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Elevated physiological arousal is associated with larger but more variable neural responses to small acoustic change in children during a passive auditory attention task

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ABSTRACT

Little is known of how autonomic arousal relates to neural responsiveness during auditory attention. We presented $N = 21$ 5-7-year-old children with an oddball auditory mismatch paradigm, whilst concurrently measuring heart rate fluctuations. Children with higher mean autonomic arousal, as indexed by higher heart rate (HR) and decreased high-frequency (0.15-0.8 Hz) variability in HR, showed smaller amplitude N250 responses to frequently presented (70%), 500 Hz standard tones. Follow-up analyses showed that the modal evoked response was in fact similar, but accompanied by more large and small amplitude responses and greater variability in peak latency in the high HR group, causing lower averaged responses. Similar patterns were also observed when examining heart rate fluctuations within a testing session, in an analysis that controlled for between-participant differences in mean HR. In addition, we observed larger P150/P3a amplitudes in response to small acoustic contrasts (750 Hz tones) in the high HR group. Responses to large acoustic contrasts (bursts of white noise), however, evoked strong early P3a phase in all children and did not differ by high/low HR. Our findings suggest that elevated physiological arousal may be associated with high variability in auditory ERP responses in young children, along with increased responsiveness to small acoustic changes.

1. Introduction

The Autonomic Nervous System (ANS) is the neural substrate of the body's stress response (Cacioppo et al., 2000). It has two main components: the Sympathetic Nervous System (SNS), involved in quick response mobilising ('fight or flight') (Cacioppo et al., 2000), and the Parasympathetic Nervous System, involved in slow-acting, response-dampening ('rest or digest') responses (Ulrich-Lai and Herman, 2009). Although the two interact largely in opposition, their function is non-additive (Janig and Habler, 2000; Lacey, 1967). One widely used peripheral index of ANS function is heart rate, which receives contributions from both the SNS and PNS, with faster HR indexing greater SNS and less PNS activity (McCabe, 2000). In addition, 'high-frequency' activity in the respiration range (e.g. 0.15-0.8 Hz) is thought to index PNS activity (Bush et al., 2011). Although some researchers have differentiated 'high-frequency' from 'low-frequency' activity (< 0.15 Hz), treating the latter as an index of SNS activity (Berntson et al., 1997), more recent research has criticised this differentiation (Reyes del Paso et al., 2013; Billman, 2013).

Research has shown that fluctuations in both long- (Richards, 1985)

and short-term (de Barbaro et al., 2016a; Wass et al., 2016) physiological arousal associate with fluctuations in visual attention (Arnsten, 2009; Liston et al., 2009; Wass, 2018). Behaviourally, increased autonomic arousal (increased SNS and decreased PNS) associates with decreased voluntary attention control and increased responsivity to salient targets, whereas lower arousal is associated with increased voluntary (endogenous) attention control (Arnsten, 2009; Liston et al., 2009; Broadbent, 1971; Alexander et al., 2007). These findings have been observed from animal research (Usher et al., 1999) and recordings of ANS function in adults (Holzman and Bridgett, 2017; Thayer et al., 2009), children and infants (Richards, 2010; Richards et al., 2011; Bacher and Robertson, 2001), including experimental manipulations of stress (Liston et al., 2009).

Non-human primate research in this area has focused on the Locus Coeruleus (LC), a brainstem area implicated in ANS control (Usher et al., 1999; Sara and Bouret, 2012). At times of elevated physiological stress, tonic firing rates in the LC are increased (McCall et al., 2015). With higher tonic firing rates, phasic (stimulus-evoked) responses become more inconsistent (Usher et al., 1999; Aston-Jones and Cohen, 2005). *Neural gain*, the degree to which neural signals are amplified or

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suppressed contingent on relevance, is lower during elevated arousal (Aston-Jones and Cohen, 2005). Atypical neural gain (Hauser et al., 2016) and hyper-tonic arousal (Sonuga-Barke et al., 2010; Imeraj et al., 2012) have both been hypothesised to be core deficits in ADHD. Phasic, stimulus-evoked activity in the LC has been associated with evoked brain components such as the P3 (Murphy et al., 2011; Nieuwenhuis et al., 2005). However, no previous research, to our knowledge, has examined the relationship between arousal and variability in neural evoked responses, in human participants (Wass, 2018).

Most previous research into physiological arousal and attention has studied attention in the visual domain. Relatively few studies have examined the relationship between physiological arousal and auditory attention - despite that auditory attention is considered a key gateway skill during language acquisition, for example (Choudhury and Benasich, 2011; Bishop, 2007). Understanding relationships between physiological arousal and auditory attention may, for example, be helpful for recognising differences in auditory processing that have been noted as a function of socio-economic status (SES) (Stevens et al., 2015, 2009), and which have been implicated in understanding individual differences in language learning capacity (Bishop, 2007; Tonquist-Uhlen, 1996; Montgomery and Windsor, 2007). Investigating this was the aim of the present paper.

We used a version of an auditory oddball paradigm in which frequently presented 500 Hz tones were interspersed with two rare variants: 750 Hz tones and broadband white noise (Kushnerenko et al., 2002a, 2007). Typically, in response to frequently presented standards, two main components can be observed in children under the age of 10 years: the P150 (P2), positive component, peaking at about 100–200 ms, and the N250 (N2), negative component peaking at about 250–350 ms or even later if merged with the subsequent N450 at faster presentation rates (Čeponien et al., 1998). The functional significance of these obligatory components in children remains to be clarified.

In adults, the source of the P2 has been located by magnetoencephalography (MEG) to the superior temporal gyri (Hari^o et al., 1987). In addition, some results indicate that the P2 at least partially reflects auditory driven output of the reticular activating system and consequently associated with the maintenance of behavioural arousal (Knight et al., 1980; Rif et al., 1991; Robinson, 1999). The P2 modulation in response to infrequent deviant in oddball paradigms was observed only in young children but not in adults (Ruhnau, 2013 #3165, Ruhnau et al., 2010). The N2 elicited by frequent repetitive stimuli ('basic' N2; Näätänen and Picton, 1986) was reported mainly in children and often denominated N250 according to its latency (Čeponien^e et al., 2001; Čeponien et al., 2002; Ceponien et al., 1998; Korpilahti and Lang, 1994). In children, the N2 amplitude was found larger in response to complex rather than simple tones (Čeponien^e et al., 2001). It is assumed to originate bilaterally in the auditory cortex of the superior temporal lobes with frontal predominance (Čeponien et al., 2002; Gomot et al., 2000). There are several studies reporting smaller N250 amplitudes in children born prematurely (Fellman et al., 2004; Gomot et al., 2007), in infants with craniofacial anomalies associated with a risk for a developmental delay (Ceponien et al., 1998; Balan et al., 2002), and in language-impaired (Tonquist-Uhlen, 1996), and dysphasic children (Korpilahti and Lang, 1994).

