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Autonomic tone in children and adults: Pupillary, electrodermal and cardiac activity at rest

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ABSTRACT

Considering the suspected involvement of the autonomic nervous system (ANS) in several neurodevelopmental disorders, a description of its tonus in typical populations and of its maturation between childhood and adulthood is necessary. We aimed to arrive at a better understanding of the maturation of the sympathetic (SNS) and parasympathetic (PNS) tonus by comparing children and adults at rest, via recordings of multiple ANS indices. We recorded simultaneously pupil diameter, electrodermal activity (EDA) and cardiac activity (RR interval and HRV: heart rate variability) in 29 children (6–12 years old) and 30 adults (20–42 years old) during a 5-min rest period. Children exhibited lower RR intervals, higher LF peak frequencies, and lower LF/HF (low frequency/high frequency) ratios compared to adults. Children also produced more spontaneous EDA peaks, reflected in a larger EDA AUC (area under the curve), in comparison with adults. Finally, children displayed a larger median pupil diameter and a higher pupillary hippus frequency than adults. Our results converged towards higher SNS and PNS tones in children compared to adults. Childhood would thus be characterized by a high autonomic tone, possibly reflecting a physiological state compatible with developmental acquisitions.

1. Introduction

Physiological reactions and human behavior are organized by the autonomic nervous system (ANS); its sympathetic (SNS) and parasympathetic (PNS) branches are activated in high and low arousal states, respectively (McCorry, 2007). Activation patterns of the SNS and/or PNS are complex, dependent on the effector (e.g. cardiac muscle, iris or sweat glands) and on its state (phasic or tonic). Historically, within the Flight or Fight framework (Cannon, 1929), phasic ANS mobilization was studied in response to fearful (Kagan et al., 1994), painful (Kleck et al., 1976) and hedonic stimuli (Francis and Kelly, 1969). More recently, Porges, in his Polyvagal theory, suggested that PNS modulation of cardiac activity reflects our capacity to disengage from and engage with the environment and to interact socially (Porges, 2001, 2003, 2007).

Phasic ANS activation is described as variation from a tonic state, also called rest, or autonomic tone; yet, compared to phasic responses, autonomic tone has remained largely unexplored in humans (Perini and Veicsteinas, 2003; Schlindwein et al., 2008) and the corresponding studies mainly focused on PNS/vagal tone (Porges, 1995, 2001, 2007). High or low autonomic tone could interfere with the generation of optimal phasic ANS responses (Porges, 1995), reducing physiological flexibility in pathological contexts (Dalton et al., 2005; Schultz et al., 2006), as has been proposed for several different disorders (Beauchaine, 2015; Bellato et al., 2020; Fanti et al., 2019; Koenig et al., 2016;

Abbreviations: ANS, Autonomic nervous system; SNS, Sympathetic nervous system; PNS, Parasympathetic nervous system; ASD, Autism Spectrum Disorder; AUC, Area Under the Curve; bpm, beat per minute; CDA, Continuous Decomposition Analysis; CPP, Comité de Protection des Personnes; ECG, Electrocardiogram; EDA, Electrodermal Activity; HR, Heart Rate; HRV, Heart Rate Variability; HF, High Frequency; LF, Low Frequency; PCA, Principal Component Analysis; PEP, pre ejection period; RSA, respiratory sinus arythmia; SD, Standard Error.

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Martineau et al., 2011; Oldenhof et al., 2019; Tonhajzerova et al., 2009).

At rest, both SNS and PNS are tonically active and provide continuous nervous inputs to a large range of organs, suggesting that the full comprehension of ANS mobilization cannot be achieved through a single ANS effector. The innervation of ANS effectors is more complex than a simple balance between the PNS and the SNS. Acquiring data simultaneously from several effectors could improve our understanding of systemic ANS functioning and equilibrium. Classically, blood pressure, skin potential, breathing rate, and especially heart rate (Garwood et al., 1982; Ingall et al., 1990; Porges, 2001) have been the most studied parameters. Among them, skin conductance is of particular interest because it is controlled only by the SNS (see Section 1.1); on the other hand, the heart presents a complex activation pattern and is under regulation of both the PNS and SNS. Together they will therefore provide complementary information, allowing for better understanding of the systemic functioning of the ANS. Pupil diameter has recently been proposed as a relevant ANS index (Fairhall et al., 2006), influenced by both the SNS and PNS, but with a simpler activation pattern. In this study, we will thus focus on these three indicators: pupil diameter, electrodermal activity (or skin conductance), and heart rate and its variability.

1.1. Autonomic control of pupillary, electrodermal and cardiac tone

Pupil diameter depends on the contractility of the iris, under PNS (constriction, e.g. pupil light reflex) and SNS (dilation; McDougal and Gamlin, 2015) control (for a recent review, see Joshi and Gold, 2020). At rest, pupil diameter decreases with age (Bradley et al., 2011; Kasthurirangan and Glasser, 2006; Tekin et al., 2018) during childhood, but not linearly: pupil size is larger in older children (12–18 years old) than in younger children (2–5 and 6–11 years old) (Winston et al., 2020). Average diameter, measured at rest, collapses phases of dilation and contraction of pupil oscillation, called hippus, at a frequency of 0.15 to 0.2 Hz (Calcagnini et al., 2000; Parnandi and Gutierrez-Osuna, 2013; Ukai et al., 1997). Autonomic hippus mechanisms are still unclear; yet, they appear to be driven by the PNS (Turnbull et al., 2017) or by the antagonism between SNS and PNS (Centeno et al., 2011; Neuhuber and Schrödl, 2011).

Electrodermal activity (EDA) reflects the activity of sweat glands, which are under unique SNS control (Dawson et al., 2017; Sequeira and Roy, 1993; Wang et al., 2018). EDA has been mainly used to study emotional reactivity, but it also reflects homeostasis maintenance (water balance and bodily temperature). A few studies have measured the number of spontaneous EDA peaks, at rest, in young adults (Kelsey, 1991; Vossel and Zimmer, 1990), and reported a large variability in the population, with individuals having either a low number of peaks (labelled as stabile) or a large number of peaks (labile). Age-related differences have been less documented for EDA and no study has directly compared children and adults. EDA tone is higher in young adults (30–40 years old) compared to older adults (50–70 years old) (Bari et al., 2020; Catania et al., 1980; Eisdorfer et al., 1980). This age effect could be linked to the modification of electrical skin properties (Boireau-Adamezyk et al., 2014), along with a maturation of sympathetic outflow regulation.

