Title: How orchids concentrate? The relationship between physiological stress reactivity and cognitive performance during infancy and early childhood

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Highlights

- The Autonomic Nervous System (ANS) plays key regulatory roles in diverse contexts.
- In Part 1 of this review we examine the relationship of the ANS to early attention.
- In Part 2 we discuss the potential bivalent role of ANS reactivity.
- We evaluate physiological reactivity within the Differential Susceptibility Theory framework.

Abstract:

The Autonomic Nervous System (ANS) is involved both in higher-order cognition such as attention and learning, and in responding to unexpected, threatening events. Increased ANS reactivity may confer both superior short-term cognitive performance and heightened long-term susceptibility to adverse events. Here, we evaluate this hypothesis within the Differential Susceptibility Theory (DST) framework. We hypothesise that individuals with increased reactivity may show heightened biological sensitivity to context, conferring both positive (development-enhancing) effects (superior attention and learning) and negative (risk-promoting) effects (increased sensitivity to unsupportive environments). First, we examine how ANS reactivity relates to early cognitive performance. We hypothesise that increased phasic ANS reactivity, observed at lower tonic (pre-stimulus) ANS activity, is associated with better attention and learning. We conclude that the evidence is largely in support. Second we discuss whether ANS reactivity to 'positive', attention-eliciting and to 'negative', aversive stimuli is a one-dimensional construct; and evaluate evidence for how the real-world environment influences physiological stress over short and long time-frames. We identify three areas where the evidence is currently inconclusive.

Keywords: arousal; stress; attention; reactivity; Differential Susceptibility Theory

1. Introduction

"Change is necessary to feeling; we are unconscious of unremitted impressions." Bain, 1859, (p.78) [1]

1.1 Measuring autonomic nervous system function in infants and children

1.1.1 What is the ANS and how do we measure it?

The Autonomic Nervous System (ANS) serves as the fast-acting, neural substrate of the body's stress response (e.g. [2-4]). It acts in concert with endocrine systems such as the Hypothalamic-Pituitary-Adrenal (HPA) axis ([2]). Relationships between the ANS and HPA and other endocrine systems are complex ([5]; [6]) and a full discussion of them is, regretfully, beyond the scope of the present paper. In this article, we focus on the ANS.

The function of all of our physiological stress systems is to allow us adaptively to respond to changing environments and situations ([7]). As part of this we show both pre-programmed, predictable, oscillatory activity and unpredictable, reflexive changes. Within the ANS, regular, periodic oscillatory activity has been documented at multiple time-scales ranging from circadian rhythms ([8, 9]) through to changes with the respiration cycle at approximately 0.5 Hz (known as RSA) (e.g. [10]; see also [11, 12]).

The majority of research, however, has studied how the ANS changes in reflexive contexts. The emphasis is on understanding how salient environmental cues can lead to a cascade of autonomic changes which are posited to optimize adaptive behaviour by response preparation ([13]; see also [14]; [2]). Reflexive ANS activity has been documented in response to different types of external events: first, events that are nonthreatening and of moderate intensity; second, events that are unexpected, intense, threatening or otherwise salient ([15-17]).

The ANS is thought to operate primarily via the norepinephrine and cholinergic neurotransmitters, and to be governed by a range of brain areas centred on the locus coeruleus

(LC) and reticular pathways in the brainstem, that communicate via thalamic and cortical projections (e.g. [18, 19]). It acts through two complementary systems - the sympathetic (SNS) and parasympathetic (PNS) nervous systems ([2]). The sympathetic nervous system (SNS) is involved in quick response mobilising ('fight or flight') responses. The parasympathetic nervous system (PNS) is involved in more slow-acting and response-dampening ('rest or digest') responses ([4]). In many cases the SNS and PNS have opposite effects, although their function is non-additive ([2, 20, 21]).

In animal research, ANS activity is often indexed by recording from the LC in the brainstem ([4, 22]). In humans, this is not possible, and so research into the ANS generally uses one of several indirect measures. Heart Rate (HR) is thought to receive contributions from both SNS and PNS, with faster HR indexing greater SNS and less PNS activity ([23]). Respiratory Sinus Arrhythmia (RSA), derived from HR, indexes the degree to which heart rate changes relative to respiratory cycles, and is thought to index PNS activity ([24]). Higher RSA (also known as increased heart rate variability, or increased vagal tone) indexes more PNS activity ([24]). Impedance cardiography (ICG) measures the Pre-Ejectile Period, the time interval between the heart beat and the outflow of blood from the aorta, and is thought to index SNS activity ([25]). A longer Pre-Ejectile Period indexes more SNS activity ([25]). Electrodermal Activity (EDA, also known as Galvanic Skin Response) is thought to measure SNS control ([26]). Higher EDA indexes more SNS activity. Pupil size is thought to be influenced by both SNS and PNS. A larger pupil size indexes more SNS and less PNS ([27]). Body movement is often traditionally included in operational definitions of physiological arousal ([28]). In addition, ERP components (such as the P3 fronto-parietal component) ([29]), frequency spectral components (theta/beta ratios and alpha fluctuations) (see [30]) and short bursts of high frequency neural activity known as micro-arousals ([31]; [32]) have all been described as neural indices of arousal. However, for reasons of space, these neural measures have not been included the present paper.

1.1.2 The ANS is involved in diverse cognitive functions

Reflexive changes in the ANS have been studied in a range of contexts. Early research from Russian electrophysiologists such as Sechenov and Pavlov focused on a cluster of responses that that were originally characterized as the 'Что такое?', or 'what is it?' response, also known as the orienting response (OR) ([14-16]). The stimulus qualities that tend to elicit strong ORs are novel, surprising, complex, and incongruous. Intensity of the stimulus is important, but within an intermediate range, it may be less important than novelty. For example, if one has been listening to a stimulus series consisting of repetitions of the same loud tone, a change to a softer tone will usually elicit a stronger OR than the preceding loud tone did ([15]). The orienting response is generally associated with changes in the *parasympathetic* branch of the ANS ([14]).

Stimuli that are unexpected or more aversive elicit another type of reaction, which early researchers characterised as a Defensive Reaction (DR) ([16]). The same type of stimulus can elicit either an OR or DR depending on its intensity or unexpectedness ([15]). Factors such as between- and within-individual variance can determine whether a particular stimulus elicits an OR or DR ([33]). Early research suggested that OR and DR are indistinguishable on some measures of response such as skin conductance, but that on heart rate change, the OR is characterised by a deceleration of rate immediately following the stimulus, whereas the DR is characterised by an acceleration ([34]). More recent research has associated the DR predominantly with the *sympathetic* branch of the ANS ([2]; although see e.g. [35]).

Because of these differing types of reaction, the ANS is studied in a range of contexts. First, it is studied in the context of 'higher-order' cognitive functions such as attention, and learning. These, we discuss in section 2 of this review. Second, it is studied in the context of adverse, unexpected or threatening events. These, we discuss in section 3 of this review.

1.1.3 The importance of understanding the ANS during infancy and early childhood

Development is a process of hierarchical elaboration in which higher-order development is built on foundations that are laid down early on ([36-38]). Early atypical development can lead to impairments in an individual's subsequent ability to learn, and to acquire new skills, in other areas. Thus, early-developing impairments can lead, cascade-like, to deficits that become progressively more severe over time ([38, 39]).

The self-regulatory functions performed by the ANS and governed by areas of the brainstem and hypothalamus are some of the earliest systems to become functionally mature ([40, 41]). Because they are involved in such a wide variety of contexts, early atypicalities in aspects of our regulatory response systems can, potentially, lead to subsequently disrupted performance and learning capacities in a variety of settings ([42-45]). Research has suggested that early differences in aspects of attention ([46-49]) and emotionality ([50]) can affect diverse cognitive, and clinical and mental health outcomes, but the role of early atypicalities in ANS function in contributing to the causation of these problems remains almost completely unexplored (although see [42, 43, 45]).

The early development of our physiological stress response is known to be influenced by both endophenotypic ([51]) and environmental ([52]) factors. This points to the vital importance of understanding individual differences in ANS function in order to improve our ability to identify high-risk individuals early in development, as well as to develop new and better-targeted interventions to help them.

In section 2 of this review we examine the relationship between the ANS and higher-order cognitive functions, such as attention. In section 3 we discuss the potential bivalent role of ANS reactivity: we assess whether the same individuals who show high physiological reactivity to sought-for stimuli in attention tasks also show high reactivity to adverse or unexpected experimental stressors.

2. Fluctuations in physiological stress and their relation to attention

In section 2.1 we review pre-existing theoretical frameworks, derived from research with animals and adult human participants, to generate predictions for how physiological stress and attention should associate during infancy and childhood. In section 2.2, prior to addressing these cross-sectional predictions, we first examine how physiological stress and attention develop longitudinally, across developmental time. In section 2.3 we evaluate our predictions for how physiological stress and attention should associate during infancy, during both typical (sections 2.3.1-2.3.3) and atypical (2.3.4) early development. In section 2.4 we evaluate our predictions for how physiological stress and attention should associate during childhood, during both typical (sections 2.4.1-2.4.3) and atypical (2.4.4-2.4.5) development. In section 2.5 we summarise our findings.

