of reduced SNS activity in boys with ADHD and co-morbid CD, (i.e., increased PEP length and reduced high-frequency respiratory sinus arrhythmia power; HF-RSA). However, the absence of a significant difference between ADHD without CD and controls, indicates

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	Significance & methodology	Parameters	ANS indicator	Number of reviewed studies using the measure
EDA	Skin Conductance Level	SCL	An electrical potential is applied to two electrodes, placed next to each other on the hand palms. The electrical current, flowing between the electrodes, is measured as an index of skin conductance. SCL is a tonic measure of skin conductance and detects slow changes over time.	Mean SCL, Change (slope) of SCL over time	Higher SCL: increased sympathetic arousal	14 studies (resting) 7 studies (task)
	Non-specific Skin Conductance Response/Fluctuation	ns-SCR ns-SCF	Methodology is the same as for SCL. Ns-SCRs are spontaneous changes (difference in SC from a baseline level) in skin conductance, which are not linked to any task-related event or stimulus. They can be measured during baseline, resting or task.	Number of ns-SCR/Fs Mean ns-SCR/Fs	Higher ns-SCR/Fs: increased phasic arousal or responsivity, but not specific to task-related stimuli or events	7 studies (resting) 1 study (task)
	Skin Conductance Response	SCR	Methodology is the same as for SCL and ns-SCRs. Similarly to ns-SCRs, SCRs are phasic changes (measured as a difference in SC compared to a baseline) but they are measured in response to a specific event or stimulus	Mean SCRs	Higher SCRs: increased phasic arousal or responsivity to specific events or stimuli	14 studies (task)
Heart rate	Heart rate	HR	Measured on electrocardiogram (ECG), it is calculated as the average number of beats per minute (BPM). Inter-beat interval (IBI) around a specific task stimulus represents a phasic change in heart rate (acceleration or deceleration)	Mean HR or IBI	Higher HR: hyper-arousal Increased stimulus-locked IBI: deceleration Reduced stimulus-locked IBI: acceleration	7 studies (resting) 19 studies (task)
	Standard deviation of normal-to-normal intervals (Heart Rate Variability; HRV)	SDNN or R-R-interval-SD	Measured by calculating the average change in the duration of the interval (in msec) between consecutive heart-beats (R-R intervals) and deriving the standard deviation of the N-N (or R-R) intervals over a time section of the ECG.	SDNN	Higher SDNN: increased HRV: increased PNS functioning: hypo-arousal	2 studies (resting) 4 studies (task)
	Root Mean Square of Successive Differences (HRV)	RMSSD	A measure of HRV which is measured as the average root square of the interval between successive peaks in ECG. Compared to SDNN, it is considered more reliable in measuring HRV.	RMSSD	Higher RMSSD: increased HRV: higher PNS functioning: hypo-arousal	5 studies (resting) 3 studies (task)
	Normal-to-normal intervals > 50 ms (% of)	NN50 (pNN50)	Measured on ECG as the number of pairs of successive IBI intervals which are different by 50 msec or more. pNN50 is the proportion of NN50, in relation to the entire number of RR intervals.	Number of NN50	Higher number of NN50 (or higher pNN50): increased HRV: higher PNS functioning: hypo-arousal	2 studies (resting)
	Pre-ejection period	PEP	Measured as the interval between the electrical depolarization of the left ventricle and the beginning of blood pumping from the same location. It reflects the time needed for the left ventricle to contract and pump blood, after the cardiac valves have closed. It is mainly influenced by activation of the SNS (it reduces when SNS activates).	PEP length	Increased PEP length: reduced SNS functioning: hypo-arousal	7 studies (resting) 8 studies (task)
	Respiratory sinus arrhythmia	RSA	Represents the association between cardiac functioning and respiratory mechanisms. It is measured as the variability of heart rate associated with breathing, with heart rate accelerating during inspiration and decelerating during expiration. Although it is likely to affect PEP, RSA is more related to PNS, being an index of cardiac vagal tone.	RSA	Increased RSA: increased PNS functioning: hypo-arousal	10 studies (resting) 10 studies (task)
	Low frequency power	LF	As a frequency domain measure, it represents the amount of spectral power between 0.04 - 0.15 Hz on the Fast Fourier Transform (FFT) spectrum of HRV. It is indicative of the baroreflex which is a modulation (acceleration or deceleration) of HR in situations when blood pressure (BP) is too low or high (respectively), with the aim of changing BP levels through modulating HR.	LF power	Increased LF power: increased baroreflex effect: increased HRV	5 studies (resting) 4 studies (task)
	High frequency power	HF	Similarly to LF, it is a frequency domain measure of HRV which analyses activity in the 0.15–0.40 Hz range. It has been linked to	HF power	Increased HF power: increased PNS functioning: hypo-arousal	5 studies (resting) 2 studies (task)

Table 1 (*continued*)

Domain	Measure	Acronym	Significance & methodology	Parameters	ANS indicator	Number of reviewed studies using the measure
	Low/high frequency power	LF/HF	cardiac-vagal activity, representing parasympathetic modulation of arousal. It is the ratio between spectral power in the low and high Frequency range (see above for specific ranges in Hz). It has been used as an index of the balance between SNS and PNS functioning (sympathovagal balance).	LF/HR ratio	Increased LF/HF ratio: sympathetic dominance / Reduced LF/HF ratio: parasympathetic dominance (however a strong debate is going on in literature, regarding the association between LF/HF ratio and ANS)	5 studies (resting) / 2 studies (task)
PUPILLOMETRY	Pupil diameter		Pupil size or diameter is measured using eye-tracking or optometrist tools, carefully considering for any confounding effects, including changes in environmental luminance or body movements. Pupil constrictions are generally associated with increase of brightness and processing of visual information situated at a close distance (due to narrowing of visual attentional focus).	Mean pupil size (tonic) / Stimulus-or event-locked changes in pupil size (phasic)	Increased tonic pupil size: increased allocation of mental resources to the external environment / Phasic pupil size dilations: increased arousal, spontaneous or in response to a stimulus	1 studies (resting) / 2 studies (task)

that these findings may be specifically related to the co-occurring presence of ADHD and CD. In support of this idea, Herpertz et al. (2003) found signs of hypo-arousal, measured through mean heart rate, in both CD and ADHD + CD, but not in ADHD-only, and also Griffiths et al. (2017) found signs of imbalance between SNS and PNS functioning at rest (i.e., increased low-frequency/high-frequency ratio; LF/HF) in ADHD (particularly in males), but this was mainly predicted by oppositional problems and not ADHD per se. This suggests that HR measures of ANS functioning may be specifically affected by the presence of co-morbid symptoms, such as conduct and oppositional behaviours, rather than inattention or hyperactivity. However, since some studies (e.g., Herpertz et al., 2001) did not find any difference between ADHD, ADHD + CD and controls, further research is needed to establish how the presence of comorbid CD/ODD affect HR measures in ADHD, at rest.

Among the studies reporting hyper-arousal, Rukmani et al. (2016) found evidence of atypical SNS-PNS balance in ADHD, by analysing measures of HRV, but only 10 children were included in each of the clinical and control groups, undermining the generalisability of the findings. Signs of hyperarousal were found by Shibagaki and Furuya (1997), who found that more children and adolescents with ADHD, than controls, showed reduced RSA, and concluded that hyper-arousal could be caused by reduced vagal tone. Leikauf et al. (2017) compared cognitively defined biotypes of ADHD described as 'impulsive-cognition' and 'inattentive-cognition' on HR and EDA measures. Overall, they found increased mean HR in in the 'impulsive-cognition' group, compared to controls, while there was no difference between the 'inattentive-cognition' group and typically developing controls. This result suggests that specific traits of ADHD, e.g., impulsivity, may be associated with different profiles of autonomic functioning at rest.

Many studies reporting no group differences between ADHD and typical controls measured mean HR, suggesting that calculating mean HR over a certain period of time may not be sensitive enough to detect signs of arousal dysregulation in ADHD. Although none of the studies on adults found group differences on HR measures (Lackschewitz et al., 2008; Oliver et al., 2012), further research is needed, given the paucity of research assessing adults.

3.1.3. Pupillometry

A clear picture of ANS functioning at rest, derived through pupillometry, did not emerge from this review, since the only study that focused on this ANS measure (Kara et al., 2013) did not find any group differences between controls and ADHD, or between ADHD and ADHD + ODD (Table 4).

3.1.4. Summary of resting state findings

Of 31 studies investigating autonomic arousal at rest, 12 showed signs of hypo-arousal, four of hyper-arousal and a large number of studies (15) did not report any significant group differences. Further research using all these measures of autonomic arousal in parallel is needed to understand the heterogeneous findings. Methodological choices, e.g., in the design of the resting-state period as a proper period of resting or as a short break between cognitive tasks, and the nature of the sample, e.g., including children with comorbid symptoms, may also be at the basis of non-significant or heterogeneous findings, which will be further discussed in paragraph 4.5.

3.2. Cognitive, reinforcement or socio-emotional tasks

Temporary changes in autonomic measures of ANS functioning in response to a particular stimulus reflect phasic modulation of the ANS and may be measured to identify the presence of atypicalities in ANS regulation. Phasic stimulus-locked autonomic responses, reviewed in this section, were measured using EDA, HR and pupillometry and during paradigms with different designs, such as cognitive tasks (e.g., attention, inhibitory control, working memory, alternative forced-choice, and sustained attention), paradigms manipulating rewards or