In addition the rare, or 'oddball' stimuli allowed us to investigate auditory change detection to both small- and large-spectral changes (Kushnerenko et al., 2013a). The response to larger spectral changes (noises or so called 'novel' sounds) is usually very consistent across subjects, representing early negativity (N1/Mismatch Negativity/MMN), followed by a large positivity (P3a) and a late negativity (LN) commencing at about 400 ms (Wetzel and Schröger, 2014). The P3a is only elicited when auditory change is large enough to trigger involuntary (bottom-up, saliency-driven) attention mechanisms and is sometimes linked to a behavioural distraction from the task and impairment in performance (Wetzel and Schröger, 2014).

The brain response to smaller acoustic changes (deviants) in

children, called the Mismatch response (MMR), can be characterized by either negative (nMMR or Mismatch negativity, MMN (Näätänen et al., 1978) or positive (pMMR) components, usually seen as an increase in N250 or P150 amplitudes in response to deviants compared to standards. Coexistence of positive and negative MMRs in children and infants presented a riddle for more than a decade for developmental researchers. Recently, however, there has been development in understanding these two components, presumably indexing different functional characteristics (Kushnerenko et al., 2002a, 2007). It has been proposed that the mismatch response associated with high attentional demands in the sound discrimination exhibits a positive polarity (pMMR) and is considered a less mature MMR response. The mismatch response associated with low attentional demands (more automatic) exhibits a negative polarity (i.e., MMN) and is considered the more mature MMR (Garcia-Sierra et al., 2016).

Both MMN and pMMR co-exist in the same age group (4–6 year old pre-schoolers) with larger and easier deviants eliciting adult-like MMNs, whereas smaller deviants elicit P-MMRs (Lee et al., 2012). Therefore, auditory change detection can occur with high or low attentional demands that are mediated by language experience (Garcia-Sierra et al., 2016; Rivera-Gaxiola et al., 2005; Friedrich et al., 2009), discriminability of the stimuli (Lee et al., 2012; Cheng et al., 2015) and maturational factors (Kushnerenko et al., 2002a; Morr et al., 2002; Maurer et al., 2003). There has been also been a discussion of whether pMMR can represent an early phase of the P3a component elicited in response to attention-getting stimuli (Kushnerenko et al., 2002a, 2007). However, this still requires further investigation.

Our research participants were 5-7-year-old children. We predicted that heightened levels of arousal would be associated with increased distractibility, potentially triggering attention mechanisms to a larger extent, in response to small acoustic changes. Therefore we predicted that a more P3a-like response, manifesting as a higher amplitude P150 component, would be observed in children with higher physiological arousal. Based on previous research (Aston-Jones and Cohen, 2005) we also predicted that increased physiological arousal would result in more variable trial-to-trial brain responses to the same stimulus.

2. Method

Participants: 39 participants were originally tested for the study. Their mean (std) age on the day of testing was 73.6 (sd 12.2) months. Although detailed demographic data were not collected it should be noted that the recruitment area for this study, Stratford in East London, is a demographically mixed area of London. The nature of our study meant that data from a number of participants were unavailable due either to technical problems with one of the recording streams, to insufficiently good quality data recording from one of the measures, or to technical problems sending event codes between the two streams. Technical problems with the ECG recording systems led to the loss of data N = 8 participants. Further technical problems led to problems with sending event codes between with ECG and EEG recording equipment (N = 7). Insufficiently good quality EEG data led to the loss of data from 8 participants. In total, ECG data were available for N = 30 participants; EEG data were available for N = 34 participants; both ECG and EEG data were available from N = 21. The age of participants who contributed both usable ECG and EEG data was 71.9 (sd 11.9) months on the day of testing.

Equipment: EEG was recorded using a high-density 128-channel HydroCel Geodesic Sensor Net (HGSN) produced by EGI (EGI, Eugene, OR). The size of the HGSN was chosen based on the child's head circumference. The EEG signal was referenced to the vertex, recorded at a 500 Hz sampling rate with band-pass filters set from 0.1 to 100 Hz using a Kaiser Finite Impulse Response filter. Prior to recording the impedance of each electrode was manually checked to ensure that they were below 100 kΩm.

ECG was recorded using a BioPac (Santa Barbara, CA) system

recording at 1000 Hz. Disposable Ag–Cl electrodes were used, placed in a modified lead II position. Stimuli were presented using E-Prime. In order to ensure accurate time-synchronisation between the EEG and ECG recording systems, simultaneous event codes were sent concurrently from E-Prime via TTL pulses to the EEG and ECG recording systems during stimulus presentation.

Procedure: The experiment consisted of 4 blocks of 100 trials. Each block consisted of: 70 ‘standard’ 500 Hz tones; 15 ‘deviant’ 750 Hz tones; 15 ‘noise’ (white-noise segments). The harmonic tones of 500 and 750 Hz fundamental frequency were constructed from the three lowest partials, with the second and third partials having a lower intensity than the first one by 3 and 6 dB, respectively. The harmonic tones were used instead of sinusoids for two reasons. Firstly, because it has been shown previously that complex tones result in larger N250 amplitudes in children than sinusoids (Čeponienė et al., 2001). Secondly, we aimed to use the same paradigm that was used in a number of longitudinal and cross-sectional studies in infants and children in order to increase our understanding of the observed previously effects (Kushnerenko et al., 2007). The duration of the sounds was 100 ms, including 5-ms rise and 5-ms fall times. The interstimulus (offset-to-onset) interval was 700 ms. The order in which the trials were presented was pseudo-randomised in order to ensure that two deviant and noise trials were always separated by at least two standard trials. In between blocks, 60-second videos were presented of actors reciting nursery rhymes to the camera, in order to allow participants to rest and to minimise the cumulative effect of fatigue over consecutive blocks. The total paradigm, including preparation, recording, breaks and EEG cap removal, lasted approximately one hour per participant. The proposal was approved, prior to the commencement of the study, by the University Research Ethics Committee at the University of East London.