2.1 Introduction and motivations for hypotheses

2.1.1 Slow-varying fluctuations in tonic stress

Researchers have, historically, contrasted two approaches to studying physiological stress. The first examines slow-varying fluctuations in tonic (or pre-stimulus) physiological stress ([53, 54]). The second examines faster-varying, or phasic, autonomic changes that are elicited in response to particular stimuli ([55, 56]). In this section (2.1.1) we consider tonic activity; in the next section (2.1.2) we consider phasic changes.

Endocrine changes including the release of corticotropin-releasing hormone and catecholamines such as norepinephrine are triggered in response to slow-varying but temporary increases in stress ([57, 58]). These neuromodulators then, in turn, mediate a variety of further changes, including more high-frequency oscillatory activity in the LC ([57]), and increased connectivity between otherwise segregated areas of the brain ([59]). Neuroimaging suggests that experimental manipulations that lead to increases in short-term stress are associated with the immediate down-regulation of areas such as the dorsolateral pre-frontal cortex that are involved in directed attention, together with up-regulation of areas including the hypothalamus,

striatum, amygdala and occipital cortices involved in bottom-up, salience-driving orienting ([59-62]).

Behaviourally, increased stress is associated with decreased voluntary control of attention and increased oculomotor responsivity to salient peripheral targets, whereas lower stress is associated with increased voluntary control ([63]; [64]; [61]). These findings have been observed using a variety of methods, including animal research ([17]), experimental manipulations of stress ([61]) and recordings of ANS function in adults ([65, 66]), children and infants ([67] [68, 69]).

For example, de Barbaro and colleagues collected continuous data in 20-minute segments while presenting a battery of mixed novel static and dynamic viewing data to a cohort of typical 12-month-old infants ([70]). They measured attention by recording the duration of infants' individual looks to the screen, and autonomic arousal by recording a composite of HR, EDA and movement (see Figure 2A). They found that fluctuations in physiological stress related to fluctuations in attention, such that increased stress was associated with shorter look durations. Using cross-correlations they showed that these associations disappeared when a time lag of more than 100 seconds was introduced between autonomic arousal and attention, suggesting that they are temporally specific (Figure 2B). Finally, also using cross-correlations, they found that autonomic activity up to 25 seconds before the onset of a look were predictive of the duration of that look, whereas the reverse was not true ([70]; [71]). This suggests that changes in autonomic arousal tend to precede subsequent changes in look duration (see also [67]).

INSERT FIGURE 1 HERE

2.1.2 Phasic, event-locked fluctuations

The research reviewed above has examined how slow-varying fluctuations in pre-stimulus (also known as tonic, or baseline) stress associate with fluctuations in cognitive

performance. These slow-varying fluctuations can occur spontaneously, and in response to cyclical and environmental factors that are not closely coupled with behavioural responses ([72]; [73]). In addition, other research has examined phasic, or reflexive ANS changes in response to experimental events (known as phasic changes), or to task-related decision processes ([17, 22]).

Early researchers studied phasic (or event-related) stress reactivity as a parameter of individual differences that was entirely independent of tonic (or pre-stimulus) stress levels ([74]). More recent research has, however, suggested that tonic (pre-stimulus) and phasic (stimulus-locked) reactivity are associated. Originally this relationship was formulated as a linear response. In humans it was noted, for example, that when a negative or unexpected stimulus was presented, the heart rate acceleratory response (or Defensive Response – see 1.1.2) observed in reaction to this stimulus was greater when the stimulus was presented at times of low pre-stimulus heart rate ([75]; see also [57]).

More recent research from Aston-Jones and colleagues has, however characterised it as a quadratic relationship. Aston-Jones and colleagues recorded, in primates, direct from the locus coeruleus (LC). Increases in tonic (prestimulus) activity levels associate with an increased rate of spontaneous firing in the LC and, via the principle of electrotonic coupling among LC neurons ([17]; [22]), to increases in the level of phasic (event-related) changes in response to particular stimuli. The relationship was found to be a U-shaped one: extreme high and low levels of tonic activity were found to associate with fewer phasic LC responses, but mid-level tonic activity was associated with more phasic responses (see Figure 2) (see also [76]).

INSERT FIGURE 2 HERE

Building on earlier formulations by Yerkes, Dodson and others ([53]), Aston-Jones and colleagues also examined how variability in tonic and phasic LC activity interact to predict behavioural differences. They suggested that high tonic LC firing rates should associate with

low phasic responsiveness ([22]). Individuals with high tonic LC should be more vigilant or stimulus-driven, and show better signal-to-noise ratios in primary cortices, increased habitual responding, increased fear conditioning and increased memory consolidation ([77, 78]). Mid-level tonic firing is associated with increased phasic responsiveness, together with superior working memory and selective attention with task irrelevant cues. Low-level tonic firing is associated with general inattentiveness, and reduced phasic responsiveness. Of note, the model is agnostic as to whether the phasic changes observed to stimulus events should be short-term *increases*, or *decreases*, in ANS – predicting merely that a change should take place and that a larger stimulus-related change associates with better performance.

In terms of their implications for understanding behaviour, this model is consistent with the research with adult populations, reviewed above (section 2.1.1) – with one exception. Whereas research with human populations has tended, almost exclusively, to compare low short-term stress with high short-term stress, the Aston-Jones model, following on from earlier work from Yerkes and Dodson ([53]) has identified three states: hyper-, hypo- and intermediate physiological stress. In adult, neuroimaging research, the behavioural phenotype of low-short-term stress is similar to the intermediate state in the Aston-Jones model([60]).

Some previous research has explicitly tested the tripartite predictions of the Aston-Jones model in adults ([79]) and other research has investigated hypo-arousal states such as sleep, sedation and disorders of consciousness ([80]). At the level of neurobiology, some research has also investigated inverted-U-shaped neural responsivity for various neuromodulatory transmitter systems such as catecholamine and acetylcholine ([76]). However, in both neurobiology (e.g. [58]) and systems-level neuroscience ([61]) the majority of the research has used a bipartite distinction between elevated and non-elevated short-term stress.

We shall return to this distinction in the Discussion (section 2.5). Here, based on a combination of the Arnsten and Aston-Jones models, and based on a more simplistic bipartite,

low/high-stress model, we make the following two predictions for how physiological stress and attention will inter-relate in human infants and children:

a) lower tonic (pre-stimulus) stress will associate with better voluntary control of attention
b) lower tonic (pre-stimulus) stress will associate with larger phasic (stimulus-related) changes

Of note, both the Arnsten and Aston-Jones approaches define high and low levels of tonic activity only relative to the average activity level *for that individual*. They do not explicitly deal with between-participant variance: the question of whether individuals who have higher, or lower, average arousal levels *relative to other individuals* tend to show greater phasic responsiveness, or different attentional profiles. For the purposes of this review, therefore, we have assumed that the model makes equivalent predictions for understanding between- as within-participant variance. We return to this point in the Discussion (section 2.5).

2.2 - Preliminary questions – change over developmental time

In the subsequent sections, we shall evaluate the two predictions, delineated above, of our models for understanding interactions between physiological stress and attention in infants (section 2.3) and children (section 2.4) respectively. Prior to this it is first necessary to examine, however, how both change independently over developmental time. Specifically: how does tonic (or baseline) autonomic arousal change over the course of typical development? Second, how do phasic (or reactive) changes to stimulus events develop with increasing age? Third, how does attention change with increasing age? Understanding how these factors change over typical development is necessary to allow us to study inter- as well as intra-individual variability, and to distinguish individual differences from developmental trends.

2.2.1 How do tonic autonomic arousal levels change with increasing age?

During the first few years of life we transition from multiple shallow sleep-wake cycles through to more stable, once-per-day cycles ([81]). Tonic heart rate increases significantly from

the 1st week to the 3rd month of life, and is stabilised at 6 months ([82]). It then decreases from typically 120 beats per minute (BPM) in 6-month-old infants to typically 70BPM in adults - although the exact development progression between infancy and childhood has not, to our knowledge, been tracked in detail.

Some authors have reported that resting RSA cannot be observed in neonates due to inconsistencies in the periodicity of the respiration cycle at birth ([83]), although others disagree ([84]; [85]). Resting RSA increases over the course of the first year ([85-87]) and has reached adult levels by 5-7 years ([88]). Less change in RSA is observed among children and adolescents aged 8 and older (e.g. [89]; [90, 91]).

Tonic pupil size is bigger in infants than in children ([92]), although again its exact developmental progression is unknown. Spontaneous fluctuations in pupil size increase with increasing age ([93]). The number of spontaneous large-wave changes in EDA was found to increase during the first 10 weeks of life ([94]) but the developmental progression of spontaneous EDA after this time has not, to our knowledge, been studied.

Research has identified spontaneous, periodic fluctuations in motor activity on a scale of minutes, that start in the foetal stage ([95]) and continue postnatally ([67]). Robertson found that these cyclic fluctuations decrease in a waking state during the first four months of post-natal life ([11]), although they continue for longer in the sleeping state. Diurnal fluctuations start *in utero* and increase in amplitude during the first 3 months of life ([96]), although the changes after that date have not to our knowledge been studied in detail. They have also been measured using actigraphs and heart rate recording ([97]) as well as cortisol ([98]).

In summary, multiple measures show a gradual increase in autonomic arousal over the first few weeks/months of life. By 12 months, all measures show arousal levels that are higher than adults, and decline subsequently to adult levels.