Table 2
Summary of results from studies measuring electrodermal activity during resting-state.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/ hyper/none
Barry et al., 2009	30	30	Children and adolescents	Resting state 5 min.	Mean SCL	ADHD < CTRL	Hypo (males only)
Barry et al., 2012[c]	18	18	Children and adolescents	Resting state 3 mins	Mean SCL	ADHD < CTRL	Hypo
Beauchaine et al., 2001[b,d]	17	22 typical; 20 CD	Adolescents	Baseline 5 min., before task start	ns-SCRs	ADHD < CTRL	Hypo (males only)
Clarke et al., 2013	104	67	Children and adolescents	Resting state 10.5 min.	Mean SCL	ADHD, defined as either excess EEG theta power OR excess beta EEG power, < CTRL	Hypo (males only)
Crowell et al., 2006[b]	18	20	Pre-school children	Resting state 5 min.	Ns-SCRs	ADHD and ODD < CTRL	Hypo
Dupuy et al., 2014	40	40	Children and adolescents	Resting state 5 min.	Mean SCL	ADHD < CTRL	Hypo (females only)
Hermens et al., 2004	35	35	Adults	Resting state 2 min.	Mean SCL	ADHD < CTRL	Hypo (females only)
Hermens et al., 2005a	70	70	Adolescents	Resting state 2 min.	Slope of SCL (rate of change), ns-SCRs	ADHD < CTRLs on rate of change in SCL	Hyper (females only)
Hermens et al., 2005b[c]	34	34	Adolescents	Resting state 3 mins	Slope of SCL (rate of change), ns-SCRs	No group differences when ADHD off-medication	None
Herpertz et al., 2001[a]	47 (26 ADHD + CD)	21	Children and adolescents	Resting state 3 mins	Mean SCL, ns-SCRs	No group differences on mean SCL. ADHD + CD < CTRl on ns-SCRs	Hypo (males only, ADHD + CD only)
Herpertz et al., 2003[a]	28 ADHD, 20 CD, 50 ADHD + CD	29	Children and adolescents	Resting state 3 mins	Mean SCL, ns-SCRs	No significant differences between groups on SCL or ns-SCRs	None (males only)
Iaboni et al., 1997[b]	18	18	Children and adolescents	Resting state 5 min.	Mean SCL	No difference between groups on mean SCL	None (males only)
Lazzaro et al., 1999	54	54	Children and adolescents	Resting state 2 min.	Mean SCL, ns-SCRs	ADHD < CTRL	Hypo
McQuade and Breaux, 2017[a,d]	23 ADHD, 7 subthreshold ADHD	31	Children and adolescents	Resting 3 mins	Mean SCL	No significant differences	None
McQuade et al., 2017[a,d]	23 ADHD, 7 subthreshold ADHD	31	Children and adolescents	Resting 3 mins	Mean SCL	No significant differences	None
Mukhopadhyay et al., 1997	10	10	Children and adolescents	Unclear	SCL fluctuations	ADHD > CTRL	Hyper
						COUNT (Hypo:hyper:none)	9:2:5

[a] Resting state measured before, during or after a cognitive task (see Tables 5–7 for cognitive task findings).
[b] Resting state measured before, during or after a reward/reinforcement task (see Tables 8 and 9 for reward/reinforcement task findings).
[c] Measured effects of an intervention (see Table 11 for results of intervention).
[d] Resting state measured before, during or after a socio-emotional task (see Table 10 for socio-emotional task findings).

Table 3
Summary of results from studies measuring heart rate during resting-state.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Beauchaine et al., 2001[b]	17 ADHD + 20 ADHD + CD	22	Adolescents	Resting state 5 minutes pre-task and 2.5 minutes between task blocks/tasks	PEP, RSA	ADHD + CD > ADHD & CTRL on PEP length. ADHD + CD < CTRL on HF RSA power	Hypo (males only, some effects only for ADHD + CD)
Crowell et al., 2006[a]	18 ADHD + ODD	20	Pre-schoolers	Resting 5 min.	PEP, RSA	ADHD + ODD > TD on baseline PEP length ADHD + ODD = TD on baseline RSA	Hypo
De Carvalho et al., 2014	28	28	Children	Resting state 20 mins	Frequency (LF, HF, LF/HF), RMSSD, NN50, pNN50	ADHD = TD on HF, LF and LF/HF ratio. ADHD > TD on NN50 ADHD > TD on Poincarre T/L	Hypo
Griffiths et al., 2017[a]	229	244	Children and adolescents	Resting state 2 min.	RMSSD, HF, LF, LF/HF	ADHD = CTRL on heart rate. ADHD > CTRl on LF/HF ratio Correlations with comorbid symptoms	Hypo (males only)
Herpertz et al., 2001[a]	21 ADHD, 26 ADHD + CD	21	Children and adolescents	Resting state 3 mins	Mean heart rate	ADHD + CD = ADHD = TD on resting mean HR	None (males only)
Herpertz et al., 2003[a]	28 ADHD, 20 CD, 50 ADHD + CD	29	Children and adolescents	Resting state 3 mins	Mean heart rate	ADHD + CD, CD < CTRl mean heart rate. No difference between ADHD and CTRL	Hypo (males only, effects in ADHD + CD and CD only)
Iaboni et al., 1997[b]	18	18	Children and adolescents	Resting state 5 min.	Mean heart rate	No group differences	None (males only)
Jennings et al., 1997[a]	40	26	Children and adolescents	Resting state (2 min.)	Mean heart rate (inter-beat interval)	Non-significantly faster heart rate in ADHD than CTRL	None (males only)
Lackschewitz et al., 2008[d]	18	18	Adults	Resting state 15 minutes	SDNN, RMSSD, Power Spectral Density, LF, HF, LF/HF	No group differences	None
Leikauf et al., 2017[a,c]	112	56	Children and adolescents	Resting state 2 min.	Heart rate, RMSSD	Two ADHD biotypes defined by cognitive profile. 'Impulsive cognition' biotype showed faster mean HR. 'Inattentive cognition' biotype showed no difference in HR. No effects for RMSSD	Hyper (specific to one bio-type)
McQuade and Breaux, 2017[a,d]	23 ADHD, 7 subthreshold ADHD	31	Children and adolescents	Resting 3 mins	RSA, RDA reactivity (RSA-R: difference between baseline RDA and task RSA)	No group differences	None
Musser et al., 2011[d]	32	32	Children	Resting state 2 min.	PEP, RSA	No group differences	None
Musser et al., 2013[d]	21 ADHD low social function; 54 ADHD high-social function	75	Children and adolescents	Resting state (length not reported)	PEP, RSA	No group difference	None
Musser et al., 2018[d,e]	42	44	Children and adolescents	Resting state (length not reported)	PEP, RSA	No group difference	None
Oliver et al., 2012	N/A	22 low-ADHD-traits; 20 high-ADHD traits	Adults	Driving simulation task	Heart period, RSA, PEP	No group differences	None
Rukmani et al., 2016	10	10	Children and adolescents	Resting state 15 min.	Heart rate, Mean & SD of NN intervals, RMSSD, NN50 (n, %), LF, HF, LF/HF	ADHD < CTRl on RMSSD, pNN50, SDNN, HF. ADHD > CTRl on LF/HF ratio	Hyper
Shibagaki and Furuya, 1997	18	49	Children and adolescents	Resting state 3 mins	RSA	More ADHD children than controls showed decreasing or no rhythmicity, derived from RSA. No group differences on RSA.	None
Tenenbaum et al., 2018[b]	69	48	Children and adolescents	Resting state 2 min.	PEP, Mean RSA	No group differences	None
Wang et al., 2013	Cohort of 88 (ADHD traits measured)		Pre-schoolers	Baseline	Power spectrum analysis of HRV	Male pre-schoolers with more inattentive/hyperactive traits showed lower sympathetic and higher parasympathetic activity	Hypo (high non-clinical traits, males only)

Table 3 (*continued*)

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Ward et al., 2015[a]	116	127	Children and adolescents	Resting state 2 min.	RSA	No group differences	None
						COUNT Hypo:hyper:none	6:2:12

[a] Resting state measured before, during or after a cognitive task (see Tables 5–7 for cognitive task findings).
[b] Resting state measured before, during or after a reward/reinforcement task (see Tables 8 and 9 for reward/reinforcement task findings).
[c] Measured effects of an intervention (see Table 11 for results of intervention).
[d] Resting state measured before, during or after a socio-emotional task (see Table 10 for socio-emotional task findings).
[e] An erratum for this paper (Musser et al., 2018) reported the same results found in the original.

reinforcement (e.g., reward versus penalty, reinforcement versus no or neutral feedback) and socio-emotional paradigms (social cognition and emotion recognition or processing). We begin by reviewing studies that measured ANS during cognitive tasks.

3.2.1. Cognitive tasks

3.2.1.1. EDA. Of 12 studies recording EDA during cognitive tasks, seven reported evidence of ANS hypo-activation in ADHD, one of hyper-activation and four of no group differences (Table 5).

Of the studies reporting hypo-activation of the ANS, three used either passive and/or active auditory attention tasks (Herpertz et al., 2001, 2003; Shibagaki et al., 1993). Shibagaki and Furuya (1997) further demonstrated that, in the passive task, the difference between ADHD and controls was greatest at the beginning of the tasks, indicating difficulties in adapting to a novel experimental situation. The studies of Herpertz et al. (2001; 2003), described in paragraphs 3.1.1 and 3.1.2, similarly found reduced skin conductance responses (SCRs) and delayed habituation of SCRs to auditory tones during a passive attention task, but this effect was only significant when comparing children with ADHD + CD to typical controls (no differences were found between controls and children with ADHD-only). Since the other studies did not measure the influence of CD, it is not clear whether those effects were mainly driven by co-occurring CD as well.

Two other studies reported hypo-activation of the ANS during sustained attention tasks (Lawrence et al., 2005; O'Connell et al., 2004). Lawrence et al. (2005) found reduced mean SCL in children and adolescents with ADHD during an adapted version of the Continuous Performance Task (CPT), suggesting reduced activation of the ANS, while O'Connell et al. (2004) found atypical phasic modulation of skin conductance in ADHD children and adolescents during a different form of CPT, the Sustained Attention to Response Test (SART). Specifically, while in control children SCRs following commission errors were increased relative to correctly withheld trials, this difference was not significant in ADHD, suggesting a lack of ANS responsivity to errors in ADHD. Considering firstly, the role of the ACC in error processing (Brown and Alexander, 2017; Sellaro et al., 2015), secondly, evidence of atypical function of brain systems that support error processing in ADHD (Johnstone et al., 2013) and thirdly, the links between ACC and ANS (Critchley and Garfinkel, 2018), the evidence reviewed here suggests that ANS dysfunction may contribute to abnormal error processing in ADHD.

One other study reported evidence of reduced EDA in ADHD (Johnstone et al., 2010) using a hybrid flanker go/no-go task designed to challenge response conflict processing and inhibitory control. In addition, these authors manipulated the effort required to pay attention to the stimulus stream by degrading the central target stimulus by either 0 %, 30 % or 60 %. Children and adolescents with ADHD showed significantly reduced mean SCL compared with matched typical controls in the non-degraded condition of the task but equivalent SCL in the 60 % degraded condition, suggesting hypo-activation of the ANS in the easier condition but typical arousal levels in the most difficult condition. James et al. (2016) found significantly reduced SCL in the baseline condition of a 4-choice RT task in the ADHD group compared with controls. In a faster paced condition with incentives for correct responses, no significant group differences were reported and the ADHD group showed a steeper increase in SCL from the baseline to the fast-incentive condition than the control group. A further analysis of this effect can be found in the next paragraph, where the impact of reward on cognitive performance is discussed. Together, these findings suggest that ADHD children may perform better in conditions with a faster event rate or that are perceptually more demanding, compared with slower, more monotonous tasks with very few cognitive or perceptual challenges.

