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1 **Title: Psychophysiological dynamics of emotional reactivity: interindividual reactivity**  
2 **characterization and prediction by a machine learning approach**

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20 **Highlights:**

- 21 • Cross-correlations between RR and tonic electrodermal activity appear during emotion.
- 22 • Interindividual variability of these cross-correlations are observed.
- 23 • One cluster of stress vulnerability with cross-correlations independent of emotion.
- 24 • Cross-correlations of the stress vulnerability cluster are dependent of anxiety trait.
- 25 • Cluster membership prediction by a machine learning model.

## 26 **Abstract**

27 The fast reaction of the autonomic nervous system (ANS) to an emotional challenge (EC) is the result of a  
28 functional coupling between parasympathetic (PNS) and sympathetic (SNS) branches. This coupling can  
29 be characterized by measures of cross-correlations between electrodermal activity (EDA) (under the  
30 influence of the SNS) and the RR interval (the interval between R peaks) (under the influence of the PNS  
31 and the SNS). Significant interindividual variability has previously been reported in SNS-PNS coupling  
32 in emotional situations, and the present study aimed to identify interindividual cross-correlation  
33 variability in ANS reactivity. We therefore studied EDA and the RR interval in 62 healthy subjects,  
34 recorded during a 24-minute EC. A Gaussian Mixture Model was used to cluster tonic EDA-RR cross-  
35 correlations during the EC. This identified two clusters that were characterized by significant or non-  
36 significant cross-correlations (SCC and NCC clusters, respectively). The SCC cluster reported higher  
37 negative emotion after the EC, while the NCC cluster reported higher scores on the Center for  
38 Epidemiologic Studies–Depression scale. The latter finding suggests that NCC is a pathological mood  
39 pattern with altered negative perception. Furthermore, a machine learning model that included three  
40 parameters indexing the functionality of both branches of the ANS, measured at baseline, predicted  
41 cluster membership. Our results are a first step in detecting dysfunctional ANS reactivity in general  
42 population.

## 43 **Keywords**

44 Emotion, cross-correlation, interindividual variability, nonlinear, autonomic nervous system, machine  
45 learning

46

## 1. Introduction

47 Emotional reactivity can be defined as the response of the autonomic nervous system (ANS) to an  
48 emotional stimulus. Typically, there is a joint reaction that involves both parasympathetic and  
49 sympathetic systems (McCraty et al., 1995). Electrodermal activity (EDA) and heart rate (HR) are  
50 physiological indices of ANS activity: EDA is under the influence of the cholinergic sympathetic system,  
51 and HR is under the influence of both sympathetic and parasympathetic systems (Kreibig, 2010). These  
52 two branches of the ANS interact closely, and the activity of one modulates the activity of the other  
53 (Thayer & Lane, 2009).

54 Examining moment-to-moment ANS responses during an emotional experience remains a methodological  
55 challenge (Golland et al., 2014; Kettunen & Keltikangas-Jarvinen, 2001). Since emotion is defined  
56 as a phasic response, several theoretical models assume that multiple patterns of body responses succeed  
57 each other during an emotional event (Scherer, 2009). Under this assumption, dynamic rather than steady  
58 point measurements are more informative. Findings from earlier studies support the idea that cross-  
59 correlation analysis can provide relevant indices of ANS activity, by comparing the dynamics of activities  
60 in both branches during an emotional experience (Golland et al., 2014).

61 Cross-correlations between EDA and HR have been used as a simplified index of ANS functioning in the  
62 past (Janig & Habler, 2000). This approach reduces the number of dimensions to be considered, and  
63 enables a continuous assessment of the balance between the two branches (Golland et al., 2014). Such an  
64 analysis is in line with the interest of nonlinear variables for each ANS signal. As there are several levels  
65 of regulation (Thayer & Lane, 2009), ANS oscillation is nonlinear (Basar & Guntekin, 2007) and can be  
66 described by appropriate indices (Reiter et al., 2020). These nonlinear variables provide an overview of  
67 the equilibrium of the system, describe its functioning and, more particularly, its flexibility (Young &  
68 Benton, 2015).

69 ANS regulation can be estimated by the Lyapunov exponent (LE), which is correlated to the size of the  
70 active biological neuronal pathway (Lajoie et al., 2014). The LE is a numeric value that characterizes the  
71 ability of a signal to be influenced (Pilant, 2020). An increase in the size of the active neuronal network  
72 leads to it being more influenced and, therefore, the LE increases (Lajoie et al., 2014). The LE is usually  
73 correlated with the Hurst exponent (HE) (Tarnopolski, 2016), which characterizes the ability of a signal to  
74 persist in the long term. This long-term memory appears to be a consequence of stability in the  
75 connectivity of an active neural network (Taylor et al., 2012).

76 SD1 and SD2 Poincaré indices reflect, respectively, short- and long-term signal variability, and provide  
77 information about the type of neural activity. When applied to the R-peak (RR) interval, short-term  
78 variability is known to be a marker of the effects of parasympathetic activity on the sinus node, since  
79 vagal effects are known to be faster than sympathetic ones (Hoshi et al., 2013; Mourot et al., 2004). SD2  
80 is influenced by both tones (De Vito et al., 2002; Hoshi et al., 2013). In the case of heart rate variability  
81 (HRV), the SD1/SD2 ratio, which represents the relationship between the two components has been  
82 shown to be correlated to the HE (Hoshi et al., 2013). Nonlinear indices can, thus, indicate the dynamic  
83 functioning of the ANS (Reiter et al., 2020) and give a precise evaluation of system flexibility, in terms of  
84 variability, memory or control under stress (Young & Benton, 2015).

85 Although dynamic approaches have been shown to be useful in reducing variability in ANS responses to  
86 emotion, interindividual variability remains significant, and appears to be a function of numerous  
87 historical, environmental, and biological factors (Andrew et al., 2017; Boissy, 1995; Fan et al., 2014;  
88 Golland et al., 2014; Hot et al., 2005; Huang et al., 2018; von Holzen et al., 2016). Furthermore, anxiety,  
89 mood, and alexithymia have been found to be associated with a lack of ANS flexibility (Agorastos et al.,  
90 2020; Hoehn-Saric & McLeod, 2000; Koschke et al., 2009; Lischke et al., 2018; Udupa et al., 2007).  
91 While overall, these differences have been described for each branch of the ANS (Charkoudian & Wallin,  
92 2014; Kirstein & Insel, 2004; Muhtadie et al., 2015), to the best of our knowledge interindividual  
93 differences in dynamic interactions between the two branches of the ANS have not been explored. More

94 specifically, questions remain not only about the functioning of each individual ANS branch, but also the  
95 dynamics of their interaction.

96 Hence, this exploratory study assesses the relevance and sensitivity of the combination of two  
97 methodological approaches: *i*) a cross-correlation analysis between the two branches of the ANS; and  
98 *ii*) the use of machine learning to identify profiles (clusters) of ANS reactivity. The first step was to  
99 identify the dynamic co-evolution of sympathetic and parasympathetic branches of the ANS during an  
100 emotional challenge (EC), and pinpoint clusters of inter-individual variability based on cross-correlations  
101 between EDA and RR intervals, measured as the tonic (e.g., skin conductance level) component of EDA.