Autonomic regulation of cardiac activity is more complex, but better documented, especially during maturation (mainly via HRV: heart rate variability). Like the pupil, the heart is innervated both by the PNS and SNS. The central PNS vagal complex (ambiguous nucleus, dorsal vagal nucleus) keeps cardiac heartbeat at rest level (Ogawa et al., 2007): approximately 50–70 beats per minute (bpm) for adults and 85–120 bpm for children (Finley et al., 1987; Finley and Nugent, 1995). The variation in PNS input on the heart is an index of our capacity to engage in and disengage from social interactions (Porges, 2001, 2007). During social interaction, while the SNS activates most autonomic effectors, the PNS decreases heartbeat (with an increased RR interval), reflecting positive engagement with the environment (Porges, 2001, 2007). In contrast, in fight or flight situation, the SNS induces heartbeat acceleration (with a decreased RR interval). Other cardiac parameters, pre-ejection period (PEP), respiratory sinus arrhythmia (RSA) and HRV, reflect different activation patterns of the SNS and PNS (Harteveld et al., 2021). Using PEP, under SNS influence, Harteveld et al. (2021) showed a linear decrease of SNS tone between age 6 months and 20 years old. Using RSA, under PNS influence, they showed a PNS tonus increase until 5 years old, followed by a plateau and a decrease during adolescence (Harteveld et al., 2021). HRV can be assessed using parameters in the frequency (low and high frequencies: LF and HF) (Shaffer et al., 2014; Shaffer and Ginsberg, 2017) domain, reflecting PNS modulation (Pomeranz et al., 1985), and using parameters in the time domain (RR interval) reflecting global ANS modulation. Consistent with RSA, LF and HF increase until age 6, decrease between age 6 and adulthood, and are stable in adulthood (Finley and Nugent, 1995; Molfino et al., 2009) which reflects undergoing developmental changes in childhood, with arousal less influenced by PNS after age 6 (Finley and Nugent, 1995; Harteveld et al., 2021). Absolute power of HF presents large intra-subject variability in children (Silva and Schalock, 2016) and decreases with age (Yeragani et al., 1994), probably reflecting the development of self-regulation (Yeragani et al., 1994; Lenard et al., 2004). All HRV PNS-dependent parameters, which reflect cardiac vagal tone, are indices of physiological and behavioral self-regulation (Geisler et al., 2013; Zeytinoglu et al., 2021).

Higher activation of the PNS at rest has been associated with more efficient attentional processing and more reactive emotional responses (Hansen et al., 2003; Calkins, 1997). In line with the prosocial development theory, the maturation of the ANS is central to the development of emotional and affective processes involved in social behavior (Porges, 2001, 2003). These processes evolve during childhood (Decety, 2010) and are crucial for the transition from childhood to adulthood (Casey, 2015; Casey and Caudle, 2013).

1.2. Autonomic control modes across different measures

The dual ANS innervation on many organs has led to the identification of different modes of autonomic control. Rather than considering the ANS as the result of strict antagonism between the PNS and the SNS, the model developed by Berntson et al. (1991, 2008) proposes that the PNS and SNS branches of the ANS lie within a theoretical two-dimensional space, with their coactivation, coinhibition, and uncoupled activation being possible. These different modes of functioning could also differ within the population according to the context (at rest or challenged) (Alkon et al., 2003), and interact with the HPA axis (hypothalamic-pituitary-adrenal; Holochwost et al., 2021).

To date, most of our knowledge on ANS regulation at rest and its functioning modes is based on studies using one or two autonomic measures. Most studies that have recorded simultaneously pupil, EDA and heart parameters did not study their correlations (Kahneman et al., 1969; Perry et al., 1989), but showed that all these parameters increased with mental task difficulty (Kahneman et al., 1969). However, in unrest condition, covariation of pupil diameter with EDA (Bradley et al., 2008; Wang et al., 2018) or with heart rate (Wass et al., 2015), and of EDA with heart rate (Bradley et al., 2008; Wang et al., 2018; Wass et al., 2015) have been reported. During activity, only one study has found a link between pupil size and EDA (indices of SNS tone) and also some PNS cardiac activity indices (Schumann et al., 2020). At rest, a positive correlation between pupillary hippus parameters and HRV parameters was also reported (Parnandi and Gutierrez-Osuna, 2013).

The ANS is extremely receptive to the environment (Bradley et al., 2008; Wass et al., 2015; Wang et al., 2018; Porges, 2004, 2007; Porges et al., 2019) and this reactivity might be partially predicted from its tone at rest (Del Giudice et al., 2011). Several physiological profiles have been proposed, depending on developmental stages and life history factors (Del Giudice et al., 2011). However, the direct comparison of SNS/PNS profiles at rest, at different stages of development, remains

under-investigated (Harteveld et al., 2021).

1.3. Goal of this study and hypotheses

Baseline autonomic regulation and cognition are dynamically linked and work together to process information, execute action, and regulate behavior (e.g. Porges, 2001, 2003; Del Giudice et al., 2011). Considering the behavioral maturation from childhood to adulthood, this theoretical framework would suggest that there is maturation of autonomic regulation that would be measurable at rest. However, a direct comparison between children and adults has only be done with HRV, and this description would benefit from complementary ANS measures that could be easier to implement, especially in individuals with a developmental disorder. The main goal of this study is thus to describe the maturation of the autonomic tone using three ANS measures (pupil size, heart rate and its variability, and electrodermal activity), modulated differently by the SNS and the PNS, in typical adults and children in a short rest paradigm.

While numerous studies have focused on cardiac vagal tone, suggesting an increase of the PNS tone until age six 6, followed by a decrease with age (Finley and Nugent, 1995; Molfino et al., 2009), the maturation of SNS control is less clear and less studied (but see Harteveld et al., 2021). Direct comparison of PNS and SNS measures at rest between children and adults will make it possible to describe both PNS and SNS maturation.

A second objective is to evaluate to what degree the parameters measured for these three effectors correlate, in order to motivate the choice of the optimal measure for the study of mental disorders. Based on the literature, we expect higher pupil diameters in individuals with more spontaneous EDA fluctuations (Schumann et al., 2020), and a correlation between HRV and pupil spectral energy, and between RR and hippus frequency, in adults (Parnandi and Gutierrez-Osuna, 2013).

Finally, pupillary hippus is under-investigated, in particular in children, and our multiple-effectors approach could help shed light on the ANS control of these oscillations. A correlation between the HF in HRV and hippus frequency (Parnandi and Gutierrez-Osuna, 2013) would confirm the hypothesis that hippus is mainly under PNS control (Turnbull et al., 2017).

2. Material and method

2.1. Participants

30 children (aged 6 to 12 years, mean age: 9.5 years ± 2.0, 16 females) and 30 adults (aged 20 to 42 years, mean age: 26.0 years ± 4.6, 17 females) were recruited locally at the University Hospital and in local schools according to the following criteria: children aged between 6 and 12, and adults aged between 20 and 45, no previously diagnosed psychiatric disorders or neurologic diseases, no learning disabilities or difficulties. No other individual information was collected. The children gave verbal consent. Their parents and the adult participants provided written informed consent according to institutional guidelines. The experiment conformed to the Code of Ethics of the World Medical Association (World Medical Association, 2013) and was ethically approved by the Comité de Protection des Personnes (CPP; protocol PROSCEA 2017-A00756-47). All the participants were recorded in the same conditions, at the Tours University Hospital, France.