Contrary to these findings, one study (Satterfield et al., 1984) reported increased SCL in children with a diagnosis of Hyperactivity (DSM-III diagnosis of Attention Deficit with Hyperactivity; ADD/H)

Table 4
Summary of results from studies measuring pupil size measures during resting-state.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Kara et al., 2013	32	24	Children	Resting-state	Pupil diameter	ADHD = CTRL COUNT (hypo:hyper:none)	None 0:0:1

passively attending to clicks delivered at either a slow or fast rate bi-naurally, which would suggest increased ANS activation, while other studies reported no group differences in EDA recorded during a cognitive task. Mayer et al. (2016), for example, used the Contingent Negative Variation (CNV) to assess response preparation during an auditory go/no-go task in adults with ADHD. Although increased reaction-times variability (RTV) and reduced CNV amplitude were found in ADHD, the groups did not differ on mean SCL or SCRs to the cue-go stimulus interval. Moreover, Dykman et al. (1982) found no group differences in mean SCL in the inter-trial interval of a stimulus-response mapping task, in which children with a diagnosis of ADHD-Hyperactive Subtype (DSM-III) with or without Reading Disorder, were required to learn a stimulus-response (S-R) mapping to a criterion level of performance, at which point the S-R mapping switched. Further studies (McQuade et al., 2017; McQuade and Breaux, 2017) did not find any association between ADHD symptoms and SCL collected during a battery of executive function, cognitive and socio-emotional tasks in children and adolescents with different levels of ADHD traits, but found a significant positive association between SCL and internalising symptoms.

In summary, the majority of studies measuring EDA during a cognitive task have found significantly reduced EDA (either mean SCL or target-locked SCR) in children and adolescents with ADHD, reflecting hypo-activation of the ANS, although four studies reported no group difference and one reported evidence of hyper-activation. The studies differ in task design and sample composition; factors that will be discussed further in paragraph 4.5.

3.2.1.2. Heart rate. Twelve studies analysed autonomic functioning during cognitive tasks in ADHD by collecting cardiac measures (Table 6). Among these, seven found signs of hypo-activation of the ANS and five found no group differences between ADHD and typical controls (none of the included studies reported hyper-activation).

In a test of the state regulation hypothesis which suggests that ADHD children are less able to increase effort allocation during cognitively boring or sustained tasks, Borger and van der Meere (2000) measured changes in heart rate (inter-beat interval; IBI) prior to and following the presentation of go and no-go stimuli. The authors found significantly reduced pre-stimulus HR decelerations in the ADHD group in the slow but not in the fast event rate condition, and a delay in the onset of HR acceleration in the slow condition, suggesting a lack of ANS regulation related to reduced motor preparation in the slow condition. In addition, power in the.10 Hz IBI frequency range was greater in ADHD than controls, in the slow condition, indicating less effort allocation during this less challenging task condition. There were no group differences in HR on no-go trials. Similarly, Jennings et al. (1997) measured HR IBIs with respect to a go-stimulus in a stop signal task and found slower go RT and increased standard deviation of RTs (RTs-SD) in the ADHD group. Furthermore, although control children showed longer IBIs (i.e., heart rate deceleration) preceding successful than failed inhibitions, suggesting greater autonomic control on trials when the response was successfully withheld, ADHD children did not show this effect. Overall, both studies assessing response inhibition found signs of hypo-arousal in ADHD, but the atypical features in ADHD were more closely related to response preparation and regulation, rather than response inhibition.

Signs of ANS hypo-activation have been reported in ADHD by studies investigating sustained attention using variants of a CPT. Children

and adolescents with ADHD showed a profile of greater RT and RTV (but not errors) compared with controls, as well as greater power in the.10 Hz heart rate frequency and poorer on-task behaviour (1999), suggesting less effort allocation and weaker ANS regulation. Using a similar paradigm, Griffiths et al. (2017) found greater LF/HF ratio during rest and task in ADHD children that, similarly to Borger et al. (1999), predicted worse task performance. The studies presented so far seem to converge on a profile of hypo-activation of the ANS in ADHD during cognitive tasks that require response control and sustained attention. However, one study (Shibagaki and Furuya, 1997) used passive and active auditory listening tasks and reported no group differences in HR during the tasks, although the ADHD group showed reduced RSA variability during a resting state condition. The analytic approach used in this paper relied upon calculating the frequency of RSA sub-types within the ADHD and control samples; the methodological approach is therefore not comparable to other studies in this review that have measured HR in relation to attention.

The only study investigating error monitoring found signs of hypo-activation of the ANS in ADHD during a task that required participants to report the global or local shape in a global/local array, interpreted as reduced sensitivity to error processing (Groen et al., 2009). Also, all groups (controls, ADHD-unmedicated and ADHD-medicated) were more accurate and gave slower responses in the feedback blocks compared with no feedback, and show similar post-error slowing, while stimulus-locked HR decelerations were greater on error trials than correct trials in controls and medicated-ADHD, but not in unmedicated ADHD. Broadly, these findings indicate reduced autonomic reactions to errors in ADHD children when unmedicated, supporting evidence presented in paragraph 3.2.1.1 and suggesting that the links between ACC and ANS may be atypical in ADHD, undermining error processing.

In another study (Leikauf et al., 2017), the authors used a battery of cognitive tasks, including Go/no-go, CPT, attention switching task, maze task, verbal memory recall task, attention inference task, motor tapping task, digit span and choice RT task, and identified two cognitive subtypes of ADHD, namely "impulsive" and "inattentive", based on their performance to the tasks. A significant difference on HR measures was found only for the impulsive-cognition subtype at rest (see paragraph 3.1.2). In contrast, the inattentive-subtype had longer/more variable RTs and omission errors and lower EEG beta power, but HR did not differ from controls. These results suggest the importance of considering subtypes within the ADHD diagnostic category, which may better explain the heterogeneity of results about arousal regulation deficits in ADHD.

Five studies (Dykman et al., 1982; Keage et al., 2006; McQuade and Breaux, 2017; Perrin et al., 2014; Ward et al., 2015) used one or more tasks assessing executive functions. Two studies reported some evidence of ANS dysfunction in ADHD. Dykman et al. (1982) measured HR in hyperactive children (with or without reading disabilities) and typically developing controls during a rewarded stimulus-response learning task. The hyperactive children showed reduced HR acceleration on trials that were less likely to lead to reward which the authors interpreted as reduced effort allocation when rewards are improbable. Ward et al. (2015) measured short term memory and found that children with higher ADHD symptoms showed worse task performance and reduced RSA withdrawal from baseline/rest to the task, which is a sign of reduced functioning of the PNS when switching from a less- to a more-attentional demanding situations. However, a positive association between good task performance and ADHD symptom scores was also

Table 5
Summary of results from studies measuring electrodermal activity during cognitive tasks.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Dykman et al., 1982	10 Hyperactive, 10 Reading Disabled, 10 Hyp + RD	10	Children and adolescents	S-R contingency task	Mean SCL 30 seconds pre and post-test and during intertrial interval	No differences between groups	None
Herpertz et al., 2001[a]	21 ADHD, 26 ADHD + CD	21	Children and adolescents	Auditory attention task (passive) and startle stimulus task	SCR to stimuli; Habituation (reduction in SCR) to stimuli	No differences between ADHD and typically developing controls. Differences were specific to ADHD + CD	Hypo (only in ADHD + CD)
Herpertz et al., 2003[a]	28 ADHD, 20 CD, 50 ADHD + CD	19	Children and adolescents	Auditory attention task (passive) and startle stimulus task	SCR to stimuli; Habituation (reduction in SCR) to stimuli	No differences between ADHD and typically developing controls. Differences were specific to ADHD + CD and CD	Hypo (only in ADHD + CD and CD)
James et al., 2016	73 + 75 siblings	72 + 72 siblings	Adolescents and young adults	4-choice RT Fast Task	SCL and SCRs	ADHD < CTRL on SCL during the slow-event rate block with no incentives, and not during fast-event rate with incentive). ADHD = TD on SCRs	Hypo
Johnstone et al., 2010	20	20	Adolescents	Flanker task with 3 levels of degradation of the central stimulus	Mean SCL	ADHD < TD on SCL (only in the non-degraded condition)	Hypo
Lawrence et al., 2005[b]	18	18	Children and adolescents	CPT-AX	Mean SCL, stimulus-locked SCR	ADHD < controls on SCL during first session (difference reduced with medication), > controls during second session. ADHD < controls on SCR (only in test phase 2)	Hypo
Mayer et al., 2016	23	22	Adults	Auditory cued go/no-go (eyes closed)	SCL	No differences between groups	None
McQuade and Breaux, 2017[a]	23 ADHD, 7 subthreshold ADHD	31	Children and adolescents	CANTAB, impossible puzzles	Mean SCL	SCL during the tasks was associated with internalising symptoms, but not ADHD symptoms.	None
McQuade et al., 2017[a]	23 ADHD, 7 subthreshold ADHD	31	Children and adolescents	CANTAB, impossible puzzles	Mean SCL	SCL during the tasks was associated with internalising symptoms, but not ADHD symptoms.	None
O'Connell et al., 2004	15	15	Children and adolescents	Sustained Attention to Response Task	SCR and SCL	No difference in SCR to commission errors and withholds in ADHD (difference was present in controls). ADHD < controls on SCR to commission errors	Hypo
Satterfield et al., 1984	138	60	Children and adolescents	Passive attention: clicks delivered binaurally while watching a video.	Mean SCL	Hyperactive > TD on SCL	Hyper
Shibagaki et al., 1993	18	49	Adolescents	Passive and active listening task	Mean SCR	ADHD < controls on SCR, especially during the first trials of the passive listening task, and on the entire active listening tasks	Hypo
						COUNT (Hypo:hyper:none)	7:1:4

a Resting-state measures obtained before, during or after the cognitive task (see Tables 2–4 for resting state findings).
b Measured effects of an intervention (see Table 11 for results of intervention).

