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**Temporal matching between interoception and
exteroception: electrophysiological
responses in a heartbeat discrimination
task**

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Abstract

Recent studies on interoception emphasize the importance of multisensory integration between interoception and exteroception. One of the methods frequently applied for assessing interoceptive sensitivity is the heartbeat discrimination task, where individuals judge whether the timing of external stimuli (e.g., tones) are synchronized to their own heartbeat. Despite its extensive use in research, the neural dynamics underlying the temporal matching between interoceptive and exteroceptive stimuli in this task have remained unclear. The present study used electroencephalography (EEG) to examine the neural responses of healthy participants who performed a heartbeat discrimination task. We analyzed the differences between EEG responses to tones, which were likely to be perceived as "heartbeat-synchronous" (200 ms delayed from the R-wave) or "heartbeat-asynchronous" (0 ms delayed). Possible associations of these neural differentiations with task performance were also investigated. Compared with the responses to heartbeat-asynchronous tones, heartbeat-synchronous tones caused a relative decrease in early gamma-band EEG response and an increase in later P2 event-related potential (ERP) amplitude. Condition differences in the EEG/ERP measures were not

significantly correlated with the behavioral measures. The mechanisms underlying the observed neural responses and the possibility of electrophysiological measurement of interoceptive sensitivity are discussed in terms of two perspectives: the predictive coding framework and the cardiac-phase-dependent baroreceptor function.

Keywords: Interoception; heartbeat perception; multisensory integration; predictive coding; baroreceptor.

1. Introduction

The central processing of internal bodily information, known as interoception, has attracted interest in psychology and neuroscience in recent years. The sensitivity to an interoceptive signal is an important factor for modulating emotional experiences (Herbert, Herbert, & Pollatos, 2011; Terasawa, Shibata, Moriguchi, & Umeda, 2013; Wiens, Mezzacappa, & Katkin, 2000). In clinical studies, hyper- or hypo-sensitivity of interoception is often reported in mental disorders related to emotion and body awareness (Herbert & Pollatos, 2012), including anxiety (Domschke, Stevens, Pfleiderer, & Gerlach, 2010), depression (Terhaar, Viola, Bär, & Debener, 2012), alexithymia (Shah, Hall, Catmur, & Bird, 2016), and eating disorders (Merwin, Zucker, Lacy, & Elliott, 2010). Various aspects of cognitive function, such as decision-making (Dunn et al., 2010), time perception (Wittmann, 2015), and self-awareness (Sel, Azevedo, & Tsakiris, 2016; Suzuki, Garfinkel, Critchley, & Seth, 2013), have also been suggested to correlate with individual differences in the interoceptive process (Craig, 2009; Seth, 2013). As such, measurement of individual

differences in interoception has far-reaching implications across various fields.

Individuals' sensitivity to interoceptive signals have been most frequently assessed in terms of cardiac perception. Behavioral tasks of heartbeat perception can be classified into two types of experimental paradigms: heartbeat tracking and heartbeat discrimination (Brener & Ring, 2016; Jones, 1994). The heartbeat tracking task typically requires participants to count the number of perceived heartbeats within a certain period (Schandry, 1981). This paradigm has been widely used in clinical studies and cognitive neuroscience to conveniently assess interoceptive sensitivity. However, despite this practical advantage, this task is susceptible to cognitive biases, such as beliefs or expectations regarding heart rate (Pennebaker, 1981; Ring, Brener, Knapp, & Mailloux, 2015).

The heartbeat discrimination task requires participants to judge whether the timing of external stimuli (e.g., tones or flashes) are synchronous with their own heartbeat. Researchers have used this paradigm with several variations regarding the number of conditions on the heartbeat-feedback interval and its temporal pattern (Jones, 1994). This paradigm has some practical disadvantages, including the requirement of a system to provide

feedback stimuli with precisely controlled timings, and a much longer experimental time than the tracking task (e.g., 20-90 min versus 5-10 min). Another important caveat of this task is its difficulty for participants; typically, only about 20-30% of participants can perform the task accurately at an above-chance level, so it tends to fail at detecting individuals who can actually perceive their heartbeat (Brener & Ring, 2016). Despite these disadvantages, the heartbeat discrimination paradigm remains a relevant methodology because it is considered to be much less influenced by the cognitive bias of participants, and is thus more objective than tracking tasks (Brener & Ring, 2016; Ring et al., 2015). Furthermore, this paradigm is also important because it reflects the function of the integrative process between interoception and exteroception, as discussed below.

Multisensory integration in the interoceptive process has received growing interest in cognitive neuroscience. For example, it has been reported that the amplitude of magnetoencephalogram activity time-locked to heartbeats is associated with the detection of visual stimuli (Park, Correia, Ducorps, & Tallon-Baudry, 2014). This suggests that central processing of an afferent visceral signal is associated and

integrated with the exteroceptive process. The effects of cardiac phases (systole vs. diastole) on perception of external stimuli have also been examined (Critchley & Garfinkel, 2015; Edwards, Ring, McIntyre, Winer, & Martin, 2009). For instance, emotionally expressive faces, particularly those expressing fear, presented during the cardiac systole period are processed with slightly more salience than those presented during the diastole period (Garfinkel et al., 2014; Gray et al., 2012). Studies on the sense of selfhood have also reported that self-attribution to visual stimuli is enhanced when their appearances covary in synchrony with participants' heartbeats (Aspell et al., 2013; Suzuki et al., 2013). Together, these findings suggest a real-time association between the interoceptive process and external stimuli.

