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Interoception is associated with heartbeat-evoked brain potentials (HEPs) in adolescents

Running Head: Interoception and HEPs in adolescents

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Highlights

- We studied the association between HEPs and interoception in adolescents.
- Interoceptive accuracy was positively associated with HEPs.
- Interoceptive sensibility was not associated with HEPs.
- HEP positivity was higher in the heartbeat condition than in the resting condition.
- Our findings suggest the function of the HEP as a neural marker of interoception in adolescents.

Abstract

Heartbeat-evoked brain potentials (HEPs) are an index of the cortical reflection of cardiac interoceptive signals. Studies which have examined interoception in adolescents with the use of HEPs are not known to the authors so far. This study investigated the function of the HEP as a marker of interoception in adolescents. EEG and ECG were recorded in 46 adolescents during a resting condition and during a heartbeat detection task. Participants were asked for confidence in their interoceptive accuracy during heartbeat perception. HEPs appeared during both conditions, showing maximal activity over frontocentral electrodes in the heartbeat condition, and highest activity over occipital locations in the resting condition. Interoceptive accuracy (IAc) was positively associated with the HEP at frontocentral locations only for the heartbeat condition. Interoceptive sensibility was not associated with the HEP. No significant association between IAc and interoceptive sensibility was revealed. Our results highlight the relevance of the HEP as a neural marker of interoception in adolescents. Its use as an indicator of vulnerability for affective, physical and mental dysfunctions during adolescence should be exploited in future studies.

Keywords: HEP; Interoceptive accuracy; Interoceptive sensibility; Adolescents.

1. Introduction

Adolescence is described as a period of increased vulnerability due to reorganizational and maturational processes of the brain, of cognitive and of behavioral systems (Steinberg, 2005). Most notably elevated probabilities for the onset and occurrence of mental disorders such as affective disorders, anxiety and eating disorders are reported (Abraham, 1999; McLaughlin, Hatzenbuehler, Mennin, & Nolen-Hoeksema, 2011; Klump, 2013; Murphy, Brewer, Catmur, & Bird, 2016; Patton & Viner, 2007; Reardon, Leen-Feldner, & Hayward, 2009; Steinberg & Morris, 2001; Hazel, Oppenheimer, Technow, Young, & Hankin, 2014; Paus, Keshavan, & Giedd, 2008; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Murphy et al., 2016). Adolescence is also a critical period for the development of interoception (Li, Zucker, Kragel, Covington, & LaBar, 2017). Atypical neural activity in interoceptive networks in adolescents is described to be associated with psychopathologies, such as substance use disorders and with physical health problems (Berk et al., 2015; Murphy et al., 2016; Mata, Verdejo-Roman, Soriano-Mas, & Verdejo-Garcia, 2015; Migliorini, Stewart, May, Tapert, & Paulus, 2013). Against this background, it might be of heightened relevance to study interoception in adolescents as a marker to indicate vulnerability for psychopathologies.

One dimension of interoception is *interoceptive accuracy (IAc)* (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015), which describes the ability to accurately detect and report internal sensations from the body (Garfinkel, Critchley, & Pollatos, 2017). IAc is frequently measured in children and adults by the performance in a heartbeat detection task (Pollatos &

Schandry, 2004; Pollatos, Kirsch, & Schandry, 2005a; Craig, 2002; Wiens, 2005; Garfinkel et al., 2015; Herbert, Pollatos, Flor, Enck, & Schandry, 2010; Schandry, 1981; Koch & Pollatos, 2014a; Koch & Pollatos, 2014b; Eley, Stirling, Ehlers, Gregory, & Clark, 2004). Previous research revealed substantial interindividual differences in IAc in adults (Garfinkel et al., 2015; Pollatos, Füstös, & Critchley, 2012; Terasawa, Moriguchi, Tochizawa, & Umeda, 2014; Pollatos, Herbert, Matthias, & Schandry, 2007; Pollatos, Herbert, Kaufmann, Auer, & Schandry, 2007; Pollatos & Schandry, 2004; Pollatos et al., 2005a; Pollatos, Kirsch, & Schandry, 2005b).

A second dimension of interoception, described as *interoceptive sensibility (IS)*, represents an individual's subjective report of the experience of own internal bodily sensations (Garfinkel et al., 2015). It can be assessed with measures of a person's subjective belief in his or her interoceptive accuracy (e.g. subjective confidence rating of IAc during an interoceptive task) or with self-report questionnaires of the extent to which individuals feel affected by their bodily signals (Garfinkel et al., 2015). As a subjective measure, IS does not necessarily correspond to behavioral indicators of IAc (Garfinkel et al., 2015).

The cortical processing of cardiac afferent signals is mirrored by the heartbeat-evoked potential (HEP), a scalp potential which can be observed contingent to the heartbeat (Schulz et al., 2015a; Pollatos & Schandry, 2004; Schandry & Montoya, 1996; Schandry & Weitkunat, 1990; Montoya, Schandry, & Müller, 1993; Schandry, Sparrer, & Weitkunat, 1986; Leopold & Schandry, 2001; Pollatos et al., 2005a; Fukushima, Terasawa, & Umeda, 2011; Schulz et al., 2015b)-. –HEPs depict positive brain waves with highest activity in the latency range of 250-600ms after the R-wave at frontal and frontocentral electrodes (Pollatos & Schandry, 2004; Pollatos et al., 2005a; Montoya et al., 1993; Schandry & Montoya, 1996; Leopold & Schandry, 2001; Schulz et al., 2015b; Park & Tallon-Baudry, 2014). Structures which were identified as generators of the HEP are the anterior cingulate, the right insula, the prefrontal cortex and the left secondary somatosensory cortex (Pollatos et al., 2005a).