102 Tonic and phasic components of EDA are underpinned by different neuroanatomical pathways and,  
103 therefore, different processes (Nagai et al., 2004; Ozawa et al., 2019). The tonic component covaries with  
104 ventromedial prefrontal and orbitofrontal cortex activities, while the phasic component is a function of  
105 activity in various regions of the brain, such as the hypothalamus, thalamus, striate and extrastriate  
106 cortices, anterior cingulate and insular cortices, and several lateral regions of the prefrontal cortex (Nagai  
107 et al., 2004; Ozawa et al., 2019). As a consequence, it is influenced by multiple inputs depending on the  
108 task, while the tonic component appears to be under the influence of attentional processes that are  
109 particularly enhanced in an emotional context (Nagai et al., 2004; Ozawa et al., 2019). These differences  
110 should make it possible to describe the ANS time course during an EC by capturing the degree of cross-  
111 correlation as a marker of autonomic adjustment. Thus, as a first step, the combination of variation in  
112 tonic EDA and RR outputs during an EC may provide a fine-grained assessment of individual emotional  
113 reactivity. Variability was characterized using physiological, sociodemographic, and psychological  
114 variables.

115 The second step in our work used a machine learning analysis to assess resting state ANS indices that  
116 best-predict emotional reactivity patterns. This is a major challenge, as cross-correlations are not observed  
117 beyond the context of emotional events (Golland et al., 2014). We used a Support Vector Machine (SVM)

118 learning method as it can combine several parameters, improving prediction capacity. This technique is  
119 particularly useful in a context where there are at least two factors (such as the two branches of the ANS).

## 120 **2. Materials and methods**

121 Results presented in this article were collected from two successive studies. The first validated the EC  
122 (Study I), and the second analyzed the dynamic cross-correlation between the two branches of the ANS  
123 during the same EC (Study II).

### 124 **2.1. Subjects**

125 Study I was conducted with 58 participants (72.5% women; mean age =  $20.84 \pm 0.49$  (standard error of the  
126 mean [SEM])), and Study II with 66 participants (88.71% women; mean age =  $20.52 \pm 0.55$ ). No  
127 significant differences were found for sociodemographic parameters between the two groups  
128 (Supplementary Table 1). Both studies were approved by the Ethics Committee of Savoie Mont Blanc  
129 University, France (CEREUS\_2017\_13). Written informed consent was obtained from each participant.  
130 Participants were recruited from among psychology students at Savoie Mont Blanc University and  
131 Grenoble Alpes University.

### 132 **2.2. Procedure**

#### 133 *Procedure common to both studies*

134 Each participant was tested individually in an experimental room. Physiological sensors for the  
135 electrocardiogram (ECG) and EDA were attached. Recording was continuous throughout the experiment.  
136 To obtain a baseline measurement, participants were asked to rest without moving, and let their mind  
137 wander with their eyes open for 10 minutes. This period was chosen in order to have enough time to  
138 calculate ANS signal parameters. Emotional state was assessed using the Affective Slider (AS) (Betella &  
139 Verschure, 2016). The AS assessment was performed before and after the 10-minute baseline phase

140 (Figure 1). Then, participants watched a 24-minute video based on extracts from the movie *The Conjuring*  
141 (Wan, 2013). This duration was chosen to ensure immersion. At the end of the video, the AS assessment  
142 was repeated. This was followed by a 15-minute recovery period, and another AS assessment. This period  
143 was chosen in order to have enough time to calculate ANS signal parameters and to observe a recovery of  
144 physiological parameters. Finally, participants were asked to report the degree to which the video they  
145 had just watched was unpleasant and scary, using two analogue scales ranging from -50 (not  
146 unpleasant/scary at all) to +50 (very unpleasant/scary), with 0 corresponding to a neutral state.

#### 147 *Differences between studies*

148 While watching the video, participants in Study I used a potentiometer to continuously evaluate their  
149 instantaneous emotional state. This real-time assessment validated the intensity of the experience.  
150 Because it was possible that this conscious activity would influence ANS reactivity (Park & Thayer,  
151 2014; Park et al., 2013), the same assessment was not performed during Study II, in which we aimed to  
152 assess dynamic ANS change.

#### 153 *Power analysis*

154 The necessary number of subjects was calculated using BiostaTGV ("BiostaTGV,"), based on a similar  
155 previous study (Golland et al., 2014). The earlier study recruited 27 subjects with the aim of observing  
156 significant cross-correlations. It found a correlation coefficient of around 0.6 during an emotional event,  
157 and standard deviation of around 0.1. In the present study, our goal was to observe at least two clusters,  
158 with a minimum difference of 15% and power of 90%, at a significance level of 0.05. The minimum  
159 number of subjects was identified as 52. This was increased by 10% for Study I (to compensate for  
160 technical problems in the emotional assessment system), and by 20% for Study II (to compensate for both  
161 technical problems and signal anomalies).

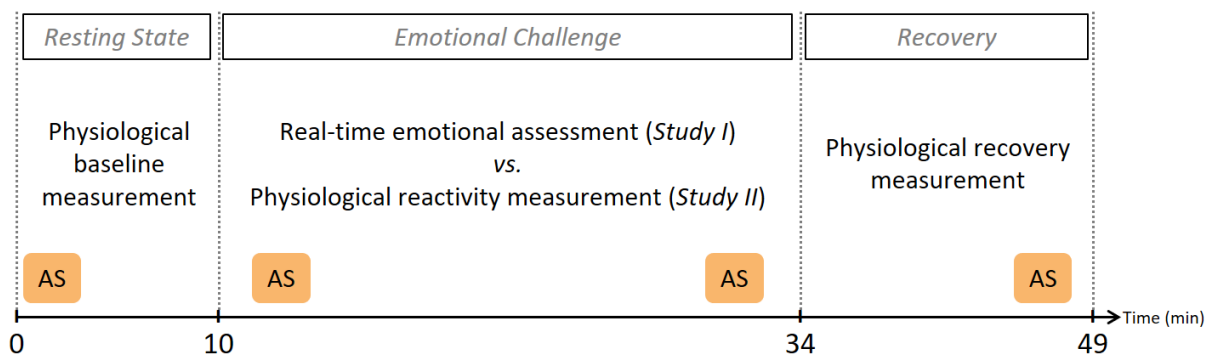


162 *Study I: Validation of the emotional paradigm*

163 A total of 58 participants were recruited. Of these, 37 provided an instantaneous emotional assessment of  
164 the movie and complete sociodemographic information; three provided an instantaneous emotional  
165 assessment and incomplete sociodemographic information (age, weight, and height were not recorded);  
166 and 18 only provided emotional assessment data.

167 *Study II: The dynamic ANS model and the machine learning model*

168 Among the 66 participants who were initially recruited, data from one was excluded due to a technical  
169 problem during the experiment (significant signal loss) and three were excluded due to a physiological  
170 anomaly (arrhythmia).