One of the important theories for the interoceptive multisensory integration is the "predictive coding framework", which has been applied in studies of interoception and related topics (Apps & Tsakiris, 2014; Barrett & Simmons, 2015; Blanke, Slater, & Serino, 2015; Seth, 2013). This view proposes that the brain primes itself for efficient and optimal information processing by creating a model of causes and consequences of the world to constantly predict or prepare for upcoming information

(Clark, 2013; Friston, 2009). A general and observable phenomenon featured by the predictive coding framework is response attenuation to predicted sensory inputs (Brown, Adams, Parees, Edwards, & Friston, 2013; Quattrocki & Friston, 2014). A well-known example of this effect is the diminished neural response to external stimuli that are caused by self-action, which are largely predictable for the perceptual brain areas receiving the afferent copy of motor commands (Blakemore, Goodbody, & Wolpert, 1998; Hughes, Desantis, & Waszak, 2013; von Holst, 1954; Wolpert, 1997). Importantly, the occurrence of predictive sensory attenuation can be an index of the cardiac interoception, particularly its sensory integration with exteroception. Considering that the brain receives signals from each heartbeat, the brain could predict the timing of external stimuli that are temporally associated with the heartbeats, and could suppress the response to those stimuli. As an important demonstration of this notion, Salomon and colleagues have shown that visual awareness (and activity of insula cortex) are significantly suppressed when visual stimuli are synchronized with the participant's heartbeat (Salomon et al., 2016).

The heartbeat discrimination task is specifically designed for the process of intero-exteroception integration for the

assessment of synchronicity judgment. Also, the cardiac perception task directly provides us with a measure of individuals' cardiac sensitivity, which is highly relevant for examining the underlying process. For these reasons, together with the findings described above, we consider the heartbeat discrimination paradigm to be an appropriate task to elucidate the detailed mechanism underlying interoceptive multisensory integration. In addition, the high temporal resolution of electroencephalography (EEG) provides an advantage for examining the temporal aspect of information integration. Thus, the present study examined scalp-surface EEG activity during the heartbeat discrimination task.

Previously, van Elk and colleagues systematically investigated event-related potential (ERP) responses in the situation of a heartbeat discrimination task (Van Elk, Lenggenhager, Heydrich, & Blanke, 2014). Specifically, they examined the N1 component elicited by tones with several kinds of heartbeat-contingent and -unrelated timings. In the heartbeat-contingent trials, a series of tones was presented with a fixed interval from the electrocardiogram (ECG) R wave. As an "external" (heartbeat-unrelated) trial, a series of tones was

presented with randomly varied intervals that resembled an ordinary heartbeat sequence. In each trial, participants judged synchronicity between the tones and their heartbeats. The results showed significant attenuation in the N1 component elicited by the heartbeat-related tones relative to the response to the external sounds, whereas it showed no difference among the heartbeat-related trials. Furthermore, the N1 attenuation by the cardiac-contingent sounds was highly correlated with the decline of N1 responses to the sounds elicited by the participants' own actions. Therefore, referring to the predictive coding framework, they discussed the findings as indicating the occurrence of predictive suppression of external stimuli in the heartbeat discrimination paradigm.

This well-designed study by van Elk et al. (2014) leaves a few issues to be further examined. First, although they showed different neural responses to heartbeat-contingent and -unrelated stimuli, they found no evidence of neural differentiation within the heartbeat-contingent conditions. In other words, the synchronicity between intero-extero signals in terms of the length of temporal gaps (i.e. whether there is an evident delay or not) failed to be detected in their analysis of N1. This result is somewhat reasonable from the viewpoint of

predictive coding; when the delays of the tones to the heartbeats are stable, the predictability of the timing of tones may not substantially differ among different lengths of delays. However, the majority of discrimination tasks have presented sequences of fixed heartbeat-sound intervals (e.g., 200 vs. 500 ms) in every condition to discriminate (Brener & Ring, 2016; Jones, 1994). Therefore the difference among those temporal gaps is expected to modulate the underlying neural activities. We suggest that the null result in their study may have resulted from the limited focus of their analysis, where only the N1 ERP component was examined. Neural responses to auditory tones can be examined at other latencies and also in the time-frequency domain of EEG. To further elucidate the neural responses to heartbeat-related stimuli, it is worth extending the analysis to time-frequency responses of EEG as well as another ERP component such as P2.

Another important issue is that it was unclear whether the neural activities underlying the heartbeat discrimination task reflected individuals' cardiac sensitivity. Their paper reported no significant correlation between the performances of the heartbeat discrimination task and the attenuation of N1 components. However, the task in their study was performed with

only one trial for each condition (seven trials in total), and this small number of trials is not sufficient for reliable scoring of task performance (Acosta & Pegalajar, 2003). Therefore, possible associations between the behavioral and neural measures remain to be examined.

The present study examined EEG/ERPs of healthy participants performing the heartbeat discrimination task. For this paradigm, it would be ideal to adjust the amount of heartbeat-stimulus asynchronous (delay) for each participant. However, it this is not possible in all cases; for example, the optimal delay is unclear for poor cardiac perceivers (Wiens & Palmer, 2001). Therefore we used a two-alternative fixed-interval version of the task because it is one of the most frequently applied methods in neuroscience and psychology (Barrett, Quigley, Bliss-Moreau, & Aronson, 2004; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015; Khalsa et al., 2008). We investigated how neural responses differed when sounds were presented at two different timings, 200-ms and 0-ms delays from the ECG R-wave, which were likely to be perceived as synchronous and asynchronous with the heartbeat, respectively (Wiens & Palmer, 2001). We examined neural measures

of sensory neural responses for auditory stimuli, including early auditory-evoked gamma response, and later ERP components of N1 and P2. Together with assessing the difference between conditions, all neural measures were tested for their association with behavioral measures of interoceptive accuracy. In addition, the interoceptive accuracy of each participant was also assessed using the heartbeat tracking task to obtain additional information about the behavioral-neural link.

2. Methods

2.1. Participants

Twenty-seven participants (14 females) aged 19–34 years (mean \pm SD: 22.89 \pm 3.02) were included in this study. Participants received 2000 yen (approximately 20 USD) for their inclusion, and all provided written informed consent before the experiments. The study was approved by the Ethics Committee of the Web for the Integrated Studies of the Human Mind, Japan (No. 25-p-15) and was conducted in accordance with standards specified in the 1964 Declaration of Helsinki.