Data analysis: The vertex-referenced EEG was algebraically re-computed to an average reference. The signal was off-line low-pass filtered at 30 Hz using a Kaiser Finite Impulse Response filter and segmented into epochs starting 100 ms before and ending 600 ms after the stimulus onset. Channels contaminated by eye or motion artifacts were rejected manually, and trials with more than 20% bad channels were excluded. The average (std) [min-max] proportion of channels excluded per trial was 0.09 (0.12) [0.01–0.45] for standard trials; 0.09 (0.10) [0.01–0.37] for deviant trials; 0.06 (0.09) [0.001–0.32] for noise trials. The mean (range) (std) number of trials included was 248 (210–270) (19) for standard; 50 (42–56) (4) to deviant; 54 (48–60) (4) for noise. This number of accepted trials has proven to be sufficient for this type of paradigm (Kushnerenko et al., 2013a; Guiraud et al., 2011; Dehaene-Lambertz and Dehaene, 1994; Friederici et al., 2007; Kushnerenko et al., 2013b, 2008).

The valid ERPs obtained for each stimulus type were first averaged to create a per-participant mean waveform. The electrode locations used are shown in Fig. 1b. Because P150 and the early phase of the P3a represent an overlapping double-peaked component in response to white noise (Fig. 1a), the amplitude and latency of the maximum positive change was measured between 100 and 300 ms post stimulus onset.¹ The following negative peak representing merged N250 and

¹ The reason for not analysing P150/P3a separately is that in children these components are often inseparable. Firstly, due to large inter-individual differences the latency windows for these peaks overlap and therefore analysing these two peaks in two separate windows we are at risk to miss the component’s maximum amplitude if it is elicited earlier or later than on the average. Secondly, in Kushnerenko et al. (2002a, b) it has been shown that there is a superposition of the positive and negative ERP components in infants and young children in the same latency range (see also Morr et al., 2002 for corroborating evidence) and an emerging negative component is often seen riding on top of the wider positivity dividing it into two subcomponents P150 and an early P3a. In the absence of this negative peak (presumably emerging N1) the response is often seen as one positive peak, so in fact the separation of this positive component into two might be artificial. Kushnerenko et al. (2002a, b,

N450 components, will be called throughout N250 and was measured as the maximum negative change between 200 and 500 ms post stimulus onset. The late negativity (LN) in response to white noise was measured in the time window from 400 to 600 ms. The amplitude was calculated as the mean amplitude \pm 20 ms around the peak amplitude. The time windows were defined based on the longitudinal and cross-sectional research using the same paradigm (Kushnerenko et al., 2007, 2002b) and the average of fronto-central channels was used as the largest MMN/P3a/LN were expected to occur over this area (Gumenyuk et al., 2005, 2004).

Raw ECG data were parsed to identify heart beats using a variable amplitude thresholding criterion. The amplitude threshold was inspected and adjusted between participants using the data visualisation illustrated in the SM (see Fig. S1). Then, automatic artefact rejection criteria were used to automatically identify artefactual beats: if the time interval between beats was less than 400 ms or greater than 1100 ms, or if the rate of change between that beat and the preceding beat exceeded 400 ms. This level was set, following visual inspection, as greater than the maximum rate of change of heart rate in vagally mediated HR changes (see Fig. S1). Following automatic parsing, data were visually inspected in order to identify erroneously identified beats. The criteria used to identify short- and large-scale variability in HR are described in the Supplementary Materials.

3. Results

In Analysis 1 we examine how between-participant variability in HR related to neural evoked responses on the Standard (Figs. 2,3), Deviant (Fig. 4) and Noise (Fig. 5) conditions. In Analysis 2 we examine how within-participant variability in HR – fluctuations in HR within the testing session – associated with altered patterns of evoked neural responses.

3.1. Preliminary analyses – descriptive

Fig. 1 shows the grand average ERPs (Fig. 1a), the electrode locations used to calculate all ERPs (Fig. 1b) and the deviant-standard waveform (Fig. 1c). ERPs to standard and deviant both consist of the P150 followed by N250, the latter being more negative displaced in the deviant compared to the standard. This can be seen in the deviant-standard difference wave with the negative peak around 200 ms. ERPs to white-noise segments also represent a typical waveform consisting of a large and prolonged positive peak (merged P150 and early phase of P3a), followed by a merged N250 and Late Negativity (LN).

Fig. S2, in the Supplementary Materials, shows the raw HR data collected during the experiment, rank ordered by mean HR obtained across the entire trial. The participants showed generally consistent inter-individual differences in mean HR across the recording session. It can also be seen that, in addition to differences in mean HR, participants showed differences both in the level of high-frequency heart rate variability (regular, vagally mediated changes in HR with the respiration cycle, known as Respiratory Sinus Arrhythmia) (Anrep et al., 1935; Porges, 2017) as well as low-frequency variability, often considered an index of sympathetic nervous system activity (Berntson et al., 1997; Billman, 2013). In the Supplementary Materials we present analyses to examine these other aspects of variability in the time series. In the main text we focus on mean HR (Analysis 1) and within-participant

(footnote continued)

2013a, b) have argued that certain amount of involuntary attention in young children can be triggered even by small acoustic change, i.e. by frequency deviants, and therefore mismatch positivity observed in children might be elicited due to recruiting of some involuntary attention mechanisms. However, in response to noise sounds the elicitation of the early P3a observed much more clearly due to more salient acoustic contrast.