Several of the parameters recorded in this study, like EDA at rest and pupillary hippus, have never been recorded in both children and adults before. The number of participants was thus estimated based on two kinds of results described in the literature: effect of age on heart rate (HR) and HRV in children and adults, and on electrodermal activity in two adult groups. Yeragani et al. (1994) showed significant differences between 11 children aged 4–12 years and 23 adults aged 21–43 years for HR and HRV parameters. Finley and Nugent (1995) also showed significant HR and HRV differences between age groups composed of 8 to 18 subjects. A significant effect of age was found on EDA by comparing groups composed of 12 to 36 younger and older adults (Catania et al., 1980; Eisdorfer et al., 1980). We thus aimed to recruit 30 participants for each group. The age range for children was determined based on several criteria: we wanted to recruit children before adolescence because of the possible hormonal impact on sudation and skin conductance recordings for example (White and Graham, 2016), and thus stopped inclusion at age 12; the lower boundary was fixed at 6-years-old based on HRV parameters, as the HRV profile changes between children younger and older than 6 (Goto et al., 1997). Moreover HRV was relatively stable between 7 and 14 years (Fukuba et al., 2009; Lenard et al., 2004). In the end, the age range in children (6–12 years old) more or less corresponded to the juvenile developmental stage (7–11) described by Del Giudice et al. (2011). We recruited young adults (20–42 years-old) based on the expected stability of skin conductance (Eisdorfer et al., 1980).

2.2. Material

The cardiac tone and the electrodermal tone were recorded by using BIOPAC MP36® (BIOPAC Systems Inc. Goleta, CA), with a constant voltage of 0.5 V and AcqKnowledge® 4.1 software. The EDA was recorded (acquisition frequency: 1 kHz, with range band: 0-5 Hz) using two 8 mm Ag/AgCl cup electrodes (EL258, Biopac Systems., Goleta CA, USA) and 0.5 %-NaCl electrode paste (GEL101; Biopac Systems), positioned on the second phalange of the index and medium finger of the right hand. The electrocardiogram (ECG) was recorded (acquisition frequency: 1 kHz, with range band: 0–35 Hz) using two disposable vinyl electrodes (EL503, Biopac Systems, Goleta CA, USA) placed on the sternum and on the right shoulder. The pupil diameter was measured by using an eye-tracking system SMI RED500® (acquisition frequency: 500 Hz) synchronized with BIOPAC MP36®.

2.3. Procedure

The recordings were all carried out in the same experiment room, in which conditions of luminosity (10 lx), hygrometry (27 % rh) and temperature (23 °C/76.4 °F) were constant. After installing all sensors (EDA, ECG), participants sat facing the eye-tracking screen (resolution: 1920 × 1080 pixels, visual angle: around 45 × 25°, infrared: $\lambda = 870$ nm, norm compliance: CE, EMC, Eye Safety). Eye calibration was performed with the visual tracking of five white points appearing on a grey screen. For the experiment, only a central black fixation cross on a grey background appeared on the screen. All participants were asked to stay still and to look at the fixation cross during the whole experiment. No chinrest was used. The experimenter and participant were separated by a panel, in order to avoid any distraction for the participants. Before starting the recording, the participants adjusted themselves to be comfortably seated in the armchair, and a period of 5 min was respected in order to stabilize the physiological constants. We then recorded simultaneously pupillary, cardiac and electrodermal tone during 5 min of rest.

2.4. Parameters and preprocessing

2.4.1. Pupil tone

The raw pupil signal was preprocessed with MATLAB® (r2016a; MathWorks). The first step of preprocessing eliminated artifacts, such as blinking and brief signal losses, via a velocity-based algorithm (Kret and Sjak-Shie, 2019; Nyström and Holmqvist, 2010). Afterwards, the resulting signal was smoothed using a median filter and a band pass filter (0.0004–0.0150 Hz). For each participant, three parameters were extracted (Fig. S1A in OSM): hippus frequency (in Hz) evaluated thanks to a Fourier transform method, hippus amplitude (mm) and median pupil diameter (mm).

2.4.2. Cardiac tone

Heart rate and heart rate variability (HRV) were analyzed by using Kubios software (Tarvainen et al., 2014). Cardiac frequency was studied by calculating the inter-beat interval (RR interval) between each QRS complex (for artifacts and more signal processing details, see OSM). The analysis was performed on the whole five-minute window, with equidistant sampling interpolation at 4 Hz. The frequency of the oscillations was evaluated on the five-minute recording by using a Fourier transform. We focused on high frequency (HF), between 0.15 and 0.4 Hz, reflecting cardiac PNS activity (Pomeranz et al., 1985), and low frequency (LF), between 0.04 and 0.15 Hz, reflecting baroreflex activity at rest, an index of vagal tone (Malliani et al., 1991; Pagani et al., 1986; Posada-Quintero et al., 2016; Shaffer et al., 2014; Shaffer and Ginsberg, 2017). For each participant, we thus obtained time domain and frequency domain parameters (Fig. S1B in OSM): RR interval (ms), LF and HF peak frequency (Hz), LF and HF absolute power (ms^2) and LF/HF ratio (absolute density LF/absolute density HF — very low frequency; Berntson et al., 1997).

2.4.3. EDA tone

Preprocessing of the electrodermal activity was performed in Ledalab (Benedek and Kaernbach, 2010), an open source software for MATLAB® (r2016a; MathWorks). The data were down-sampled to 10 Hz and bandpass-filtered with a first order Butterworth filter and cut-off frequencies of 5 Hz (Bach et al., 2009). Artifacts due to noise were corrected by using the spline interpolation. To ensure a conservative estimate of residual variance, we did not exclude non-responses (Staib et al., 2015). We used a Continuous Decomposition Analysis (CDA) to analyze four EDA parameters (Fig. S1C in OSM): area under the curve (EDA AUC, μS·s) for the whole five-minute, amplitude of EDA peaks (μS), number of EDA peaks and tonic component of EDA (μS), based on Standard Deconvolution method (Benedek and Kaernbach, 2010; Boucsein, 2012).

2.5. Statistical analyses

Considering the number of participants, we explored only the effect of age on our measures. Other factors, like sex, were not taken into consideration here (see OSM for statistical analysis including the sex).

All statistical analyses were performed in JAMOVI® (version 2.2.1.0) and XLSTAT® (version 2020.1.2). The normality of the distribution of the data was verified by using the Shapiro Wilk test and the homogeneity of the variance was verified by using the Levene test. LH and HF absolute power, amplitude of EDA peaks and EDA AUC, differed greatly among individuals, therefore they were logarithmically transformed before performing the statistical analysis (Benedek and Kaernbach, 2010; Sinnreich et al., 1998; Young and Leicht, 2011). We tested the effect of age on autonomic parameters in two steps. First, the effect of 'age group' as a categorical factor (children vs. adults) on pupil, cardiac and EDA parameters was evaluated using a Student *t*-test. Secondly, when a significant effect of 'age group' was found, we performed linear regressions with 'individual age' (as a continuous factor) and pupil, cardiac, and EDA parameters within each group. Finally, autonomic intra-subject covariations of the different parameters were tested with non-parametric Spearman correlations, and significant *p*-values were corrected according to the number of correlations performed (the *p*-value was multiplied by the number of correlations performed and the *p*-value obtained is then indicated by p_{corr}).

In order to examine the hypothesis of differential ANS profiles that could evolve with maturation, we used parameters that statistically distinguished children from adults. For each group (children/adults), each parameter was transformed into a *z*-score, followed by a Principal Component Analysis (PCA) based on Spearman correlations without rotation. Finally, a hierarchical cluster analysis (Ward's method, Euclidian distance) on the PCA contribution of observations was performed. We also tested the same approach on the all 13 recorded parameters. After the cluster analysis, we performed a MANOVA to compare the groups obtained, completed by corrected ANOVAs on each parameter defining the profile (indicated by p_{corr}).