2.2. Heartbeat tracking task

Participants performed two types of heartbeat perception tasks during EEG and ECG recordings. Although the primary focus of this study was the heartbeat discrimination task, the heartbeat tracking task was executed first because the discrimination task explicitly informs the participants of their heart rate, which could affect the tracking task performance. In the tracking task, the participants were seated in a dimly lit, electrically shielded sound-attenuation room. The participants were asked to count their own heartbeats during designated periods, and to verbally report the number of beats at the end of each trial. The start and end of the trial periods were signaled acoustically. Following a practice trial (10 s), the experiment was conducted using three trials of different lengths (25 s, 40 s, and 60 s). The sequence of trials was randomized for each participant. The task score was calculated by comparing the reported and actual number of heartbeats using the following formula (Herbert, Pollatos, & Schandry, 2007; Sueyoshi, Sugimoto, Katayama, & Fukushima, 2014):

$$\text{tracking task score} = \frac{1}{3} \sum \left(1 - \frac{|\text{recorded heartbeats} - \text{counted heartbeats}|}{\text{recorded heartbeats}} \right).$$

This equation yields the degree to which the number of subjective heartbeats matches that of actual heartbeats; when

the two are equal, the score is 1 (maximum), and when no heartbeat is perceived, the score is 0 (minimum). Scores were calculated for each trial, and the average of the three trials was used as the final score of this task for each individual.

2.3. Heartbeat discrimination task

Participants sat in the same room, on the same chair for the tracking task. A 22-in computer monitor was placed in front of the participants, and a numeric keyboard was set on a table to the right of the participant's chair. The heartbeat discrimination task contained three conditions: synchronous, asynchronous, and silent. In the synchronous and asynchronous conditions, participants were asked to judge whether a series of tones (800-Hz square-wave tone with 100-ms duration) was synchronized with their own heartbeat. In the synchronous condition, the tones were delivered 200 ms after an individual's ECG R waves appeared. In the asynchronous condition, the tones were delivered at the moment of (i.e., no delay to) each R wave. These settings were determined based on established knowledge of the heartbeat discrimination task, where stimuli presented with a 200-300-ms delay after the appearance of R waves are most likely to be perceived as being synchronous with an individual's own heartbeat (Ring & Brener, 1992; Wiens & Palmer, 2001). The

inter-stimulus interval was approximately 857 ms on average, which corresponds to the inter-heartbeat intervals of the participants (see also the Results section). An average of 75 - 76 tones were presented in the both conditions. The silent condition delivered no tones and measured participants' baseline neurophysiological state. After the participant pressed a key on the keyboard to initiate a trial, the display first indicated whether the tones would be presented in the current trial. Each of the trial periods lasted for 65 s, during which the computer monitor presented a white fixation cross centered on a black background. During this presentation, stimulus tones were delivered for the synchronous and asynchronous conditions, and no stimulus was presented in the silent condition. At the end of the synchronous and asynchronous trials, the computer display prompted the participants to report their judgment on the synchrony by pressing a corresponding key. Each condition comprised six trials; the whole task comprised 18 trials in total with the three conditions presented in pseudo-randomized order.

By calculating the ratio of hits and false alarms, the task score was quantified as A prime (A'), which is a nonparametric version of the sensitivity index (analogous to d') of signal

detection theory (Aaronson & Watts, 1987; Grier, 1971). This value is obtained by estimating the receiver-operation curve by a single combination of hit and false-alarm rates, and it ranges from 0 to 1, where a value of 0.5 corresponds to a chance level and a value of 1 corresponds to perfect discrimination (for an example of usage of this index in the heartbeat discrimination task, see Harver, Katkin, & Bloch, 1993).

2.4. Electrophysiological recordings

EEG was recorded from 65 electrodes with a Geodesic Sensor Net and Netstation System (EGI Inc., OR, USA), sampled at 1000 Hz with a 0.01-Hz high-pass filter. All recordings were initially referenced to the vertex. ECG was recorded using a physiological amplifier Polyam-ECGIIA (Nihon-Santeku Co. Ltd, Japan) with Ag/AgCl electrodes that were placed on the left and right wrists (i.e., Lead-I derivation). Its output signals were connected to the Polygraphic Input box of the EEG amplifier (EGI Inc.). The same ECG signals were branched and sent to a custom-made heartbeat-feedback device (MaP1985HDF, Nihon-Santeku Co. Ltd.), which detected the rising point of ECG R waves and

generated the stimulus tones with a programmed delay (200 or 0 ms) from each R wave.

2.5. EEG analysis

EEG and ECG during the heartbeat discrimination task were analyzed. Offline processing of EEG data was performed using Vision Analyzer 2.0 (Brain Products GmbH, Germany). Data were applied a 100-Hz high-frequency filter and down-sampled to 256 Hz. After removing epochs with large motion artifacts by observation, eye movements and electromyogram artifacts were further removed by means of independent component analysis. The data were then re-referenced to the average of all electrodes and segmented into 1600-ms epochs based on the timing of the of ECG R wave, including an 800-ms pre-R-wave period. Only segments within ± 200 μ V in each channel were further analyzed.