The occurrence of HEP activity is independent of the conscious perception of cardiac activity: As poor as well as good heartbeat perceivers show HEP activity, it is assumed that the heartbeat signal is constantly monitored by the brain (Schandry & Montoya, 1996; Park & Tallon-Baudry, 2014). However, psychological factors, such as IAc, attention and motivation manipulate HEP activity (Schandry & Montoya, 1996; Yuan, Yan, Xu, Han, & Yan, 2007; Montoya et al., 1993; Weitkunat & Schandry, 1990). As studies with adults showed higher HEP amplitudes in individuals with high IAc as compared to low IAc (Pollatos & Schandry, 2004; Pollatos et al., 2005a; Montoya et al., 1993; Schandry et al., 1986) and significant relationships between IAc and HEP amplitudes (Pollatos & Schandry, 2004; Katkin, Cestaro, & Weitkunat, 1991), HEPs are assumed to reflect interindividual differences in cardiac IAc (Pollatos & Schandry, 2004; Pollatos et al., 2005a; Montoya et al., 1993; Schandry et al., 1986). The significance of the HEP as a neural marker of interoceptive processing was confirmed in different studies with adults, showing that HEPs are affected by processes related to the interoceptive network, such as food deprivation (Schulz et al., 2015a), or pain (Shao, Shen, Wilder-Smith, & Li, 2011). However, there is a lack of research concerning the cortical processing of cardio-afferent information in adolescents. There are no studies known to the authors so far which have examined interoception in adolescents with the use of HEPs. To our knowledge, currently two studies exist which have shown HEPs in children (Immanuel et al., 2014; Baumert et al., 2015).

As a theoretical framework we suggest an own model, named “MINP”, to describe the relationship between interoception, cognitive and physiological processes. We assume four levels of interoception, so called “Working **M**odel”, “**I**nteroceptive Processing”, “**N**euronal Processing” and “**P**hysiological State”. As suggested by predictive coding models

(Friston et al., 2013; Friston, Stephan, Montague, & Dolan, 2014; Quattrocki & Friston, 2014; Seth, Suzuki, & Critchley, 2012), the highest level is assumed to constitute a working model matching interoceptive signals from the body with interoceptive prediction signals in the brain. The second level refers to the model of Garfinkel and colleagues (Garfinkel et al., 2015), including the independent dimensions IAc, IS and interoceptive awareness (IAw). We added a fourth dimension, interoceptive evaluation (IE) as described as an evaluation of feelings related to one's own interoception (Pollatos, Herbert, Mai, & Kammer, 2016). All four dimensions are assumed to be influenced by Level 1. The third level consists of the neuronal processing of different interoceptive modalities. We assume that on this level, the neuronal processing of heartbeat signals is reflected by HEPs (Pollatos & Schandry, 2004; Pollatos et al., 2005a), but that also other interoceptive signals, such as respiration are reflected by neuronal correlates, e.g. by respiratory-evoked potentials (Davenport, Chan, Zhang, & Chou, 2007; Davenport, Cruz, Stecenko, & Kifle, 2000; Webster & Colrain, 2000). As IAc was described as a basic concept (Garfinkel et al., 2015) as well as in accordance to reported relationships between IAc and HEPs (Pollatos & Schandry, 2004; Katkin et al., 1991) we assume IAc to be associated with the HEP. Due to previous research showing ambivalent findings regarding relationships between physiological interoceptive markers including the HEP, and IS (Baranauskas, Grabauskaite, & Griskova-Bulanova, 2017; Mallorquí-Bagué et al., 2014), we postulate that IS might be associated with some neuronal markers, but that this should not be necessarily the case. The fourth and most basic level of our model is called "Physiological State", referring to Forkmann and colleagues (Forkmann et al., 2016) who described the state of cardiovascular activation as basic level of interoceptive processing. We assume that this state could be influenced by different mechanisms. Related to cardiac perception, we define the physiological state to be determined by the activity of the mechanoreceptors of the heart (baroreceptors) from where afferent bodily signals are projected to the brain stem, the thalamus and to the insular cortex in the brain, containing a representation of bodily signals (Craig, 2002). Accordingly, this level is assumed to influence all higher levels of the model by bottom-up projections. *Figure 1* illustrates our model.

-----------------------Please Insert Figure 1 here. --------------------------

The present study aimed to encounter the lack of research regarding the relation of interoception and the HEP in adolescence. We examined cortical cardiac signal processing by assessing HEPs in a sample of adolescents during a heartbeat perception task and during a resting condition. Based on findings in adults, we assumed the presence of HEPs during both conditions, showing maximal amplitudes at frontal and frontocentral electrodes (hypothesis I) (e.g Pollatos & Schandry, 2004; Pollatos et al., 2005a; Leopold & Schandry, 2001). As described in previous studies (Schulz et al., 2015b) we expected higher HEP amplitudes during the heartbeat perception condition as compared to the resting condition (hypothesis II). Taking into consideration the positive association between IAc and the HEP in adults (Pollatos & Schandry, 2004), we assumed that IAc would be positively associated to the magnitude of HEP amplitudes during a heartbeat detection task in adolescents (hypothesis IIIa). However, we expected no association between IAc and HEPs during a resting condition (hypothesis IIIb). On the basis of research showing missing relationships between physiological and subjective measures of interoception (Baranauskas et al., 2017; Mallorquí-Bagué et al., 2014) we expected that IS would not be associated with HEPs in the heartbeat condition (hypothesis IV). Based on previous findings showing independence of behavioral and subjective measures of interoception (Garfinkel et al., 2015; Forkmann et al., 2016), we assumed that IAc and IS would not be related (hypothesis V).

2. Methods

2.1 Participants

Fifty-four adolescents (28 female, 26 male) between 12 and 17 years were recruited via advertisement, associations, e-mail and schools to participate in the study. Participants received a 15€ cinema voucher for their participation. Exclusion criteria were chronic or acute heart diseases, other physical or mental health diseases, neurological diseases and current intake of medication. All participants and their parents provided written informed consent. The current study was approved by the ethics committee of Ulm University. Due to technical failure and poor EEG data quality eight participants had to be excluded; the final sample consisted of forty-six adolescents (24 female, 22 male; mean age 14.2 years, SD 1.6, range: 12-17).

2.2 Experimental Procedure

After arrival, participants were informed about the experiment and their informed consent was obtained. Afterwards, the participants' height and weight were assessed. Then, the participants were seated in a sound-attenuated chamber, which was connected to the neighboring equipment room by intercom. Active electrodes for EEG, ECG and EOG were attached.