171  
172 **Figure 1: Experimental procedure for both studies. AS: Affective Slider assessment.**

### 173 **2.3.Sociodemographic data**

174 Sociodemographic variables included age, weight, height, tobacco use, consumption of caffeine and  
175 psychotropic substances, medical treatments, sleep habits and sports practice.

### 176 **2.4.Psychological assessment**

177 The psychological assessment was based on a set of standardized instruments that included the following  
178 three questionnaires:

- 179 i. The Spielberger Trait Anxiety Inventory (STAI): a 20-item assessment in which higher scores  
180 indicate more trait anxiety (Spielberger, 1983).
- 181 ii. The Toronto Alexithymia Scale (TAS): a 20-item assessment in which higher scores indicate  
182 greater alexithymia (Loas et al., 1995). Three dimensions were evaluated: difficulty in identifying  
183 feelings, difficulty in describing feelings, and thoughts oriented toward external reality.
- 184 iii. The Center for Epidemiologic Studies–Depression (CES-D) scale: a 20-item assessment in which  
185 higher scores indicate a higher level of depressive symptoms (Fuhrer & Rouillon, 1989).

## 186 **2.5. Affective Slider assessment**

187 Participants' instantaneous emotional state was evaluated with the AS (Betella & Verschure, 2016). This  
188 assessment consists of two analogue scales, one addressing emotional valence, the other Arousal. In both  
189 cases, scales range from –50 (very negative) to +50 (very positive), with 0 corresponding to a neutral  
190 state. This measure was recorded between tasks (Figure 1).

## 191 **2.6. Real-time emotional assessment**

192 A real-time emotional assessment was carried out while participants watched the video in Study I.  
193 Subjects continuously moved a linear home-made potentiometer. Values ranged from 0 (minimal  
194 intensity) to 40 (maximal intensity). The sampling frequency was 2 Hz. A higher sampling frequency  
195 would have been possible, but would not have been relevant, given that we were seeking to measure a  
196 conscious, explicit behavioral response. The response was then normalized for each subject as a  
197 percentage of maximum intensity.

## 198 **2.7. Physiological measures**

199 The ECG was recorded with sensors placed on the chest, according to the DII standard Einthoven  
200 derivation. EDA was recorded by placing electrodes on the last phalanx of the index and middle fingers of  
201 the non-dominant hand. The signal was acquired by ECG 100 and GSR 100 amplifier modules connected

202 to a BioPac MP150 (BioPac Systems, Inc., CEROM, Paris, France). Acquisitions were performed with  
203 AcqKnowledge 4.1 software at a sampling frequency of 1000 Hz. ECG and EDA signals were recorded  
204 during the entire experiment and then transferred to MATLAB software (Mathworks, r2018a, Natick,  
205 Massachusetts, USA) for tonic and phasic EDA and RR post-acquisition processing.

## 206 **2.8. Physiological signal preprocessing**

207 R peaks were first detected automatically by an algorithm based on wavelet detection, and then  
208 comprehensively manually checked. In one case, peaks could not be manually identified, and the  
209 recording was considered artifacted and excluded. The EDA signal was first separated into phasic and  
210 tonic components by a validated algorithm (Greco et al., 2016), before being down-sampled from  
211 1000 Hz to 2 Hz to allow it to be aligned with the interpolated inter-beat interval (IBI). Finally, it was  
212 smoothed by a moving median algorithm with a 10-point moving window, as previously reported  
213 (Golland et al., 2014). Both components of the time series were then detrended and normalized as  $z$ -  
214 scores, as recommended for cross-correlation analysis (Box et al., 2016; Golland et al., 2014).

## 215 **2.9. Physiological signal analysis**

### 216 **2.9.1. IBI time series**

#### 217 *2.9.1.1. Temporal analysis of RR intervals*

218 The following temporal components of HRV were calculated from RR intervals: mean RR (the mean of  
219 RR intervals in ms); SDNN (the standard deviation of normal-to-normal RR intervals in ms); RMSSD  
220 (the root mean square of successive differences in ms); and HRV-TI (the Heart Rate Variability  
221 Triangular Index).

222            *2.9.1.2. Frequency analysis of IBI time series*

223            RR intervals were interpolated to a 2 Hz IBI time series that was then detrended. A fast Fourier transform  
224            using the Welch method with a moving window and an overlap of 50% was used to calculate spectral  
225            components of HRV parametric analyses: Very Low Frequencies (VLF): 0.002–0.04 Hz; Low  
226            Frequencies (LF): 0.04–0.15 Hz; and High Frequencies (HF): 0.15–0.5 Hz. VLF, LF and HF were  
227            calculated as a percentage of the sum of VLF+LF+HF.

228            2.9.2. HF time series

229            The 2 Hz detrended IBI time series was analyzed using a continuous wavelet transform. Following the  
230            method reported in the literature, a Morse wavelet with symmetry parameter equal to three, and time-  
231            bandwidth product equal to 60 were used. HF power was extracted as a percentage of the sum of  
232            VLF+LF+HF, after exclusion of the cone of influence. The previously-described nonlinear algorithms  
233            were applied, and Poincaré indices, the HE, and the largest LE were calculated as described earlier. These  
234            nonlinear indexes of HF time series have previously been described (Hoshi et al., 2013; Yeragani et al.,  
235            2002).

236            *2.9.2.1. Nonlinear analysis of HF time series*

237            Poincaré indices SD1 and SD2, the HE, and the LE of the HF time series were calculated.

238            **Poincaré indices**

239            Nonlinear Poincaré indices SD1 and SD2 describe the variability of the Poincaré plot, and were calculated  
240            from RR intervals. SD1 and SD2 provide an estimate of the dispersion of points perpendicularly, and  
241            along the line of identity, respectively. They therefore represent short- and long-term variability in the  
242            analyzed signals, respectively.

243            **The Hurst exponent**

244 The HE evaluates the long-term memory of a process (Tarnopolski, 2018). Its interpretation is a function  
245 of its value. A value above  $\frac{1}{2}$  suggests a persistent process that has long-term memory and a value below  
246  $\frac{1}{2}$  suggests a non-persistent process with a short-term memory (Tarnopolski, 2016). The HE was  
247 calculated using a detrended moving mean algorithm, which was chosen because of its simple, closed-  
248 form processing (Tarnopolski, 2018).

### 249 **The largest Lyapunov exponent**

250 The largest LE ( $\lambda$ ) indicates the exponential divergence/ convergence of an initially-considered point in a  
251 dynamic system in its phase space, within a time limit of infinity (i.e., the degree of sensitivity to initial  
252 conditions) (Tarnopolski, 2018). Considering two points close to the phase plane at times  $t=0$  and  $t=t$ , and  
253 the distances between these points in the  $i^{\text{th}}$  direction, the LE is estimated as follows:

$$254 \lambda_i = \lim_{t \rightarrow \infty} \frac{1}{t} \log_2 \frac{\|\delta x_i(0)\|}{\|\delta x_i(t)\|}$$

255 where  $\|\delta x_i(0)\|$  and  $\|\delta x_i(t)\|$  are the Euclidean distances between the two points in the  $i^{\text{th}}$  direction at times  
256  $t=0$  and  $t$ , respectively (Pilant, 2020; Tarnopolski, 2018). The limit  $t \rightarrow \infty$  is replaced by  $t$  that is  
257 sufficiently large, leading to the finite time LE (Pilant, 2020; Roth, 2009).