2.5.1. Gamma oscillations

The time-frequency analysis for the auditory-evoked gamma activity was performed using a complex Morlet's wavelet transformation on the R-wave-based EEG segments described above for each condition separately. The parameters of the wavelet analysis were as follows: Morlet parameter $c = 5$, frequency

range from 2 to 80 Hz in 1-Hz logarithmic steps, and Z-transformed with respect to the reference period between -450 and -250 ms of an R wave (this baseline period was chosen as it showed least deflection of the ECG). To obtain evoked (phase-locked) gamma activity, the spectral powers (μV^2) were calculated from the averaged ERP segments for each condition (Cohen, 2014). Finally, to remove cardiac field artifact (i.e., volume conduction of ECG), silent condition data were subtracted from those of synchronous and asynchronous conditions for each subject. The gamma activity was quantified as the mean values of 35-50 Hz (wavelet layers 62-67) for the 30-100-ms time window. This temporal window was chosen based on the peak latency of the gamma response (~65 ms post-stimulus) and from published studies (Gandal et al., 2010; Pantev et al., 1991). To increase S/N of the data and to overcome individual differences in the topography of the gamma response, we pooled the data of three channels centered on FCz (channels 4, 7, and 54) where the gamma responses were maximal.

2.5.2. Auditory-evoked ERPs

To obtain auditory-evoked ERPs (N1 and P2 components), the R-wave-based segments described above were averaged for each condition separately. Similar to the calculation of the gamma

activity, the averaged waveforms of the silent condition were subtracted from synchronous and asynchronous conditions to remove cardiac artifacts. These ECG-corrected ERPs were then baseline-corrected regarding 100-ms pre-stimulus periods (for raw ERP waveforms, see Supplemental Figure S1). Auditory-evoked N1 and P2 were identified as the most negative and positive peaks in the 70-140-ms and 150-250-ms post-stimulus latencies, respectively. Magnitudes of those components were quantified as the mean amplitudes of the 10-ms time windows centered over the peak latencies for each individual. We chose this quantification as it is tolerant of high-frequency noise and individual variation in peak latency. The N1 data were analyzed using the average values of three channels with maximal amplitude across conditions, FCz, AFz, and Fz. Likewise, P2 was assessed by averaging values of Cz, CP1, and C1.

2.6. Cardiac analysis

To assess possible changes in cardiac activity among all conditions, the mean heart rate (HR) and heart rate variability (HRV) in the trial periods of the discrimination task were calculated and averaged for each condition separately.

Considering that the trial period (65 s) was too short to apply frequency analyses, HRV was evaluated as the coefficient of variation (CV) (Sandercock, Bromley, & Brodie, 2005). The CV was calculated by dividing the standard deviation by the mean value of the HR time series from each trial.

2.7. Statistical analysis

Neural differences between the conditions were assessed with a *t*-test (synchronous vs. asynchronous) for each auditory-evoked neural response. Correlation between the neural responses and the task score was assessed by Pearson's *r*. This analysis was performed for the heartbeat discrimination and tracking tasks separately. The behavioral data of the heartbeat discrimination task for one female participant was not recorded because of a system problem; thus, the analyses of behavior and behavioral-neural associations lack one sample for the discrimination task. Statistical threshold for the null-hypothesis testing was $p = 0.05$, with correction for multiple testing by means of the false discovery rate (FDR; Benjamini & Hochberg, 1995) within the *t*-tests and correlation tests independently.

3. Results

3.1. Task performances

The mean score \pm SD of the heartbeat discrimination task (A') was 0.73 ± 0.17 (range: 0.333-0.958), with no sex differences ($t(24) < 1$, $p = 0.37$, $d = 0.35$). For the heartbeat tracking task, which assessed only behavioral measures, the mean score was 0.64 ± 0.25 (range: 0.054-0.98), where scores were significantly higher in males than females ($t(25) = 2.16$, $p = 0.028$, $d = 0.89$). Correlations between scores of the two tasks were not significant ($r(24) = 0.32$, $p = 0.11$).

3.2. Cardiac measures

Averages of HR for each condition across participants were 69.87 ± 8.25 for synchronous, 69.88 ± 8.24 for asynchronous, and 71.72 ± 7.95 for silent trials. Average CV values representing HRV were 0.066 ± 0.025 , 0.064 ± 0.022 , and 0.065 ± 0.016 for synchronous, asynchronous, and silent conditions, respectively. There were no significant differences between synchronous and

asynchronous conditions for either HR ($t(26) = -0.09, p = 0.93, d = 0.002$) or CV ($t(26) = 1.079, p = 0.291, d = -0.088$).

3.3. Condition differences of neural measures

Mean values of each neural measure (EEG and ERP) for both synchronous and asynchronous conditions, and the results of t-tests on the condition differences are shown in Table 1. As can be seen in Figure 1, the evoked gamma power was greater for the asynchronous than synchronous condition ($t(26) = -2.32, p = 0.028, d = -0.44$). Grand-averaged waveforms for ERPs (N1 and P2) for each condition are presented in Figure 2. The amplitudes of the N1 component were not significantly different between the conditions ($t(26) = 1.16, p = 0.26, d = 0.16$). The P2 component was significantly greater in the synchronous condition than in the asynchronous condition ($t(26) = 2.88, p = 0.008, d = 0.31$).

3.4. Association between neural and behavioral measures

Each of the neural measures were tested for their correlation with the discrimination task score for each

condition, and the difference between them (Table 2, supplemental Figure S2). The condition differences in all neural measures showed no significant correlation with the task score. Separate examinations of each condition indicated that the magnitude of evoked gamma power and N1 showed trends of negative association with the task score with uncorrected p -values (Table 2; note that the N1 component is a negative potential, thus positive correlation coefficients with the N1 amplitude mean inverse association with the task score). However, these correlations were not significant with the FDR correction for multiple testing (gamma, corrected p -values were 0.13, 0.14, and 0.29; N1, corrected p -values were 0.13, 0.11, and 0.78, for synchronous and asynchronous conditions and the condition difference, respectively). Additionally, because increased cardiac activity correlates with higher performance on interoception tasks (Cameron, 2001), the correlations were tested with HR and HRV as control variables to rule out the possible influence of individual differences in cardiac activity. These analyses showed comparative results (Supplemental Table S1), suggesting that the behavioral-neural associations (Table 2) are not likely to be accounted for by cardiac activity.