All results are expressed as means with standard error (SD), with effect size expressed in Cohen's D (*d*) for Student *t*-test, r^2 for linear regression and *r* for Spearman's correlation. A sensitivity analysis performed in G*Power® 3.1 revealed that we could expect, with our number of participants ($n = 59$), to detect medium to large effects with 80 % power: $d = 0.74$ for Student *t*-test, $r^2 = 0.22$ ($f^2 = 0.28$) for linear regressions in the child and adult groups, $r = \pm 0.38$ for Spearman correlations in child and adult groups. For the MANOVA between the two child clusters, the sensitivity analysis revealed that we could expect $f^2 = 0.67$ with 80 % power.

3. Results

Due to technical problems, the recordings failed for one child. A total of 29 children and 30 adult participants were thus recorded and analyzed.

3.1. Pupil tone

As pupillary hippus has never been evaluated in children, we illustrated the recording of pupil at rest in Fig. S2 (in OSM).

Hippus frequency was significantly higher for children (0.22 ± 0.05 Hz) than for adults (0.18 ± 0.05 Hz) ($t(57) = 2.93$, $p < 0.01$, $d = 0.76$; Fig. 1), but no significant linear variation with 'individual age' was reported in children ($r^2 = 0.03$, $p = 0.34$) nor in adults ($r^2 = 0.02$, $p = 0.42$). Hippus amplitude was not significantly different between age groups ($t(57) = 1.65$, $p = 0.10$; children: 0.28 ± 0.06 mm, adults: 0.24 ± 0.07). Median pupil diameter was significantly higher for children (5.58 ± 0.76 mm) than for adults (4.76 ± 0.81 mm) ($t(57) = 4.10$, $p < 0.001$, $d = 1.07$), and tended to increase linearly with 'individual age' in children ($r^2 = 0.12$, $p = 0.06$), but not in adults ($r^2 = 0.03$, $p = 0.33$). No sex effect was reported on pupillary parameters (see OSM).

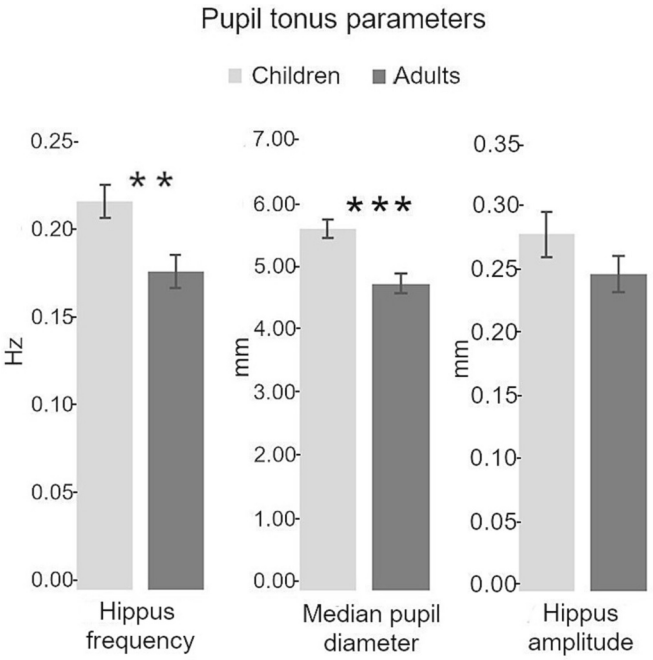

Fig. 1. Pupil tonus parameters in children and adults. Histograms represent the mean values (±standard error) of pupillary hippus frequency (in Hz), hippus amplitude (in mm) and median pupil diameter (in mm), extracted for both children (light grey/left columns) and adults (dark grey/right columns). $^{**}p < 0.01$, $^{***}p < 0.001$.

No significant correlations were observed among the three pupil parameters in children or in adults (children: median pupil diameter and hippus amplitude ($r = -0.02$, $p = 0.88$), median pupil diameter and hippus frequency ($r = -0.05$, $p = 0.78$), hippus frequency and hippus amplitude ($r = 0.05$, $p = 0.76$); adults: median pupil diameter and hippus amplitude ($r = -0.08$, $p = 0.72$), median pupil diameter and hippus frequency ($r = -0.09$, $p = 0.65$), hippus frequency and hippus amplitude ($r = -0.11$, $p = 0.53$).

3.2. Cardiac tone

RR interval was lower (i.e. the heartbeat faster; Fig. 2) for children (713.99 ± 16.59 ms) than for adults (881.53 ± 26.59 ms) ($t(57) = 5.30$, $p < 0.001$, $d = 1.38$) and increased linearly with 'individual age' in children ($r^2 = 0.40$, $p < 0.001$), but not in adults ($r^2 = 0.06$, $p = 0.18$).

For the HRV parameters (Fig. 2), an 'age group' effect was reported only on LF peak frequency, HF absolute power and LF/HF ratio. LF peak frequency was higher for children (0.106 ± 0.023 Hz) than for adults (0.091 ± 0.026 Hz) ($t(57) = 2.37$, $p = 0.02$, $d = 0.61$) but no variation with 'individual age' was reported (children: $r^2 = 0.01$, $p = 0.57$; adults: $r^2 = 0.05$, $p = 0.25$). HF absolute power tended ($t(57) = 1.76$, $p = 0.083$) to be higher for children (in log scale: 3.08 ± 0.07 ms^2) than for adults (in log scale: 2.89 ± 0.07 ms^2), but no variation with 'individual age' was reported (children: $r^2 = 0.07$, $p = 0.16$; adults: $r^2 = 0.02$, $p = 0.49$). LF/HF ratio was lower for children (0.52 ± 0.12) than for adults (1.68 ± 1.63) ($t(57) = 2.49$, $p = 0.016$, $d = 0.65$) and tended to increase linearly with 'individual age' in adults ($r^2 = 0.11$, $p = 0.08$) but not in children ($r^2 = 0.01$, $p = 0.59$). No significant effect of 'age group' on HF peak frequency ($t(57) = 1.38$, $p = 0.17$; children: 0.26 ± 0.0 Hz; adults: 0.23 ± 0.01 Hz) and on LF absolute power ($t(57) = 0.59$, $p = 0.55$; in log scale; children: 2.95 ± 0.06 ms^2; adults: 2.89 ± 0.07 ms^2) were reported. A sex effect was reported on RR interval and LF/HF ratio (see OSM).

In children, RR interval correlated with both LF ($r = 0.47$, $p_{corr} = 0.05$) and HF ($r = 0.49$, $p_{corr} = 0.03$) absolute power, but not with LF ($r = -0.12$, $p = 0.51$) or HF ($r = -0.15$, $p = 0.42$) peak frequency or with the LF/HF ratio ($r = -0.06$, $p = 0.73$). LF/HF ratio correlated (or tended to) negatively with LF peak frequency ($r = -0.43$, $p_{corr} = 0.05$) and with HF absolute power ($r = -0.43$, $p_{corr} = 0.09$), but not with HF peak frequency ($r = -0.17$, $p_{corr} = 0.36$) or LF absolute power ($r = 0.19$, $p = 0.31$). HF absolute power did not correlate with HF peak frequency ($r = -0.35$, $p = 0.23$), nor did LF absolute power correlate with LF peak frequency ($r = -0.02$, $p = 0.89$).