258 LE values above 0 are associated with chaos, and correspond to a deviation that grows exponentially as  
259 the number of iterations increases. Values equal to 0 are associated with a periodic or quasiperiodic  
260 signal, and indicate that deviation from the orbit remains steady regardless of the number of iterations  
261 (Dämmig & Mitschke, 1993). Among the numerous algorithms used to estimate LE, we selected Pilant's  
262 algorithm because of its simplicity and the closed form processing (Pilant, 2020). Non-MATLAB users  
263 can download and read the algorithm using a standard text editor.

264 2.9.3. EDA time series

265 Poincaré indices, the HE, and the LE were calculated as described earlier for tonic EDA time series.

266 **2.10. Correlation analysis**

267 Sampling frequencies for the two signals were aligned. The 2 Hz detrended IBI time series was filtered  
268 below 0.04 Hz in order to remove low components insufficiently present in 60 s window. The last time  
269 series were then normalized as z-scores. A cross-correlation analysis between the IBI time series and the  
270 tonic EDA time series was performed for each subject using moving windows according to Golland et al.  
271 (Golland et al., 2014). Briefly, the analysis is based on short ( $t=60$  s) overlapping ( $\Delta t=30$  s) time  
272 segments. For each segment, and for each individual the maximum correlation (within  $\pm 5$ -s lags) was  
273 identified between the two series. In each case, a nonparametric bootstrapping procedure with surrogate  
274 data allowed us to control the statistical significance of the result. Surrogate data were obtained by  
275 randomizing segments in the time series. This procedure was repeated 1000 times. As described in  
276 previous work (Golland et al., 2014), the statistical likelihood of a cross-correlation in each time window  
277 was assessed nonparametrically using the Wilcoxon rank sum test against synthetic control data. Obtained  
278  $p$ -values were corrected for multiple comparisons using the false discovery rate (FDR) procedure  
279 (Benjamini & Hochberg, 1995).

280 **2.11. Clustering**

281 2.11.1. Evaluation of the optimal number of clusters

282 Clusters of subjects with the same emotional response were identified from cross-correlations between the  
283 RR interval and the tonic EDA signal observed during the eight, intensely emotional 60 s windows of the  
284 movie (4–5, 6–7, 8–9, 10–11, 12–13, 17–18, 19–20, and 21–22 min). Values were calculated for each  
285 individual. The clustering of subjects was performed on these last 8 variables by using the Calinski–  
286 Harabasz algorithm for Gaussian model mixture distribution as available in MATLAB software. The

287 Calinski–Harabasz non-supervised cluster solution algorithm was chosen as it uses clustering criteria  
288 based on the ratio of variances to provide a robust heuristic index (Andrade et al., 2020). Thus, a well-  
289 defined cluster has a large between-cluster variance and a small within-cluster variance. The optimal  
290 number of clusters is chosen according to a criterion based on these parameters. One to six cluster  
291 solutions were tested. The maximum number of iterations to reach convergence was set at 1000, and a  
292 diagonal covariance matrix was used. Solutions with the best fit were considered optimal. This solution  
293 without *a priori* has retrieved an optimal number of 2 clusters.

#### 294 2.11.2. Cluster membership

295 Membership of one of the two clusters was determined from the eight cross-correlation values that  
296 determined the dynamics of each individual’s responses using a Gaussian Mixture Model. This method  
297 was selected to study interindividual variability as, by definition, the latter follows a Gaussian  
298 distribution. MATLAB’s *cluster* algorithm was used, with the maximum number of iterations to reach  
299 convergence set at 1000. Here again, a diagonal covariance matrix was used. The Gaussian model assigns  
300 query data points to the multivariate normal components that maximize the component posterior  
301 probability, given the data. The method established the following cluster membership: cluster 1 (n=30)  
302 and cluster 2 (n=32).

#### 303 2.12. Machine learning

304 The ability of baseline parameters to predict the distribution of subjects within clusters was trained and  
305 cross-validated using a linear kernel SVM model. The linear kernel is widely used due to its robustness.  
306 To further increase robustness, a classical cross-validated model was used. First, data were randomly  
307 partitioned into 10 sets. Then, for each set, the algorithm reserved the set as validation data, and trained  
308 the model on the other nine sets. The out-of-sample misclassification rate was used to assess performance.

### 309           **2.13.       Statistical analysis**

310       Statistical analyses were performed with MATLAB, Cohen's effect sizes were calculated with G\*Power.  
311       One-way factorial analyses of variance (ANOVAs) were performed to compare means of the two clusters.  
312       As the duration of baseline, EC, and recovery phases were different, repeated measures ANOVAs could  
313       not be used to compare HRV results because most parameters are a function of the sample size. Other,  
314       time-insensitive parameters were analyzed with repeated measures ANOVAs for Time and Group main  
315       effects, and their interaction. Time effects identified changes in measures between baseline, EC, and  
316       recovery. Group effects identified differences between clusters 1 and 2. Group×Time effects reflect the  
317       combined effects of Time and Group. When the ANOVA revealed a significant effect, partial eta squared  
318       and Cohen's f effect size were calculated to estimate its size. According to the work of Schäfer and  
319       Schwarz applied to psychology domain, we considered that an effect size of 0.2 as small, higher than  
320       0.4 as medium and higher than 0.6 as large (Schafer & Schwarz, 2019). Partial eta squared of 0.01  
321       indicates a small effect, of 0.06 a medium effect and 0.14 a large effect. Clusters were characterized by  
322       the mean value of the cross-correlation during each window. This was linked to other psychological data  
323       using Pearson correlations for each cluster.

324       For categorical variables, Chi-Square independence tests were used. When significant, a Cohen's w effect  
325       size was calculated. According to basic rules for Cohen's w, a w of 0.10 indicates a small effect, of 0.30 a  
326       medium effect and 0.50 a large effect (Cohen, 1988).