At first, we assessed a resting condition for a duration of 5 minutes. Participants were instructed to sit comfortable in their chair and to relax. They were also allowed to close their eyes. A heartbeat tracking task (Schandry, 1981) was following to assess *IAc* (Garfinkel et al., 2015). The heartbeat perception task comprised one training interval of 10 s and four heartbeat-counting phases (intervals lasting for 25, 35, 45 and 60 seconds), which were separated by two resting phases of 20 s. During the intervals, participants were instructed to concentrate on their own heart activity and to silently count their heartbeats. Participants were not allowed to take their pulse or to try other manipulations which could facilitate the detection of their heartbeats. The beginning and the end of the counting intervals were signaled by the test supervisor. Immediately after the stop signal, participants were asked to verbally report the number of counted heartbeats. Participants obtained no information about the length of the counting intervals and about their performance.

At the end of the heartbeat tracking task, the participants rated their confidence regarding their perceived IAc as a measure of *IS*. Participants were asked to make their judgements verbally on a ten-point Likert scale with a range from 1 to 10, where one endpoint was labeled “No confidence at all” while the other endpoint was named “Complete confidence” (Garfinkel et al., 2015).

2.3 Psychophysiological Recording

During the heartbeat perception task, EEG activity was recorded continuously from 62 leads, using the Easy-Cap electrode system (Falk Minow Services, Germany) with nonpolarizable active Ag/AgCl electrodes at equidistant positions. Cz served as a reference and the ground electrode was attached at the electrode position F4. Horizontal and vertical electrooculograms (EOG) were recorded. Impedances were maintained below 5kΩ. The signals were amplified using an active amplifier system (Brain Products, Germany) and digitized at a sampling rate of 1000Hz. EEG data were hardware filtered between 0.16Hz (10s time constant) and 1000Hz during the acquisition.

ECG was measured with a nonpolarizable Ag/AgCl electrodes placed at the right clavicula and left chest. ECG activity was recorded equivalent to the EEG using an active amplifier system (Brain Products, Germany) with a sampling rate of 1000 Hz, and were hardware filtered between 0.016Hz and 1000Hz during the acquisition.

2.4 Data analysis

2.4.1 Analysis of ERP and ECG data

All steps of ECG and EEG analysis were conducted with Brain Vision Analyzer 2.1 (Brain Products, Germany). EEG data were visually inspected. ECG R-waves were detected offline semi-automatically in ECG raw data. The detected R-waves were used to create average artifact subtraction templates for the cardiac artifact (CA) correction in the EEG data (Allen, Polizzi, Krakow, Fish, & Lemieux, 1998). An extended infomax independent component analysis (ICA) was performed to remove residual CAs and eye-movement artifacts (Terhaar, Viola, Bär, & Debener, 2012; Maister, Tang, & Tsakiris, 2017). Other possibilities to reduce the residual CA are the CSD transformation (Terhaar et al., 2012; Pollatos et al., 2005a; Pollatos & Schandry, 2004) or the HAC method (Waser & Garn, 2013). ICA has been proven to efficiently extract and remove the CA (Terhaar et al., 2012; Debener, Hine, Bleeck, & Eyles, 2008; Viola et al., 2009) so that reliable HEP signals can be regained. Independent components (ICs) representing CA, lateral eye-movements and eye-blink activity were detected semi-automatically. The ICs representing CA can be identified based on their topographic pattern (Terhaar et al., 2012; Viola et al., 2009). Since difficulties in identifying clear heartbeat related EEG topographies were reported (Viola et al., 2009), we imposed two additional criteria in order to enhance the validity of the identified CA independent components. For both additional criteria, the ICs data were first segmented by the detected R-wave. For the first criteria, we conducted a Fast Fourier Transform (FFT) to get a frequency spectrum of the ICs (Welch, 1967). To identify heart-rate related activity, the averaged data were inspected for a peak within the frequency range of 0.7 to 2 Hz in the power spectrum. We expected a peak in this range based on conversion of the resting heart rate and former research (Iriarte et al., 2003). As a second criterion for ECG artifact detection, the average of the R-wave segmented ICs were visually inspected regarding the magnitude of R-peak. For the CA-related IC, we expect to see a clear R-peak waveform in the average of the IC segments. Based on the combined criteria of the topography, spectrum properties within 0.7 to 2 Hz and magnitude of R-wave in the segmented IC data, the ICs were identified as ECG artifacts. *Fig. 2* demonstrates the topography, as well as the frequency spectrum and the averaged R-wave segmented ICs, for the classified cardiac artifact related ICs.

----------------------Please Insert Figure 2 here. -------------------------

Following ICA analysis, EEG data were filtered (0.05-20 Hz). EEG data were examined for muscular artifacts and other sources of artifacts. Within an automatic artifact rejection trials were rejected from the analysis if the voltage exceeded ± 50 µV/ms in any channel. Trials contaminated by artifacts were eliminated. EEG data were segmented relative to the detected R-wave-triggers, whereby segments were built in epochs ranging from 200 ms before the R-wave-trigger to 1300 ms after the R-wave-trigger. After baseline correction (200 ms pre R-wave-trigger as baseline), average brain waves were computed in the R-triggered EEG segments. Based on data-driven visual inspection for maximal brain activity and overlapping with selected time frames of previous studies (Terhaar et al., 2012; Schulz et al., 2015b; Schulz et al., 2015a) we decided to choose a time window of 360 to 500 milliseconds after the R wave for calculating the averaged HEP.

RR-interval times were calculated from the ECG to determine mean heart rate (HR). ECG waves were segmented for the time window of 360-500 ms after the R peak to calculate mean T-wave amplitudes.

2.4.2 Analysis of IAc and IS

IAc was determined with the heartbeat perception score, which was built as a mean score across the four intervals according to the following equation (Pollatos & Schandry, 2004; Pollatos et al., 2005a):

Perception Score = 1/4 ∑ (1- (|recorded heartbeats – counted heartbeats|)/ recorded heartbeats)

Higher scores indicate higher IAc, whereby a maximum score of 1 indicates an absolute IAc (Pollatos & Schandry, 2004; Pollatos et al., 2005a).

Mean values of confidence judgements were calculated as a measure of *IS*.