2.2.2 How do phasic changes in autonomic arousal relative to stimulus events change with increasing age?

Even young infants demonstrate phasic ANS changes relative to experimenter-controlled stimulus events ([99]). For example, new-born infants show heart rate decelerations relative to low-intensity tones ([100]), although RSA changes are less obvious ([100]), and movement decelerations have been noted relative to new stimulus onsets ([101]). EDA changes have also been demonstrated in 10-week-old infants in response to auditory stimuli ([94]; see also [102]). EDA responses to a heel prick increase in magnitude during the first month after birth ([103]).

Several researchers have shown that phasic ANS changes also increase in magnitude during the first year of life. Morrongiello and Clifton found that changes in HR relative to the presentation of a sound were more consistent in 5-month-old than in newborn infants ([104]). Byrne & Miller found that 6-month-olds showed a larger HR decelerative response to the onset of a new stimulus than 3-month-olds, although no difference was found for body movement decelerations ([105]). Hernes and colleagues found that the likelihood of infants showing a EDA response to an auditory stimulus increased from 8% to 50% between birth and ten weeks of age ([94]).

Calkins and Keane found that between 2 and 4.5 years there was high stability in RSA suppression in response to challenge tasks at both ages. Modest cross-age stability in RSA suppression was also observed, along with a significant decrease in the magnitude of RSA suppression across age ([106]).

In summary, convergent research has shown that, whilst even young infants show phasic changes in physiological stress relative to stimulus events, the magnitude of these changes increases over the course of the first year of life. Little research has examined how the magnitude of phasic changes in physiological stress to stimulus events changes between infancy and adulthood.

2.2.3 How does attention change with increasing age?

Endogenous (voluntary) attention control has also been reported to increase through the first year ([107]). At birth, infants attend primarily to salient physical characteristics of their environment or attend with nonspecific orienting ([108]). Responsiveness to external stimuli develops rapidly through the first year, but voluntary, endogenous attention is generally thought to be largely absent until 12 months ([107]). However, other research has questioned this ([109-111]). For example, Richards examined the blink reflex, a response to high-intensity short-duration stimuli based on short-latency reflex pathways involving first-order neurons in the sensory pathways and brainstem cranial nerves ([112]). Selective attention to one stimulus modality enhances the blink reflex to a stimulus of that modality and attenuates the blink reflex to stimuli in other modalities - so this attenuation of the blink reflex may also be used as an index of the amount of higher-order selective attention. Between 8 to 26 weeks, Richards found a clear increase in the enhancement of the blink reflex for the modality-match conditions and an increase in the attenuation of the blink reflex for the modality-mismatch conditions. This suggests an enhancement in selective attention across this age range ([113]).

Research with older children has found that attention control continues to mature through childhood. Some aspects of attention control, such as steady-state inhibition, are robustly detectable even in young children ([114]), but other aspects, such as cognitive flexibility (switching between rules) show a slower developmental trajectory ([114, 115]). Unlike autonomic arousal, the development of attention control has been extensively researched through childhood and adolescence, and a large number of studies have examined longitudinal developmental trends ([116]).

In summary, endogenous (voluntary) control of attention is thought to be rudimentary, but detectable using sensitive measures, during the first year of life. Thereafter, it is thought to increase.

2.3 – Physiological stress and cognitive performance in infants

In this section, we assess our predictions for understanding infant development by asking the following three questions: first, behaviourally, is better performance observed at lower levels of tonic (baseline) physiological stress? Second, are larger phasic (reactive) changes observed at lower levels of tonic (baseline) physiological stress? Third, are larger phasic (reactive) changes associated with better performance? Separately, we then explain the fit of the model for understanding atypical development.

2.3.1 Behaviourally, is better performance observed at lower levels of tonic (baseline) physiological stress?

RSA is commonly used to index 'tonic' PNS control (lower physiological stress ⇔ more PNS ⇔ more RSA). Studies have suggested that 4-6-month infants with greater RSA (indexing greater PNS control) show better recognition memory ([117]; see also [118]). 3-6-month-old infants with high RSA look longer than low RSA infants at a central stimulus in the presence of a distracting stimulus during sustained attention ([119]; see also [120]).

The findings noted in section 2, however, suggest one important caveat to these findings: they only examined individual differences between individuals from the tonic (time-invariant) perspective. Given that both resting RSA and voluntary control of attention increase with increasing age, these could simply reflect that infants who were generally more developmentally advanced show both greater RSA and greater attention control, without there being a direct association between the two.

2.3.2 Are the larger phasic (reactive) changes observed at lower levels of tonic (baseline) physiological stress?

The majority of studies in this area have measured RSA to index PNS control. Porges and colleagues found that newborn infants with high RSA responded to the onset of a stimulus tone with greater heart rate acceleration, and to the offset of the tone with greater heart rate deceleration ([85]). A second study obtained similar findings when subjecting infants to

changes in illumination ([121]). Other studies have also found that, in older infants, infants with higher RSA showed larger heart rate decelerations during sustained attention ([122]; [123], [10]). These findings suggest that greater reactivity is observed at lower general levels of autonomic arousal (increased PNS ⇔ decreased arousal ⇔greater reactivity).

2.3.3 Are larger phasic (reactive) changes associated with better performance?

Across several studies Richards and colleagues have shown that greater (larger amplitude) HR decelerations, measured relative to both externally defined events (experimenter-defined stimulus presentations) and internally defined events (infants' looks to and away from the target), index better stimulus encoding (reviewed [68, 69], see Figure 3). For example, infants are better able to recognise material that was presented during phases of heart rate decelerations ([117]; [124]). Infants are also less distractible during heart rate decelerations ([125, 126]).

INSERT FIGURE 3 HERE

Bornstein and Suess found that larger attention-related decreases in RSA (associated with a suppression of PNS activity in response to the presentation of a new stimulus) associated with more efficient habituation and with shorter looking ([88]). Similarly, DeGangi and colleagues found that greater RSA decreases during administration of the Bayley Scales associated with higher Mental Development Index scores in infants ([127]). However, DiPietro and colleagues reported that infants who reacted to the stimulus with *increased* vagal tone (indicating phasic increases in PNS influence) were more often engaged in focused examination of an object ([128]). Richards and Casey discuss phasic *increases* in PNS influence during attention phases (which are the posited cause of the HR decelerations discussed above) ([122]). Thus, for RSA, convergent evidence suggests that increased phasic changes in RSA associate with better stimulus encoding. However, some of this research is inconsistent as to whether the

relationship was one of an increase or a decrease in autonomic arousal relative to the stimulus event. (Recall that the Aston-Jones model, described in section 2.2 above, predicts that a larger phasic LC response associates with better quality attention, but is agnostic as to whether the phasic change should be that of an increase, or a decrease in activity.)

Wass and colleagues measured infants' spontaneous visual attention (looks to and away from the screen) while presenting a stimulus battery consisting of mixed static and dynamic viewing materials to a cohort of typical 12-month-old infants ([129]). At the same time, they measured physiological stress via a composite of heart rate, galvanic skin response, head velocity and peripheral movement levels. They found that infants with generally more labile autonomic profiles showed more visual attention (longer look durations) (see Figure 4). Infants who showed more visual attention also showed greater phasic autonomic changes relative to attractive, attention-getting stimulus events. They also found that four sessions of attention training, which led to increased visual sustained attention, led to concomitant increases in autonomic arousal lability ([129]).

INSERT FIGURE 4 HERE

Friedman and colleagues examined how body movement patterns during looking at 1- and 3 months relate to parent-reported attention problems at 8 years ([130]). They found that infants who showed greater phasic deceleration in body movement at the onset of looking were less likely to show parent-reported attention problems at 8 years ([130]). This is consistent with a model that increased phasic ANS changes associate with better performance. Similarly, Robertson & Johnson examined the relationship between body movement changes during habituation and performance on that task ([131]). They distinguished between 'suppressors', for whom the typical decrease in body movement at the onset of looks persisted into the looks, and 'rebounders', for whom the initial decrease was more transient and movement quickly

returns above baseline. Suppressors and rebounders did not differ on measures of looking during habituation, but, when the stimulus changed, rebounders looked more than suppressors.

In conclusion, research has shown that individuals who show increased phasic autonomic arousal changes to a sought-for stimulus show better voluntary control of attention and superior stimulus encoding. Recent findings ([129]) have also shown that attention training, which increases infants' visual attention (look durations to the screen) also leads to greater phasic changes in autonomic profiles, suggesting a bidirectional effect.

2.3.4 Atypical development

A number of studies have shown that early atypicalities in the auditory brainstem response, a brain area strongly implicated in the neural control of physiological stress (see section 1), can predict later atypicalities in aspects of social behaviour and inhibition ([45]; [42, 43]). These atypicalities are, however, not ones of hypo- or hyper-arousal, but rather of inconsistent stimulus responses. Further, no research has investigated whether infants with atypical early brainstem responses show different patterns of phasic responses to experimenter-controlled stimuli during later development.