Table 6
Summary of results from studies measuring heart rate during cognitive tasks.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Borger et al., 1999	21	16	Children and adolescents	Sustained attention task	Mean HR, Mean power in the.010 Hz component	No differences between groups on mean HR. ADHD > CTRl on 0.10 Hz component (ADHD: reduced effort allocation)	Hypo (males only)
Borger and van der Meere, 2000	27	22	Children and adolescents	Go/no-go task (response inhibition)	Mean IBI around go and no-go stimuli; Mean power in the.10 Hz component	No difference between groups on mean IBI. ADHD < CTRl on HR deceleration (in the slow condition, not in the fast). ADHD > CTRl on delay in IBI acceleration after go stimulus presentation, in the slow condition. ADHD = CTRl on HR deceleration after No-Go stimuli, when compared to Go. ADHD > CTRl on.10 Hz component (slow condition), indicating less effort allocation	Hypo (males only)
Dykman et al., 1982	10 Hyperactive, 10 Reading Disabled, 10 Hyp + RD	10	Children and adolescents	S-R task (executive functions, set shifting)	HR rate, inter-trial interval changes in HR	No differences between groups on HR. Hyperactive and RD > CTRl on inter-trial interval changes in HR (reduced effort allocation in the clinical groups)	Hypo
Griffiths et al., 2017[a]	229	224	Children and adolescents	CPT-IP (sustained attention)	RMSSD, HF, LF, LF/HF	ADHD > TD on LF/HF during the task (lower LF/HF during task predicted better performance). No differences between groups in RMSSD, HF or LF	Hypo
Groen et al., 2009	16 + 16	18	Children and adolescents	Global/local task (error processing)	Stimulus-locked IBI	Unlike TD and ADHD-with-MPH, ADHD-unmedicated did not show increased HR deceleration/acceleration effect on error trials, compared to correct trials	Hypo
Jennings et al., 1997[a]	40	26	Children and adolescents	Stop Signal Task (response inhibition)	Go-stimulus-locked IBI	Unlike CTRL, ADHD did not show longer IBIs preceding successful inhibition, than failed inhibitions (heart rate deceleration before successful inhibition)	Hypo (males only)
Keage et al., 2006	129	129	Children and adolescents	Trail making, verbal memory (executive functions; working memory)	Mean HR	No significant differences between groups	None
Leikauf et al., 2017[a,b]	112	56	Children and adolescents	Go/no-go, switching, CPT, maze, verbal memory recall, verbal inference, motor tapping, digit span, choice RT	Heart rate, RMSSD	No significant differences between groups	None
McQuade and Breaux, 2017[a]	23 ADHD, 7 subthreshold ADHD	31	Children and adolescents	CANTAB (executive functions), impossible puzzles	RSA, RDA reactivity (RSA-R: difference between baseline RDA and task RSA)	No group differences on HR measures.	None
Perrin et al., 2014	19 children; 20 adults	34 children; 22 adults	Children and adults	Tower of London (executive functions)	Amplitude and latency of HR acceleration and deceleration	No significant differences between groups	None
Shibagaki and Furuya, 1997[a]	18	49	Children and adolescents	Passive and active auditory attention task	HR, stimulus-locked HR acceleration and deceleration	No significant differences between groups	None
Ward et al., 2015[a]	116	127	Children	Forward and backward Short Term Memory Task (executive functions; working memory)	RSA	No significant differences between groups. Higher probability of ADHD diagnosis and poor STM performance was associated with lower RSA withdrawal from rest to task.	Hypo
						COUNT (Hypo:hyper:none)	7:0:5

[a] Resting-state measures obtained before, during or after the cognitive task (see Tables 2–4 for resting state findings).

[b] Measured effects of an intervention (see Table 11 for results of intervention).

found, but only when RSA withdrawal from rest to task was increased. This finding suggests that reduced responsivity of the PNS branch of the autonomic system in the transition from a baseline rest period to a task may undermine task performance in ADHD.

The remaining three studies measuring executive functions (EF) found no group differences in cardiac measures of ANS activity. McQuade and Breaux (2017) used several experimental paradigms, including an executive function battery and other socio-emotional tasks (see below, paragraph 3.2.3) but only found effects relating to EDA (see paragraph 3.2.1.1), not HR. In a study designed to measure HR and electrophysiological responses (P3a amplitude and latency) to distractor stimuli in a working memory task, Keage et al. (2006), found no HR differences between groups. Perrin et al. (2014) measured HR in a wide age range of children and adults with ADHD and controls while they performed an age-adjusted version of the Tower of London (TOL) task but found no significant differences between groups on HR acceleration or deceleration, or task performance. The authors conclude that ADHD may not suffer from an EF planning deficit and that the task may have been excessively engaging, since feedback was given on each trial, so this may have reduced any arousal regulation difficulties in ADHD. Overall, the findings suggest that ANS function is generally typical in ADHD during EF tasks, although this may depend on task complexity.

3.2.1.3. Pupillometry. Only two studies measured pupil size during cognitive tasks (Table 7). One reported signs of hypo-arousal in ADHD (Wainstein et al., 2017), while the other reported no differences between ADHD and controls (Karatekin et al., 2010).

Pupil size was reduced among off-medication children and adolescents with ADHD performing a visuo-spatial working memory task (Wainstein et al., 2017), compared to controls, but the difference was absent when on-medication (see paragraphs 3.3 and 4.6 for a discussion about the effects of medication). Moreover, a correlation between within-trial pupil size and performance (i.e., accuracy and RTV) was found in the ADHD group, suggesting the presence of signs of hypo-activation of the ANS in ADHD and specific difficulties in allocating a constant and appropriate level of attentional resources during tasks involving executive function abilities, which may be improved by medication. In the other study (Karatekin et al., 2010), pupillary responses (i.e., pupil dilations to visual stimuli) were equivalent in children and adolescents with ADHD, during a pro- and anti-saccade task, compared to typically developing controls.

3.2.1.4. Summary of cognitive task effects. Twenty-three studies analysed autonomic arousal during a cognitive task. Among these, 14 found signs of hypo-activation of the ANS, one study found signs of hyper-activation, while eight found no group differences and one reported mixed findings dependent on the autonomic measure. The majority of studies reporting signs of hypo-activation of the ANS measured EDA. Summarising, the hypothesis that children with ADHD have difficulties up-regulating autonomic arousal during cognitively challenging tasks, with consequent negative outcomes on behaviour and performance, is supported by the majority of the studies included in this review. However, as will be discussed in paragraph 4.5, the nature of the cognitive task or the presence of motivational factors (such as feedback; see paragraph 3.2.2), appears to influence the profile

of impairments found in ADHD.

3.2.2. Reward/reinforcement

Eleven studies included in this review, measured the association between reward/reinforcement and ANS functioning, in ADHD, by investigating the effects of rewards/reinforcers on some aspect of cognition, such as attention or inhibitory control, or the effect of changing the frequency or magnitude of rewards and penalties.

3.2.2.1. EDA. Two studies (out of eight using EDA) found signs of hypo-activation of the ANS in ADHD, one found signs of hyper-activation and five reported no group differences (Table 8).

Iaboni et al. (1997) were among the first to test the hypothesis that the Behavioural Inhibition System (BIS), introduced by Gray (1981), is deficient in ADHD. In their study, children performed a simple RT task and were initially rewarded before the reward contingencies were extinguished and then reintroduced. SCL (which was averaged for each block as an index of SNS activity and a measure of BIS activation) increased as soon as rewards were extinguished in controls, but not in children with ADHD, indicating inefficient regulation of the ANS in response to a change in reinforcement contingencies (see results from HR measures in paragraph 3.2.2.2). A similar version of this task was used by Beauchaine et al. (2001) who reported no group differences between children with ADHD, ADHD + CD and controls on SCRs to reward extinction. The reason for the discrepant findings between these studies is unclear.

Besides reporting reduced SCL during a no-incentive slow condition of a forced-choice response task, James et al. (2016) (see paragraph 3.2.1.1), found a significant increase in SCL and an improvement in task performance in a fast, incentivised condition in the ADHD group only, not in control children. The effect of this was to equate the SCL and performance of the ADHD and control group suggesting that ANS activity and attention are enhanced by faster event rates and incentives, although these two factors cannot be dissociated within that particular paradigm. Conversely, two studies measuring relationships between inhibitory control and EDA (Crone et al., 2003; Desman et al., 2008) found no group differences between ADHD and controls on SCRs during a go/no-go task under five different conditions of reinforcement (Desman et al., 2008) or in response to different levels of punishment (Crone et al., 2003). In these studies, SCRs were calculated over multiple trials, rather than locked to a specific stimulus and may have been insensitive to more subtle fluctuations in skin conductance during the task. Moreover, the emphasis was on inhibitory control, whereas in James et al. (2016), the primary focus of the task is on response selection.

In a study measuring the effects of rewards on time estimation/reproduction, Luman et al. (2008) found that children with ADHD did not respond to reinforcement as controls did (i.e., by improving estimation accuracy when given rewards). However, RTV and SCR amplitude were normalised in response to reinforced feedback, compared to feedback-only, in the ADHD group, suggesting that reinforcement enhanced ANS activity and improved time estimation in this group. One study (Wilbertz et al., 2013) investigating ANS activity during delay aversion, an often-reported feature of ADHD (Van Dessel et al., 2018), found increased SCL (i.e., hyperarousal) during the delay interval in adults

Table 7
Summary of results from studies measuring pupil size measures during cognitive tasks.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect hypo/hyper/none
Karatekin et al., 2010	26 ADHD	48 typical; 29 psychosis	Children and adolescents	Pro- and Anti-saccade task	Pupil diameter	ADHD = TD controls and psychosis	None
Wainstein et al., 2017	28	22	Children and adolescents	Visuo-spatial Working Memory task	Pupil diameter	Off-medication ADHD < CTRL On-medication ADHD = CTRL	Hypo
						Count (hypo:hyper:none)	1:0:1

Table 8

of results from studies measuring electrodermal activity during tasks involving reward processing.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Beauchaine et al., 2001 [a]	17	22 typical; 20 CD	Adolescents	Choice RT + reinforcement	ns-SCRs to extinction	No group differences	None (males only)
Crone et al., 2003	22	22	Children and adolescents	Hybrid go/no-go flanker task	SCRs during task blocks with and without punishment.	No significant differences between ADHD and controls on the increase of SCRs after punishment, positive and negative feedback.	None
Desman et al., 2008 (study 1)	19	19	Children and adolescents	Go-No Go task + reinforcement	SCR	No differences between groups	None
Iaboni et al., 1997 [a]	18	18	Children and adolescents	Choice RT + reinforcement	Mean SCL	No differences between groups. ADHD children showed no change in SCL between reward and extinction (in controls, increase of SCL between reward and extinction and decrease from extinction to reward).	Hypo (males only)
James et al., 2016	73 + 75 siblings	72 + 72 siblings	Adolescents and young adults	4-choice RT Fast Task + incentives	SCL and SCRs	ADHD < CTRL on SCL (only at slow-event rate with no incentives and not during fast-event rate with incentive). ADHD = TD on SCRs	None
Luman et al., 2008	25	30	Children and adolescents	Time reproduction task	SCR	ADHD: reduced SCR in the feedback-only condition, compared with reinforcement (effect not significant in CTRL)	Hypo
Wilbertz et al., 2013	12	12	Adults	Monetary incentive delay task	SCL, SCRs	ADHD > CTRL on mean SCL during delays. ADHD = CTRl on SCRs after loss or gain.	Hyper
Wilbertz et al., 2017	28	28	Adults	Probabilistic anticipation of monetary loss & gain	SCRs	No differences between groups on SCR	None
						COUNT (hypo:hyper:none)	2:1:5

[a] Resting state measured before, during or after the task (see Tables 2–4 for resting state findings).

Table 9

Summary of results from studies measuring heart rate during tasks involving reward processing.