2.4.3 Statistical analysis

Mean voltages of the averaged HEP amplitudes were investigated for eight aggregated scalp sectors, based on region: frontal (FP1, AF3, F1, F5, F7, F9, FT7, FT9, F9/FT9, FPz, AFz, Fz, FP2, AF4, F2, F6, F8, F10, FT10, FT8, F10/FT10), frontocentral (FC3, FC5, FCz, FC4, FC6), central (C1, C2, C3, C4, C5, C6), centroparietal (CP1, CP2, CP3, CP4, CP5, CP6, CPz), parietal (P1, P2, P5, P6, P7, P8, P9, P10, Pz), temporal (T7, T8, TP7, TP8, TP9, TP10), parietooccipital (PO3, PO4), occipital (O1, O2, O9, O10, Oz). In consideration of the factor laterality, sixteen additional clusters were investigated, formed by region and hemisphere: frontal left (FP1, AF3, F1, F5, F7, F9, FT7, FT9, F9/FT9), frontal right (FP2, AF4, F2, F6, F8, F10, FT10, FT8, F10/FT10), frontocentral left (FC3, FC5), frontocentral right (FC4, FC6), central left (C1, C3, C5), central right (C2, C4, C6), centroparietal left

(CP1, CP3, CP5), centroparietal right (CP2, CP4, CP6), parietal left (P1, P5, P7, P9), parietal right (P2, P6, P8, P10), temporal left (T7, TP7, TP9), temporal right (T8, TP8, TP10), parietooccipital left (PO3), parietooccipital right (PO4), occipital left (O1, O9), occipital right (O2, O10). Differences in mean HEPs between scalp locations were investigated for each condition using a 8 x 2 repeated measures ANOVA with eight levels of scalp sectors (frontal, frontocentral, central, centroparietal, parietal, temporal, parietooccipital, occipital) and two levels of laterality (left, right). Post hoc analysis were conducted using *t* tests for dependent samples with Bonferroni-correction. For all ANOVA tests with repeated measures and more than one degree of freedom, uncorrected F-values as well as Greenhouse-Geisser corrected *p* values and epsilon values are reported. The normally distribution of the data was investigated using the Kolmogorov-Smirnov test (Field, 2009). Separate correlation analyses reporting Spearman-Rho correlation coefficients (r_s) (Field, 2009) were conducted to explore the association between *IAc/IS* and each HEP during the heartbeat condition or the resting condition. Moreover, possible associations between *IAc* and *IS* were examined using Spearman-Rho correlation coefficients (r_s). Critical alpha levels were fixed for all analyses to .05 with a confidence interval of 99.5.

Paired t-tests with Bonferroni-correction were calculated to investigate differences in the magnitude of heartbeat evoked brain activity in the heartbeat condition compared to the resting condition. Due to the multitude of comparisons in the t-tests comparing activities of different electrode clusters, critical alpha levels were fixed for those analyses to .006 with a confidence interval of 99.99. ECG amplitudes were averaged for the time window of 360-500 ms. All analysis were conducted with SPSS 24.0 (IBM, Inc.).

3. Results

3.1 IAc

The mean IAc score was .67 (SD =.17, Min = .33, Max = .97). The median of IAc was .64.

3.2 IS

The mean value of *IS* was 4.99 (SD = 1.87, Min = 1, Max = 8). The median was 5.0.

3.3 HEP

Scalp distribution of the HEP - resting condition

We neither observed a main effect of laterality [F(1,45) = .59, p = .45] nor of scalp sector [F(2.99, 134.5) = .87, p = .46]. We assessed a significant interaction effect of laterality and scalp sector [F(4.28, 192.79) = 2.49, p = .041, ηp^2 = .052]. Post hoc tests revealed marginally higher activity at the right hemisphere showing marginally higher activity at occipital (M = - .008 µV, SD = .73) compared to frontocentral electrodes [M = - .18 µV, SD = .44, t(45) = - 1.95, p = .057]. For the left hemisphere higher activity was observed for frontocentral electrodes (M = - .10 µV, SD = .45) as compared to temporal electrodes [M = - .31 µV, SD = .81, t(45) = 2.32, p = .025] as well as higher activity for centroparietal (M = -.10 µV, SD = .41) as compared to temporal electrodes [t(45) = 2.10, p = .041]. Regarding descriptive statistics, highest brain activity was observed over occipital electrodes followed by parietooccipital and parietal locations. Table 1 depicts mean averaged HEP amplitudes for all investigated scalp sectors.

Scalp distribution of the HEP - heartbeat condition

We neither observed a main effect of laterality [$F(1,45) = 2.47$, $p = .123$] nor of scalp sector [$F(2.82, 127.5) = .71$, $p = .54$]. There was also no significant interaction effect of laterality and scalp sector [$F(4.43, 199.41) = 1.63$, $p = .163$]. Regarding descriptive statistics, highest brain activity was observed over frontocentral electrodes followed by central and occipital locations (see Table 1). *Fig. 3* depicts topography maps of HEPs for the heartbeat detection task and for the resting condition for the sample of the current study.

-----------------------Please Insert Table 1 here. --------------------------

-----------------------Please Insert Figure 3 here. --------------------------

HEPs during the resting condition compared to the heartbeat condition

HEPs during the heartbeat condition were significantly more positive as compared to the resting condition for the frontocentral and central electrode cluster [frontocentral: resting c. M = - 1.14 µV, SD = 3.60, heartbeat c. M = .08 µV, SD = .15, $t(45) = 2.35$, $p = .023$, $d = .48$; central: resting c. M = - .30 µV, SD = .74, heartbeat c. M = - .04 µV, SD = .56, $t(45) = 2.23$, $p = .031$, $d = .40$]. For all the other electrode locations, no significant differences in mean HEPs were observed (*ps* < .05).

3.4 Correlations

Results of Kolmogorov-Smirnov tests revealed significant deviations from normal distribution for averaged heartbeat-evoked brain activities for both the heartbeat and the resting condition (ps = .000041 - .03). Also data of IS were not normally distributed ($p = .000499$).