In adults, the RR interval correlated only with LF peak frequency ($r = -0.46$, $p_{corr} = 0.05$) but not with LF ($r = 0.19$, $p = 0.30$) or HF ($r = 0.28$, $p = 0.12$) absolute power, or HF peak frequency ($r = -0.03$, $p = 0.83$) or the LF/HF ratio ($r = 0.14$, $p = 0.41$). LF/HF ratio did not correlate with HF absolute power ($r = -0.41$, $p_{corr} = 0.1$), LF absolute power ($r = 0.36$, $p_{corr} = 0.2$), LF ($r = 0.04$, $p = 0.82$) or HF ($r = -0.24$, $p = 0.19$) peak frequency. HF absolute power did not correlate with HF peak frequency ($r = -0.27$, $p = 0.14$), nor did LF absolute power correlate with LF peak frequency ($r = 0.16$, $p = 0.37$).

3.3. EDA tone

The number of EDA peaks was higher for children (53 ± 34) than for adults (31 ± 25) ($t(57) = 2.93$, $p = 0.005$, $d = 0.76$) (Fig. 3A), but no variation with 'individual age' was reported (children: $r^2 = 0.001$, $p = 0.87$; adults: $r^2 = 0.001$, $p = 0.92$). The distribution of the number of EDA peaks across the population is illustrated in Fig. 3B, showing that both adults and children could present very few spontaneous peaks (stabile individuals) or large numbers of peaks (labile individuals). Moreover, children presented higher EDA AUC (1.27 ± 0.69 μS·s) than adults (0.86 ± 0.60 μS·s) ($t(57) = 2.27$, $p = 0.02$, $d = 0.61$) (Fig. 3A), but no variation with 'individual age' was reported (children: $r^2 = 0.001$, $p = 0.64$; adults: $r^2 = 0.001$, $p = 0.94$).

No significant effect of 'age group' on the amplitude of EDA peaks ($t(57) = 1.30$, $p = 0.20$; log scale; children: 0.75 μS ± 0.49; adults: 0.79 μS ± 0.51) and on tonic component of EDA ($t(57) = 0.86$, $p = 0.39$; children: 3.17 ± 2.43 μS; adults = 3.88 ± 3.25 μS) were reported. No sex effect was reported on EDA parameters (see OSM).

In children, EDA AUC showed a positive correlation with the amplitude of EDA peaks ($r = 0.95$, $p_{corr} < 0.001$) and the number of EDA peaks ($r = 0.93$, $p_{corr} < 0.01$), which also showed a positive correlation between each other ($r = 0.90$, $p_{corr} < 0.01$). No significant correlation was observed between the tonic component of EDA and EDA AUC ($r = 0.16$, $p = 0.38$), the amplitude of EDA peaks ($r = 0.19$, $p = 0.31$) or the number of EDA peaks ($r = 0.12$, $p = 0.51$). In adults, the EDA AUC showed a positive correlation with the number of EDA peaks ($r = 0.96$, $p_{corr} < 0.01$), but not with the amplitude of EDA peaks ($r = -0.12$, $p = 0.49$). No significant correlation was reported between amplitude of EDA peaks and the number of EDA peaks ($r = -0.08$, $p = 0.64$). The tonic component of EDA correlated with EDA AUC ($r = 0.68$, $p_{corr} < 0.001$) and the number of EDA peaks ($r = 0.70$, $p_{corr} < 0.01$) but not with the amplitude of EDA peaks ($r = 0.23$, $p = 0.20$).

3.4. Maturation of the ANS profiles

In order to examine the hypothesis of differential ANS profiles that could evolved with maturation, we used the seven parameters that were statistically different between children and adults (median pupil diameter, hippus frequency, RR interval, LF peak frequency, LF/RF ratio, EDA AUC and number of EDA peaks) to perform PCA then clustering analyses. The PCA analysis on the data from the children group showed

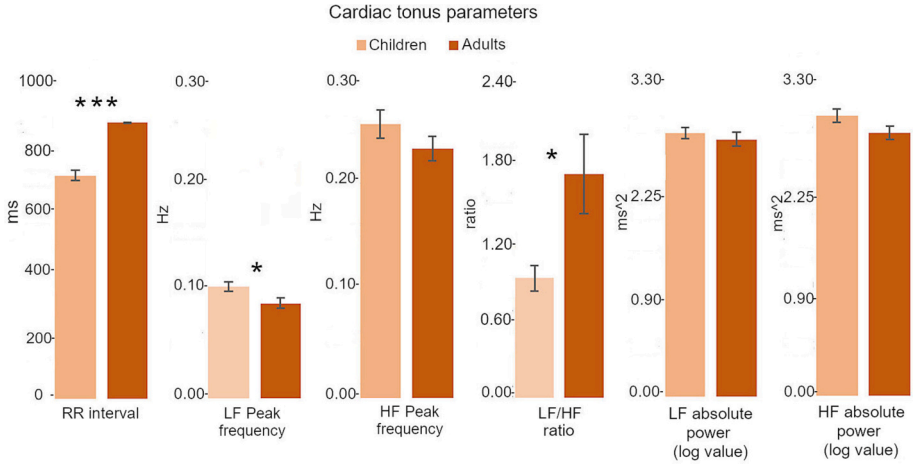

Fig. 2. Cardiac tonus parameters in children and adults. Histograms represent the mean values (±standard error) of RR interval (in ms), LF peak frequency (in Hz), HF peak frequency (in Hz), LF/HF ratio, LF absolute power (log scale, in ms^2), HF absolute power (log scale, in ms^2), extracted for both children (light orange/left columns) and adults (dark orange/right columns).
*$p < 0.05$, ***$p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