Along similar lines, Cohen and colleagues tested the auditory brainstem response as a prospective risk factor for subsequent development of Autism Spectrum Disorders (ASD) ([132]; see also [44]). They found that children who had an early atypical brainstem response, together with a preference for high rates of visual stimulation at four months, were more likely subsequently to develop ASD ([132]). A number of possible neural mechanisms have been discussed for the abnormal patterns of stress-related change observed, involving reticular and thalamic areas ([132]; [133]). Behaviourally, this may relate to findings from Wass and colleagues who found that 8-month-old infants who were later diagnosed with ASD showed more frequent eye movements, together with a reduced inability to modulate eye movement frequencies as a function of viewing time ([134]). These behaviours are consistent with tonic hyper-stress, although physiological stress was not explicitly tested in this study.

In conclusion, although some research exists pointing to relationships between early autonomic arousal and subsequent atypicalities, no research has examined these questions from the perspective of our research questions for this review.

2.4 – Physiological stress and cognitive performance in children

In this section, we assess our predictions for understanding child development by asking the same three questions as in the previous section: first, behaviourally, is better performance observed at lower levels of tonic (baseline) physiological stress? Second, are larger phasic (reactive) changes observed at lower levels of tonic (baseline) physiological stress? Third, are larger phasic (reactive) changes associated with better performance? Separately, we then evaluate how our predictions fit to explain atypical development

2.4.1 Behaviourally, is better performance observed at lower levels of tonic (baseline) physiological stress?

Typical 3.5-year-old children with higher resting RSA (higher PNS ⇔ lower physiological stress) show better performance on executive function tasks ([135]). Similarly, in 6-13-year-old children, higher resting RSA associates with better performance on working memory and reaction time tasks ([136]). Higher resting RSA during infancy has also been shown to relate to better cognitive outcomes during childhood ([137]). Suess and colleagues measured resting RSA in a cohort of typical 9-11-year-old children and recorded performance on the Continuous Performance Task (a measure of sustained attention) ([138]). They found that higher RSA and lower heart rate associated with better performance on early (but not later) blocks of the task.

No research using methods other than RSA has, to our knowledge, addressed this question explicitly. However, some other indirect evidence is available. For example, some research has examined how circadian rhythms affect performance on cognitive tasks in children ([139]). The findings suggest that tasks with high voluntary (executive) demands show greater diurnal variability than tasks that are relatively more subserved by involuntary networks, such as pattern detection tasks ([139]). However, autonomic arousal was not explicitly measured, and arousal changes in children as a function of circadian rhythms have not been tracked in detail (see [140] for analogous work with adults).

Other indirect evidence comes from studies that used questionnaires to assess negative affect in children. Performance on voluntary attention tasks, such as a spatial conflict task, shows inverse correlations with negative affect in children of pre-school age ([141]; [142] see also [143]; [144]). Again, physiological stress was not directly measured in these studies, although other research has shown associations between autonomic arousal and questionnaire-based assessments of negative affect ([5]).

In conclusion, research has again suggested that lower autonomic arousal (increased PNS) is associated with better cognitive performance. In addition, there is some evidence that certain tasks, putatively those with a larger 'executive' component, show larger variance with changing levels of autonomic arousal than others.

2.4.2 Are larger phasic (reactive) changes observed at lower levels of tonic (baseline) physiological stress?

A number of authors have reported linear relationships between baseline RSA and vagal withdrawal, such that higher RSA (lower autonomic arousal) is associated with increased withdrawal during a behavioural challenge in young children ([135, 145]). However Suess and colleagues found no association between RSA and the amplitude of RSA decelerations during attention in children ([148]). To our knowledge no research using methods other than RSA has addressed this question.

2.4.3 Are larger phasic (reactive) changes associated with better performance?

Again, the only research to have addressed this question in children has used RSA. Results are inconsistent in two aspects (see [146-148]). First, in the direction of effects: whether results show that phasic *increases* or *decreases* in RSA are considered to associate with 'better' performance. Second, in whether the results observed are linear (larger RSA change considered 'better') or quadratic (intermediate levels of RSA change associated with 'better' performance).

Greater RSA withdrawal in response to various laboratory challenges has been associated with increased sustained attention, engagement during challenge tasks, on-task behaviours in the classroom, and cognitive functioning, as well as more adaptive emotion regulation strategies ([149]; [150]; [106, 151]; [136]; [138]). Similarly, Becker and colleagues reported that better performance on an EF task was associated with greater RSA withdrawal among elementary school students ([152]). However, Utendale and colleagues found that greater EF skills were associated with *lower* RSA withdrawal among 5- and 6-year-olds, a relationship further moderated by children's externalizing problems ([153]). Staton and colleagues observed no relationship between RSA reactivity and cognitive performance in 6-13-year-old children ([136]). And Sulik and colleagues reported that while RSA withdrawal was linked to better EF performance, the associations between changes in RSA levels and EF skills varied across three different EF tasks ([154]).

Studies described in the paragraph above have all documented linear relationships between RSA reactivity and performance. However, some other studies have observed quadratic relationships. For example, Marcovitch and colleagues observed a quadratic relationship in typical 3.5-year-old children, such that intermediate levels of RSA withdrawal during a number recall test associated with better performance ([135]). And 'excessive' RSA reactivity to challenges has been observed in psychiatric samples of internalizing and externalizing children, adolescents, and adults ([155]; [156]; [157]; [158]).

Obradović & Finch suggested than one reason for these inconsistent results may be that RSA studies tend to study change over relatively long time-scales (minutes) ([146]). This may mean that a number of different subcomponent processes (initial withdrawal, maintenance of change, recovery) are all included in the measure of RSA withdrawal ([148]). By using piecewise growth curve modelling to examine change in RSA within the challenge period, they found that children with strong 'cool' EF skills showed curvilinear withdrawal during the challenge period, whereas those with lower levels showed curvilinear increases. But for 'hot' EF skills a different result was observed: those with higher EFs showed an inverted U-shaped

trajectory (i.e. gradual, curvilinear RSA augmentation followed by mild RSA withdrawal), whereas those with lower hot EF skills displayed a U-shaped trajectory of RSA reactivity (i.e. gradual, curvilinear RSA withdrawal followed by mild RSA augmentation).

In conclusion, a number of studies have found that increased phasic (reactive) changes are associated with better performance. However, other studies have suggested that 'excessive' phasic (reactive) changes are markers of psychopathology. This is inconsistent with our predictions, which state that increased phasic reactivity should be associated with better performance.

2.4.4 Atypical development - ADHD

Atypical physiological stress has been noted in a number of aspects of child developmental psychopathology. In particular, lower RSA has been identified in a range of atypical populations, such as those with conduct disorder and depression ([159]). Here, however, we concentrate on two well-researched clinical conditions: 1) Attention Deficit Hyperactivity Disorder, which has been suggested to involve tonic hyper-arousal, and 2) Autism Spectrum Disorders, which are thought to involve more complex patterns of atypical autonomic arousal.

Children with Attention Deficit Hyperactivity Disorder (ADHD) move their heads more than typical children, and show more linear and less complex movement patterns ([160]; see also [161]). 24-hour analyses of heart rate also show that heart rate levels were overall higher in the ADHD group – with largest effects during afternoon and night ([162]). Findings for RSA are, however, inconsistent, with some authors reporting lower RSA in children with ADHD ([163]) and others reporting no difference ([164]; [165]). Abnormal circadian patterns in children with ADHD have also been found using salivary cortisol ([30]). Although not completely consistent, these findings have led a variety of researchers to speculate that the pathophysiology of ADHD involves hyperactivation of the LC ([166]; [30]; [167]) (although see also [168] for a contrasting approach).

Research into phasic autonomic changes in children with ADHD has generally shown that children with ADHD show smaller phasic ANS changes relative to stimulus events. For example, Groen and colleagues examined HR decelerations during the performance of a selective attention task in which feedback was given. They observed enhanced HR decelerations in response to errors in typical children but not in those with ADHD. However, a Methylphenidate-treated ADHD group showed HR decelerations similar to those seen in typical controls ([169]). Boerger and van der Meere examined HR changes during Go/No-Go performance in children with ADHD and typical controls. They found no evidence of decreased HR decelerations relative to the onset of the No-Go signal, but they did find that heart rate decelerations before the onset of Go signals, which are believed to reflect motor preparation, were less pronounced in the ADHD children ([165]; see also [164]). Using a similar model, O'Connell and colleagues examined EDA responses to errors in children with ADHD. They found reduced EDA responses in the ADHD group and that sustained attention errors were predicted by EDA amplitudes ([170]).

2.4.5 Atypical development - ASD

Autism Spectrum Disorders (ASD) may show a more complex pattern. There are some reports of hyper-tonicity similar to that suggested for ADHD. For example, Bal and colleagues found a faster tonic heart rate in children with ASD ([171]; see also [172]). They also reported lower amplitude RSA (suggesting decreased PNS contribution) (although [173] failed to replicate this). Anderson and Colombo noted increased tonic pupil size in a small sample of 23-70-month-old children with ASD ([174]). This can be compared to studies identifying increased brain metabolic activity at rest in individuals with ASD, suggesting a failure to deactivate at rest ([175]).