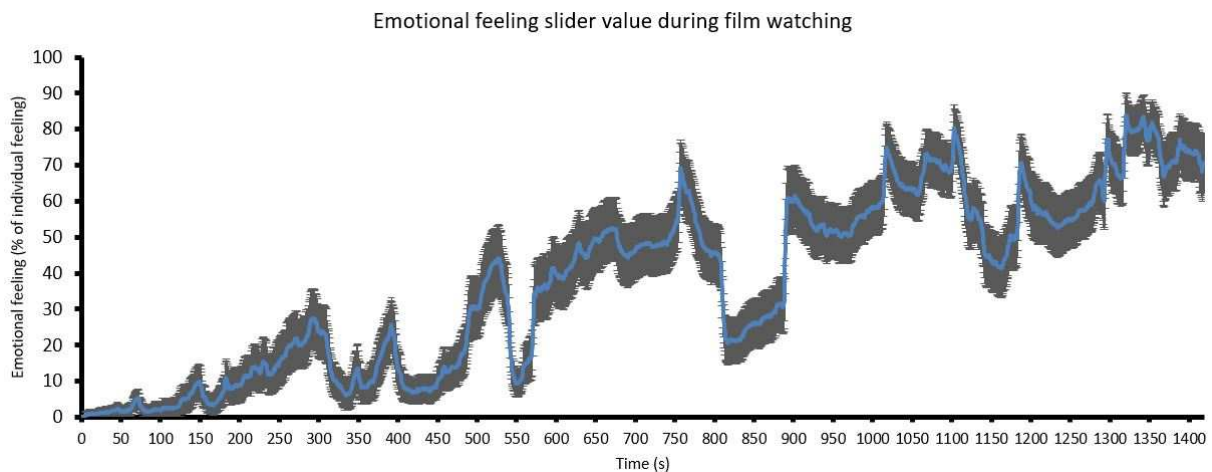
327       The predictive power of each variable was assessed with receiver operating characteristic (ROC) curves.  
328       The cut-off was associated with an area under the curve (AUC) above 0.8. Significance was set at  $p < 0.05$ .  
329       As for cross-correlation,  $p$ -values were corrected for multiple comparisons using the FDR procedure  
330       (Benjamini & Hochberg, 1995). Data are presented as mean  $\pm$  SEM.



331 **3. Results**

332 **3.1. Study I: Validation of the EC**

333 As they watched the video, subjects evaluated real-time emotional intensity (Figure 2). Our result  
334 highlighted a progressive increase in global intensity as a function of time, along with a few bursts. As  
335 cross-correlations between EDA and the RR interval have previously only been observed during  
336 emotional bursts (Golland et al., 2014; Hsieh et al., 2011), this result confirmed that the EC was an  
337 efficient way to study cross-correlations between the two branches of the ANS.



338

339 **Figure 2: Emotional intensity as a function of time.** Emotional intensity was expressed as a percentage  
340 of individual feeling measured using a potentiometer (see Materials and Methods). The blue line  
341 represents the mean for all subjects. Black bars represent the 95% confidence interval.

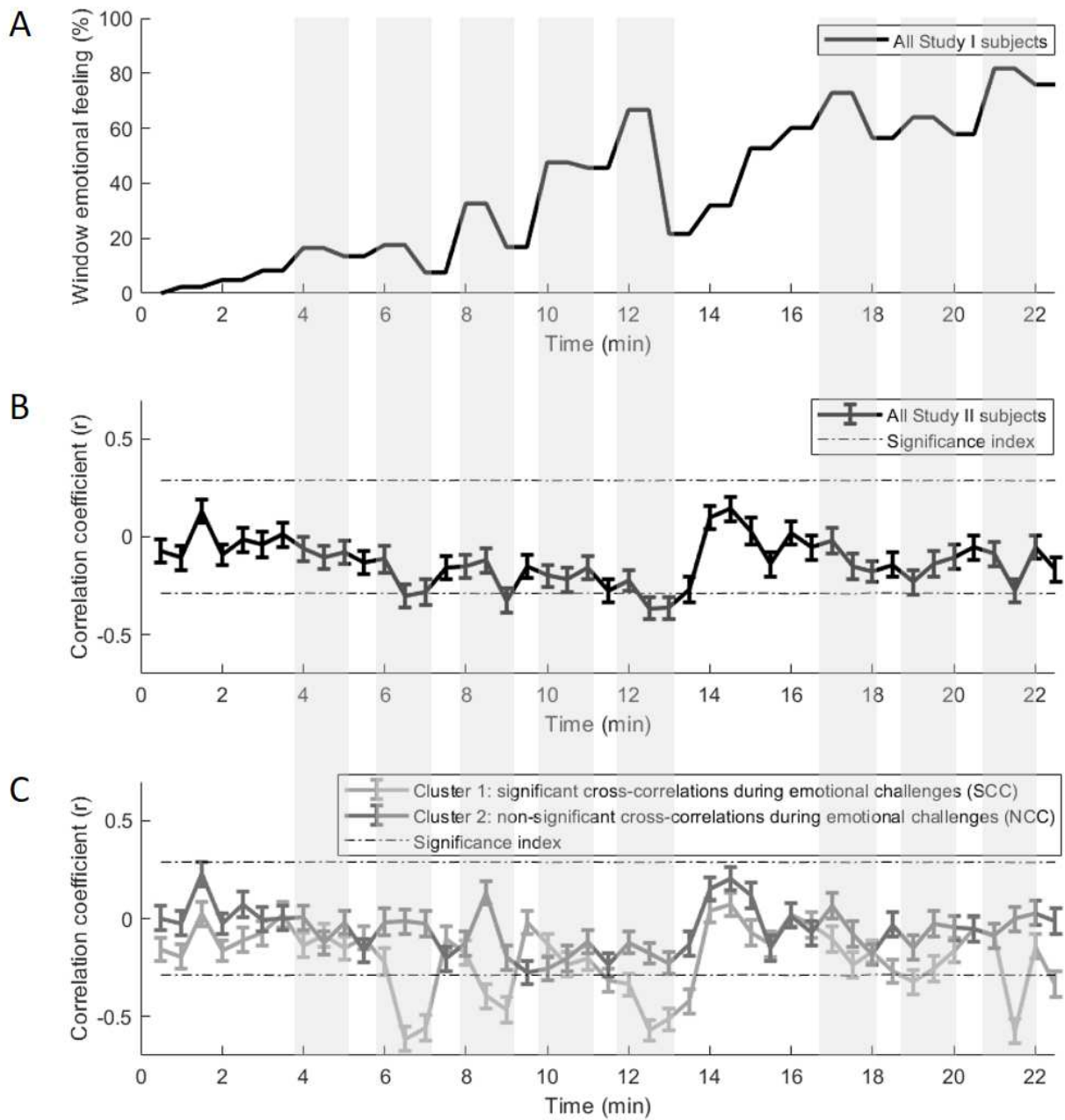
342 **3.2. Study II: Evaluation of the autonomic dynamic during the EC**

343 **3.2.1. Physiological identification of emotional bursts during the EC**

344 In order to align the self-reported emotion scores obtained in Study I (Figure 2) with cross-correlation  
345 results, we calculated mean self-reported emotion intensity for each 60 s window (Figure 3.A). This  
346 identified eight windows with peak emotional intensity (4–5, 6–7, 8–9, 10–11, 12–13, 17–18, 19–20, and

347 21–22 min; Figure 3.A). Significant negative cross-correlations between the RR interval and tonic EDA  
348 (i.e., low RR and high EDA) were only observed in two windows: 12–13 min ( $r=-0.36 \pm 0.05$ ,  $p < 0.05$ );  
349 and 12 min 30 s to 13 min 30 s ( $r=-0.35 \pm 0.06$ ,  $p < 0.05$ ; Figure 3.B).