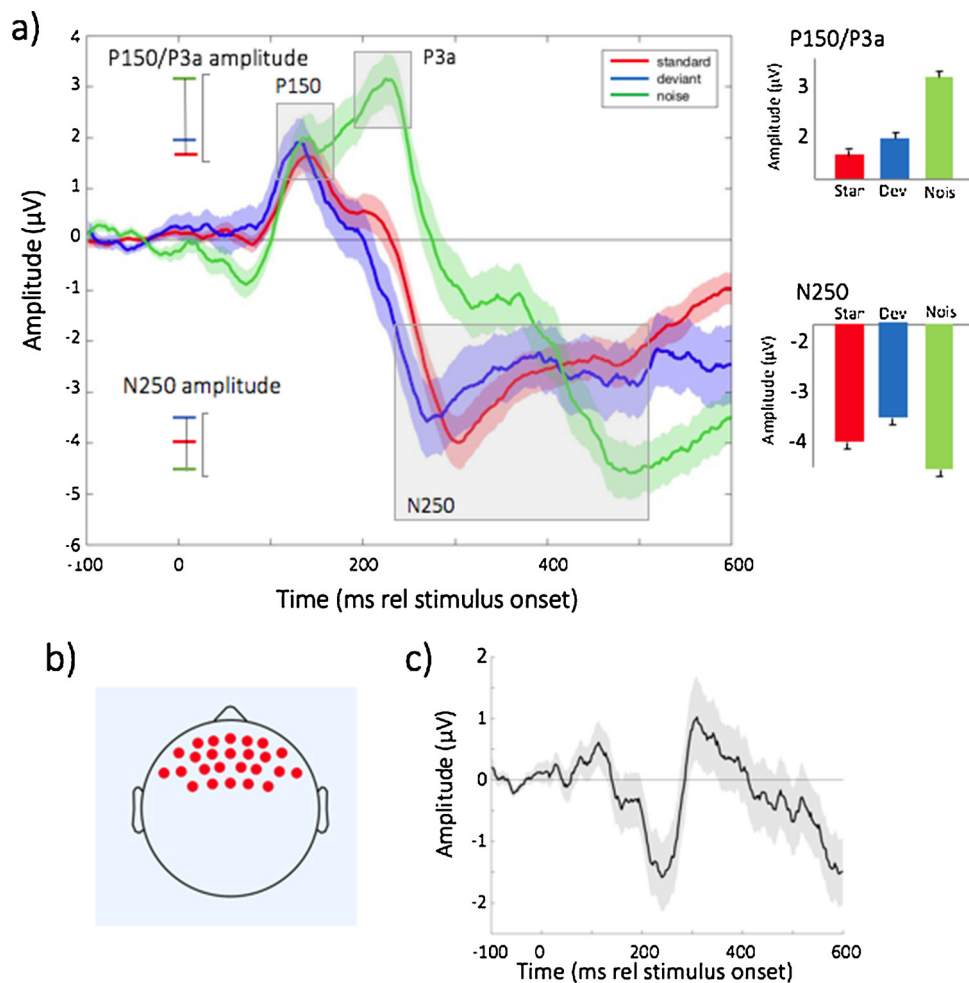


Fig. 1. a) Left - grand average ERPs. Shaded areas represent the error bars, calculated as the Standard Error of the Mean. Right - amplitudes for the P150/P3a and N250. b) Electrode locations used to calculate all ERPs. The locations used are marked red. c) Deviant-Standard difference wave (grand average). Shaded areas represent the error bars, calculated as the Standard Error of the Mean.

variability in HR (Analysis 2).

3.2. Analysis 1 – between-participant variability in HR

In Analysis 1 we examine how between-participant variability in HR related to participant responses on the Standard (Figs. 2,3), Deviant (Fig. 4) and Noise (Fig. 5) conditions.

3.2.1. Standard

Fig. 2c shows the mean ERP responses for the standard trials, subdivided using a median split by mean HR across the testing session. Although the latency of the N250 component is similar between the two groups, the amplitude is lower for the high HR group. Topoplots (Fig. 2a and b) indicate that this effect was observed consistently across all fronto-central channels. Fig. 2d shows the bivariate relationship between mean HR and N250 peak amplitude. (For this, and all subsequent bivariate relationships reported below, normality plots were conducted; but these have not been reported throughout for reasons of space. Because not all data were found to be parametrically distributed, the more conservative nonparametric Spearman's test was used throughout, for consistency.) The bivariate relationship between mean HR and N250 peak amplitude was found to be $\rho(20) = .49$, $p = .027$, suggesting that higher mean HR is associated with lower amplitude N250 responses on Standard trials.

In order further to investigate why smaller average N250 responses were observed in participants with higher HR, we investigated the

hypothesis that participants with higher HR might show increased *between-trial variability* in evoked responses. First, the peak amplitude ERP responses were calculated trial by trial, and pooled into high HR and low HR groups, based on a median split. Individual trials more than 2 IQR +/- the mean were excluded. Separate histograms were computed for each distribution and compared (Fig. 3c). The median results are similar: $-10.2\mu\text{V}$ for both the high and low HR groups. But the high HR group shows both more high and low values than the low HR group, along with a longer tail. In order to quantify these differences ex-Gaussian distributions were fitted, as described in the Supplementary Materials section 2.iii (Lacouture and Cousineau, 2008). In brief, these analyses suggested that the model responses were similar across the two populations (as shown by similar μ components of the ex-Gaussian), but that both τ (exponential component) and σ (the variance of the Gaussian component) were larger in the high HR group.

Second, we calculated the average between-trial variance in N250 amplitude, by computing the N250 peak amplitude individually for each trial presented, log transforming the data, and calculating the standard deviation between trials. A significant relationship was observed between mean HR and between-trial variance in N250 amplitude $\rho(20) = .46$, $p = .045$, suggesting that participants with higher mean HR showed greater between-trial variance in N250 amplitude (Fig. 3a). A marginally non-significant bivariate relationship was identified when comparing between-trial variance in N250 peak amplitude and N250 amplitude, suggesting that participants with greater between-trial variance in N250 amplitude showed lower average N250