Schoen and colleagues examined phasic EDA changes in children with high-functioning ASD in response to presentation of mixed sensory stimuli. They identified two subgroups - a hyper-aroused group that showed increased attention-related changes and faster

latencies, and a hypo-aroused subgroup that showed lower changes and slower latencies ([176], see also [177]). Ben-Sasson and colleagues noted strikingly similar results in a behavioural analysis looking at sensory sensitivities ([178]; see also [179]). They reported co-occurring auditory hyper- and hypo-sensitivity symptoms in children with ASD, and suggested that both of these problems may be explained by a common mechanism, namely a dysfunctional autonomic arousal system that compromises the ability to regulate an optimal response ([178]). Schaff and colleagues found that, whereas typical children showed a decrease in RSA in response to challenging stimuli, children with ASD did not (Schaff et al., 2013).

In conclusion, results from children with ADHD are largely consistent with our predictions. Children with ADHD have been suggested to show hyper-tonic activation, together with reduced phasic responsiveness and poorer top-down control of attention. Results from children with ASD are thought to be more complex, with the possibility of hyper- and hypo-aroused subgroups.

2.5 Summary - how well does the evidence fit the predictions?

We have reviewed the relationship between: 1) an individual's level of tonic (baseline) physiological stress; 2) the degree of phasic (reactive) change they show relative to sought-for stimuli; and 3) levels of cognitive performance. We predicted that: a) lower tonic (pre-stimulus) physiological stress would associate with better performance and b) lower tonic (pre-stimulus) physiological stress would associate with larger phasic (stimulus-related) changes.

As we described above (section 2.1.2), the theoretical frameworks that we used as the basis for our predictions mainly concern within-participant variability. The evidence that we reviewed has been consistent with these predictions. Within participants, slow-varying increases in physiological stress associate with decreases in focused attention ([70]). Increased phasic heart rate decelerations, both in reaction to external stimuli and endogenously triggered (during a look) are associated with better stimulus encoding and reduced distractibility (sections

2.3.1, 2.3.2, 2.3.3). In infants, training attention has been shown to lead to concomitant increases in autonomic lability ([180]) (see section 2.3.3).

We have also reviewed evidence, consistent with our predictions, that has examined between-participant variability. Behaviourally, in infants, best performance tends to be observed in individuals with *lower* tonic physiological stress; larger phasic changes are observed in individuals at *lower* tonic physiological stress; and better performance is observed in individuals who show *larger* phasic autonomic changes (sections 2.3.1-2.3.3). These have been observed in typical infants by measuring RSA – both pre-stimulus (tonic) and phasic (event-related) RSA changes. Similar patterns, of increased variability associating with better attention, have also been shown in infants for other measures, such as movement ([129]). In typical children evidence consistent with these hypotheses has been obtained in studies that use RSA to index physiological stress (2.4.1, 2.4.2, 2.4.3). Evidence into atypical development has suggested that children ADHD may show a pattern of elevated tonic physiological stress and reduced phasic autonomic changes, which is consistent with our hypotheses (section 2.4.4). Evidence from other conditions such as ASD is more mixed (section 2.4.5).

In the Introduction (sections 2.1.1 and 2.1.2) we noted one inconsistency in the prior literature, which was that, whereas some previous research takes a linear approach that differentiates two levels of stress (high vs low), other research takes a quadratic approach that differentiates three levels (hypo-, intermediate, and hyper-). Of the literature we have reviewed only a few studies ([135, 176]) have discussed the hypo-aroused phenotype predicted by Aston-Jones and colleagues. The majority have taken a linear approach to defining autonomic arousal, differentiating high vs low physiological stress.

There are, however, a number of possible explanations for why hypo-arousal may have been present, but undetected by the studies that we have reviewed. The first is that the majority of the research, particularly with children, has used a single measure, RSA, to quantify autonomic arousal, and it is unclear whether RSA is sensitive to hypo- as well as hyper-arousal. It may be that other research using, for example, movement patterns, might be more sensitive

to both extremes. The second is that infants and children may have a tendency, relative to adults, towards hyper-tonic arousal. (A finding not directly empirically investigated (see section 2.2.1), but to which many parents of young children would testify.) What is in effect a normal curve thus becomes positively skewed, making the positive linear trend stronger than the quadratic effect. A third possibility is that the specific demands of testing (attending a lab, wearing equipment) or excluding trials in which no response was given mean that hyper-arousal is over-represented relative to hypo-arousal in experimental samples, and that hypo-arousal might be observed more in naturalistic contexts (such as the classroom) than it is in the lab. A fourth possibility is that the quadratic effect exists but studies are underpowered to recognize it.

One further limitation to the predictions that we laid out at the start of this review is that the three elements that are connected – tonic (baseline) physiological stress, phasic (reactive) stress responses and performance – are treated as showing unitary co-variance. However it may be that the influence of physiological stress on performance is stronger in some individuals than others ([181]). Metin and colleagues, for example, examined how changing event rate (the rate of stimulus presentation) affects performance both in typical children and in children with ADHD ([182]). (Event rate was used as a proxy for autonomic arousal, since fast-paced stimuli were considered to be more arousing.) Results showed that altering the event rate ('increasing arousal') had a larger effect on performance in children with ADHD than in typical children, which they interpreted as suggesting that performance in children with ADHD may be disproportionately affected by changes (either increases or decreases) in autonomic arousal. Similarly we might predict that, due to asymmetric patterns of brain maturation (with subcortical attention networks developing before cortical attention networks) ([183]; [184]), stress-attention interactions might be stronger in infants than in older children. If proven, such a finding would be hard to incorporate into the theoretical frameworks that we have laid out (section 2.2).

3. Bivalent effects of physiological stress reactivity?

In Section 3.1 we describe Differential Susceptibility Theory (DST). We explicate how different researchers have defined biological sensitivity to context using different criteria, of which physiological reactivity is one candidate amongst several. In section 3.2 we outline three questions that need answering in order to understand the mechanisms through which heightened physiological reactivity might have the bivalent effect predicted by DST. In the subsequent three sections, we address these questions in turn. In section 3.3 we ask: is stress reactivity a one-dimensional construct? In other words, do the same individuals who show heightened reactivity to 'positive', attention-eliciting stimuli also show heightened reactivity to 'negative', aversive stimuli? In section 3.4 we address the mechanistic details of how heightened stress reactivity might confer increased susceptibility to adverse environments. We ask: if increased physiological reactivity is a mechanism that confers increased susceptibility to the negative effects of the environment, then what, exactly, are these negative environmental influences? And how do individuals higher in physiological reactivity react differently to them? In section 3.5 we consider how heightened physiological reactivity to short-term adverse events might lead either to higher long-term stress, or to increased (maladaptive) stress reactivity.

3.1 Different ways of defining susceptibility – plasticity, temperament and reactivity

Differential Susceptibility Theory (DST) suggests that some individuals are more susceptible than others to *both* negative (risk-promoting) and positive (development-enhancing) environmental conditions ([51, 185, 186]). Individuals with high biological sensitivity to context show superior long-term outcomes in positive environments, but worse long-term outcomes in negative environments; children with lower sensitivity show a lesser influence of environment on long-term outcomes.

Some researchers working within this framework have used *physiological reactivity* to index biological sensitivity to context (see [187] for a review). As with the studies that we reviewed in section 2, physiological reactivity in these studies is usually assessed by measuring

the degree of ANS (HR or RSA) or HPA axis (cortisol) change to an experimental stressor in the lab (see [188]). Environment is assessed, for example, via life histories, questionnaires, or video-coding of parent-child interactions. A variety of types of long-term outcome have been investigated, such as physical and mental health (e.g. [189]), and socioemotional and cognitive competencies, but an increasing number of studies are focusing on outcomes such as academic performance or performance on executive function tasks ([187]). Thus, for example, Skowron and colleagues examined RSA responses to a social challenge task in 161 children aged 3-5 years, of whom half had been exposed to childhood maltreatment. To the same children they also administered experimental assessments of inhibitory control, using age-appropriate Stroop tasks. They found that elevated parasympathetic reactivity during a parent–child interaction was associated with less optimal performance on EF tasks in 3- to 5-year-olds exposed to maltreatment, and with more optimal performance among non-maltreated children ([190]; see also e.g. [191-195]). This suggests that high physiological reactivity may confer an advantage in settings where the long-term environment is supportive, and a disadvantage in settings where it is not.

In the remainder of section 3 we evaluate the theoretical and empirical viability of using physiological reactivity to index biological sensitivity within the framework of DST. Before we do this, however, it is important to note that not all researchers working within the framework of DST define biological sensitivity in this way. Other researchers have used different criteria to index biological sensitivity; at the moment, overlap between these techniques is somewhat limited. First, some researchers use *genetic* criteria to assess an individual's level of sensitivity to their environment (e.g. [185, 196, 197]). For example, children with less efficient dopamine-related genes were found to perform worse in negative environments than comparison children without the "genetic risk", but they also profited most from positive environments ([197]). In genetics, biological sensitivity is typically conceptualized in terms of plasticity ([196, 198, 199]). Relationships are generally investigated over long-term time-scales, in order to examine the life-long relationship between genetics,

environment and cognitive and behavioural outcomes; however, other research has also found relationships consistent with these findings over shorter time-frames. For example, adults and children with higher levels of candidate genes involved in the manufacture of dopamine and other catecholamines have been found to show greater increases in cortisol in response to a social stress test ([200, 201]).

Second, another body of research has used questionnaire-based assessments of *temperament* ([202]) to index an individual's level of biological sensitivity to context. For example, a meta-analysis found that children with high negative affect were more sensitive to parenting style than others, although associations were only present when the trait was assessed during infancy ([203]). Again, relationships tend to be investigated over life-long time-scales, but how these individuals differ over shorter time-frames is a question that has received relatively little research (although see e.g. [204]).