350 As our earlier work had identified that significant cross-correlations are only observed during emotional  
351 events (Golland et al., 2014), we limited the search for interindividual variability in cross-correlations  
352 between the RR interval and tonic EDA to these eight bursts. An automated analysis of the optimal  
353 number of clusters for these eight cross-correlations identified two: cluster 1 ( $n=30$ ); and cluster 2 ( $n=32$ ).  
354 Significant cross-correlations were found among individuals in cluster 1 during the EC, but not cluster 2  
355 (Figure 3.C). Therefore, cluster 1 was labelled the “significant correlation cluster” (SCC), and cluster 2  
356 the “non-significant correlation cluster” (NCC). Finally, no significant cross-correlation was observed for  
357 either cluster at baseline or recovery (Supplemental Figures 1A to D).

359  
360361 **Figure 3: Cross-correlations between tonic EDA and the RR interval during the EC.**362 **A, B, C:** Vertical gray zones represent the eight emotional peaks during the EC. Results are expressed as  
363 mean  $\pm$  SEM. Dotted horizontal lines represent FDR-corrected upper and lower limits of significance

364 ( $q < 0.05$ ). **A:** Mean emotional intensity as a percentage for overlapping windows (Study I). **B:** Cross-  
 365 correlation coefficients ( $r$ ) for overlapped windows (window size = 60 s, with an overlap of 50% between  
 366 two windows) for all subjects in Study II. **C:** Cross-correlation coefficients ( $r$ ) for overlapped windows  
 367 (window size = 60 s, with an overlap of 50% between two windows) for each cluster (Study II).

### 368 3.2.2. Physiological characterization of clusters

369 No difference was observed between clusters at baseline or recovery. However, Table 1 shows that during  
 370 the EC the SCC group was characterized by a less chaotic distribution (LE) of tonic EDA ( $F(1,60)=9.5$ ,  
 371 **FDR-corrected  $p < 0.05$ , observed power=0.86, partial eta-squared=0.14, Cohen's  $f=0.53$** ). Results for all  
 372 tested physiological variables are reported in Supplementary Table 2.

373 **Table 1: Physiological results as a function of cluster and measurement time.** Results are expressed  
 374 as mean ( $\pm$  SEM). As the three measurement periods (baseline, EC, and recovery) are not of the same  
 375 duration, a repeated measures ANOVA cannot be used. Only significant results after FDR correction  
 376 ( $q < 0.05$ ) for the one-way ANOVA for each period are shown.

	Baseline				EC				Recovery			
	Significant correlation cluster (SCC)	Non-significant correlation cluster (NCC)	p-Value corrected by FDR of 1-way ANOVA	Observed power	Significant correlation cluster (SCC)	Non-significant correlation cluster (NCC)	p-Value corrected by FDR of 1-way ANOVA	Observed power	Significant correlation cluster (SCC)	Non-significant correlation cluster (NCC)	p-Value corrected by FDR of 1-way ANOVA	Observed power
	<b>EDA signal</b>											
LE tonic EDA	1.34 ( $\pm$ 0.07)	1.28 ( $\pm$ 0.07)	$F(1,60)=0.32$ ; $p=0.80$	0.09	<b>1.78 (<math>\pm</math> 0.04)</b>	<b>1.51 (<math>\pm</math> 0.08)</b>	<b><math>F(1,60)=9.5</math>; <math>p=0.045</math></b> <b>partial eta-squared=0.14</b> <b>Cohen's <math>f=0.53</math></b>	<b>0.86</b>	1.41 ( $\pm$ 0.05)	1.33 ( $\pm$ 0.07)	$F(1,60)=0.77$ ; $p=0.71$	0.14

### 378 3.2.3. Psychological characterization of clusters

379 Psychological characterization consisted of reported emotional intensity at different times of the  
 380 procedure, and an initial psychopathological self-report questionnaire. Table 2 shows AS scores, and  
 381 highlights that the NCC group perceived the EC less negatively than the SCC group ( $F(1,60) = 11.50$ ,  
 382 **FDR-corrected  $p < 0.01$ , observed power=0.92, partial eta-squared=0.16, Cohen's  $f=0.63$** ).

383 **Table 2: Reported AS as a function of cluster.** *p*-values are calculated with repeated measure ANOVAs  
 384 of Valence and Arousal, and a one-way ANOVA with FDR correction ( $q < 0.05$ ) for the overall evaluation  
 385 of emotion. Results are expressed as mean ( $\pm$  SEM).

		Significant correlation cluster (SCC)	Non-significant correlation cluster (NCC)	Statistics
Valence	Before baseline	19.40 ( $\pm$ 2.16)	18.44 ( $\pm$ 2.97)	Repeated ANOVA: interaction $F(3,180)=0.91$ ; $p=0.44$ ; observed power=0.25 group effect $F(1,60)=1.35$ ; $p=0.25$ ; observed power=0.21
	After baseline	12.53 ( $\pm$ 2.37)	17.84 ( $\pm$ 2.60)	
	After video	-4.7 ( $\pm$ 3.66)	0.75 ( $\pm$ 3.31)	
	After recovery	5.63 ( $\pm$ 1.98)	9 ( $\pm$ 2.63)	
Arousal	Before baseline	-6.87 ( $\pm$ 2.93)	0.88 ( $\pm$ 3.31)	Repeated ANOVA: interaction $F(3,180)=1.61$ ; $p=0.19$ ; observed power=0.42 group effect $F(1,60)=0.01$ ; $p=0.93$ ; observed power=0.05
	After baseline	-20.83 ( $\pm$ 3.25)	-20.91 ( $\pm$ 3.68)	
	After video	18.97 ( $\pm$ 3.11)	13.97 ( $\pm$ 3.75)	
	After recovery	-9.37 ( $\pm$ 3.48)	-13.13 ( $\pm$ 4.75)	
Final evaluation	Unpleasant video feeling	10.43 ( $\pm$ 4.18)	4.53 ( $\pm$ 3.94)	1-way ANOVA: $F(1,60)=1.06$ ; $p$ corrected=0.31; observed power=0.17
	Scary video feeling	18.7 ( $\pm$ 2.98)	9.47 ( $\pm$ 3.78)	1-way ANOVA: $F(1,60)=3.62$ ; $p$ corrected=0.09; observed power=0.46
	Negative video feeling	<b>15.8 (<math>\pm</math> 3.23)</b>	<b>-3.06 (<math>\pm</math> 4.46)</b>	1-way ANOVA: <b><math>F(1,60)=11.50</math>; <math>p</math> corrected=0.003; observed power=0.92</b> <b>partial eta-squared=0.16; Cohen's <math>f=0.63</math></b>

386

387 Table 3 highlights that the NCC group scored higher on the CES-D scale than the SCC group, indicating  
 388 more depressive symptoms.

389 **Table 3: Psychological indicators as a function of cluster.** *p*-values were calculated using a one-way  
 390 ANOVA. Results are expressed as mean ( $\pm$ SEM).