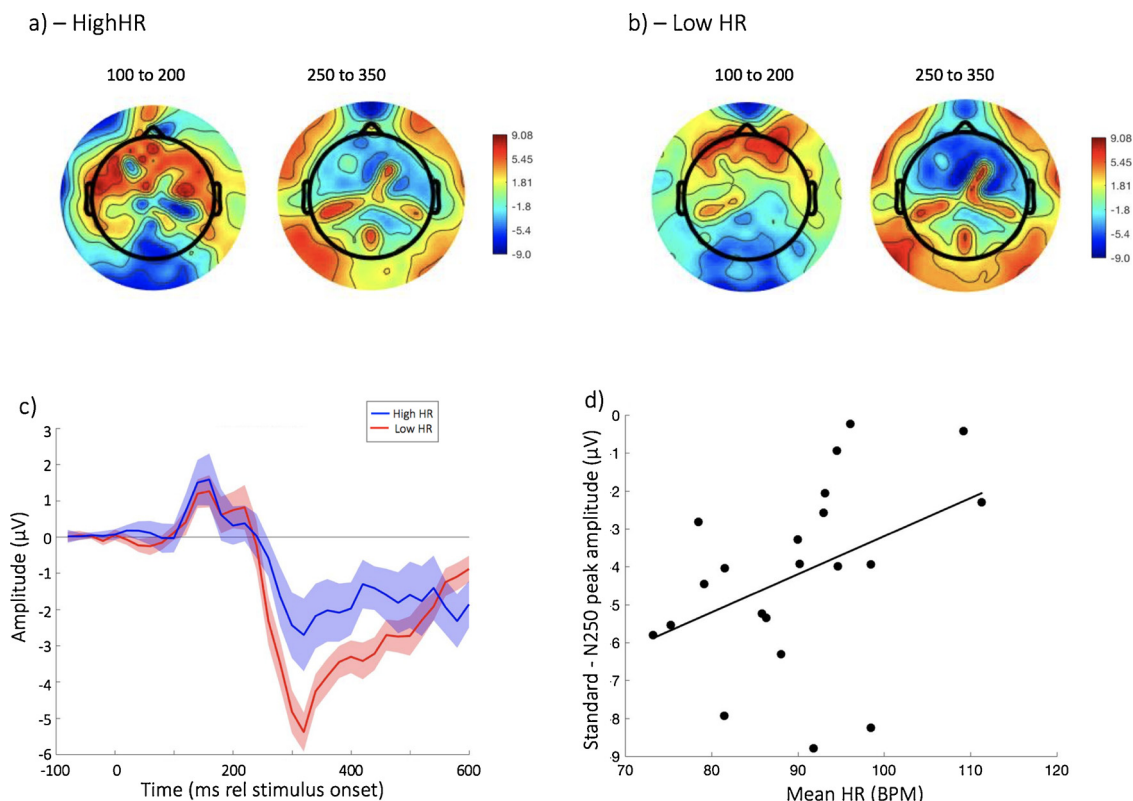


Fig. 2. a and b) - topoplots for responses to the Standard trials, split by the participants' mean HR across the entire testing session. The figure above each time plot indicates the mean time of each bin, in ms, relative to stimulus onset. Only the time intervals 100–200 ms and 250–350 ms, corresponding to the main ERP peaks, are shown. Results for other time intervals are shown in the SM (Fig. S6). The colour bar indicates the voltage, in μV . a) High HR group; b) Low HR group. c) ERP response to the Standard trials, subdivided into the low HR group (red) and the high HR group (blue) and downsampled to 20 ms. Shaded areas represent the error bars, calculated as the Standard Error of the Mean. d) Scatterplot showing the significant relationship observed between mean HR and peak amplitude of the N250 on Standard trials.

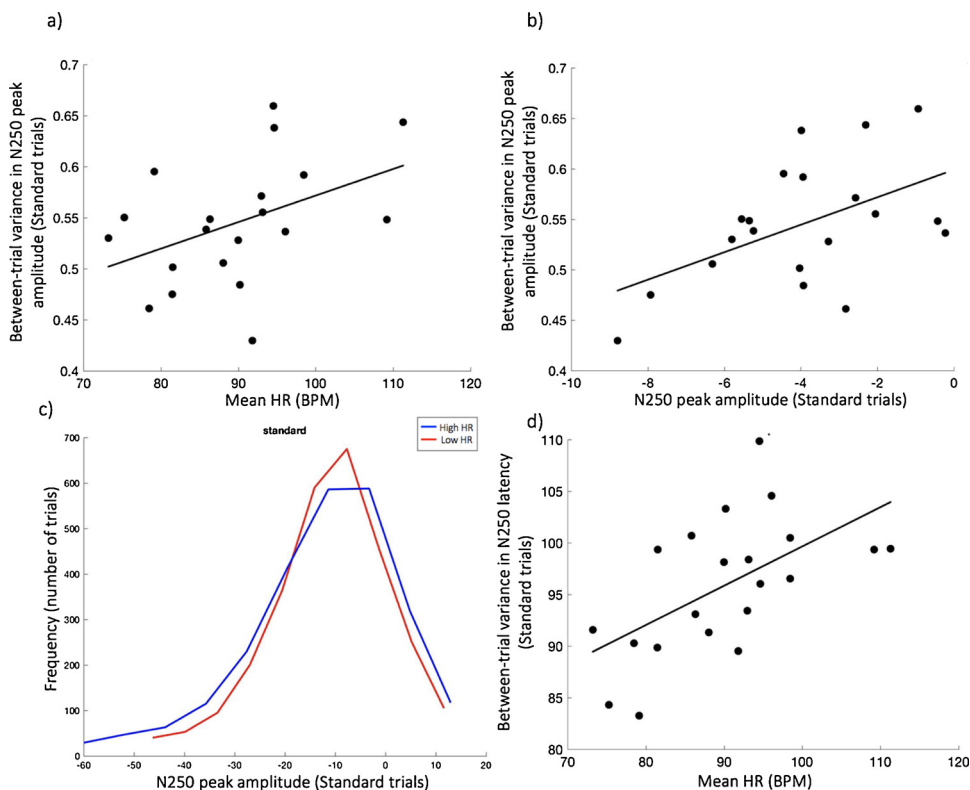


Fig. 3. a) Scatterplot showing the relationship between mean HR and between-trial variance in N250 amplitude. b) Scatterplot showing the relationship between N250 peak amplitude and between-trial variance in N250 amplitude. c) Histogram showing the distributions of ERP amplitude responses observed across all Standard trials, sub-divided into the low average HR group and the high average HR group. Although the modal response is similar, the high HR group show greater variability in responses. d) Scatterplot showing the relationship between mean HR and between-trial variance in N250 latency.