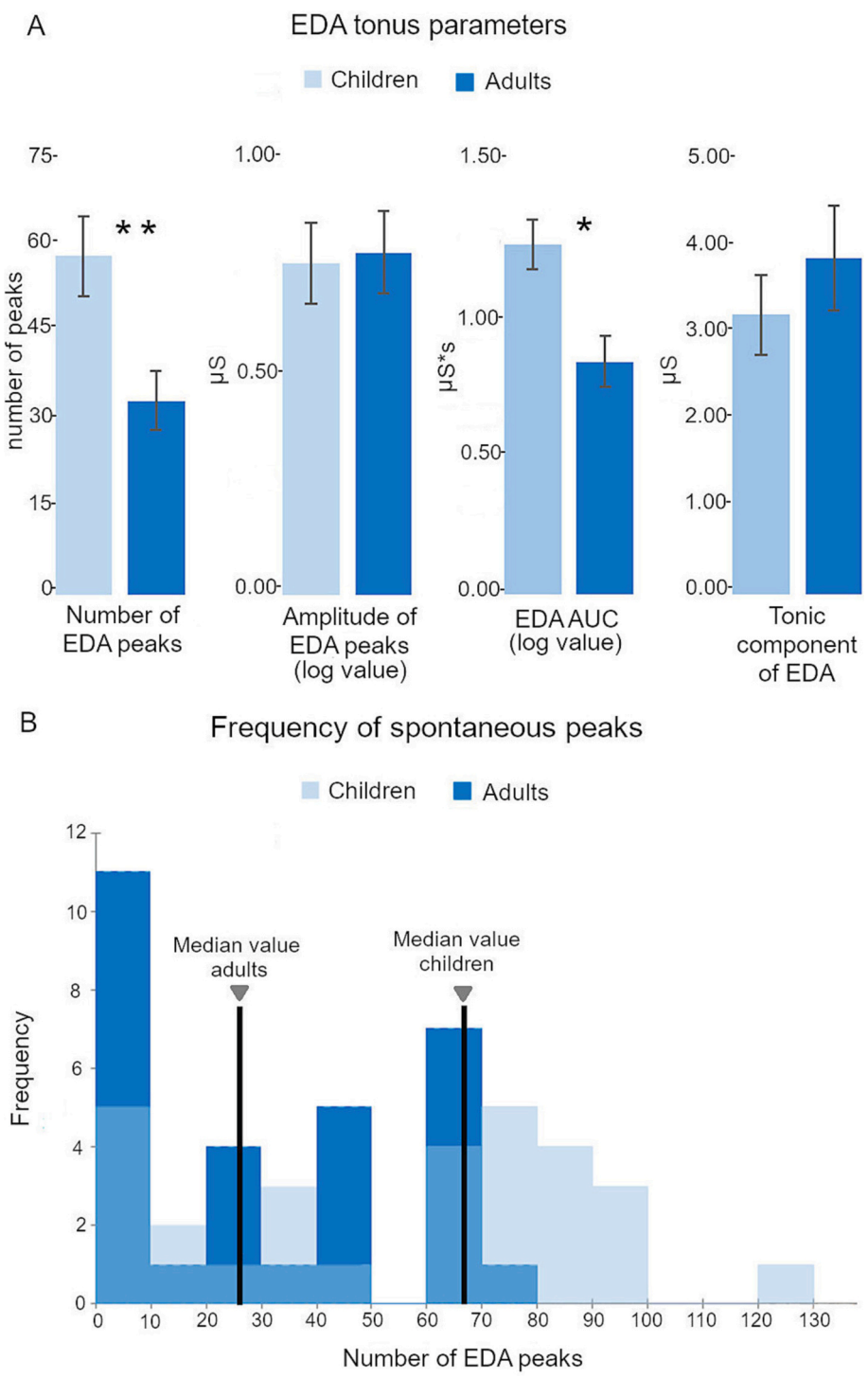

Fig. 3. EDA tonus parameters in children and adults. A. Histograms represent the mean values (±standard error) of the number of EDA peaks, amplitude of EDA peaks (log scale, in μS), EDA AUC (log scale, in μS·s), and tonic component of EDA (in μS), extracted for both children (light blue/left columns) and adults (dark blue/right columns). *$p < 0.05$, **$p < 0.01$. B. Distribution of the frequency of EDA peaks (bins of ten events) for the 5 min recording in children (light blue) and adults (dark blue). Black bars represent median values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

that four factors explained 86.5 % of the variability. The first factor grouped EDA AUC, number of EDA peaks and hippus frequency. The second factor grouped LF peak frequency and LF/HF ratio. The third factor was dominated by the RR interval, and the fourth by the median pupil diameter. The cluster analysis based on these four PCA factors revealed the existence of two profiles (Fig. 4A), with a comparable number of individuals (Group 1 $n = 14$, Group 2 $n = 15$), but which were not strikingly different (dissimilarity < 8 for the first node separating the two groups). The cluster analysis revealed that the first PCA factor was the one driving the definition of the two groups, with a large variability along the three parameters that contributed to this factor (Fig. 4A, dispersion of the dotted grey lines). However, when testing each parameter separately, the mean for these three parameters was not significantly different between the two groups. The two groups were statistically different (MANOVA, $F_{7,21} = 4.01$, $p = 0.006$, $f^2 = 0.51$) and the specific parameter driving this difference was the RR interval ($F_{1,27} = 19.56$, $p_{corr} < 0.001$, $\eta^2 = 0.42$). While RR interval was shown to increase with age, the two groups did not significantly differ according to age ($t(27) = 0.48$, $p = 0.63$).

The PCA analysis on the data from the adult group showed that four factors explained 84.7 % of the variability. The first factor grouped EDA AUC, number of EDA peaks and RR interval. The second factor grouped

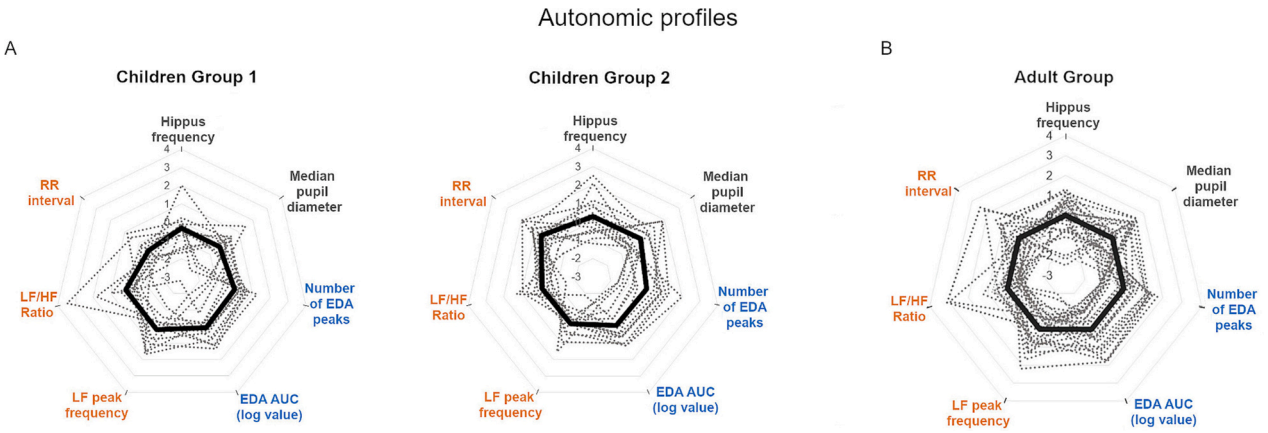

Fig. 4. Autonomic profiles in children (A) and adults (B). Radar charts represent the mean values (black line) for the seven chosen parameters in the three groups. Dotted grey lines represent all the individuals of the group. All data are presented in z-scores.

hippus frequency and LF peak frequency. The third factor was dominated by the LF/HF ratio, and the fourth by the median pupil diameter. However, the cluster analysis based on these four PCA factors revealed no differential profiles in the adult group, at least with a number of clusters reasonable considering the size of our population. Moreover, the clustering revealed that adults were overall less dissimilar (dissimilarity < 4 for the first four nodes) compared to children (dissimilarity > 7 for the first node separating the two groups). The overall adult group is presented in Fig. 4B.

As we did not observe an effect of maturation on these profiles, we also checked that none of the remaining parameters (i.e. the parameters that were not significantly different between the children and adult groups) would contribute to the definition of specific ANS profiles. We thus applied the same approach (PCA and clustering) on the complete set of 13 parameters in both children and adults. This approach did not contribute to a better explanation of the variability in each group, neither for PCA factors nor for the clustering.