Correlation analyses revealed a significant positive association between IAc and the HEP at frontocentral electrodes for the heartbeat condition ($r_s = .452$, $p = .002$). Considering the factor laterality, significant relations were assessed between IAc and HEPs at left and right frontocentral electrodes for the heartbeat condition (left: $r_s = .492$, $p = .001$, right: $r_s = .306$, $p = .039$). No significant correlations were detected between IAc and HEPs for the resting condition ($ps > .05$). IS was not associated with HEPs for the heartbeat condition ($ps > .05$).

Fig. 4 exemplarily illustrates the association between the HEP and IAc by depicting mean HEP amplitudes during the heartbeat detection task for individuals with high (n = 10) or low levels of IAc (n = 10). *Fig.5* exemplarily illustrates topographic maps of HEPs during the heartbeat detection task for individuals with high (n = 10) or low levels of IAc (n = 10). Individuals with high levels of IAc were identified as the 10 subjects of the sample with highest values of IAc. Individuals with low levels of IAc were identified as the 10 subjects with lowest values of IAc. Groups were only built for illustration.

----------------------Please Insert Figure 4 here. -------------------------

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Fig. 6 exemplarily illustrates mean HEP amplitudes during the resting condition for subjects with high (n = 10) or low levels of IAc (n = 10). *Fig.7* exemplarily depicts topographic maps of HEPs during the resting condition for individuals with high (n = 10) or low levels of IAc (n = 10). Groups of high vs. low IAc were only built for illustration.

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No significant association was revealed between IAc and IS ($r_s = .16$, $p = .283$).

3.5 ECG Analysis

Mean heart rate for the heartbeat condition was 72.4 bpm (SD = 10.6, Min = 49.6, Max = 103.5 bpm). There was no significant association with IAc ($r = -.012$, $p = .935$).

4. Discussion

The current study is the first that investigated HEPs in adolescents related to their interoception. Our findings illustrate the meaning of the HEP as a valid neuronal marker of interoception in adolescence.

4.1 Study Aim I: Investigation of topography and amplitude of the HEP during heartbeat condition and during resting condition

In accordance with hypothesis I HEPs were present during both the heartbeat detection task as well as during the resting condition in the latency range of 360-500ms post R-wave. Regarding scalp distribution, hypothesis I was only partly confirmed for the heartbeat condition in descriptive statistics, as we observed highest activity over frontocentral electrodes followed by central locations. During the resting condition, however, maximal amplitudes appeared over occipital locations. Our results for the heartbeat condition are in accordance with previous studies in adults reporting highest HEP amplitudes over frontal, frontocentral and central electrodes (Pollatos & Schandry, 2004; Pollatos et al., 2005a;

Montoya et al., 1993; Schandry & Montoya, 1996; Leopold & Schandry, 2001; Schulz et al., 2015b; Park & Tallon-Baudry, 2014) as well as in consistence with studies with children describing HEPs at the central electrode location (Immanuel et al., 2014; Baumert et al., 2015). Findings for the resting condition are in line with research on adults describing the HEP as being present even without an explicit attentional focus on one's cardiac activity (Schandry & Montoya, 1996; Park et al., 2015) as well as in line with studies in children describing HEPs during sleep (Baumert et al., 2015; Immanuel et al., 2014). In consideration of a dipole source localization study of Pollatos and co-workers (Pollatos et al., 2005a), the frontocentral activity pattern in the current study might reflect sources in the interoceptive network, including the anterior cingulate or the insular cortex. Functional imaging studies identified the insula, the anterior cingulate and the medial frontal/dorsal cingulate as cerebral correlates of cardiovascular arousal and as parts of a neural network for processing cardiac signals, being also associated with IAc (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Cameron & Minoshima, 2002; Pollatos, Schandry, Auer, & Kaufmann, 2007). According to Pollatos and colleagues (Pollatos et al., 2005) dipole strength in the right insula and the anterior cingulate was positively correlated with IAc.

In consistence with hypothesis II we detected higher HEP positivity during the heartbeat condition as compared to the resting condition over frontocentral and central locations. The results are in accordance with previous research (Schulz et al., 2015b) and indicate that HEP positivity in the heartbeat condition was manipulated by criteria related to the heartbeat task, such as an attentional focus on heartbeat perception.

Mean HEP amplitudes in the current study were within a negative range. Some research groups also described negative HEP amplitudes (Montoya et al., 1993; Schandry & Weitkunat, 1990; Fukushima et al., 2011). This effect might be related to the age group of the participants investigated, other factors explaining possible location differences refer to the use of different reference channels. However, HEPs are of positive polarity in the current study, which is consistent with the majority of previous research and indicates that the potential was manipulated by external factors, such as an attention focus on the heartbeat (Pollatos & Schandry, 2004; Pollatos et al., 2005a; Montoya et al., 1993; Schandry & Montoya, 1996; Leopold & Schandry, 2001; Schulz et al., 2015b; Park & Tallon-Baudry, 2014; Schulz et al., 2015a).

4.2 Study Aim II: Relation between dimensions of interoception and the HEP in the light of a new model of interoception

In line with hypothesis IIIa and IIIb HEP positivity was positively associated with IAc in the heartbeat condition at frontocentral locations, whereas no associations were observed in the resting condition. These findings, together with results of hypothesis II indicate the validity of the HEP as a neuronal marker of interoception in adolescence and should be pointed out as the core results of the current manuscript. Those results are consistent with previous research in adults, showing positive associations between HEP amplitudes and IAc in adults (Pollatos & Schandry, 2004; Katkin et al., 1991) and are in line with findings of individuals with high IAc showing higher HEP activity than individuals with low IAc (Pollatos & Schandry, 2004; Pollatos et al., 2005; Montoya et al., 1993). According to our findings, we would support the assumption that HEP activity mirrors IAc (Pollatos & Schandry, 2004; Pollatos et al., 2005a; Montoya et al., 1993; Schandry et al., 1986). The fact that the degree of the ability to detect visceral-afferent (cardiovascular) signals of one's own body is reflected in the HEP has already been confirmed for different interoceptive signals which all influence the HEP, such as hunger, pain and affective states (Fukushima et al., 2011; Schulz et al., 2015a; Shao et al., 2011; Couto et al., 2015; MacKinnon, Gevirtz, McCraty, & Brown, 2013).