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/ none
Beauchaine et al., 2001[a]	17	22 typical; 20 CD	Adolescents	Manual response RT task	PEP, RSA	ADHD + CD < CTRL on PEP reactivity to reward. However, no significant differences between ADHD and CTRL	Hypo (males only)
Crone et al., 2003	22	22	Children and adolescents	Hybrid go/no-go flanker task + feedback	Feedback-locked HR changes	ADHD < CTRL on HR difference between positive and negative feedback (HR was faster after positive feedback)	Hypo
Crowell et al., 2006[a]	18 ADHD + ODD	20	Pre-schoolers	Recording of psychophysiological reactivity to reward during playing with shape-based commercially available game	PEP, RSA	ADHD + ODD > TD on during-game PEP length ADHD + ODD = TD on during-game RSA	Hyper
Desman et al., 2008 (study 1)	19	19	Children and adolescents	Go-No Go task + reinforcement	Mean heart rate for each reinforcement condition	No significant differences between groups	None (males only)
Iaboni et al., 1997[a]	18	18	Children and adolescents	Choice RT task – Reward and Extinction	Mean HR	More rapid habituation to reward in ADHD. HR deceleration after extinction of rewards was reduced in ADHD, compared to CTRL	Hypo (males only)
Luman et al., 2007	18	18	Children and adolescents	Time reproduction task	HR acceleration and deceleration; feedback-locked IBI; HRV	No differences between ADHD and CTRL on HR response to feedback. Unlike CTRL, no initial deceleration after feedback in ADHD	Hypo
Luman et al., 2008	25	30	Children and adolescents	Time reproduction task	HR acceleration and deceleration; feedback-locked IBI; HRV	No differences in heart-rate responses to feedback, however faster reactivity to feedback in ADHD	Hyper
Tenenbaum et al., 2018[a]	69	48	Children and adolescents	Balloon Analog Risk Taking task	Mean PEP and RSA	ADHD and ADHD + ODD < CTRL on PEP lengthening and RSA increase (these were mostly explained by CD and ODD symptoms).	Hypo
Wilbertz et al., 2013	12	12	Adults	Monetary incentive delay task	Mean HR during delay	ADHD > TD COUNT (hypo:hyper:none)	Hyper 5:3:1

[a] Resting state measured before, during or after the reward task (see Tables 2–4 for resting state findings).

with ADHD, suggesting that stressful but engaging situations may over-activate ANS functioning, an opposite reaction to low stimulation settings such as resting or monotonous, simple cognitive tasks. In a later study (Wilbertz et al., 2017), the authors reported an increased neural response to monetary loss in adults with ADHD during a probabilistic monetary loss or gain paradigm, but did not find any group differences in SCR. The discrepant results are difficult to reconcile but suggest that delay may be more aversive in ADHD, eliciting a more pronounced ANS response. Alternatively, as the monetary loss paradigm was a passive task (requiring no response), the lack of SCR response may reflect the different response requirements of the two paradigms.

3.2.2.2. Heart rate. Among the nine studies analysing the impact of positive or negative reward/reinforcement on autonomic measures of HR functioning (Table 9), five reported hypo-activation of the ANS to reward, three reported hyper-reactivity and one found no group difference between ADHD and controls.

During a time production paradigm, Luman et al. (2007) found that children with ADHD generally showed HR deceleration following response feedback, while controls showed an initial acceleration followed by a deceleration, suggesting atypical modulation of ANS activity in ADHD when preparing to make a response following feedback. In addition, the authors reported evidence of reduced mental effort when incentives were not provided to children with ADHD (reflected in reduced low frequency HRV in the reward and response cost conditions, compared to neutral). A second study (Luman et al., 2008, described in paragraph 3.2.2.1), however, found different results, i.e., no group differences in HR or HR response to reinforcement and a trend for ADHD children to show HR acceleration following reinforcement, compared with controls, which would indicate ANS hyper-responsivity to reinforcement in ADHD. Similar results showing hyper-responsivity of ANS in response to reward, were also found by Wilbertz et al. (2013), who found that adults with ADHD had increased heart rate during a frustration-inducing monetary incentive task and during a delay period, and these effects were associated with self-reported impatience, boredom and negative affect (and with increased SCL, see paragraph 3.2.2.1).

Iaboni et al. (1997) found that children with ADHD showed an equivalent increase in HR compared with controls, when rewards were introduced during a motor response task, but the decrease in HR after successive trials was more rapid in ADHD, which was interpreted as more rapid habituation to reward. Once rewards were extinguished, the control group showed the expected HR decrease but this was delayed in the ADHD group, suggesting hypo-responsivity to changes in reinforcement contingencies. This is partially in line with the EDA findings published in the same paper and, taken together, they suggest that HR may be more sensitive, compared to EDA, to changes in an experimental context where cognitive and reward processing mechanisms are involved. Similarly, Crone et al. (2003) found signs of reduced changes in HR in response to different reinforcement contingencies in ADHD, suggesting that children with ADHD show a reduced ANS response to reinforcers.

Three studies explicitly investigated the influence of comorbidities on ANS function in ADHD. Beauchaine et al. (2001) designed a manual response task, where male adolescents with ADHD and conduct disorder pressed a button in response to a single-digit visual stimulus. Performance was initially rewarded before being extinguished, reinstated and extinguished again. In addition to this, participants watched a video showing an escalating conflict between peers. Although the authors did not find any difference in task performance, reduced autonomic reactivity to reward (reduced PEP reactivity) was related to levels of aggression in ADHD/CD, compared to controls, suggesting hypo-activation of SNS, but there was no significant difference between ADHD-only and controls. Some limitations of this study are the small sample size and the absence of female participants. Tenenbaum et al. (2018) similarly focused on ADHD and CD/ODD, and found that

increased reward sensitivity (measured using the Balloon Analogue Risk-Taking Task), lengthening of PEP and reduced RSA withdrawal were explained by comorbid CD and ODD symptoms, and not by hyperactivity or inattention, in a sample of children with ADHD. In addition to these studies, Crowell et al. (2006) found signs of autonomic hyper-activation both at baseline and in association with reward, during a tablet-based game played by pre-schoolers with ADHD + ODD. However, it is not fully clear if these effects were mainly driven by symptoms of ADHD, ODD or both.

Lastly, Desman et al. (2008) reported no significant group differences in HR (and EDA, described above) during a Go-No Go task: all children (controls and ADHD) showed an increase in HR in the reward and response cost conditions, compared to the neutral condition, but there were no group differences. It should be noted, therefore, that measuring autonomic arousal at the block level (mean heart rate was used in this study) may have reduced sensitivity compared to measuring phasic changes, i.e., through the analysis of stimulus-locked variations in heart rate. Also, the medication washout period for some of the children on medication was less than 24 h, which may have been too short to remove the possibly normalising effects of medication on ANS function.

3.2.2.3. Summary of reward/reinforcement task effects. Of 11 studies assessing autonomic responses to reward or reinforcement in ADHD, three showed signs of hypo-activation of the ANS, two found hyper-activation, three did not find any group difference and three showed mixing results depending on the ANS measure. Group differences on ANS reactivity to reward (hypo- or hyper-) were more likely when HR measures were used, than EDA. Hypo-reactivity to reward was more likely in tasks that measured extinction to reward or some aspect of response control, whereas hyper-responsivity was more likely during time estimation and frustration, suggesting an emotional reaction during the task. However, the findings were inconsistent between studies and seem also to be influenced by comorbid symptoms of ODD, as will be discussed in paragraph 4.5.

3.2.3. Socio-emotional tasks

Ten studies measuring ANS functioning during a socio-emotional task (Table 10) were included in this review because of the important role of emotional dysregulation and social impairments in ADHD. There were too few studies to create specific categories for social and emotional tasks and so we have collapsed across them here to create a 'socio-emotional' category.

3.2.3.1. EDA. Conzelmann et al. (2014), by using EDA measures, found signs of hypo-sensitivity to social information in children and adolescents with ADHD, when presented with a series of pictures of positive, negative or neutral valence. Within the ADHD group, children who were unmedicated showed significantly reduced pre-stimulus SCL and reduced post-stimulus SCRs, compared with controls and medicated ADHD children (see paragraphs 3.3 and 4.6 for a discussion of medication effects). The other two studies investigating EDA (McQuade and Breaux, 2017; McQuade et al., 2017) found no significant relationships between ADHD symptoms and SCRs during socio-emotional tasks (see below, paragraph 3.2.3.2, for results about HR).

3.2.3.2. Heart rate. Among the eight studies which analysed HR measures during socio-emotional paradigms, three reported hypo-reactivity to the tasks, three reported increased autonomic reactivity, while two did not find any differences between ADHD and controls (Table 10).

A number of studies in this area have attempted to induce emotions and measure ANS reactivity following emotion-induction. In one study, Musser et al. (2018) measured autonomic arousal during an interaction between children/adolescents and their parents by using a frustration-

Table 10
Summary of results from studies measuring electrodermal activity and heart rate during socio-emotional tasks.

EDA measures

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Conzelmann et al., 2014[b]	80	22	Children and adolescents	Positive, negative and neutral valence task	Mean SCL and SCRs	ADHD-no-MPH < ADHD-with-MPH and TD on Baseline SCL. ADHD-no-MPH < ADHD-with-MPH and TD on SCRs to emotional pictures	Hypo (males only)
McQuade and Breaux, 2017[a]	N/A	61 Low- vs High-ADHD traits	Children and adolescents	Social rejection	SCL	No association between SCL and ADHD traits. SCL to the tasks was associated with internalising symptoms.	None
McQuade et al., 2017[a]	N/A	61 Low- vs High-ADHD traits	Children and adolescents	Social rejection	SCL	No association between SCL and ADHD traits.	None
						COUNT (hypo:hyper:none)	1:0:2