	Significant correlation cluster (SCC)	Non-significant correlation cluster (NCC)	Statistics
STAI-Trait	44.87 ( $\pm$ 1.86)	49.17 ( $\pm$ 1.75)	1-way ANOVA: $F(1,60)=2.82$ ; $p$ corrected=0.25; observed power=0.38
CES-D	<b>15.7 (<math>\pm</math>1.73)</b>	<b>22.72 (<math>\pm</math>2.1)</b>	<b>1-way ANOVA:</b> <b><math>F(1,60)=6.53</math>; <math>p</math> corrected=0.05; observed power=0.71;</b> <b>partial eta-squared=0.10; Cohen's <math>f=0.41</math></b>
TAS-20: difficulties in identifying feelings	16.37 ( $\pm$ 1.05)	18.28 ( $\pm$ 1.27)	1-way ANOVA: $F(1,60)=1.33$ ; $p$ corrected=0.31; observed power=0.21
TAS-20: difficulties in describing feelings	13.47 ( $\pm$ 0.93)	13.94 ( $\pm$ 0.93)	1-way ANOVA: $F(1,60)=0.13$ ; $p$ corrected=0.72; observed power=0.06
TAS-20: thoughts oriented toward external reality	16.8 ( $\pm$ 0.76)	15.47 ( $\pm$ 0.66)	1-way ANOVA: $F(1,60)=1.76$ ; $p$ corrected=0.31; observed power=0.25

391

### 392 3.2.4. Health behavior in clusters

393 While no difference was found between the two clusters with respect to sociodemographic characteristics,  
 394 health behaviors did differ (Table 4). Specifically, those in the NCC cluster were more likely to smoke  
 395 than those in the SCC cluster.

396 **Table 4: Demographics and health behavior as a function of cluster.** *p*-values were calculated using a  
 397 one-way ANOVA or  $\chi^2$  test. Results are expressed as mean ( $\pm$  SEM).

	Significant correlation cluster (SCC)	Non-significant correlation cluster (NCC)	Statistics
Age (year)	20.73 ( $\pm$ 1.08)	20.34 ( $\pm$ 0.51)	1-way ANOVA: F(1,60)=0.11; <i>p</i> corrected =0.97; observed power=0.06
Height (cm)	166.37 ( $\pm$ 1.13)	166.38 ( $\pm$ 1.35)	1-way ANOVA: F(1,60)=0.00; <i>p</i> corrected =1; observed power=0.05
Weight (kg)	62.57( $\pm$ 2.32)	63.06 ( $\pm$ 3.41)	1-way ANOVA: F(1,60)=0.01; <i>p</i> corrected =0.98; observed power=0.05
Gender	3 men / 27 women (10%)	4 men / 28 women (12.5%)	$\chi^2$ <i>p</i> corrected =0.97; power (1- $\beta$ )=0.06
<b>Smoking</b>	<b>2 yes / 28 no (6.7%)</b>	<b>13 yes / 19 no (40.6%)</b>	<b><math>\chi^2</math> <i>p</i> corrected =0.03; power (1-<math>\beta</math>)=0.88; Cohen's <i>w</i>=0.55</b>
Coffee or energy drink use	8 yes/ 22 no (26.7%)	14 yes / 17 no (45.2%)	$\chi^2$ <i>p</i> corrected =0.46; power (1- $\beta$ )=0.32
Drug use	6 yes / 24 no (20%)	8 yes / 24 no (25%)	$\chi^2$ <i>p</i> corrected =0.97; power (1- $\beta$ )=0.08
Regular sports	20 yes / 10 no (66.7%)	17 yes / 15 no (53.1%)	$\chi^2$ <i>p</i> corrected =0.56; power (1- $\beta$ )=0.19
Slept well the previous night	21 yes / 9 no (70%)	25 yes / 5 no (83.3%)	$\chi^2$ <i>p</i> corrected =0.51; power (1- $\beta$ )=0.23
Bedtime	11:55 p.m. ( $\pm$ 19 min)	11:49 p.m. ( $\pm$ 30 min)	1-way ANOVA: F(1,60)=0.02; <i>p</i> corrected =0.98; observed power=0.05
Waking hour	7:03 a.m. ( $\pm$ 12 min)	7:49 a.m. ( $\pm$ 19 min)	1-way ANOVA: F(1,60)=4.11; <i>p</i> corrected =0.22; observed power=0.51
Sleep duration (seconds)	25738 ( $\pm$ 1575.2)	28800 ( $\pm$ 1671.6)	1-way ANOVA: F(1,60)=1.77; <i>p</i> corrected =0.51; observed power=0.26
Sleepy today	12 yes / 18 no (40%)	15 yes / 17 no (46.9%)	$\chi^2$ <i>p</i> corrected =0.97; power (1- $\beta$ )=0.08
Concentration difficulties	5 yes / 25 no (16.7%)	15 yes / 17 no (46.9%)	$\chi^2$ <i>p</i> corrected =0.07; power (1- $\beta$ )=0.72

398

### 399 3.2.5. Functional patterns in clusters

399

400 To study each cluster individually, we summarized cross-correlation dynamics as the mean for each  
 401 emotional burst for each participant (a cross-correlation reduction). This identified that (negative) cross-  
 402 correlation values were higher among the SCC cluster ( $r=-0.37\pm 0.03$ ) than in the NCC group  
 403 ( $r=-0.07\pm 0.03$ ; F (1,60)=69.89,  $p<0.001$ , **partial eta-squared=0.54, observed power=1.00, Cohen's**  
 404 **f=0.85**). This variable can be used to study functional correlates in each cluster by testing Pearson  
 405 correlations between it and psychological variables or subjective emotion. In the following, only  
 406 significant results are reported.

407 In the NCC cluster, no correlation was found between mean cross-correlations during emotional bursts  
 408 and subjective emotion or psychological variables. However, in the SCC cluster, they were correlated  
 409 with subjective valence after video recording ( $r=0.43$ , corrected  $p<0.05$ ), unpleasant emotions ( $r=-0.49$ ,  
 410 corrected  $p<0.01$ ), and feeling scared ( $r=-0.45$ , corrected  $p<0.05$ ). This finding indicates that the stronger

411 the negative cross-correlation between the RR interval and EDA while watching the movie, the greater  
412 the perception of unpleasantness and feeling scared.

### 413 3.2.6. Predicting clusters from baseline data with machine learning

414 First, ROC curves were used to evaluate the predictive power of each baseline variable individually. The  
415 prediction of clusters using physiological variables or a single factor (identified by factor analysis)  
416 yielded AUCs no higher than 0.63. These values are considered poor, as good predictive power is  
417 associated with an AUC above 0.8. Then, a machine learning model was used to predict the distribution  
418 of subjects within the two clusters using baseline physiological variables. The machine learning algorithm  
419 automatically chose variables with the most predictive power. The search for new variables ended when  
420 no additional variable increased the predictive power of the model (the list of variables is given in  
421 Supplementary Table 2).

422 The cross-validated SVM model resulted in a prediction of 74.19% using only three baseline  
423 physiological variables: the HE of tonic EDA; the percentage of HF; and the LE of HF. Two nonlinear  
424 variables were automatically chosen by the model, suggesting that the nonlinear characteristics of both  
425 EDA and HF signals are important baseline characteristics in predicting cross-correlation ANS  
426 functioning during the EC. However, and interestingly, no difference between clusters was observed at  
427 baseline for these variables when they were considered independently (Supplementary Table 2).