During the resting condition participants were not instructed to focus on their interoceptive sensations. Accordingly, in this condition IAc was not associated with HEP positivity. In sum, our finding of related IAc and HEP positivity only for the interoceptive condition underpins the assumption of the HEP as a marker of interoception in adolescence, being modulated by an attentional focus on interoceptive signals, such as the heartbeat. Previous studies in adults are in line with this assumption, describing an attentional focus on the heartbeat, high motivation in heartbeat detection as well as IAc as relevant factors to manipulate HEP amplitudes (Montoya et al., 1993; Yuan et al., 2007; Schandry & Montoya, 1996; Weitkunat & Schandry, 1990; Pollatos & Schandry, 2004; Katkin et al., 1991; Pollatos et al., 2005a).

In hypothesis IV we assumed that IS would not be associated with HEP amplitudes in the heartbeat condition, which could be confirmed in the current study. Our results are in line with previous studies showing that self-report measures of interoception are not related to physiological measures of interoception (Mallorquí-Bagué et al., 2014) nor to the HEP (Baranauskas et al., 2017). However, it is important to consider that Baranauskas and colleagues also found one out of eight self-report scales of interoception, the Not-Worrying scale of the MAIA (Mehling et al., 2012), to positively correlate with the HEP (Baranauskas et al., 2017). The authors concluded that scales and HEPs assessed different facets of interoception which are not directly related (Baranauskas et al., 2017). This might also be an explanation for the findings of the current study. Especially in the current study IS was assessed as the self-report of participants' confidence in their own IAc, which is again a different facet of IS (Garfinkel et al., 2015) which has not been investigated related to HEPs to the authors' knowledge so far. Another explanation might be the young age of the sample which might have been associated with difficulties in estimating one's own IAc and which has been described as one limiting factor in previous studies showing that 5-12% of the children were unable to sense any of their heartbeats (Koch & Pollatos, 2014a; Eley et al., 2004; Eley, Gregory, Clark, & Ehlers, 2007).

Referring to Garfinkel and colleagues (Garfinkel et al., 2015) we assumed in hypothesis V that the dimensions of interoception (IAc and IS) would be independent. This could be confirmed for the current study as IAc and IS were not related and this was also confirmed by previous research groups (McFarland, 1975; Whitehead, Drescher, Heiman, & Blackwell, 1977; Garfinkel et al., 2015).

In the light of our results we can confirm several assumptions of the postulated "MINP"-Model. At first, we confirmed the independence of IAc and IS. The HEP should be pointed out as the central outcome variable of the current study as we could show that it was associated with behavioral dimensions of interoception, such as IAc, but not with subjective dimensions, such as IS. This is in line with the "MINP" model considering an additional level of neuronal markers, including brain potentials (such as the HEP) which are related to dimensions of interoception. As mean heart rate, which can be subsumed as "Physiological state" variable, was not related to IAc, we further exclude cardiovascular arousal, as proposed by Forkmann and colleagues (Forkmann et al., 2016), as mediating variable for the relation of IAc and the HEP. However, our model should necessarily be validated in future studies. It might be of particular interest to examine possible relations between the HEP and other dimensions of interoception, such as IS, IAw and IE. Moreover, it might be of relevance to investigate in a regression model whether the HEP might also serve as a predictor of different components of interoception. To conclude, we postulate the HEP as one relevant neuronal marker of interoception which should necessarily be considered in recent models and in upcoming research on interoception.

In summary, this is the first study validating the HEP as a neuronal marker of interoception in adolescents. Being associated with interoception, the HEP might serve to indicate poor interoception in adolescents. Consequently, it might be a useful tool to detect ~~a~~ vulnerability for affective, physical and mental dysfunctions during adolescence, related to atypical interoception (Murphy et al., 2016).

In future studies, the HEP should also be investigated as a marker of developmental processes of interoception or as an index of atypical interoception in clinical samples. Also its relation to the processing of emotion or pain, being closely associated with interoception (Garfinkel et al., 2017), should be considered in future studies in adolescents.

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Author notes

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Abbreviations

bpm = beats per minute, **CA** = cardiac artifact, **ECG** = electrocardiography, **EEG** = electroencephalography, **EOG** = electrooculography, **ERP** = event-related potential, **HEP** = heartbeat-evoked brain potential, **IAc** = interoceptive accuracy, **IS** = interoceptive sensibility.

Table 1. Mean averaged amplitudes of HEPs (μV) for investigated scalp locations for the resting condition and for the heartbeat condition.

	N = 46	
Scalp location	Resting condition M (SD)	Heartbeat condition M (SD)
Frontal	-0.41 (1.80)	-0.21 (1.64)
Frontocentral	-1.14 (3.60)	0.08 (0.99)
Central	-0.30 (0.74)	-0.04 (0.56)
Centroparietal	-0.28 (1.04)	-0.14 (0.96)
Parietal	-0.23 (1.67)	-0.20 (1.43)
Temporal	-0.43 (1.36)	-0.27 (1.26)
Parietooccipital	-0.21 (1.42)	-0.20 (1.28)
Occipital	-0.12 (2.29)	-0.04 (2.12)