HR measures

First author, year	ADHD n	Control n	Age group	Paradigm	ANS measure	Main findings	ANS group effect Hypo/hyper/none
Bubier and Drabick, 2008	N/A	63 TD boys, ADHD and ODD traits assessed but not with clinical measures.	Children	Affective decision making and emotion-inducing task	RSA, PEP	Among males, reduced decision making skills were associated with symptoms of hyperactivity and impulsivity, and this was mediated by reduced sympathetic activation in the emotion-inducing task	Hypo (only males)
Lackschewitz et al., 2008[a]	18	18	Adults	Tier Social Stress Test	SDNN, RMSSD, Power Spectral Density, LF, HF, LF:HF	ADHD < CTRL in the stress phase, and on HR increase during anticipation of stress; ADHD > CTRL on decline from stress phase to the first post-stress phase	Hypo
McQuade and Breaux, 2017[a]	N/A	61 Low- vs High-ADHD traits	Children and adolescents	Social rejection task	RSA, RDA reactivity	ADHD symptoms were associated with reduced RSA withdrawal in response to social rejection, after controlling for ODD and internalising symptoms	Hyper
Musser et al., 2011[a]	32	32	Children and adolescents	Emotion induction and suppression task	PEP, RSA	No differences between ADHD and CTRL on PEP; ADHD < CTRL on increase of RSA from baseline to negative suppression condition. Positive induction condition: RSA increased from baseline, in ADHD, while it decreased from baseline, in controls.	Hypo
Musser et al., 2013[a]	21 ADHD-low-social-skills; 54 ADHD-high-social-skills	75	Children and adolescents	Emotion induction and suppression task	PEP, RSA	ADHD > CTRL > ADHD-low-social-skills on mean PEP length throughout the task. (ADHD = CTRL) > ADHD-low-social-skills on RSA increase from baseline to induction and suppression of negative emotions. ADHD-only showed RSA increase from baseline to positive induction condition; CTRL & ADHD-low-social-skills: RSA decrease	Hyper
Musser et al., 2018[a,c]	42	44	Children and adolescents	Parent-Child Interaction Task	PEP, RSA	No differences between ADHD and CTRL on mean PEP. ADHD > CTRL on RSA withdrawal between baseline and task	Hyper
Oliver et al., 2012[a]	N/A	22 low-ADHD-traits; 20 high-ADHD traits	Adults	Driving simulation task	Heart period, RSA, PEP	No differences between low- and high-ADHD-traits	None
Waschbusch et al., 2002	17 ADHD; 23 CD/ODD; 20 ADHD + CD/ODD	115	Children and adolescents	Reaction to verbal provocation task	Heart rate, event-locked R-R intervals	No differences between ADHD and CTRL	None
						COUNT (hypo:hyper:none)	3:3:2

[a] Resting state measured before, during or after the social task (see Tables 2–4 for resting state findings).
[b] Measured effects of an intervention (see Table 11 for results of intervention).
[c] An erratum for this paper (Musser et al., 2018) reported the same results found in the original.

Table 11
Summary of studies investigating the effect of ADHD medication or interventions on arousal measures.

First author, year	Sample (ADHD)	Age group	ANS measure	Main findings
Barry et al., 2012	18	Children and adolescents	Resting-state EDA	This study looked at the effects of caffeine, not medication. Although ADHD and TD showed similar increase of SCL during resting-state, after caffeine administration, in ADHD this increase was not dependent on the dose, while in TD it was.
Conzelmann et al., 2014	45 un-medicated + 35 with prescribed MPH	Children and adolescents	EDA during socio-emotional task	Children with ADHD under MPH were similar to TD, while unmedicated children with ADHD showed reduced baseline SCL during the socio-emotional task and SCRs in response to emotion-inducing pictures, compared to controls and ADHD + MPH.
Groen et al., 2009	16 un-medicated + 16 with prescribed MPH	Children and adolescents	HR during cognitive task	HR decelerations on error trials during a global/local task (selective attention) were found in controls, but not in the unmedicated ADHD group. However, children with ADHD and under MPH, show normalised HR decelerations to errors and in response to feedback after errors, similarly to controls.
Hermens et al., 2005b	34	Adolescents	Resting-state and EDA measured during an attentional task	No effect of MPH on EDA measures during resting at eyes-closed. During the auditory oddball task, MPH maintained SCL constant throughout the task, in ADHD (up-regulation of arousal), while the decrease of SCL with task ongoing was larger in unmedicated ADHD, than controls.
Lawrence et al., 2005	18	Children and adolescents	EDA during cognitive task	MPH normalised any group difference on SCL (ADHD < controls when unmedicated) and reduced SCR (which was similar to CTRL when ADHD were unmedicated) during CPT.
Leikauf et al., 2017	112	Children and adolescents	Resting-state HR; HR during cognitive task	Two bio-types identified based on cognitive performance. The impulsive biotype had a greater response to ATX treatment (measured only as a reduction of symptoms), compared with inattentive.
Wainstein et al., 2017	28	Children and adolescents	Pupil size measured during a cognitive task	MPH increased pupil size during the task, in ADHD. Pupil size was reduced between ADHD-off medication and controls, and normalised (no significant difference) between ADHD-on medication and controls.

inducing paradigm (Parent-Child Interaction Task). They found excessive RSA withdrawal in the ADHD group when switching from baseline to the challenging task, reflecting PNS dysregulation and hyper-reactivity to frustration. An earlier study by the same group (Musser et al., 2011) measured induction or suppression of positive or negative emotions and found, in the control group, an increase of RSA from baseline to the negative-emotion suppression condition, reflecting PNS withdrawal and a decrease in RSA from baseline to the positive-emotion induction condition. These emotion-condition effects were absent in ADHD, therefore the authors concluded that ADHD is associated with PNS hypo-activation but intact sympathetic functioning (no significant results were found for PEP). A further study (Musser et al., 2013) used a similar paradigm and investigated whether co-occurring callous and unemotional traits (CUT), measured as pro-social behaviours, influenced the findings in ADHD. Children with ADHD with atypical pro-social behaviours showed reduced sympathetic function (increased PEP) and PNS function (reduced RSA) throughout the entire task compared to controls, while those with typical pro-social behaviours showed increased SNS activity (shorter PEP) throughout and also significantly increased PNS activation during the positive induction condition. These results suggest that ADHD children with typical pro-social behaviours exhibit increased SNS and PNS activity during emotional tasks, while those with low pro-social behaviours (indicative of the presence of CUT) show SNS and PNS hypo-arousal. This is consistent with evidence of reduced ANS reactivity in those with conduct disorder (Fanti et al., 2019).

The association between socio-emotional abilities and cognitive performance has been investigated by McQuade and Breaux (2017), who analysed HR in a series of experimental paradigms, including an executive function battery, aimed at inducing frustration. Overall, they found that ADHD symptoms were correlated with reduced RSA withdrawal in response to social rejection, which would suggest a reduced ability to down-regulate autonomic arousal in response to negative emotions. Furthermore, children with poor EF showed better social and academic skills if they demonstrated higher RSA withdrawal during the frustration tasks, suggesting that the ability to efficiently regulate PNS may be related to successful compensation of EF deficits, mitigating their impact on adaptive functioning. However, there was no direct group comparison and the overall sample included only males, limiting the generalisability of the study findings to females with ADHD. Furthermore, the tasks did not tackle everyday failure experiences making it difficult to interpret their relevance to general emotion regulation.

Lastly, among two studies investigating the impact of comorbid symptoms on ANS functioning, Waschbusch et al. (2002) assessed reactions to verbal provocation during a competitive computer game in boys with ADHD, ADHD + CD/ODD, CD/ODD. Although there were no differences between pure ADHD and controls, the comorbid group (ADHD + CD/ODD) showed a more pronounced ANS response to provocation (faster HR acceleration after losing points during game-play). In another study (Bubier and Drabick, 2008), the association between traits of ADHD and ODD, and HR measures, was investigated through an affective decision making and emotion-inducing task in typically developing children and adolescents. Among male participants, reduced decision-making skills (lower proportion of advantageous compared to disadvantageous choices) were associated with reduced sympathetic activation (increased PEP length) during exposure to emotion-inducing stimuli. Moreover, reduced sympathetic arousal during the socio-emotional task was associated with traits of hyperactivity and impulsivity, but not ODD, indicating an association between traits of hyperactivity/impulsivity, SNS dysfunctioning and decision-making skills.

3.2.3.3. Summary of socio-emotional task effects. Nine studies investigated autonomic arousal in ADHD during a socio-emotional task. Among these, four found signs of hypo-reactivity during the tasks, two found signs of hyper-reactivity and two did not find any group differences. The studies targeted different aspects of social

information and emotion processing making it difficult to draw firm conclusions about the profile of ANS regulation in ADHD in relation to socio-emotional processing, as later discussed in paragraph 4.5.

3.3. Effects of medication and other interventions

Six studies investigated the effects of ADHD medication, e.g., methylphenidate (MPH), five of which found signs of *normalisation* of ANS functioning (Table 11). Two studies (Hermens et al., 2005b; Leikauf et al., 2017) measured autonomic arousal at rest and did not find any effect of MPH on EDA (Hermens et al., 2005b) or HR measures (Leikauf et al., 2017). Most of the other studies have instead investigated the effects of stimulant medication during cognitive (Groen et al., 2009; Lawrence et al., 2005; Leikauf et al., 2017), socio-emotional (Conzelmann et al., 2014) or attentional tasks (Hermens et al., 2005b; Wainstein et al., 2017). Conzelmann et al. (2014), for example, showed that unmedicated children with ADHD had reduced baseline SCL during a socio-emotional task and reduced SCRs in response to emotion-inducing pictures, while there was no significant difference between ADHD on-medication and controls. Groen et al. (2009) measured the effect of MPH on HR measures during a cognitive task, and found HR decelerations to errors and in response to feedback after errors in both children with ADHD on MPH and controls, while these decelerations were not present when the ADHD children were unmedicated. Similarly, autonomic measures during an auditory oddball task have been collected by Hermens et al. (2005b), who showed that MPH maintained SCL at a more constant level throughout the task, in ADHD, while a decrease in SCL, over time, was present in unmedicated children with ADHD. Using SCL, Lawrence et al. (2005) found similar results during an attentional task, so that children with ADHD, when unmedicated, showed reduced SCL compared to controls, but this difference was not evident when they were medicated. The only study using pupillometry (Wainstein et al., 2017) found increased pupil size during a cognitive task, when children and adolescents with ADHD were on medication, compared to when they were not.

One other study focused on analysing the effects of caffeine (Barry et al., 2012) and found that in controls and children/adolescents with ADHD, caffeine increased SCL at rest. However, while in controls this increase was dependent on the dose, in ADHD it was not, suggesting reduced sensitivity to the dose of caffeine, which is a natural stimulant, in ADHD. Since this was the only study investigating caffeine, a clear conclusion cannot be fully supported.

Summarising, results from these studies support the hypothesis of hypo-arousal in ADHD, since most of them showed some up-regulating or *normalising effects* of stimulant medication on measures of ANS functioning, in ADHD, which will be further discussed in paragraph 4.3.

4. Discussion

4.1. Summary and interpretation of main findings

We conducted a systematic review of the literature to identify studies which measured ANS functioning in ADHD at rest and during tasks of cognition, reward/reinforcement and socio-emotional processing. Overall, our review of 55 studies produced 91 findings comparing ANS measures in people with traits of ADHD (clinical or subclinical) against typical controls (see SM3 for a summary). The findings were heterogeneous: 39 of 91 findings (43 %) were null, 12 of 91 (13 %) were in the direction of hyper-arousal in ADHD and 40 of 91(44 %) were in the direction of hypo-arousal in ADHD. Although mixed, the pattern overall suggests that findings of either hypo-arousal or no group difference were more prominent than hyper-arousal in these studies. Moreover, the effects were partly task- and measure-dependent with a greater likelihood of hypoarousal in resting state studies measuring EDA than those measuring pupil size or HR in the resting state, a greater tendency for hypo- than hyperarousal when cognitive tasks required sustained

attention and response regulation, and a greater likelihood of hypoarousal in reward tasks in studies using HR than EDA measures.