We also performed the same analyses on the performance of the heartbeat tracking task (Table 3). Similar to the discrimination task score, the tracking task score tended to show a correlation with the amplitude of ERP components, especially N1 ($p = 0.038$ and $p = 0.004$ for synchronous and asynchronous conditions, respectively). However, most of these correlations were not significant after FDR correction, except N1 for the asynchronous condition (corrected $p = 0.039$). Partial correlations analyses by controlling HR and HRV again show similar results (Supplemental Table S2).

4. Discussion

The present study examined EEG/ERP responses to heartbeat-synchronous (200-ms delay from the R wave) and -asynchronous (0-ms delay) tones. The EEG/ERP indexes showed significant differences between conditions, and also some weak correlations with the task performances. We will first discuss a trend of correlations between the neural and behavioral data because they showed a common pattern across conditions, and thus can illuminate a general nature of the present task. Following that,

we will discuss several issues on the neural differentiation between the conditions.

4.1. Relationship to the task performance

The behavioral data (task scores) in this study were comparable to earlier studies in terms of the mean and deviation (Aronson, Barrett, & Quigley, 2006; Barrett et al., 2004; Harver et al., 1993). The present EEG and ERP data indicate tendencies of negative correlations between the magnitude of neural responses (specifically, evoked gamma and N1) and the task score in both the heartbeat-synchronous and asynchronous conditions (Table 2). These associations were unlikely to be accounted for by individual differences in cardiac activity (HR or HRV, Table S1). Although the correlations were not statistically significant with the FDR-corrected threshold, this pattern of negative association was consistent in both conditions for the two earlier neural responses. The score of the other prevailing interoception task (i.e., the heartbeat tracking task) also suggested the same direction of association with the neural measures. However, the correlation between the scores of the two behavioral tasks was not statistically significant. This lack of

correlation between the two types of paradigms has been observed in several previous studies (e.g. Phillips, Jones, Rieger, & Snell, 1999; Schulz, Lass-Hennemann, Sütterlin, Schächinger, & Vögele, 2013). Some researchers have argued that the tracking task may be more prone to the influence of subjective belief or cognitive bias (Pennebaker, 1981; Ring & Brener, 1996). Another inconsistency between the tasks was related to the gender difference. The heartbeat tracking task showed higher score in males compared to females, as in many previous studies (e.g. Katkin, Blascovich, & Goldband, 1981; Pennebaker & Roberts, 1992). However, the discrimination task did not show the male superiority, maybe because of the high task difficulty and the floor effect. Despite the paradigms' heterogeneity, the data obtained from both types of heartbeat perception task indicated the same direction of association with the EEG/ERP data, suggesting that this behavioral-neural link is worth considering in the interpretation of the overall results.

Our results were in line with those of the former study (van Elk et al., 2014), which examined interoception-exteroreception integration based on the view of interoceptive predictive coding. As described before, the results of van Elk et al. (2014) showed N1 suppression by tones with fixed

intervals from heartbeats, relative to the response to heartbeat-unrelated sounds. They interpreted this neural suppression as a reflection of the interoceptive predictive processing on the heartbeat-contingent stimuli. It is generally considered that the degree of predictive sensory suppression should correspond to the accuracy of prediction of the stimuli timing. Therefore, if the reduced N1 in their study reflects the interoceptive predictive suppression, it is logically anticipated that better interoceptive accuracy, which corresponds to better predictability of the stimuli timing, should correlate with greater attenuation in the neural response to cardiac-related tones. The data of this study, in which all stimuli were heartbeat-contingent, support this idea. The present data suggest that the magnitude of evoked-gamma and N1 responses in both conditions were negatively correlated with the task performances. This means that the participants who were better at perceiving their heartbeat tended to exhibit greater EEG/ERP suppression to the heartbeat-contingent tones.

This interpretation does not contradict the assumed properties of the EEG/ERP responses. The early auditory-evoked gamma and N1-P2 ERPs are all considered to largely reflect sensory-perceptual processes, which are mainly generated in the

primary auditory areas (e.g., for gamma: Karakaş & Başar, 1998; N1: Vaughan & Ritter, 1970; P2: Hegerl, Gallinat, & Mrowinski, 1994). Previous electrophysiological studies have suggested that individual responses are not functionally identical, but the differences in their nature have not been clear (Başar, 2013; Key, Dove, & Maguire, 2005). In general, early activity in sensory cortical areas reflects initial processing of input stimuli, while later activity in the sensory areas also reflects processing of backward signals returning from other (higher) areas, and is more likely to be modulated by contextual or cognitive factors (Garrido, Kilner, Kiebel, & Friston, 2007; Lamme & Roelfsema, 2000; Ponton, Eggermont, Kwong, & Don, 2000). In the present study, the amplitude of the later P2 component was not associated with interoceptive accuracy. This result may be related to predictive coding, which could be associated with interoception, only modulating the initial processing of auditory stimuli (indicated by the evoked gamma and N1). In contrast, the later stages of the process, which could be a blend of several backward signals, may not reflect the predictive process.

Taking the issues discussed above into account, particularly for the data of the gamma and N1 responses, we

consider that both the previous (Van Elk et al., 2014) and current studies support the notion that predictive suppression processing takes place in the heartbeat discrimination paradigm. The former study showed this by comparing conditions with cardiac-related, unrelated, and self-generated tones. The present study expanded this by assessing the influence of interoceptive accuracy of individuals.

4.2. Neural differentiation of the heartbeat-tone timing

One of the main purposes of this study was to elucidate the neural differentiation of heartbeat-synchronous and -asynchronous sounds, which were both cardiac-contingent but had different lengths of delays from the heartbeats. Consistent with van Elk et al. (2014), the present study detected no significant difference in N1 amplitude between the two types of fixed-delay (0 and 200 ms) conditions. Rather, the results revealed that the neural differentiation occurred in the earlier gamma-frequency activity and later P2 component. Evoked gamma was attenuated, whereas the P2 amplitude was magnified, in response to the heartbeat-synchronous tones compared with the asynchronous

tones. Based on the discussion above, we consider that the suppression of the early response (i.e., gamma activity) reflects the primary neural response to the heartbeat-synchronous tones.