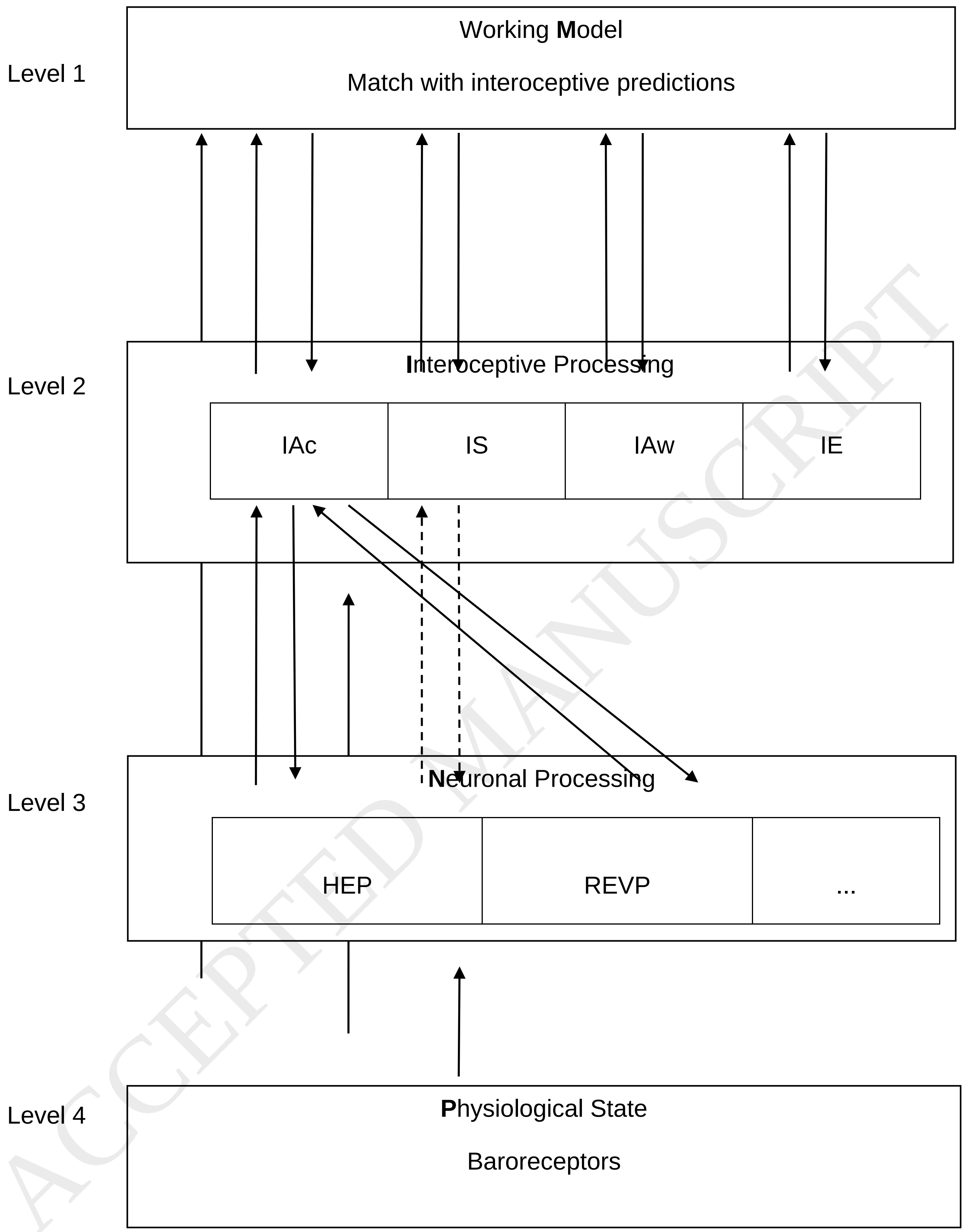

Figure 1. MINP- Model of interoception. Illustrated are assumed associations of different levels of interoception. Arrows drawn through indicate assumed associations between variables. Dotted arrows indicate the assumption of possible but not necessary associations.

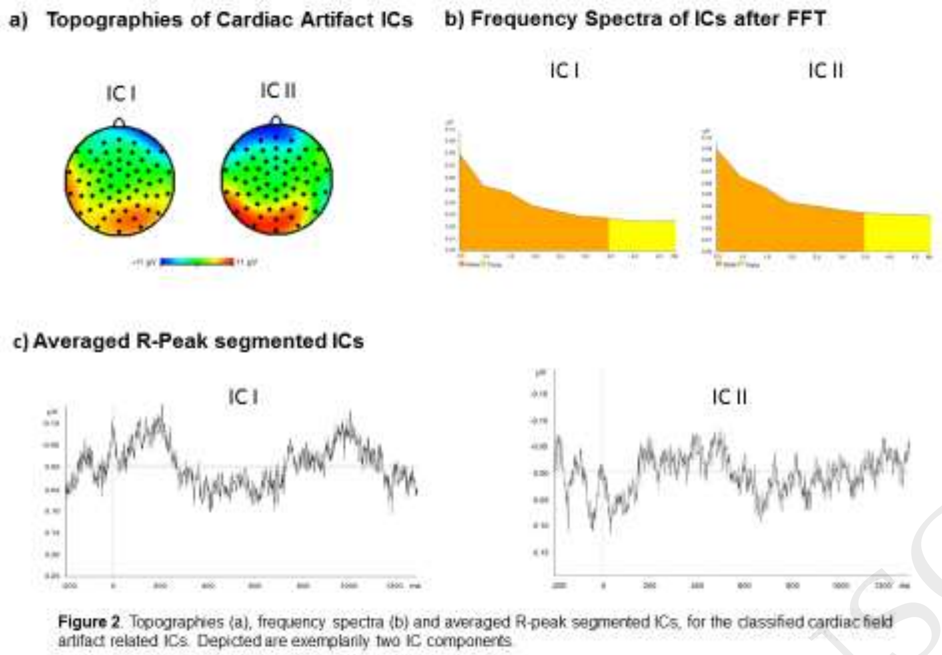

Figure 2. Topographies (a), frequency spectra (b) and averaged R-peak segmented ICs, for the classified cardiac field artifact related ICs. Depicted are exemplarily two IC components.

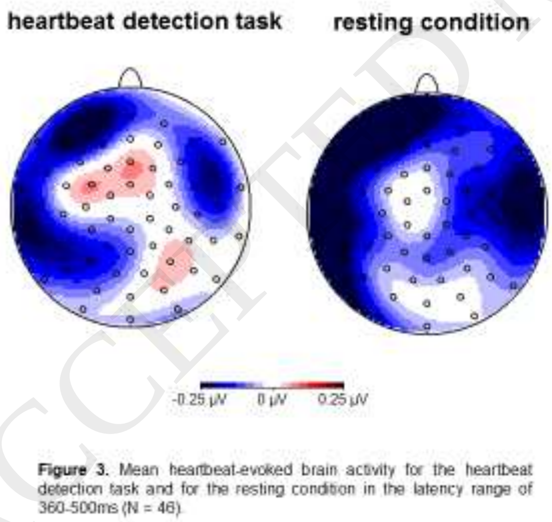

Figure 3. Mean heartbeat-evoked brain activity for the heartbeat detection task and for the resting condition in the latency range of 360-500ms (N = 46).