3.5. Correlations between the different ANS measures

Considering the number of pupil, EDA and cardiac parameters tested in this study, we restricted our exploration of correlations between the ANS effectors. First, we performed non-parametric Spearman correlations between the three tone levels: median pupil diameter, tonic component of EDA, and RR interval. In children and adults, no significant correlation was observed between median pupil diameter and tonic component of EDA (children: $r = -0.10$, $p = 0.60$; adults: $r = -0.25$, $p = 0.18$), median pupil diameter and RR interval (children: $r = -0.07$, $p = 0.69$; adults: $r = 0.25$, $p = 0.89$) and tonic component of EDA and RR interval (children: $r = -0.03$, $p = 0.85$; adults: $r = -0.46$, $p = 0.02$).

To better understand the ANS control of pupillary hippus, we tested precise hypotheses according to the literature (1.3) and we performed correlations between the hippus frequency, hippus amplitude, HF absolute power, RR interval, the number of EDA peaks and EDA AUC. In children, we found a positive correlation between the hippus frequency and the number of EDA peaks ($r = 0.49$, $p = 0.03$) and the EDA AUC ($r = 0.48$, $p = 0.04$). No significant correlation was found between the hippus frequency and the HF absolute power ($r = -0.25$, $p = 0.18$) or the RR interval ($r = 0.39$, $p = 0.15$). No significant correlation was found between hippus amplitude and either the number of EDA peaks ($r = -0.09$, $p = 0.63$) or EDA AUC ($r = -0.19$, $p = 0.30$). In adults, we did not obtain any significant result: no significant correlation was found between the hippus frequency and either the number of EDA peaks ($r = 0.002$, $p = 0.99$), or EDA AUC ($r = -0.07$, $p = 0.70$), or HF absolute power ($r = 0.11$, $p = 0.53$), or RR interval ($r = 0.09$, $p = 0.62$). No significant correlation was found between hippus amplitude and either the number of EDA peaks ($r = 0.33$, $p = 0.35$) or EDA AUC ($r = 0.29$, $p = 0.11$).

4. Discussion

4.1. Cardiac tone decreases with maturation

Our cardiac results, obtained with a short five-minute recording previously shown to provide replicable individual values (Sinnreich et al., 1998), mainly confirmed what had already been described in the literature. The RR interval (e.g. Finley and Nugent, 1995) was significantly lower in children than in adults, i.e. children had a faster heartbeat (around 84 bpm) than adults (around 68 bpm), with values consistent with measures from similar age groups (children: Finley and Nugent, 1995; Garavaglia et al., 2021; Goto et al., 1997; Lenard et al., 2004; Silva and Schalock, 2016; Yeragani et al., 1994; adults: Garavaglia et al., 2021; Voss et al., 2015; Yeragani et al., 1994). We observed a linear increase of the RR with age in the children group but not within the adult group, that could reflect the relative stability of heartbeat in young adults (Garavaglia et al., 2021). This maturation of heartbeat frequency, potentially related to the increase of body mass (Garavaglia et al., 2021) or to the maturation of autonomic cardiac regulation, could be better understood in the light of the HRV results. We found significantly higher LF peak frequency, a tendency to higher HF absolute power and lower LF/HF ratio in children compared to adults (as in Finley and Nugent, 1995, and Yeragani et al., 1994), but no effect of age on the other HRV parameters (contrary to Yeragani et al., 1994). This difference with the literature could be due to the fact that our recordings were in a sitting position, whereas most studies record HRV in a supine position (which was not possible in our study due to the simultaneous recording of the pupil), or the length of the recordings. The parameters which distinguished children from adults – the RR interval, LF peak frequency, HF absolute power and LF/HF ratio – are difficult to interpret in terms of PNS and SNS control. Indeed, while LF has long been considered a SNS index, and LF/HF the reflection of the SNS/PNS balance, this interpretation has been challenged by several studies. LF is now considered as mainly determined by the parasympathetic activity at rest (Billman, 2013; Reyes del Paso et al., 2013; Shaffer and Ginsberg, 2017). A higher LF peak frequency in children would not indicate a higher sympathetic tone as suggested by Montano et al. (2009), but rather a higher PNS tone that would be confirmed by our tendency of higher HF absolute power (index of tonic cardiac outflow) in children than in adults. Overall, our results would thus suggest that PNS modulation of cardiac activity decreases with maturation (in line with the attenuation of the baroreflex with age; Lenard et al., 2004). This interpretation would fit with the one proposed by Yeragani et al. (1994), of a reduction of PNS influence associated to a diminished cholinergic

modulation between children and adults. As in the present study, these authors also observed an increase in LF/HF ratio between children and adults (Yeragani et al., 1994). Our results would also fit with the dynamic of PNS tone maturation described in Harteveld et al. (2021) considering the age of our population. We cannot exclude that the changes in LF/HF ratio and RR interval with age also involve a SNS component, while not directly quantifiable. The increase in LF/HF ratio associated with the decrease in LF peak frequency with age, suggests also that other parameters are at play, including parameters contributing to the very low frequency in HRV components. This very low frequency has been proposed to reflect mainly PNS influence, sympathovagal balance, renin/angiotensin system (Taylor et al., 1998), and other unidentified factors (Billman, 2013). Moreover, we cannot neglect the existence of an intrinsic cardiac nervous system (Achanta et al., 2020; Aksu et al., 2021; Fedele and Brand, 2020; Kerna et al., 2021; Shen, 2021), and the influence of neuromodulators or hormones (Benarroch, 2013), which challenge the simplistic definition of LF/HF as an index of both SNS and PNS components.

Globally, some HRV indices of our study point towards higher PNS tone in children that decreases with maturation, at least after 6–12 years old (Harteveld et al., 2021). This could be interpreted as a more stable ANS balance in adults, and an increase in consistency in cardiac parameters with age (Garwood et al., 1982). This result is relevant for the use of ANS cardiac parameters in a developmental context, especially in individuals with neurodevelopmental disorders. For example, PNS-HRV parameters at rest are frequently lower in autism spectrum disorder (ASD) than in the typically developed population (Cheng et al., 2020), and it is crucial to quantify the respective impact of age and autism in these differences.

However, the cardiac parameters we used do not allow specific quantification of SNS maturation. It would be interesting to complement our measures with the evaluation of PEP to evaluate the influence of the SNS on cardiac activity at rest (Harteveld et al., 2021).

4.2. Electrodermal tone decreases with maturation

Our study is one of the first to directly compare child and adult EDA during rest. A higher sympathetic tone in children was reflected by the higher number of EDA peaks and larger EDA AUC in children compared to adults. Venables and Mitchell (1996) did not report an effect of age between ages 5 and 25, but their study used very different methods as well as a very different definition of EDA tone compared to ours.

We found, both in children and in adults, a correlation between EDA AUC and the number of EDA peaks, suggesting these two parameters are highly redundant. EDA AUC could be more relevant as it also correlates with the amplitude of EDA peaks in children, and with the tonic component of EDA in adults.

These EDA results are crucial to complement the interpretation of our cardiac results, as they allow for access to pure SNS components, pointing towards a decrease of both PNS and SNS tones with age and suggesting global maturation of the ANS.