This early neural modulation can be functionally interpreted in the view of two lines of research. From the view of the predictive coding framework, the variation in magnitude of neural responses may reflect the different degree of predictive suppression between the conditions. However, the current data provide no evidence for (or against) this interpretation. The raw data of the evoked gamma and N1 measures did tend to correlate with the task score. However, the degree of condition differences (synchronous vs. asynchronous) of these measures failed to show significant correlations with the task score, thus providing no evidence for a relationship between the neural differentiation and predictive coding. However, it is possible that this lack of correlation could have resulted from practical limitations (e.g., a lack of statistical power) in obtaining neural and behavioral data that are strong enough to detect a weak association. We do not think there is sufficient evidence to exclude the predictive suppression mechanism as a

potential explanation for the neural differentiation of heartbeat-synchronous and -asynchronous tones in this study.

The other important line of research for interpretation of the present findings is the perceptual effects of baroreceptor signals. Baroreceptors are stretch sensors within the walls of major vessels, and their activity covaries with systole-diastole phases of the heart (Duschek, Werner, & Reyes del Paso, 2013; Garfinkel & Critchley, 2016). The physiological and subjective responses to simple and salient bodily stimuli, such as painful or startle stimuli, are attenuated when they are delivered during the systole phase (pain modulation: Dworkin et al., 1994; Edwards, McIntyre, Carroll, Ring, & Martin, 2002; McIntyre, Kavussanu, & Ring, 2008; startle modulation: Schulz et al., 2009), which can be explained by the effect of baroreceptor responses. Shortly after the heart constricts and blood pressure rapidly increases, these sensors activate and cause a phasic attenuation of the central nervous system, partly via autonomic nervous system modulation (Duschek et al., 2013). Our study used sound stimuli with either a 200-ms or 0-ms delay after the ECG R wave, and these tones can be regarded as events in systole and diastole cardiac phases, respectively. Accordingly, the heartbeat-synchronous tones in the present study correspond to

the systole phase of the heart. Therefore, the current result of gamma suppression can be explained by the systole-inhibition effect produced by baroreceptor activity. The baroreceptor mechanism does not necessarily rely on conscious perception of heartbeats. Thus, this explanation is unaffected by the lack of correlation between the discrimination task score and the condition differences of the neural measures.

There is another issue regarding the relationship between the cardiac-phase effect and the present data. As mentioned above, the effect seems to reflect perceptual insensitivity during the systole phase. However, recent studies have reported that some types of perception, especially visual recognition of fearful faces, are enhanced during the systole phase, rather than suppressed (Garfinkel et al., 2014; Gray et al., 2012). This means that the perceptual influence of the cardiac phase varies depending on the input and subsequent processing. Although some factors, such as arousal or expectation, are known to modulate the effect of the baroreceptor response (Martins, Ring, McIntyre, Edwards, & Martin, 2009; McIntyre, Edwards, Ring, Parvin, & Carroll, 2006), there has not been a consensus on why specific types of visual emotion perception are differently affected by the cardiac phase. We hypothesize that

the difference in the cardiac effect could arise from differences in the latency of perceptual processing. Specifically, fast, reflective responses to painful or startling stimuli would be suppressed, whereas processes requiring more time and cognitive resources, such as visual recognition or intensity rating of fearful stimuli, would be enhanced at the systole phase. This hypothesis implicating latency effects is in accordance with the current results. The EEG and ERP data of this study showed attenuation of the early response (gamma activity occurred with <100 ms latency) and amplification of the later component (P2 elicited with >150 ms latency) to sounds during the systolic phase compared with the diastolic phase. Considering that the stimuli used in this study were simple neutral tones, however, it is too speculative to connect the findings with those of pain or fear responses. Still, such a speculation demonstrates the potential benefit of high temporal resolution EEG/ERP measurements, which could further reveal the detailed time course of multisensory interoceptive integration in future studies. Furthermore, the detail of neural modulation (e.g. which of magnitude and phase of the activity is underlying) should also be elucidated together.

4.3. Limitations and future directions

Our results were largely interpreted with regard to the concept of predictive sensory attenuation. However, the present study did not include an "unpredictable" heartbeat-noncontingent sequence of tones as a comparison condition, which would strengthen the support for the prediction coding framework. Previous studies on methodological refinement of the heartbeat discrimination paradigm have attempted to vary the heartbeat-sound intervals for a heartbeat-asynchronous condition (Davis, Langer, Sutterer, Gelling, & Marlin, 1986; Hantas, Katkin, & Reed, 1984; Katkin et al., 1981), which has been shown to reduce the task difficulty in some cases (Davis et al., 1986). However, these methods still have drawbacks (Jones, 1994). For example, participants were able to judge the synchronicity based solely on irregularity of the temporal pattern of the stimulus sequence, rather than the temporal matching between sounds and heartbeat sensations. There is also a possibility that the variable intervals in a heartbeat-asynchronous condition can provide a tone at the moment of the heartbeat, confusing participants. Because of these issues, the variable-interval methods have rarely been used in current interoception studies including our present research. However, considering the

interoceptive predictive framework, future studies examining the neural mechanisms of the heartbeat discrimination task would benefit from the use of a stimulus sequence that is not contingent on heartbeat.