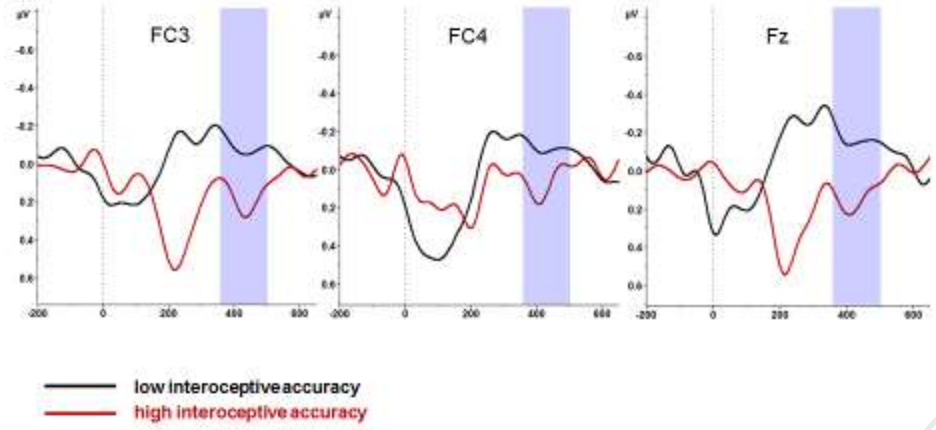

Figure 4. Event-related potentials of heartbeat-evoked brain activity in the latency range of 360-500ms during the heartbeat detection task. Depicted are grand averages (GAs) of subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

Figure 4. Event-related potentials of heartbeat-evoked brain activity in the latency range of 360-500ms during the heartbeat detection task. Depicted are grand averages (GAs) of subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

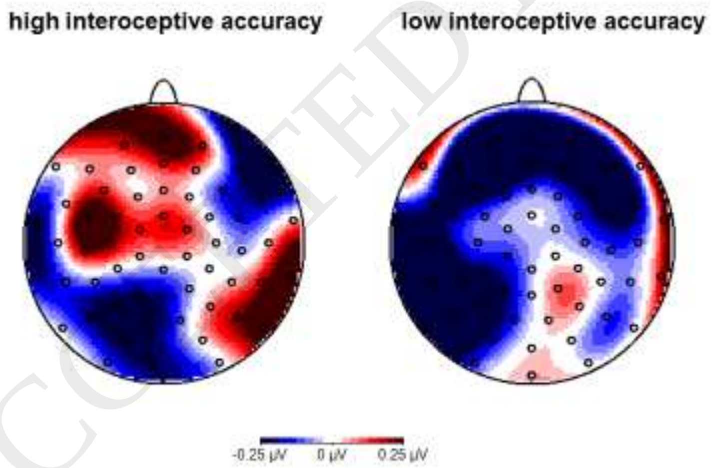

Figure 5. Mean heartbeat-evoked brain activity for the heartbeat detection task in the latency range of 360-500ms for subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

Figure 5. Mean heartbeat-evoked brain activity for the heartbeat detection task in the latency range of 360-500ms for subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

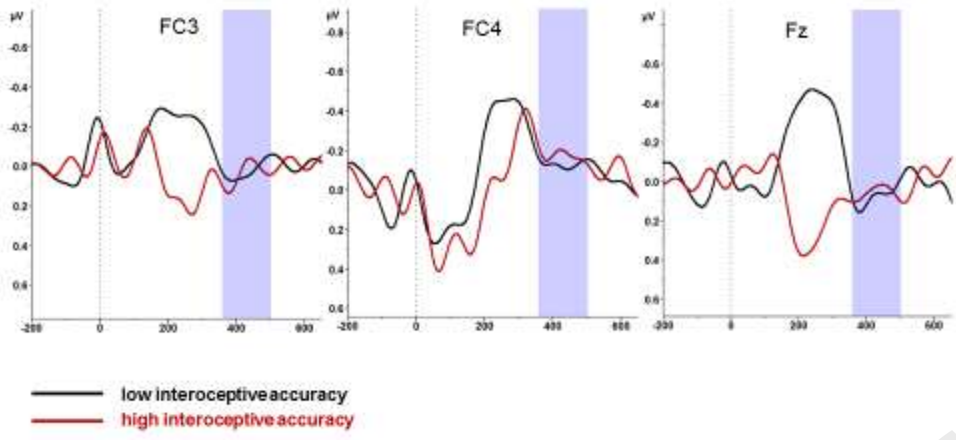

Figure 6. Event-related potentials of heartbeat-evoked brain activity in the latency range of 360-500ms during the resting condition. Depicted are grand averages (GAs) of subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

Figure 6. Event-related potentials of heartbeat-evoked brain activity in the latency range of 360-500ms during the resting condition. Depicted are grand averages (GAs) of subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

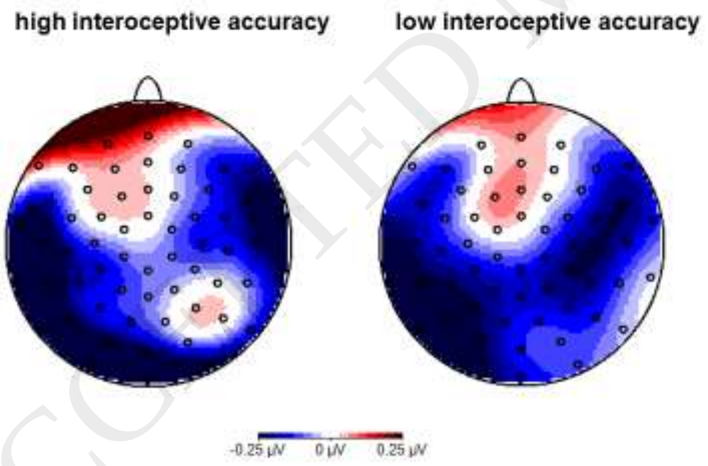

Figure 7. Mean heartbeat-evoked brain activity for the resting condition in the latency range of 360-500ms for subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).

Figure 7. Mean heartbeat-evoked brain activity for the resting condition in the latency range of 360-500ms for subjects with high (n = 10) or low levels of interoceptive accuracy (n = 10).