The greater predominance of effects of hypo-arousal compared with hyper-arousal, in studies that reported a group difference, suggests reduced autonomic arousal in ADHD which is in line with theoretical models proposing arousal (dys)regulation as an important factor in the pathology of ADHD (Geissler et al., 2014; Kuntsi and Klein, 2012; Sara and Bouret, 2012; Sergeant, 2000). The review enabled us to address the three main questions set out in the introduction. Firstly, we found evidence of ANS dysfunction in ADHD (question 1) either in the direction of hypo- or hyper-arousal, in 52 of 91 findings reported across the 55 studies included in this review. Secondly, most of the significant group differences were for hypo-activation of the ANS in ADHD rather than hyper-activation (question 2). Lastly, our review identified findings of ANS dysfunction in ADHD during resting-state and during experimental tasks requiring the processing of cognitive, rewarding or socio-emotional information, indicating reduced functioning of the ANS at rest and impaired adaptation of arousal in response to task demands (question 3). We now consider these findings in more detail.

4.2. Resting state findings

The evidence of atypical functioning of the ANS during rest indicates that insufficient resources are allocated to spontaneous neural activity in situations where attention is not focused on a single task or event. Among the studies reporting a group difference at rest, more reported hypo- than hyper-arousal and this was particularly clear for studies using EDA. Fewer studies using HR measures reported a group difference and the findings from pupillometry studies were inconclusive. Since EDA is thought to be a more pure measure of SNS activity, than PNS, this pattern of findings suggests under-activation of the SNS at rest in ADHD. This is consistent with evidence of abnormal resting state brain activity in ADHD, including increased slow-wave EEG power (Barry et al., 2003, 2009) and reduced functional connectivity within and between resting-state brain networks, including the DMN (Rubia, 2018).

It is important to emphasise that a number of studies included in this review reported no group differences on any ANS measure during resting state. These heterogeneous findings undermine the theory that arousal is impaired in ADHD. Interestingly, more recent evidence from EEG studies also calls into question the reliability of the findings of increased slow relative to fast EEG waves in ADHD (see Saad et al (2015) and Loo and Makeig (2012) for reviews) indicating that ANS and CNS arousal may not be consistently impaired in ADHD. Although much effort has been invested in trying to validate specific EEG biomarkers of ADHD, such as increased theta-beta ratio (TBR), studies have been inconsistent in showing a clear association between TBR and ADHD diagnosis (Saad et al., 2015). A recent review of the literature by Newson and Thiagarajan (2018) revealed that atypical EEG profiles, such as increased power at lower frequencies and decreased power at higher frequencies, seem to be shared by individuals with different conditions (e.g., ADHD, OCD and schizophrenia) and not specific to ADHD. Alternatively, there may be sub-groups within the ADHD population who are more or less likely to be characterised by atypical arousal, but equally plausible is the possibility that atypical ANS is driven by other factors commonly associated with ADHD, rather than ADHD itself.

Most studies that investigated the relationships between measures of ANS functioning, such as changes in heart rate and HRV, electrodermal activity and pupil size, and the CNS, focused on sleep or on the sleep-wakefulness transition. A review of the literature by de Zambotti et al. (2018), for example, showed that CNS and ANS measures couple during sleep, so that brain oscillatory activity parallels fluctuations in cardiac activity. Huang et al. (2018) instead focused on the period before sleep onset and found that a reduction of activity of the ANS (reflected in reduced mean HR and SCL over time) paralleled the

decrease in vigilance and wakefulness before sleep onset, calculated through an EEG-based algorithm. Conversely, Barry et al. (2005, 2007, 2008) investigated the relationships between EEG spectral power and SCL during resting-state and found that increased alpha power was associated with reduced SCL during eyes-closed resting-state, while switching to eyes-open caused an increase in SCL and a decrease in alpha power. These findings suggests that specific measures of CNS and ANS activity are likely to change in parallel between different states of vigilance and, therefore, they may similarly reflect different states of arousal.

4.3. Findings from studies using cognitive, reward/reinforcement or socio-emotional tasks

The evidence of hypo-activation of the ANS during cognitive tasks described in this review is consistent with previous findings of greater RTV (Kofler et al., 2013) and response errors in ADHD, which are exacerbated when task stimuli are presented at a slower event rate (Metin et al., 2012). This suggests dysfunction in the brain systems linking ANS activity with cognitive functioning (Aston-Jones and Cohen, 2005; Sara and Bouret, 2012), particularly when upregulation of ANS activity is required to support performance during long or monotonous tasks. This is consistent with models of ADHD which propose that arousal regulation difficulties represent a core pathway or mechanism underlying the cognitive and behavioural features of ADHD (Geissler et al., 2014; Kuntsi and Klein, 2012; Sergeant, 2005). The findings of ANS hypoarousal are also consistent with evidence of poorer performance when cognitive tasks have a slow event rate (Metin et al., 2012; Wiersema et al., 2006) and suggest that lower ANS activity may be one factor that contributes to poorer performance of people with ADHD when tasks require sustained attention and response regulation. It has also been suggested that a general state of hypo-arousal in ADHD may be compensated through maladaptive strategies such as hyperactive motor behaviours and sensation seeking. These auto-regulatory strategies are therefore used to stabilize vigilance by creating a stimulating environment. This is likely to be especially true in situations where regulation of arousal is more difficult, for example during mentally challenging or boring situations, but it may vary significantly from person to person and according to the level of general tiredness. In support of this interpretation, the tasks most likely to elicit autonomic hypoarousal in ADHD were tasks of attention requiring an infrequent response to a rare target or tasks of response control, rather than tasks requiring complex executive functions such as planning or working memory.

The review also identified atypical ANS response to rewards and reinforcers. There was a predominance of findings of hypoarousal in studies using HR measures but studies using EDA did not show consistent results with many studies reporting no group differences. The findings from the HR studies are consistent with research showing reduced responsivity to rewards in ADHD and with broader models which hypothesise that atypical reward processing represents a core deficit in ADHD (Sonuga-Barke, 2002; Sonuga-Barke and Halperin, 2010). Interestingly, ANS hyper-responsivity to rewards was reported in some studies that combined rewards with performance of a cognitive task, so that the introduction of rewards increased ANS functioning and improved performance in ADHD. This indicates that impaired arousal regulation in ADHD may be malleable by motivational incentives, consistent with previous evidence showing the effects of motivational incentives on electrophysiological (Groom et al., 2010, 2013) and fMRI correlates (Liddle et al., 2011) in ADHD. However, this review also highlights the importance of considering the way in which rewards are delivered; several studies showed reduced sensitivity to reinforcers in ADHD, indicating that the timing, nature and size of these may need to be optimised.

The findings from studies using socio-emotional tasks were highly heterogeneous and too few in number to draw strong conclusions. Given that these behaviours are characteristically atypical in disorders such as CD/ODD with which ADHD is highly comorbid, it will be important to explore the extent to which the brain systems supporting these links between ANS and socio-emotional processing are affected in these conditions.

It is important to point out that many of the effects from studies using cognitive, reward/reinforcement and socio-emotional tasks reported in this review were null effects. It proved difficult to identify methodological parameters that might be more likely to elicit hypoactivation of the ANS compared with no group differences (see Section 4.5 below for further consideration of methodological factors). The predominance of null findings is at odds with theories of arousal dysregulation in ADHD which propose that such dysregulation contributes to cognitive and behavioural features of the condition. The null findings may be driven by task design, measurement error or small sample sizes. Further research is needed to clarify the role of ANS in cognition more broadly and in ADHD to determine whether it is more important in some cognitive functions than others, or whether it is simply a correlate of these cognitive features but not causally related to them.

4.4. The findings of the review in relation to models of arousal

The findings of this review may be usefully considered in the context of broader models of the relationships between ANS and behaviour. The maintenance of a task-focussed state is dependent upon adjustments of arousal during a task. Animal studies investigating the LC-NE system (Aston-Jones and Cohen, 2005) have shown that an initial phasic LC-NE response to a novel or salient stimulus is usually extinguished quite rapidly if the stimulus proves not to be sufficiently rewarding, so that the phasic LC-NE response habituates and exploratory non-task-focussed behaviours, e.g., low vigilance, emerge. Conversely, if the stimulus is evaluated as rewarding or salient, the phasic mode is maintained through frequent firing bursts of LC-NE neurons and release of NE, supporting sustained attention over time (Gompf et al., 2010). The evaluation of costs and benefits associated to a stimulus or a situation, mainly involves the vmPFC, Orbito-Frontal Cortex (OFC) and the Anterior Cingulate Cortex (ACC) (Aston-Jones and Cohen, 2005), which have a top-down regulatory role on LC and send efferent signals to maintain or interrupt the activation of LC-NE system in the phasic mode. Previous research has consistently shown evidence of impaired maintenance of attention in ADHD (Cubillo et al., 2012) and the evidence presented in this review suggests that ANS hypo-activity may be an important component of this dysfunction, potentially contributing to a failure of the LC-NE system to maintain a task-focussed state. Moreover, studies included in this review indicate that impaired error processing reportedly previously in ADHD (Shiels and Hawk, 2010) is reflected in weaker ANS responses to errors. One possibility requiring further investigation is that hypo-activation of the ACC in response to errors previously reported in ADHD (Fallgatter et al., 2004; Liotti et al., 2005; Rubia et al., 2019) may undermine the phasic LC-NE response and the consequent upregulation of arousal to increase attention and reduce the chance of further errors. The established links between ACC, vmPFC and the ANS (Critchley and Garfinkel, 2018) suggest that impairments in error processing, ACC hypo-activation and reduced ANS responsivity to errors may be crucially linked in ADHD. Further research is needed to investigate more closely the links between ANS activity and the neural systems supporting cognition in ADHD.

Besides the cortical and subcortical systems responsible for attentional and cognitive processes, other neural pathways and brains structures, e.g., the amygdala and limbic regions, have been shown to be involved in processing of rewards and socio-emotional stimuli (Murray, 2007). Moreover, an association between autonomic mechanisms, brain and emotional responses (such as facial expressions) has been proposed by the polyvagal theory (Porges, 2009), which suggests that atypical functioning of different ANS mechanisms may be

linked to difficulties in regulating socio-emotional and communication behaviours. The findings of this review indicate that the ANS response to these socio-emotional contexts are atypical in ADHD but the relative lack of research in this area precludes a detailed understanding of the role of the ANS in this aspect of ADHD.