Another limitation of the present study was that it only examined associations with primary scores of behavioral tasks. Garfinkel et al. (2015) classified three facets of interoception measures by means of questionnaires and behavioral experiments (Garfinkel et al., 2015). In their model, subjective belief concerning participants' interoception assessed using questionnaires (termed interoceptive *sensibility*) and objective performance on behavioral tasks such as heartbeat perception tasks (termed interoceptive *accuracy*) are explicitly distinguished. Meta-level accuracy of individuals' self-performances regarding interoceptive behavioral tasks (termed interoceptive *awareness*) is also separated from other processes. This three-facet model is currently influential among interoceptive studies, and was recently extended with including implicit behavioral as well as physiological markers (Critchley & Garfinkel, 2017). The present study assessed only one facet (accuracy) among these multiple aspects of interoception, highlighting the need for further examination of the

relationship with other facets of interoception (e.g., sensibility and awareness).

Finally, this study examined individual differences solely regarding interoceptive accuracy. However, other factors, such as individual differences in the baroreceptor response, could also influence the neural and behavioral measures in the heartbeat discrimination task. To examine the possible contribution of this factor (e.g., Schulz et al., 2009), future research on the cardio-intero information integration should assess the baroreflex sensitivity in terms of, for example, temporal association between the HR and blood pressure of participants (La Rovere, Pinna, & Raczak, 2008).

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Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Tables

Table 1. Average values in each condition and the condition differences of neural measures.

	Mean values (SD)		Difference
	Synchronous	Asynchronous	<i>T</i> (26)
Evoked gamma	10.29 (12.78)	21.12 (32.16)	-2.32 *
N1	-1.42 (1.65)	-1.66 (1.24)	1.16
P2	1.76 (1.14)	1.40 (1.20)	2.88 *

* $p < .05$ (corrected)

Table 2. Correlation coefficients (Pearson's r) of the heartbeat discrimination task score with each neural measure.

	Synchronous	Asynchronous	Difference (A. vs S.)
Evoked gamma	-.405 ^a	-.374 ^b	.283
N1	.401 ^a	.485 ^a	.059
P2	-.139	-.162	.057

^a $p < .05$, ^b $p < .10$ (uncorrected)

Note: The marking for statistical significance levels are not corrected for multiple comparison.

When the p -values of these correlation tests were corrected to account for false discovery rate, no result reached significance. A. vs S., the difference between conditions (Asynchronous- minus Synchronous-condition) for each neural measure. Also note that the correlation coefficients for the N1 amplitude should be interpreted inversely because N1 is a negative potential, indicating negative correlations to the task performance.

Table 3. Correlation coefficients (Pearson's r) of the heartbeat tracking task score with each neural measure.

	Synchronous	Asynchronous	Difference (A. vs S.)
Evoked gamma	-.346 ^c	-.244	.141
N1	.401 ^b	.532 ^a	.006
P2	-.369 ^c	-.291	-.109

^a $p < .01$, ^b $p < .05$, ^c $p < .01$ (uncorrected)

Note: All information is provided in an identical manner to Table 2.

Figures

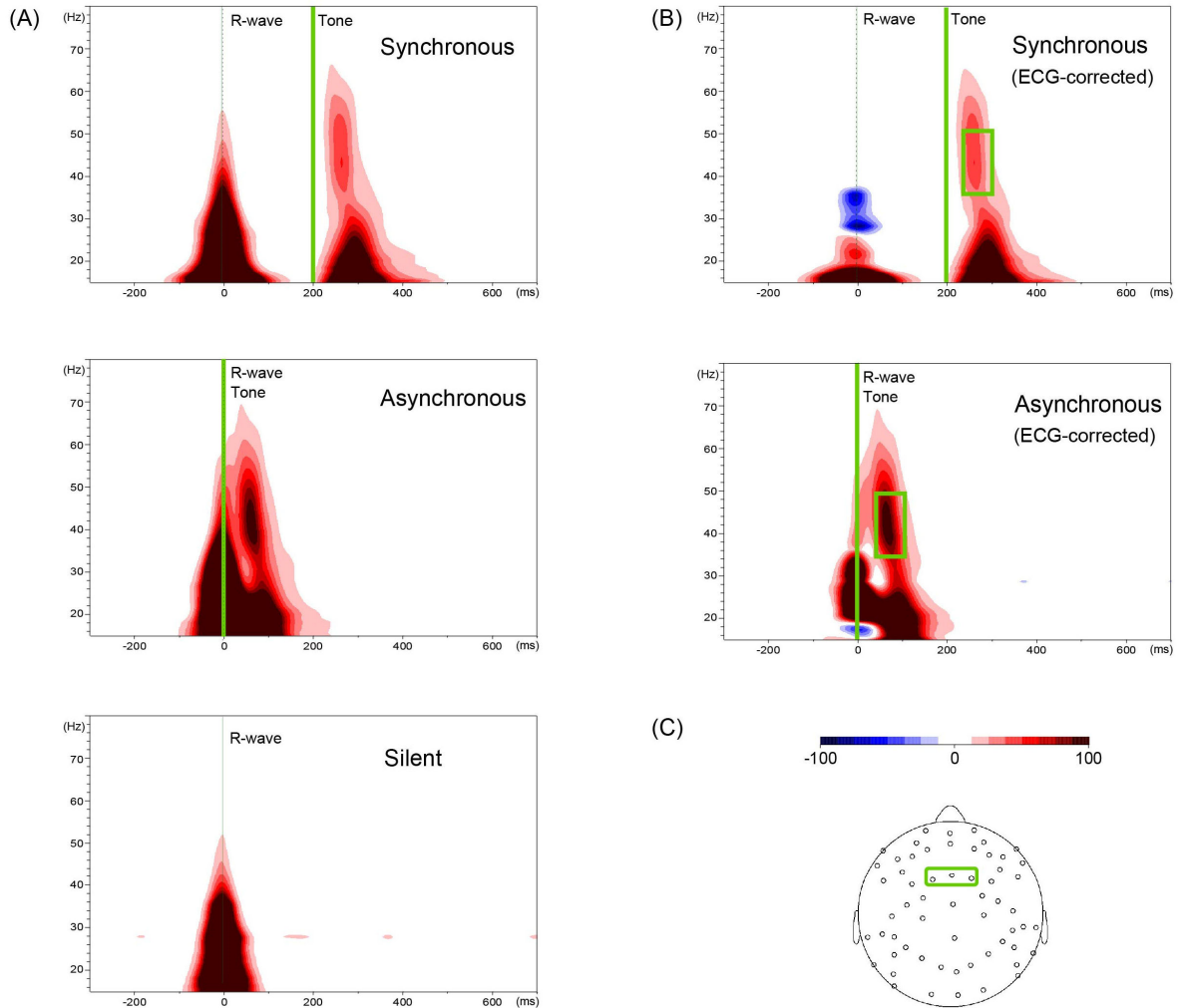


Figure 1: Evoked responses time-locked to the R waves of electrocardiogram (ECG) for each condition.