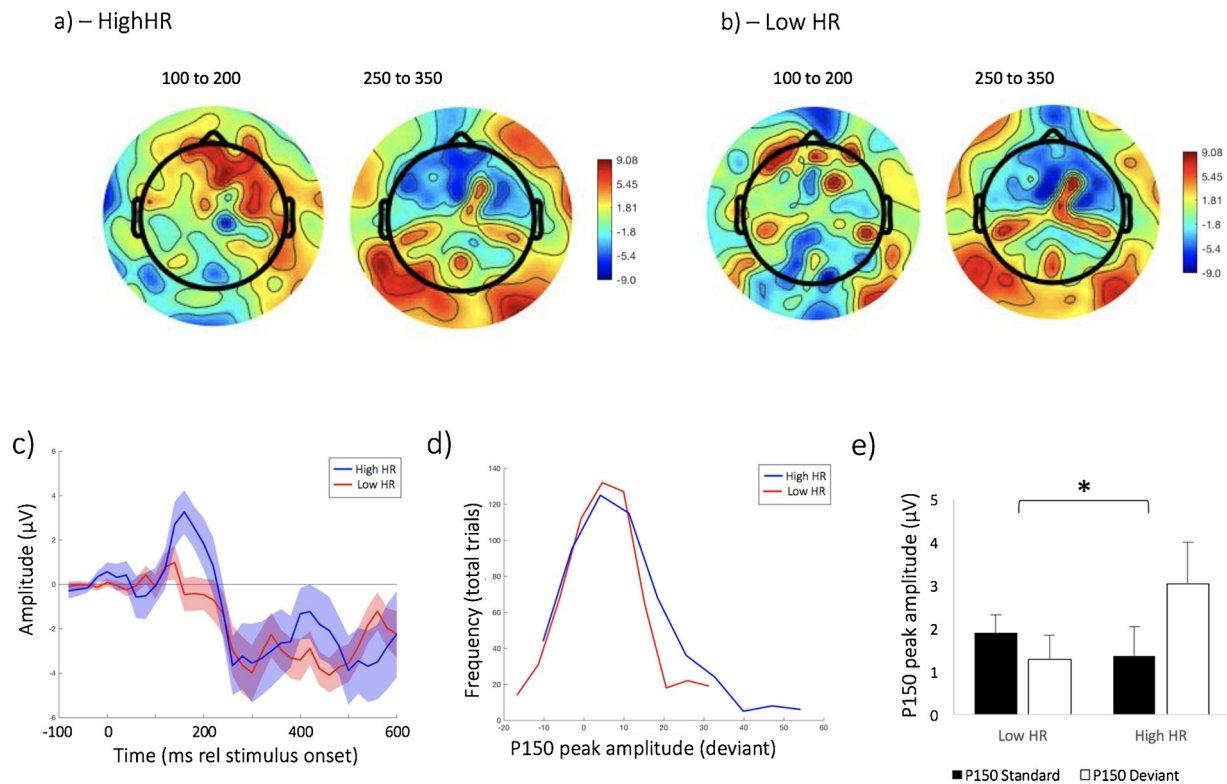


Fig. 4. a) and b) - topoplots for responses to the Deviant trials, split by the participants' mean HR across the entire testing session and binned into 100 ms time intervals. The figure above each time plot indicates the mean time of each bin, in ms, relative to stimulus onset. Only the time intervals 100–200 ms and 250–350 ms, corresponding to the main ERP peaks, are shown. Results for other time intervals are shown in the SM (Figure S6). The colour bar indicates the voltage, in μV . a) High HR group; b) Low HR group. c) ERP response to the Deviant trials, subdivided into the low HR group (red) and the high HR group (blue) and downsampled to 20 ms. Shaded areas represent the error bars, calculated as the Standard Error of the Mean. d) histogram showing the distributions of ERP P150/P3a amplitude responses observed across Deviant trials, sub-divided into the low average HR group (red) and the high average HR group (blue). e) Bar chart showing the P150 standards observed for the Standard and Deviant trials, split by low HR and high HR groups. Error bars represent the Standard Error of the Mean. The star indicates the results of the mixed ANOVA described in the main text ($p < .05$).

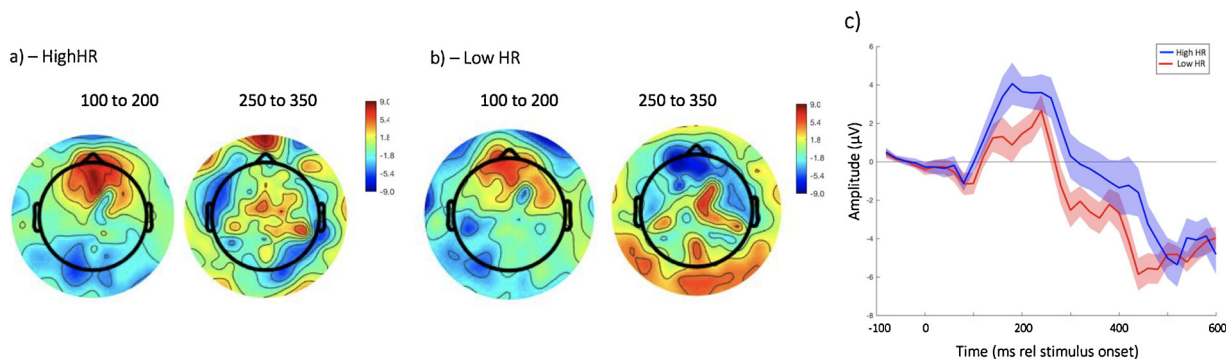


Fig. 5. a) and b) - topoplots for responses to the Noise trials, split by the participants' mean HR across the entire testing session and binned into 100 ms time intervals. Only the time intervals 100–200 ms and 250–350 ms are shown. Results for other time intervals are shown in the SM (Fig. S6). The figure above each time plot indicates the mean time of each bin, in ms, relative to stimulus onset. The colour bar indicates the voltage, in μV . a) High HR group; b) Low HR group. c) ERP response to the Noise trials, subdivided into the low HR group (red) and the high HR group (blue) and downsampled to 20 ms. Shaded areas represent the error bars, calculated as the Standard Error of the Mean.

peak amplitude responses $\rho(20) = .42$, $p = .067$ (Fig. 3b). Identical relationships were observed between mean HR and the latency of the peak amplitude: participants with higher mean HR showed increased variability in the latency of the peak N250 response $\rho(20) = .60$, $p = .005$ (Fig. 3d) and participants with increased variability in the latency of the peak N250 response showed smaller average amplitude N250 responses $\rho(20) = .62$, $p = .003$.

Overall, these results suggest that the modal responses are similar across the two populations, but that response variability was larger in the high HR group. Thus, despite the fact that large amplitude

responses were marginally *more* common in the high HR group (Fig. 3c), the greater between-trial variability both in the peak amplitude and the latency of the peak amplitude in the high HR group (Fig. 3a and d) leads to lower average response amplitudes.