Some previous research has examined the inter-relationships between genetically defined plasticity, temperament, and physiological reactivity ([5, 52, 199, 205]); however, a full discussion of this is, regretfully, beyond the scope of this review. For the remainder, we concentrate, therefore, on using physiological reactivity to index biological sensitivity within the framework of DST.

3.2 Can increased physiological reactivity render some individuals more susceptible to both negative (risk-promoting) and positive (development-enhancing) environmental effects? Three questions that need answering.

As described above, a number of authors have provided evidence suggesting that increased physiological reactivity may render some individuals more susceptible to both negative (risk-promoting) and positive (development-enhancing) environmental effects. But how, exactly, might physiological reactivity have this bivalent effect? Here we focus on three questions.

First, in the next section (3.3), we discuss: is stress reactivity a one-dimensional construct? In other words, do the same individuals who show a large autonomic change to a negative stimulus (mild experimental stressors such as arm restraint) also show a large autonomic change to a positive stimulus (such as a new item to be memorized in a working memory task, or a novel image in a habituation task)? In order to countenance that physiological reactivity may have a bivalent effect it appears a prerequisite to hold that physiological reactivity is a one-dimensional construct. If we do not hold this, and we accept that physiological reactivity to 'negative' and 'positive' stimuli are unrelated, then it appears impossible to countenance that reactivity *per se* could have a bivalent effect.

In the next section, (3.4) we discuss the different types of environmental effects that are thought to influence long-term outcomes within the framework of Differential Susceptibility Theory. We ask: is there evidence that these specific real-world environmental factors actually cause changes in physiological stress? And we discuss the problem of construct validity: whether the types of experimental stressors used to measure stress reactivity within the lab measure individual differences in physiological reactivity to 'real-world' environmental stressors.

In the final section (3.5) we consider how, exactly, increased sensitivity to real-world stressors over shorter time-frames might confer adverse effects over longer time-frames.

3.3 Is stress reactivity a one-dimensional construct?

We know that, in addition to showing responsiveness to sought-for, expected stimuli (see section 2), the ANS also shows responsiveness to adverse or unexpected environmental stressors. Researchers as far back as Pavlov ([16]) have distinguished between the Orienting Response (discussed in section 2) and the Defensive Response – a set of ANS changes that occur in response to stimuli that are unexpected, aversive, or intense. In recent research, these types of responses are generally measured using widely used and standardised experimental stressors – such as, with infants, the still face paradigm ([206]) or, with children, a transparent

barrier task, in which an attractive toy is made visible, but inaccessible, to a child ([207]) (see section 3.4).

Do the same individuals who show a large autonomic change to a negative stimulus (mild experimental stressors such as arm restraint) also show a large autonomic change to a positive stimulus (such as a new item to be memorised in a working memory task, or a novel image in a habituation task)? If stress reactivity is to be thought of as having a bivalent effect, then addressing this question appears essential.

Current approaches to answering this question from a neurobiological perspective would, probably, answer it in the affirmative. Researchers focus on the manufacture of catecholamines, such as norepinephrine and dopamine (see section 2.1.1 and 2.1.2). Candidate gene studies have shown that individuals with higher levels of genes (such as the COMT Val^{158}Met polymorphism) involved in catecholamine manufacture show higher cortisol reactivity to social stress tests ([200, 201]). Norepinephrine and dopamine have also been extensively implicated in positive, attention-related changes of the type discussed in section 2 ([17, 22]).

However, researchers who have studied physiological stress reactivity from the perspective of ANS function would not necessarily concur. Whereas early responses to studying the ANS generally posited a uni-dimensional construct of autonomic arousal that increased linearly from a coma state to complete dysregulation ([53, 55, 208]; see [33]), more recent research has increasingly identified fractionation, and differentiation, within our physiological stress responses ([20, 209]). The ANS is known to contain subdivisions – most notably the parasympathetic and sympathetic subdivisions ([2, 23]), that show different patterns of responses in different contexts ([6, 20]; [210, 211]). Thus, for example, different types of defensive behaviours – confrontational defence, flight and quiescence – can be triggered in different individuals, and in response to different settings. Each of these carries with it a distinct pattern of ANS activity ([210]).

Does the more recent research that has identified the fractionation and differentiation of stress responses mean that early research that treated autonomic arousal as a one-dimension construct is entirely wrong? Not necessarily. At the neural level, distinct mechanisms for the control of the parasympathetic and sympathetic branches of the ANS have been identified, both in terms of neuroanatomy ([4, 212]) and neuromodulation ([2]). At the same time, though, much of the research into neural control of ANS function through the LC and other brain areas continues to treat the sympathetic and parasympathetic branches as functioning, at least partially, in opposition to one another ([213]). And although there is evidence for fractionated and differentiated ANS responses in infants and children (e.g. [6]), there is also evidence that different peripheral ANS measures do, to a degree, show unitary covariance ([71, 214]). The conclusions of Graham and Jackson, writing in 1970, may still be correct today: "the unidimensionality argument [...] is probably not an all-or-nothing matter, but, like many earlier arguments concerned with general versus specific factors, a question of the relative proportions of variance that can be accounted for by a single common factor in comparison with the variance accounted for by the sum of specific factors" ([99]).

Some prior behavioural evidence is consistent with the idea that individuals who show greater reactivity to negative stimuli (stressors) also show greater reactivity to positive stimuli (interesting and engaging stimuli). Specifically, higher levels of RSA have been associated with increased reactivity to both positive, and negative, stimulus events. For example, newborns with higher RSA also exhibit larger cortisol responses to a heel-stick procedure for drawing blood, suggesting greater stress reactivity ([215]). In response to circumcision, newborn males with high RSA exhibited greater pain reactivity, as assessed by heart rate acceleration and fundamental cry frequencies ([216]). Similar findings have been observed in research examining behavioural reactivity. For example, high RSA infants subjected to a pacifier withdrawal procedure cried more than their low RSA counterparts ([217]). In a sample of premature infants DiPietro and Porges reported greater behavioural reactivity for high RSA neonates in response to a feeding procedure requiring a tube run through the nose or mouth

([128]). Evidence previously reviewed (see sections 2.3.2 and 2.4.2) suggests that infants and children with RSA show greater phasic reactions to interesting and engaging stimuli, along with better attention performance. Thus, RSA may reflect the capacity to engage in both a positive, and a negative, manner ([155]).

However, this previous research comes from separate studies that have examined relationships between RSA and short- and long-term behavioural outcomes in different settings. None of the studies reviewed above have examined whether the same individuals who show high reactivity to a 'positive' stimulus also show high reactivity to a 'negative' stimulus. This leaves open a variety of important questions. It is, for example, still an open question as to whether the associations previously noted between RSA and reactivity are best thought of as short-term, within-individual changes – such that individuals who are in a temporarily calm state at the time of testing show different behavioural responses - or as static, time-invariant features of individual differences.

Recently, we examined physiological stress reactivity and attention in a cohort of typical 12-month-old infants ([129]). Physiological stress was indexed using a combination of heart rate, electro-dermal activity and movement. Reactivity was indexed to both negative, mildly aversive stimuli (a video of another child crying) and to positive, attention-eliciting stimuli (e.g. short, appealing TV clips). Attention was indexed by recording the duration in infants' looking behaviours towards the stimulus presentation area. We found that infants who were generally more attentive showed greater phasic autonomic changes to attractive, attention-getting stimulus events, a faster rate of change of both look duration and of autonomic arousal, and more general oscillatory activity in autonomic arousal. However, these same infants who showed *greater* reactivity to the positive stimuli showed *less* reactivity to the negative stimulus. Infants who showed greater reactivity to the negative stimulus showed a markedly different attentional profile, and shorter attention durations ([129, 218]).

To further investigate this, we applied four sessions of attention training to a subset of the infants (24 trained, 24 active controls). Consistent with previous correlational research

([122]) we found that concomitant increases in autonomic lability were observed following training. However, these changes appeared only present when positive stimuli were examined. Attention training led to changes in autonomic responsiveness to positive stimuli but to no changes in reactivity to negative, mildly aversive stimuli ([129]).

These findings appear inconsistent with previous research, which suggests that infants with high RSA should show greater reactivity to both positive and negative stimuli. In our data, high RSA was associated with greater reactivity to positive stimuli, but this was negatively correlated with reactivity to negative stimuli. These findings may, in some respects, be comparable with those from other research that has examined, using an intervention-type design, whether the same individuals show enhanced susceptibility to both negative and positive types of feedback ([219]). They found, inconsistent with the predictions of DST, that some individuals were affected more by negative feedback than others – but that these same individuals were not more affected by positive feedback, too. Differential susceptibility "for better and for worse" was not supported by the data.

In summary, therefore, most recent research emphasizes that autonomic stress response systems tend to be fractionated and differentiated. If physiological reactivity is to be thought of as conferring both negative (risk-promoting) and positive (development-enhancing) effects of the environment, then it must be thought of as a one-dimensional construct. Our current understanding of autonomic function may be inconsistent with this claim. By comparing behavioural studies that have examined the effects of RSA in different contexts, it appears, however, that individuals higher in RSA may show increased engagement in both a positive, and a negative, manner. But other research has pointed to two negatively correlated phenotypes: high RSA was associated with *greater* reactivity to positive stimuli, but with *less* reactivity to negative stimuli. Future research should examine this question in more detail.