4.3. Pupil tone and ANS influence on the hippus

Our study is the first to report the existence of an hippus both in children and adults, with a frequency between 0.13 and 0.34 Hz in children and 0.05 and 0.2 Hz in adults, with an amplitude around 0.25 mm. These values are comparable to previously reported results of a mean hippus frequency between 0.15 and 0.2 Hz in adults (Calcagnini et al., 2000; Parnandi and Gutierrez-Osuna, 2013; Ukai et al., 1997). These data suggest a minimal recording time of 2 to 3 min to properly evaluate the pupil at rest (to obtain a minimum of 10–15 cycles).

We observed higher hippus frequency in children than in adults. Previous studies have attempted to identify the implication of the SNS and PNS on hippus, with no converging results. Ohtsuka et al. (1988) suggested a PNS influence on hippus, while Turnbull et al. (2017) did not observe a change in hippus frequency following local PNS antagonist application in humans. Considering the correlations we observed in children between hippus frequency, on one hand, and EDA AUC or the number of EDA peaks, on the other hand, our results suggest a SNS influence on hippus frequency that would decrease with maturation. We did not find a correlation between hippus frequency and HF peak frequency, as could be expected from a PNS control hypothesis (Ohtsuka et al., 1988).

Greater SNS influence in children would also explain the larger median pupil diameter we observed in children compared to adults. Our results nonetheless confirm that maturation of pupil diameter is complex, as suggested by the literature. Indeed, while children had larger pupils than adults, as in Tekin et al. (2018), we also found a positive regression of median pupil diameter with age within the child group, confirming the observations of Silbert et al. (2013) and Winston et al. (2020). Looking closely at Tekin et al.'s (2018) data, we can notice that pupil diameter increases until early adulthood before decreasing, suggesting that the difference we found between children and adults is dependent on the age range chosen for our population sample. This evolution probably reflects ANS maturation but also, possibly, other anatomical factors such as iris volume change (Jouzdani et al., 2013). Median pupil diameter is a parameter that is difficult to compare across studies because it is directly influenced by room luminosity (10 lx in our study, allowing us to obtain a median diameter of around 5 mm in our experimental context, optimally between the extreme physiological values of 2–8 mm). There is no indication yet that luminosity could influence hippus, making hippus frequency an interesting parameter to study SNS maturation. However, it does not allow for a specific description of PNS maturation.

4.4. ANS profiles

We were able to define two groups of children based on several ANS parameters, even if their ANS signatures were not strikingly different. The PCA analysis showed that the main factor explaining variability in children and contributing to the distinction between the two clusters, was composed of EDA AUC, number of EDA peaks and hippus frequency, i.e. SNS parameters. Logically, our correlation analyses showed that these three parameters were also positively correlated between each other. A complementary statistical analysis also stressed the difference in RR interval between the two groups. For the adult group, no subgroups could be defined and the clustering analysis suggested more homogeneity in our ANS parameters. This is coherent with the more stable ANS balance we already described for adults, and the suggestion in the literature that, globally, adults become more stable with age (Garwood et al., 1982).

Interestingly, EDA parameters were, in both children and adults, the ones contributing the most to the individual variability description. This could appear counterintuitive as, being solely regulated by the SNS, we could expect low variability at rest, with few external stimuli to adjust to. On the other hand, without the PNS influence, the spontaneous variations of SNS tonus may be more evident to detect. We can suppose that EDA activity at rest likely reflects intrinsic processes and internal states, and would benefit from complementary evaluation of personal factors like anxiety (Minnick et al., 2020). Nonetheless, we found a clear age effect on SNS tonus, even without considering these factors. Our results thus suggest that EDA, an index of SNS tonus and reactivity, is of primary importance in the description of ANS profiles at rest.

We cannot exclude that we did not capture the full ANS profiles existing in the general population. Indeed, we recruited participants in a limited location (University, University hospital and neighboring schools), that could present a socio-demographic bias. According to Del Giudice et al. (2011), four different physiological profiles should be present in the population, based on the level of stress encountered during development. Our population sample probably reflected only the low to moderate stress environments, that should translate into

moderate to high PNS basal state and moderate SNS basal state according to the Adaptative Calibration Model (Del Giudice et al., 2011).

4.5. Limitations and future orientations

Our study presented several limitations. First, some physiological parameters would need to be taken into consideration for futures studies, especially in the field of neurodevelopmental disorders. In particular, body mass index can differ from the typical population in ASD (Mouridsen et al., 2002) and is related to HRV parameters (Koenig et al., 2014; Molfino et al., 2009) but also to sympathetic influence on the pupillary activity (Segal et al., 2022). Moreover, without being linked to the sexual difference in corpulence, HRV differs according to gender (Antelmi et al., 2004; as we observed in our study, see OSM) and would be, to a lesser degree, influenced by the menstrual cycle (Vallejo et al., 2005). In addition to these physiological parameters, other factors should be integrated, such as time of the day to control for the influence of circadian rhythm on HRV (Bonnemeier et al., 2003; Massin, 2000) and on pupillary activity (Bonmati-Carrion et al., 2016). Related to the circadian cycle, sleep quality could be included because of the impact of the fatigue on HRV parameters (Tran et al., 2009). The level of anxiety (without being pathological) influences EDA (Naveteur et al., 1987) and HRV (Miu et al., 2009) parameters, and should also be taken into account in subsequent studies. Finally, psychiatric or metabolic diseases could also be considered in future directions. However, to measure the impact of these multiple factors, multivariate studies should be performed on large cohorts, much larger than the population sample in this study, and also include adolescents.

Despite the limitations of our study, in terms of number of participants and lack of consideration of some parameters, the simultaneous recording of several ANS effectors was a first step in the observation of the ANS profiles that could reflect individual signatures and be affected in some specific populations like in neurodevelopmental disorders.

5. Conclusions

For the first time, we recorded simultaneously at rest three peripheral effectors under the ANS influence, the heart, skin conductance and pupil, both in children and adults. Although ANS parameters are frequently used in neuroscience, especially to study psychiatric and neurodevelopmental disorders, we lacked until now a full picture of their characteristics at rest, which are crucial to understand before studying their reactivity. Our results aimed to fill this gap in typical children and adult populations, a first necessary step before considering using the ANS parameters to assess patients with psychiatric or neurodevelopmental conditions. In particular, we proposed a novel description of pupillary hippus in children, which would mainly be influenced by the sympathetic branch of the ANS at rest.

Our results converge towards both high sympathetic and parasympathetic tones in children compared to adults. With age, physiological and cognitive adjustments are observed, in particular towards more self-regulation and the development of emotional and affective processes involved in social behavior (Porges, 2004). This cognitive and emotional maturation process could be associated to the ANS tonus maturation we describe and this association should be explored in the future. Hypothetically, if tonus is high, energy is more dispersed towards reacting to any external stimulus, while lower ANS tonus in adulthood could be associated with more integrated responses to the environment. This high ANS tonus in childhood could provide the appropriate physiological underpinning for developmental acquisitions (Mayes, 2000). The PNS and SNS tonus indices could thus be interesting to correlate with explicit changes in behavior observed from childhood to adulthood. Future studies, involving cognitive and emotional regulation tasks or evaluations, and including adolescents, would allow for investigation of the link between self-regulation profiles and autonomic indices at rest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2022.07.009.

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