3.2.2. Deviant

Fig. 4c shows the mean ERP responses for the deviant trials, subdivided using a median split by mean HR across the testing session. It can be seen that the P150/P3a component appears to show a larger positivity in the high HR group. The topoplots (Fig. 4a and b) indicate

that this effect was observed consistently across fronto-central channels. In order to assess whether a larger P150/P3a was observed to the deviant relative to the standard trials, the P150/P3a peak amplitude was directly compared between the standard and deviant conditions, and subdivided by participant mean HR (Fig. 4e). A mixed ANOVA with P150/P3a amplitude as the DV, condition (Standard vs Deviant) as within-participants factor and HR group (Low vs High) as between-participants factor indicated a significant interaction between condition and group $F(1,19) = 9.9$, $p = .025$, partial $\eta^2 = .24$. Post-hoc analyses using paired-sample t-tests indicated that the P150/P3a was higher to deviant than standard trials in the high HR group $t(9) = 2.30$, $p = .047$, Cohen's $d = 0.79$ but not the low HR group $t(10) = 1.01$, $p = .34$, Cohen's $d = 0.28$.

In order further to investigate why larger average P150/P3a responses were observed in participants with higher HR, we again investigated between-trial variability in evoked responses. Peak amplitude ERP responses were calculated trial by trial, and pooled into high HR and low HR groups, based on a median split. Individual trials more than 2 IQR +/- the mean were excluded. Separate histograms were computed for each distribution and compared (Fig. 4d). Ex-Gaussian distributions were fitted (see Supplementary Materials section 2.iii) (Lacouture and Cousineau, 2008). These results suggest that, whereas the modal responses were again similar between the two groups (shown by the similar μ components), the increased mean P150/P3a amplitudes observed in the high HR group were associated with a sub-group of trials with a high response amplitude, manifesting as an increased τ (exponential component).

3.2.3. Noise

Fig. 5c shows the mean ERP responses for the Noise trials, subdivided using a median split by mean HR across the testing session. Fig. 5a and b show topoplots split by mean HR. An identical series of analyses were conducted to those reported for the Standard and Deviant condition, including a mixed ANOVA with condition (Standard vs Deviant) as within-participants factor and HR group (Low vs High) as between-participants factor were conducted, but no significant group differences were observed. In addition neither the latency ($\rho(20) = .17$, $p = .47$) or the amplitude ($\rho(20) = .21$, $p = .36$) of the Late Negativity component showed a significant relationship to mean HR.

3.2.4. Relationship between HR variability and ERP responses

In the Supplementary Materials we examine how low- and high-frequency variability in our ECG data relate to the ERP responses observed. Robust individual differences in both low- (< 0.15 Hz) and high- (0.15–0.8 Hz) frequency variability could be obtained, as indicated by strong correlations between time and frequency domain estimates (Fig. S7). As expected (Cacioppo et al., 2000), high-frequency variability, which is thought to index vagal/parasympathetic influence, showed strong associations with mean HR ($\rho = -0.76$) (Fig. S7d) (lower HR associated with increased high-frequency variability). Virtually identical patterns of association with the ERP responses were observed for high-frequency variability as were observed for mean HR: increased high-frequency variability was associated with larger N250 Standard responses and reduced P150/P3a Deviant responses (Figs. S8, S9). In addition, increased low-frequency variability was also associated with smaller amplitude N250 Standard responses (Figure S8b), although no relationship was observed between low-frequency variability and P150/P3a Deviant responses (Fig. S8e).

3.3. Analysis 2 – within-participant changes in HR

Our main analyses presented above look at between-participant differences based on mean HR recorded across the entire testing session. In addition, we also looked at whether similar patterns could be identified when we examined within-participant variability – i.e. fluctuations in HR within a particular individual, within a testing session.

Results for this analysis are given in the Supplementary Materials section 2.iv (Fig. S10). In brief, highly comparable patterns of results were observed. Trials where HR was high showed smaller amplitude N250 Standard responses – albeit with a smaller effect size than the between-participant analyses. For P150/P3a Deviant responses, a directionally similar result (larger amplitude associated with higher HR) was observed but the effect was not significant. Of note, because these analyses examine within-participant variability (comparing high and low HR trials within a testing session, separately for each participant), these findings are entirely independent of the results in the Analysis 1, which examine between-participant differences.

4. Discussion

We used an ERP paradigm to measure passive auditory attention in 5-7-year-old children whilst concurrently measuring between- and within-participant variability in heart rate (HR). Our results had two main features of interest: first, children with higher physiological arousal showed smaller amplitude N250 responses to Standard tones, which follow-up analyses suggested was due to increased within-participant variability in neural responsiveness in the high-arousal group. Second, children with higher physiological arousal showed larger amplitude P150/P3a responses to Deviant tones. Responses to noise showed a response with much larger early P3a phase across all children, with no significant differences related to heart rate. We shall discuss our two main findings in turn.

First, Fig. 2 illustrates the significant negative relationship observed between mean HR and N250 response amplitudes to 500 Hz tones. High-frequency variability in HR, thought to index Respiratory Sinus Arrhythmia (Parasympathetic Nervous System control) was associated negatively with mean HR (Fig. S7d) and showed the same pattern: more high-frequency variability associated with larger N250 amplitude (Fig. S8). We also examined within-participant variability in HR in a separate analysis that controlled for differences in mean HR. Consistent with the results of Analysis 1, we found that, within each testing session, trials with higher HR showed reduced N250 responses to standard tones (Fig. S10), albeit with a smaller effect size than noted in the between-participant analyses.

Between participants, elevated HR was associated with increased trial-to-trial variability for both response amplitudes (Fig. 3b) and response latencies (Fig. 3d). Previous research has reported that when single-trial ERPs are averaged, the amplitude of a peak in the average ERPs is inversely related to the trial-to-trial variability in latency of that peak (Thomas et al., 1989), consistent with the relationship we observed in our data (Fig. 3c). Our results were consistent with this. Thus, despite that the response histogram showed *more high-amplitude* evoked responses in the high HR group (Fig. 3c), the averaged evoked responses in the high HR group were lower (Ouyang et al., 2016).