## 428 **4. Discussion**

429 The goal of this study was to identify the dynamical coevolution of SNS and PNS during an EC and to  
430 describe clusters interindividual variability based on dynamical cross-correlations between EDA and RR  
431 intervals. Our study addresses two challenges. First, it is not possible to assess both moment-to-moment  
432 emotional state, and the true emotional level when attention is focused on the emotional event (Park &

433 Thayer, 2014; Park et al., 2013). Second, the self-assessment of emotion can itself be considered as a  
434 cognitive regulation task that may reduce intensity. Thus, we ran two studies, one to assess subjective  
435 emotion (Study I), and the second to record objective emotion (Study II). Our results highlight cross-  
436 correlations between tonic EDA and RR signals, and the existence of two profiles linking the two  
437 branches of the ANS during an EC. The first is characterized by sympathetic activation coupled with  
438 parasympathetic deactivation that marks the most emotionally-intense moments. The second is  
439 characterized by a lack of functional coupling within the ANS, associated with low emotional feeling  
440 during the EC and marked depressive symptomatology. Moreover, an exploratory machine learning  
441 analysis allowed us to categorize and predict these two clusters based on ANS measurements taken at  
442 rest.

443 Our study supports previous findings (Golland et al., 2014), which show that emotional arousal is  
444 associated with cross-correlations between HR and EDA signals. In the present study, a decrease in the  
445 RR interval duration was associated with a fast, transient disequilibrium between sympathetic and  
446 parasympathetic systems that favored the sympathetic system during an EC. The cross-correlation  
447 between these two variables underlies the functional coordination (or coupling) of the two branches of the  
448 ANS.

#### 449 **4.1. Interindividual variability in dynamic emotional reactions**

450 At the same time, our study goes further, and demonstrates the existence of two clusters of cross-  
451 correlations using a data-driven approach. These interindividual differences have not been reported  
452 previously, probably because individuals with no significant cross-correlations were excluded in earlier  
453 studies, or were masked in a group analysis (Golland et al., 2014).

454 Specifically, the existence of two clusters suggests that there is a difference in ANS flexibility with  
455 respect to the interplay between its two branches (Young & Benton, 2015). Interindividual variability  
456 underlying variation in flexibility has already been identified using a clustering *p*-technique applied to



457 cardiovascular activity (Friedman & Santucci, 2003). The two autonomic branches of the ANS are  
458 mutually inhibiting and globally antagonistic (Burnstock, 2008), and this can occur at different levels of  
459 regulation, highlighting the global flexibility of brain function (Bornemann et al., 2019; Ondicova &  
460 Mravec, 2010; Young & Benton, 2015).

461 In the present study, the SCC cluster was characterized by greater chaos (higher LE) in tonic EDA  
462 compared to the NCC group, suggesting that the sympathetic nervous system has a more complex  
463 regulatory network (Lajoie et al., 2014) and is more sensitive to initial recording conditions. Hence, this  
464 higher degree of chaos is consistent with a higher level of regulation. As tonic EDA is under the influence  
465 of both the ventromedial prefrontal and orbitofrontal cortices, one or both could account for this finding.  
466 Medial orbitofrontal cortex activity, which is involved in subjective emotional experience, is lower in  
467 depressive patients, while activity in lateral orbitofrontal and ventromedial cortices is increased (Koenigs  
468 & Grafman, 2009; Rolls, 2019). These changes in the neural network could account for our observed  
469 changes in tonic EDA. Functional neuroimaging studies would supplement our initial cluster  
470 characterization and clarify the role of the cortices.

471 From a psychological point of view, those in the SCC cluster reported fewer depressive symptoms,  
472 suggesting good mental health. Furthermore, we observed an association between mean cross-correlations  
473 and emotional valence after the EC, notably with respect to unpleasant and scary variables, indicating  
474 congruency between the physiological reaction and emotional feeling as the movie was watched. These  
475 observations are in line with Thayer and Lane who reported that individuals with high resting HRV  
476 produce more context-appropriate emotional responses (Thayer & Lane, 2009). Furthermore, reduced  
477 HRV and flexibility have been associated with depression (Sgoifo et al., 2015).

478 In contrast, members of the NCC cluster reported higher levels of depressive symptoms (on the CES-D).  
479 **Depressive symptoms difference between SCC and NCC was characterized by a medium effect size,**  
480 **nevertheless has to be considered since the mean level of NCC almost reached the threshold for**

481 depression (Morin et al., 2011). This depressive dimension is consistent with their propensity to smoke  
482 (Fluharty et al., 2017), and a lack of autonomic flexibility reflected in an aberrant vagal response under  
483 challenge (Agorastos et al., 2020). Depressive symptoms have long been associated with undifferentiated  
484 negative emotions (Willroth et al., 2020). Overall, unlike the SCC cluster, we did not observe congruency  
485 between the autonomic dynamic and emotion.

#### 486 **4.2. Predicting emotional reactions**

487 Predicting cluster membership on the basis of emotional regulation is not possible with a single variable.  
488 Classic one-dimension methods using ROC curves are insufficient. Thus, we used a machine learning  
489 technique to aggregate the pertinent dimensions. This revealed that three physiological baseline variables  
490 (including nonlinear dimensions of both EDA and HF time series) were able to predict up to 74% of high-  
491 and low-degree cross-correlation clustering and, therefore, the quality of emotional regulation under EC  
492 conditions. This prediction level is very close to the 80% threshold indicating good prediction ability. The  
493 fact that only three variables were used suggests good reproducibility. Moreover, these three variables  
494 appear to be important baseline predictors of the dynamics of parasympathetic activity (through the HF  
495 value), sympathetic persistence (through the HE of the tonic EDA), defined as the ability of the  
496 sympathetic system to maintain the same long-term kinetic, and parasympathetic determinism (through  
497 the LE of the HF), defined as the ability of the parasympathetic system to be exponentially disturbed.

498 While none of these baseline variables considered individually can identify the two clusters, their  
499 combination can. It should be noted that they reflect both sympathetic and parasympathetic markers,  
500 which is consistent with the idea of a co-dynamic ANS response to an EC.

#### 501 **4.3. Limitations**

502 Our machine learning model is deliberately simplified to ensure its robustness and make it possible to  
503 draw conclusions. A better prediction level could be obtained with more a complex separation plan which

504 could be justified in context of the use of nonlinear variables. However, any generalization would require  
505 a larger cohort to be valid. Second, this exploration of the characteristics of interindividual variability is a  
506 pilot study and although promising, our results must be confirmed by further work. Another study of  
507 interindividual variability based specifically on cardiovascular responsivity has identified a greater  
508 number of clusters (four or five) in the context of three other laboratory stressors, suggesting that the  
509 clustering solution might differ as a function of the stressor (Allen et al., 1991). Finally, our study is  
510 limited by the fact that the majority of participants were young female students. It is possible that anxio-  
511 depressive factors are more frequent in this group than in the general population (Dahlin et al., 2005).

#### 512 **4.4. Conclusions**

513 Despite the limitations noted above, our results are a promising step forward in the study of the  
514 psychophysiological processes that are involved in various chronic pathologies that affect both mental  
515 and somatic health.

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717 The authors declare no competing interests.

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### 720 **6.4. Data and material availability**

721 All algorithms and the video are available on reasonable request from the corresponding author.