3.4 How do real-world stressors affect short- and long-term physiological stress

If increased physiological reactivity is to be thought of as a mechanism that confers increased susceptibility to the negative effects of the environment, then what, exactly, are these environmental effects? And how do individuals higher in physiological reactivity react differently to them?

Previous research has examined how negative parenting behaviours, such as parenting with high levels of expressed emotions ([220]), parental emotional dysregulation ([221]), childhood maltreatment ([190]) or marital conflict ([194, 222, 223]) can affect long-term stress outcomes (see also [199]). This research has not directly examined the relationship between short- and long-term stress. To do this, it would be necessary to measure children's' physiological responses during the stressful events, and compare it with their long-term stress behaviours. Rather, it has examined the negative parenting behaviours after the event, using questionnaires, and separately measured stress reactivity in the lab. Putatively, though, if it were possible to measure reactivity while the events were taking place, we might observe that children who show greater reactivity to real-life negative events over a time-frame of seconds or minutes show greater long-term adverse effects of stress, when measured separately in the lab.

Similarly, other recent research has shown that certain populations of children, such as those from low socio economic status backgrounds, are more likely to be exposed to noisy, chaotic, and unpredictable living environments during early life ([219-221]). Over longer time-frames, these same populations also show altered physiological stress reactivity during later life ([6, 222]). Again, though, no research has directly investigated whether noisy, chaotic living environments actually directly influence children's' stress. It is possible that factors such as sudden loud, and unexpected noises in the home environment can lead to short-term stress responses over a time-frame of seconds, or minutes (see [102]); but this question has not been directly investigated. It is also possible that children who show greater moment-to-moment sensitivity to noisy home environments show increased long-term environmental influences. Again, though, this question has not been directly investigated.

A third category of 'real-world' stressors are, though, events that take place over much longer time-scales. For example, Obradovic and colleagues examined how family adversity, as measured via questionnaires of financial stress, affects children ([194]). Other research has examined factors such as having multiple father figures in the home ([224]), having a family member be a victim of a crime ([225]), or so on. It is unclear whether the types of physiological changes expected in response to these long-term factors are the same, or different, to the changes expected over shorter time-scales. Further, it is unclear whether the effects of these long-term stressors operate, in effect, via the mediating influences of short-term stress responses – such as, for example, that parents experiencing financial stress are more likely to have marital conflict.

As previous researchers have noted ([89, 154, 226]), almost all of our understanding of physiological stress in children comes from research conducted in lab settings, using one of a small set of standardised experimental stressors. These include, with infants, the still face paradigm ([206]) or, with children, a transparent barrier task, in which an attractive toy is made visible, but inaccessible, to a child ([207]). These techniques have the advantage that, because they are standardised and controlled, the same measures can also be compared between different studies and sites. But they have the disadvantage that the actual measures being testing may bear little resemblance to the types of situation actually encountered in real-world settings. Furthermore, when multiple lab experimental stressors are administered to a single cohort, consistent inter-individual differences in stress reactivity are not observed ([226]). This calls in to question whether stress reactivity, even to 'negative' events, is a one- or multi-dimensional construct. Of note, similar questions of face validity apply equally to the 'positive' stimuli used in lab-based assessments of attention and learning, as we discuss further in section 4).

In summary, it appears that no previous research has examined how individuals with higher physiological stress reactivity actually react differently to real-world events as they take place. As a result of this, our current knowledge of what specific real-world environmental

factors cause physiological stress responses is currently limited. The problem that multiple risk factors tend to co-occur (such that a family experiencing financial hardship would, presumably, show higher marital conflict) makes it hard to differentiate short- and long-term influences on childhood stress. More naturalistic studies, studying stress fluctuations in real-world settings in the home, may, in future, help to understand this better.

3.5 How does increased short-term reactivity associate with altered long-term stress responses?

In this section, we consider: what are the mechanisms by which increased reactivity to adverse events over shorter time-frames gives rise to poorer outcomes over longer time-frames? We consider how increased short-term reactivity can lead to increased long-term stress. And we consider one seeming asymmetry in the model. This is that increased short-term reactivity to adverse events is thought to lead to long-term increases in stress; but increased short-term reactivity to 'positive', sought-for stimuli is not thought to lead to similar long-term effects. Why does heightened reactivity to 'negative' events lead to altered long-term stress, whereas heightened reactivity to 'positive' events does not?

Previous animal research has suggested that, over shorter-time frames, repeated evocation of a stress response leads to habituation, or diminution of that response ([4]). However, over longer time-frames, repeated evocation of a stress response causes hyper-sensitivity – i.e. increased stress reactivity in response to particular stimuli ([4]). Behavioural research with humans has, similarly, suggested that individuals exposed to more stress during early life show elevated stress reactivity during later life. For example, Cao and colleagues observed positive associations between maternal emotion dysregulation and a child's dark-enhanced startle response ([201, 221, 227, 228]). In addition to long-term hyper-sensitisation of stress *reactivity,* increased exposure to stress is also thought to lead to long-term increases in levels of tonic, resting physiological stress. Thus, increased life-long stress has two consequences: higher tonic, resting stress and increased stress reactivity (cf [229]).

Other research has suggested that this relationship may be curvilinear, such that both low, and high, levels of early stress exposure are associated with increased stress reactivity ([230, 231]). This research has mainly examined between-individual variability in stress exposure - such that individuals exposed to more early-life stress show elevated stress reactivity later in development. However, the same mechanisms might putatively explain how endophenotypic variability in short-term stress reactivity can mediate the relationship between total stress exposure and long term stress reactivity – such that, for those individuals who show a bigger reaction to a given stressor, the effect of long-term hypersensitization on stress responses is greater.

This research has, though, focused on negative stress responses. One area that appears unclear, is why, if stress reactivity is to be thought of as a one-dimensional construct (see section 3.3), then increased stress-related changes to positive, sought for stimuli do not lead to long-term hyper-reactivity in the same way that increased stress-related changes to negative, unexpected stimuli do. There is, to our knowledge, no evidence that 'positive', attention-related physiological changes can become hypersensitized through repeated exposure; and yet there appears no theoretical reason to predict why this would not be observed.

As previously noted, one further challenge here is that of integrating research findings across studies that have explored phasic (reactive) change across multiple time-scales. Aston-Jones and colleagues (see 2.1) recorded phasic changes to stimuli on a time-scale of milliseconds, whereas most of the studies that examine RSA reactivity over a time-scale of minutes. Should we think of these different studies as observing one phenomenon over multiple different time-scales, or as multiple different phenomena, to which different sets of theoretical principles apply? It may be the latter: as a number of authors have noted, recording RSA reactivity over long time-periods means that distinct physiological processes of reactivity and recovery contribute to the reactivity measure ([146, 232]). Consequently, researchers have called for more dynamic analytic approaches to investigating individual differences in physiological response trajectories ([146, 188, 233]). One possibility might be that atypical or

high-risk populations, who are known to show lower tonic (baseline) RSA, might show small initial reactivity combined with a failure of subsequent regulatory/compensatory processes. Examining change on a more fine-grained time-scale will allow us to address these questions.

In summary, previous research suggests that repeated evocation of a stress response leads to two sorts of long-term changes: increased levels of tonic, long-term physiological stress and hyper-sensitization of the stress response. It is unclear, however, why, if physiological stress reactivity is to be thought of as a one-dimensional construct, then these putative long-term effects should apply to negative (adverse) stress exposure, but not to positive physiological stress responses.

4. Directions for future work

In section 2 of this review we examined the hypothesis that increased phasic ANS reactivity, which is observed at lower levels of pre-stimulus ANS activity, is associated with better performance on cognitive assessments of attention. We concluded that the evidence was largely in favour of this hypothesis, but we also noted a variety of gaps in the literature, and directions for future work. Specifically:

i) one area that has received relatively little attention is the hypo-aroused subgroups predicted by the Yerkes-Dodson and Aston-Jones frameworks (see section 2.1.2). In section 2.5 we discussed a number of possible reasons for this. Future research should address this question in more detail.

ii) future work should explicitly examine change on different time-scales (see section 3.5). Conducting this research is essential in order to allow us to distinguish reactivity from other processes such as maintenance of change, and recovery ([146]).

iii) previous research has suggested that, whereas voluntary, 'top-down' attention control is highest during mid-level autonomic arousal, some aspects of memory encoding

should be better during hyper-arousal ([60]). Some recent findings are consistent with this ([218]). Future research should explore in more detail the strengths, as well as the weaknesses, of the hyper-aroused behavioural phenotype.

iv) the majority of the research that we have reviewed has focused on using RSA to index autonomic arousal. There may be limitations on the utility of RSA – such as constraints on time-frame over which change can be analysed, and the possibility that RSA may not be sensitive to hypo-, as well as hyper-arousal. Future research should further develop our understanding of other measures of autonomic arousal ([214]).

v) almost all previous research in this area has examined attention and learning using artificial, lab-based paradigms. These generally include, for example, discrete 'edges' (such as a stimulus appearing suddenly, from against a blank background); physiological changes are generally studied relative to these artificial 'edge' events (although see [68]), and yet these 'edges' are almost invariably absent in real-world settings. More ecologically valid work, studying how attention and learning are accompanied by concomitant physiological changes in real-world settings, is needed.

vi) finally, the implications for intervention of this work remain to be investigated. The correlational evidence we have presented suggests that, in a hyper-aroused child, decreasing short-term arousal should associate with improved performance, along with increased phasic reactivity. If future work does provide evidence consistent with the existence of the hypo-aroused subgroups predicted by the Aston-Jones framework, then the opposite prediction can also be made: that, for hypo-aroused children, increasing short-term arousal should associate with improved performance, along with increased phasic reactivity. Both of these predictions arising from the model remain, to our knowledge, largely unexplored.