One possible artifactual explanation of our findings is that the children with higher HR moved more during testing, which may have contributed to the increased variability in our results (Georgieva et al., 2017). However, this appears unlikely because our participants were seated during recording, and any trials containing gross movement artefact were excluded by our artefact rejection techniques. Further, it is unclear how movement artefact would contribute to the presence both of larger, and smaller N250 responses, as well as to both smaller average ERPs in one condition and larger ERP responses in another.

Previous studies have noted high levels of variability in ERP studies with infants and children (Bishop, 2007; Kushnerenko et al., 2002a, 2007). However, the present results are, to our knowledge, the first demonstration that increased variability in neural evoked responses associates with elevated physiological arousal. Consistent with this, previous research with non-human primates has identified systematic relationships between an individual's level of pre-stimulus physiological arousal and the consistency of the phasic responsiveness that they show to relevant stimuli (Usher et al., 1999). Other research has

suggested that at times when pre-stimulus arousal is higher, neural gain, the degree to which neural signals are amplified or suppressed contingent on relevance, is reduced (Aston-Jones and Cohen, 2005; Hauser et al., 2016; Aston-Jones et al., 2007). Our results may be consistent with this – albeit that ERPs represent the summed activity of populations of neurons (Harris et al., 2014), whereas most previous research has measured responses from single-cell recordings (Usher et al., 1999).

The present results may also, potentially, be consistent with behavioural research focusing on conditions such as ADHD that has identified links between arousal and response time variability (Johnson et al., 2007; Kofler et al., 2013; Hicks et al., 1989; Wainstein et al., 2017). For example, Wainstein and colleagues recorded pupil size, which is thought to index physiological arousal (Loewenfeld, 1993) in children with ADHD and found that, at times when pupil size was higher, response time variability on a visuospatial working memory task was increased. Bluschke and colleagues have also identified increased intra-participant variability in neural responses during a conflict monitoring in patients with ADHD (Bluschke et al., 2017).

The second novel aspect of our findings was the elevated P150/P3a response that we observed in the high-arousal group in response to rare, 15% 750 Hz deviant tones. This larger mean response was observed despite the fact that the trial-to-trial variability in the high HR group was higher (Fig. 4d); and, as discussed above, greater trial-to-trial variability is typically associated with a lower averaged response. The enhanced P150 (P2) in response to deviants has repeatedly been reported in the literature (Näätänen et al., 1978; Maurer et al., 2003; Seery et al., 2014) and was referred to as positive mismatch response (pMMR). Several hypotheses about its nature and functional significance have been discussed (Wetzel and Schröger, 2014; Ruhnau et al., 2013). One hypothesis interpreted positive MMR as an inverted MMN (Maurer et al., 2003), however the mechanism of such inversion is not clear. Another proposal suggests that the positive MMR reflects an early P3a, a mechanism governing or initiating an attention shift to the distracting stimuli in environment (Kushnerenko et al., 2002b; Čeponienė et al., 2004). One more proposed explanation was based on the close temporal proximity (or overlap) of the positive MMR and the P2, and suggested that the positive mismatch response reflects a modulation of the P2 component (Ruhnau et al., 2010).

Finally, there is an interpretation offered independently by two research teams (Kushnerenko et al., 2002a; Morr et al., 2002; Kushnerenko et al., 2002b), which does not rule out the above discussed ones. Since scalp-recorded ERPs represents contributions from different concurrent generators with different relative strengths or maturation rates, the observed ERP waveform represents a sum of the overlapping superimposed positive and negative deflections, with one potentially obscuring another depending on the relative strength of the generator (Kushnerenko et al., 2002a, b). Morr and colleagues illustrated how polarity of the resulting mismatch response would depend on relative strengths of positive and negative generators depending on deviance size and children age (Morr et al., 2002).

Interpreting our results, we hypothesize that here we also have inter-relation between negative (N250/MMN) and positive generators (P150/P3a). For example, in response to ‘noise’ (Fig. 1a), which is thought to trigger the involuntary attention shift due to the saliency of the stimulus (Wetzel and Schröger, 2014), one can see that the P150 is almost merged with the following P3a. We can hypothesize that in trials with high HR, the overall brain excitability was higher and therefore more prone to involuntary attention. Thus, even small acoustic contrasts (frequency deviant) could potentially elicit a P3a-like response, which due to a larger amplitude could obscure the N250/MMN generator response and contribute to the scalp-recorded amplitude of the P150. The increased positivity in high HR group could be reflecting higher attentional demands as discussed in several recent studies (Garcia-Sierra et al., 2016; Rivera-Gaxiola et al., 2005) and less automatic auditory change detection (which should have resulted in

negative MMN) in high arousal state.

Although novel, our findings are consistent with previous research into the relationship between physiological arousal and change detection. Whereas the detection of sought-for stimuli (targets on a stimulus detection task) is generally thought to show an inverted-U-shaped relationship with physiological arousal, with optimal performance observed at intermediate levels (Aston-Jones and Cohen, 2005; Yerkes and Dodson, 1908; McGinley et al., 2015), it is known that during hyper-arousal, neural systems involved in exogenous, salience-driven orienting become more active. This leads to a shift from ‘top-down’, more frontally mediated control at lower levels of physiological arousal to ‘bottom-up’ control by low-level aspects of the sensory stimulus at higher levels of arousal (Arnsten, 2009; Liston et al., 2009). Consistent with this, greater neural responsiveness to small acoustic changes has been shown in adults with PTSD (Morgan and Grillon, 1999), and heightened physiological arousal has also been discussed in relation to auditory hypersensitivity in Autism Spectrum Disorders (Jones et al., 2009); although see (Rogers and Ozonoff, 2005).

Overall, our findings demonstrate the complex relationships between physiological arousal and cognitive performance (Arnsten, 2009; de Barbaro et al., 2016b). Sensitivity to small acoustic changes may confer advantages in certain learning situations – reduced sensitivity to change has been identified, for example, as a risk factor for conditions such as dyslexia (Baldeweg et al., 1999) and SLI (Rinker et al., 2007). However, inconsistent stimulus responses have, independently, been implicated in a diverse range of conditions, such as ADHD and ASD (Geurts et al., 2008). Further investigating the relationship between physiological arousal and auditory attention, and its potential long-term impact on learning in cognitive domains such as language, should be a goal for future research.

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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.dcn.2018.12.010>.

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