4.5. Methodological factors in task design, data analysis, sample size and characteristics

To obtain a clearer picture of ANS functioning in ADHD, in this review, we investigated whether specific methodological choices made during task design and analyses could explain the heterogeneity of results. Traditional research settings, e.g., fMRI or EEG laboratories, provide a naturally stimulating environment that may increase arousal, although it was difficult to determine whether this affected the studies reviewed here. Moreover, although it could be argued that arousal at rest may depend on whether a task of some sort is expected to follow on, resting-state autonomic dysfunctions were found in ADHD irrespective of whether a cognitive task was presented before or after. Similarly, the length of the resting-state period was found not to impact ANS functioning, with studies equally likely to report hypo- or hyper-arousal with both short and long resting periods.

When evaluating methodological choices regarding the analyses of measures of ANS functioning, studies which analysed measures at block-level (e.g., averaged over a long period of time, rather than stimulus-locked measurements), were less likely to report group effects, suggesting that this approach may not be sufficiently sensitive to detect phasic variations of autonomic functioning. Besides this, the most consistent evidence of hypo-arousal at rest came from studies measuring EDA, which is thought to be a pure measure of SNS activity, since the sweat glands are primarily innervated by adrenergic receptors (Berntson et al., 1997). Even when using cognitive tasks, signs of hypo-arousal were predominantly found in ADHD through EDA, with only one study showing hyper-arousal. Although HR may be less sensitive to detect primary deficits of SNS or PNS at rest, signs of hypo-arousal were found in ADHD during cognitive tasks when HR was measured concurrently. Tasks which were more likely to be associated with arousal dysregulation were those involving sustained attention, error monitoring and response inhibition, especially if presented at a slow pace, while null effects seem to emerge from more challenging paradigms, e.g., involving executive functions or fast paced tasks.

Studies which analysed autonomic arousal during the processing of social information were very different from one another, making it difficult to interpret the results emerging from the present review. It could be that some effects, e.g., hyper-reactivity, were mainly driven by the challenging nature of the situation and not by its social features. If this were the case, signs of hypo-arousal found during socio-emotional tasks may resemble difficulties in allocating energetic resources according to the context of the task, instead of specifically reflecting hypo-sensitivity to social stimuli. Since emotional dysregulation and atypical social abilities are key behavioural features of ADHD, it will be important to focus on this domain in future research and develop paradigms that challenge these processes more precisely.

Other methodological issues found in some of the studies were regarding the sample characteristics. For example, although the sample size of studies included in this review was variable (10 to almost 500), there was no clear relationship between sample size and the presence or directionality of effects on ANS measures. Moreover, 14 studies only included single-gendered participants (13 only males and 1 only females), giving rise to evident issues of generalisability to the ADHD population.

Another important but overlooked aspect of research into ADHD is the influence of comorbid symptoms. Although conduct (CD), oppositional-defiant (ODD) and Autism Spectrum (ASD) disorders, are some of the most frequently reported comorbidities in ADHD (Jensen and Steinhausen, 2015), only few of these studies explained how they controlled for the presence of these symptoms (see Table 12 in supplementary Materials, SM2, for a summary). About 22 studies (out of 56) excluded individuals with ADHD and comorbid ODD or CD, while symptoms of ASD were not explicitly measured in 33 studies and children with ASD were excluded from 22 studies. Further research is therefore needed to enlighten the mechanisms underlying the interaction between ANS functioning, ADHD and comorbid symptoms, bearing in mind that excluding children with comorbid symptoms may reduce the impact of potential confounding factors but narrow the possibility of generalising any results. Moreover, there may be important avenues for the identification of sub-groups based on biomarkers such as ANS activity that cut across traditional diagnostic boundaries and that lead to alternative ways of clustering subgroups of patients based on similar profiles (Collins et al., 2011).

Studies focusing on children with subthreshold traits of ADHD or analysing the association between continuous levels of symptoms and arousal measures have been included in this review, however in most of the cases the results were not significant. There were very few studies taking this approach and of those included here, most did not include participants from across the spectrum, tending instead to recruit participants with a range of scores at the typical end of the dimension. It is too early to say therefore whether ANS dysfunction is related to ADHD as a continuous trait measure. Further research is needed to address this question. Including broader samples of children with different presentations of ADHD symptoms (e.g., inattentive-only, hyperactive-only and combined), clinical and sub-threshold symptoms; and comorbid symptoms may better represent the vast clinical heterogeneity of ADHD symptomatology and inform about ANS and cognitive functioning in children with different symptom profiles.

4.6. Effects of medication

Some of the studies included in our review focussed on analysing the impact of medication on ANS functioning. Stimulant medication for ADHD, e.g., MPH, is usually a first-choice treatment for ADHD (NICE, 2018) but, together with well documented findings of improvement in cognitive performance (Coghill et al., 2014) and reduction of hyperactivity and impulsivity (Faraone and Buitelaar, 2010), it also has an effect on ANS functioning, for example increasing HR and blood pressure (Liang et al., 2018) and giving rise to difficulties in sleeping (Storebo et al., 2015).

Results from the studies included in this review are in line with the hypo-arousal theory of ADHD, and indicated that stimulant medication, e.g., MPH, may up-regulate or *normalise* a general state of hypo-arousal in ADHD. However, studies were divergent when fully reviewed (e.g., planning different washout periods, taking different decisions about leaving some children on medication during the testing, within-sample differences in medication history), therefore, further research is needed to investigate the relation between effects of ADHD medications on cognitive, behavioural and arousal mechanisms. Moreover, there were no studies investigating the effect of non-stimulant medication such as atomoxetine, clonidine or guanfacine. Non-stimulants, particularly clonidine and guanfacine, are likely to have an opposite effect on ANS functioning, i.e., reducing HR and blood pressure (see, for example, Sayer et al., 2016) compared with stimulants, but they have similar benefits on cognitive performance and ADHD symptoms. Further research directly comparing the effects of stimulants and non-stimulants could further illuminate the relationships between ANS activity and cognition in ADHD and may also help identify sub-groups, given that individuals with ADHD are often more responsive to one type of medication than the other.

4.7. Implications, limitations and future directions

Although recent developments in imaging technology are improving localisation and functional imaging of the LC and its connections with

other regions, the small size and deep location of this structure make it hard to image, even in adults. Therefore, measuring other indices of LC-NE involvement, such as measures of ANS functioning at rest and during cognitive tasks, may give some insights into the functioning of the LC at any age and in neurodevelopmental populations, including ADHD. Previous findings suggesting that specific measures of CNS and ANS activity are likely to change in parallel between different states of vigilance (e.g., de Zambotti et al., 2018; Huang et al., 2018; Barry et al., 2005, 2007, 2008) should be followed up by further research to better explain the relationships between measures of CNS activity, such as EEG, and the ANS. Therefore, future studies should focus on carefully designing experimental situations where autonomic (e.g., HR, EDA and pupillometry), neuroimaging (e.g., EEG or fMRI) and behavioural measures are collected, during periods of resting-state and cognitive or attentional tasks, both in ADHD and neurotypical individuals.

Knowing the associations between specific signs of ANS dysfunction in individuals with different symptomatological profiles, may help clinicians in making more reliable and objective diagnoses, e.g., in the case of children with ADHD and comorbid ASD, or CD/ODD. Moreover, increasing our knowledge about the effects of different medical interventions on ANS functioning, may be helpful to study the response to stimulant and non-stimulant ADHD medication and try to develop innovative treatments which benefit both ANS and cognitive functioning and limit the undesirable side effects.

This review also suggests that manipulating the nature of rewards and reinforcers provided to individuals with ADHD may help them to up-regulate their attentional and arousal state, with evident benefits in many settings, such as schools or workplaces, and positive effects on productivity and academic achievement, quality of life and social interactions. Equally, this could be applied to the home environment. However, further research in this field is needed to develop innovative programs for parents, teachers and employers, who can implement strategies to optimise arousal regulation. In many cases, medication may still be the preferred first-line treatment. It is therefore imperative in future research that the modes of action of currently available ADHD medications are better understood. In this review, we only found papers assessing the effects of stimulants on ANS activity. Further research assessing the effects of non-stimulants (e.g. atomoxetine, guanfacine, clonidine) on ANS activity and on the LC-NE system is needed particularly as these medications are often more effective in individuals who do not respond to stimulants, lending weight to the possibility of subtypes within ADHD, and they target the LC-NE system (Minzenberg et al., 2008). Similarly, there are non-pharmacological interventions under development that are also likely to impact an arousal regulation deficit such as exercise interventions (Ng et al., 2017) and neurofeedback (Arns et al., 2014). Reviewing the evidence on each of these interventions is beyond the scope of this review but it will be important to test the effects of these interventions on autonomic and central nervous system markers of arousal.

Although the results of this review offer some useful factors to consider in the design of future studies, there are some limitations to address. First of all, the vast heterogeneity in the design of the studies and/or in the methodology of data collection prevented us from carrying out a meta-analysis. There is also likely to be a bias in the inclusion of studies in that we only selected peer-reviewed publications. This increases confidence in the reliability of the findings from individual studies included in this review but there may be unpublished findings that would give valuable information. Since this is likely to be a common limitation of most review studies, we encourage open science and pre-registered studies with clear hypotheses to facilitate the inclusion of unpublished analyses, (including null findings) in future literature reviews. Moreover, since we could not properly investigate the potential effects of sex and age on ANS activity in ADHD due to the vast heterogeneity of samples characteristics and/or missing information in the published full texts, we strongly advise that these characteristics are made a focus of future investigations in this area.

We conclude our review by indicating some interesting areas of research which we think should be targeted in future studies, in order to obtain more knowledge about the relation between behaviour, cognition, attention and autonomic arousal mechanisms in ADHD:

1 Measuring different presentations of ADHD symptoms, both qualitatively (e.g., comparing inattentive-, hyperactive- and combined-presentations of ADHD) and quantitatively (e.g., comparing children with different levels of impairment and adaptive functioning), to verify the presence of similarities and differences on their autonomic arousal profiles;

2 Measuring co-morbid symptoms in ADHD, such as ASD or OCD/ODD, instead of excluding individuals with comorbid conditions, to identify profiles of autonomic functioning in different symptom profiles;

3 Assessing the effects of age and gender on ANS activity under different paradigms;

4 Investigating the specific effects of medical and non-medical intervention on short- and long-term changes in autonomic arousal in individuals with ADHD, and measuring the positive or negative impact of different types of information (e.g., reward or feedback) on arousal regulation;

5 Investigating underlying mechanisms of socio-emotional processing in ADHD, at neural, behavioural and electrophysiological level, and evaluate the impact of co-occurring symptoms of CD and ASD on these mechanisms;

6 Combining neuroimaging, electrophysiological and behavioural measures in different experimental situations, such as cognitive-attentional tasks and resting-state, and use them to derive subtypes based on physiological arousal patterns, cognitive function and symptom profile.

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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.2019.11.001.

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