In section 3 we discussed the potential bivalent role of ANS reactivity, and the potential of physiological reactivity as a mechanism for explaining how endophenotypic stress reactivity

can confer an advantage in settings where the long-term environment is supportive, and a disadvantage in settings where it is not. We identified a number of areas of investigation for future research.

i) First, we argued that more research should explicitly examine whether the same individuals who show increased reactivity to positive (interesting, engaging) stimuli also show higher reactivity to negative (aversive) stimuli (see section 3.3). We argued that recent research into autonomic stress responses may be inconsistent with the idea that stress reactivity is a one-dimensional construct, and that the behavioural evidence on this question is currently mixed.

ii) second, future work should explore whether 'real-world' experimental stressors lead to the same types of moment-by-moment changes in physiological stress as shown using experimental, lab-based stressors (see section 3.4). Although the paradigms used for assessing stress reactivity in the lab (such as the still face paradigm) have the strengths of standardization and consistency, their weakness is that the lack ecological validity. The fact that no previous research has studied children's' actual physiological changes to real-world adverse events means that a number of vital questions remain unanswered – such as which types of adverse event influence physiological stress most strongly.

iii) third, future work should explicitly examine the relationship between stressors that operate over long time-scales (such as family poverty) and stressors that operate over shorter time-scales (such as sudden, unexpected noises or parenting with high levels of expressed emotions) (see section 3.4). Future work should examine which time-scale of stressor has the biggest effect on short- and long-term levels of physiological stress, and whether, for example, the effects of long-term stressors (e.g. poverty) may be mediated by the effects of short-term stressors (e.g. parental expressed emotions).

iv) finally, there is considerable evidence that, by maturity, atypical physiological stress and stress reactivity may be a transdiagnostic risk marker for psychopathology ([229]).

But very little previous research has investigated how for this increased risk is attributable to early-emerging, endophenotypic vulnerabilities in physiological stress reactivity. Improving our ability to identify high-risk individuals early in development, and to develop new and better-targeted interventions to help them, should be an urgent goal for future research.

Figures

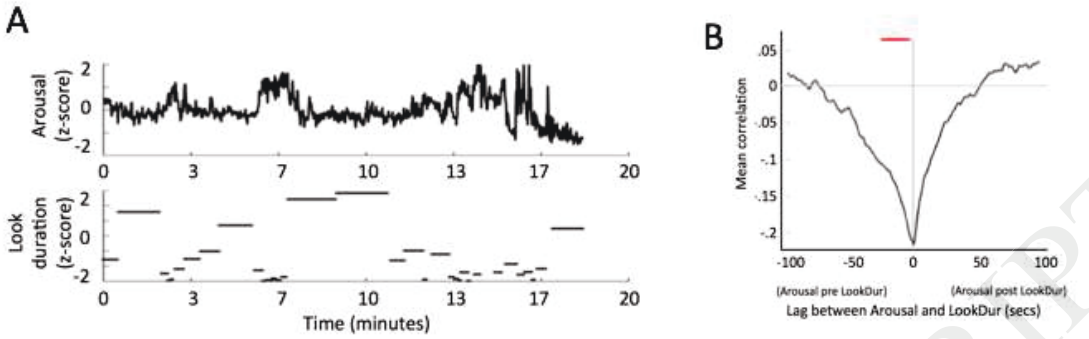

Figure 1: A) sample of raw data from the study from de Barbaro and colleagues. Infants were presented with a 20-minute battery of mixed static and dynamic viewing materials, and their changing autonomic arousal levels (top plot) and durations of looks to the stimulus presentation area (bottom plot) were measured. B) Cross-correlation plot showing how the relationship between autonomic arousal and look duration changes as a function of varying the time-interval between them. X-axis indicates the time-lag between the two variables. Y-axis indicates the correlation observed between the two variables, when one was time-lagged relative to the other. Coloured dots above the plot indicate whether a significant relation was observed at each time-lag p<.05). Three aspects of the results can be seen. First, at time 0 (no lag), a negative relationship can be seen, suggesting that, at moments of high autonomic arousal, look durations tend to be lower. Second, this relationship disappears when a lag of more than 100 seconds is introduced between the two variables, suggesting that it is temporally specific. Third, the lag is asymmetric: autonomic activity levels up to 25 seconds before the onset of a look were predictive of the duration of a look, whereas the reverse was not true. This suggests that changes in autonomic activity tend to precede changes in look duration. Figures adapted from ([70]).

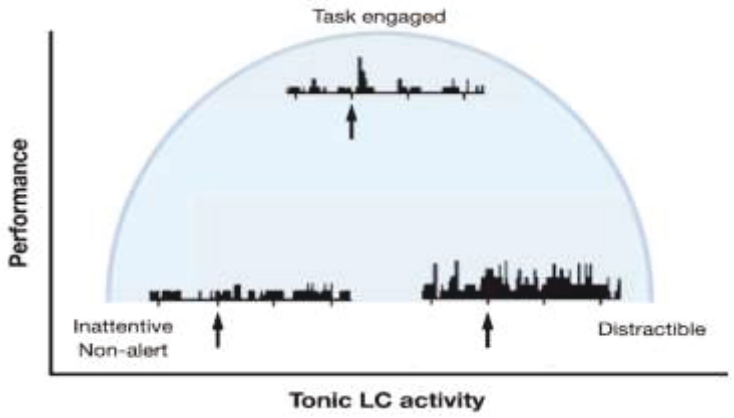

Figure 2: Schematic from Aston-Jones and Cohen. At mid-level, Tonic LC activity, phasic (event-related) LC changes are greater and the capacity to maintain focused attention is increased. At both hypo- and hyper-tonic arousal, phasic LC changes are reduced and the capacity to maintain focused attention is lower (Figure from [22]).

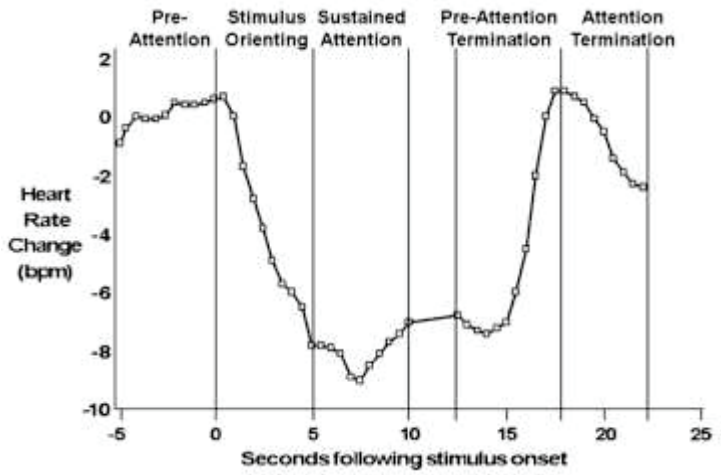

Figure 3: Heart-rate defined during a look in 3-6-month-old infants. Not all looks are accompanied by concomitant decelerations in heart rate; but those that do show better stimulus encoding ([234]) and reduced distractibility ([125]). Figure from ([122]).

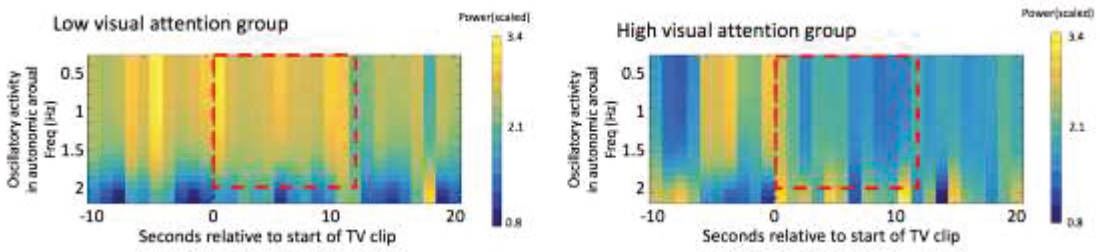

Figure 4: Autonomic arousal was measured in a cohort of 12-month-old infants by recording heart rate, electrodermal activity and movement. Oscillatory activity in autonomic activity was calculated, epoch by epoch, using a Fourier transform; results are shown as a spectrogram. (Yellow indicates that greater power was observed at that frequency in that time window; Blue, that lower power was observed.) The two spectrograms both show changes in autonomic activity relative to a stimulus event: the start of a new, attention-eliciting TV clip. The left plot shows the changes observed in a subgroup of infants who, across the whole stimulus battery, were generally more attentive to the stimulus materials. The right plot shows the same changes in a subgroup who were less generally attentive. Figure from ([129]).

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