(A) Evoked time-frequency responses of each condition are aligned to the timing of the R wave of ECG, normalized by z-

transformation. Vertical green lines indicate auditory stimulus timing. The heartbeat-evoked response that appeared in the silent condition data also appeared in the data for the synchronous and asynchronous conditions. (B) Data of the synchronous and asynchronous conditions for analysis, where the data of the silent condition was subtracted to extract auditory-evoked responses. Green rectangles indicate the time and frequency ranges used for statistical analyses of gamma activity. (C) Color scale of the time-frequency plot; the green rectangle indicates the position of the electrodes on a participant's head, which was centered on the FCz channel, from which the averaged data were analyzed.

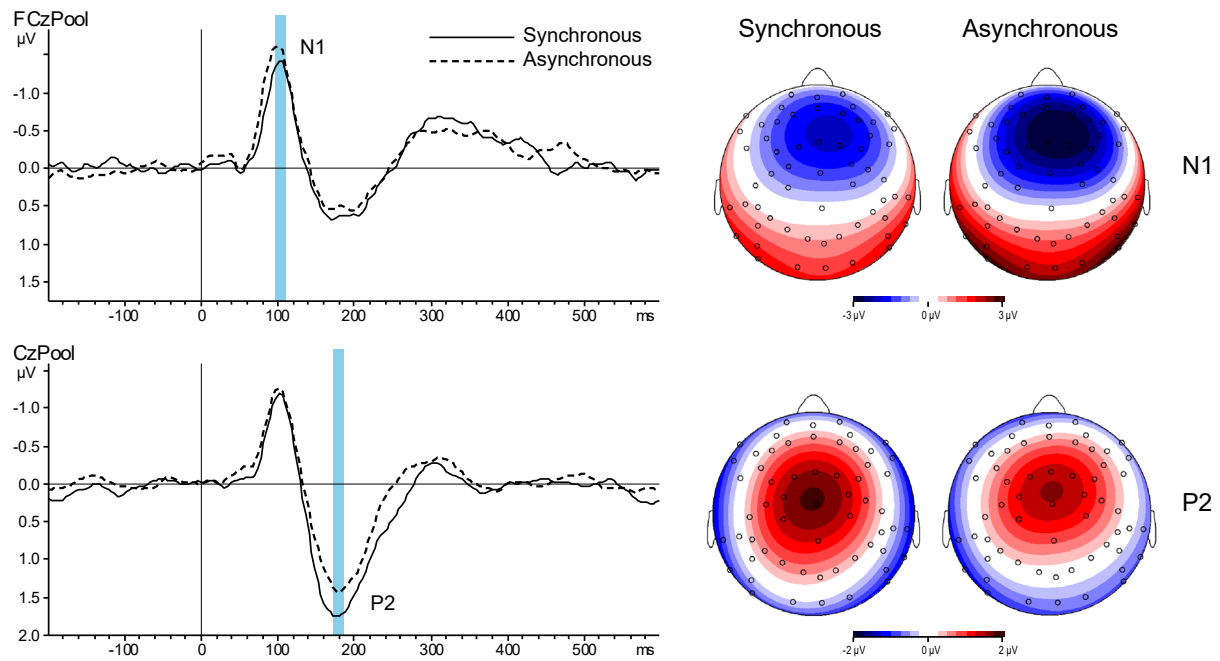


Figure 2. Auditory-evoked event-related potential (ERP) waveforms and scalp distribution for each condition.

The waveforms were corrected for ECG contamination by subtracting those of the silent condition. For the time scales, 0 ms corresponds to the onset of tones. N1 and P2 amplitudes were quantified as the average of three electrodes centered on FCz and Cz, respectively. Data from the pooled electrodes are depicted. The blue-shaded areas overlaid on the waveforms show the periods with which mean amplitudes of the ERP component were calculated for the statistical tests.

Supplemental materials

Table S1. Partial correlation coefficients (Pearson's r) of the heartbeat discrimination task score with each neural measure.

	Synchronous	Asynchronous	Difference (A. vs S.)
Evoked gamma	-.416 ^a	-.375 ^b	.219
N1	.407 ^a	.493 ^a	.040
P2	-.141	-.216	.023

^a $p < .05$, ^b $p < .10$ (uncorrected)

Table S2. Partial correlation coefficients (Pearson's r) of the heartbeat tracking task score with each neural measure.

	Synchronous	Asynchronous	Difference (A. vs S.)
Evoked gamma	-.320	-.247	.106
N1	.395 ^c	.535 ^a	-.001
P2	-.406 ^b	-.331	-.129

^a $p < .01$, ^b $p < .05$, ^c $p < .10$ (uncorrected)

Common notes for Tables S1 and S2: These values are partial correlation coefficients, which control the variables of heart rate and heart rate variability. The p -values represent significance levels that were not corrected for multiple comparison. When the p -values of these correlation tests are corrected to account for false discovery rate, no differences reached significance. A. vs S., the difference between conditions (Asynchronous- minus Synchronous-condition) for each neural measure. Also note that the correlation coefficients for the N1 amplitude should be interpreted inversely because N1 is a negative potential, indicating negative correlations to the task performance.

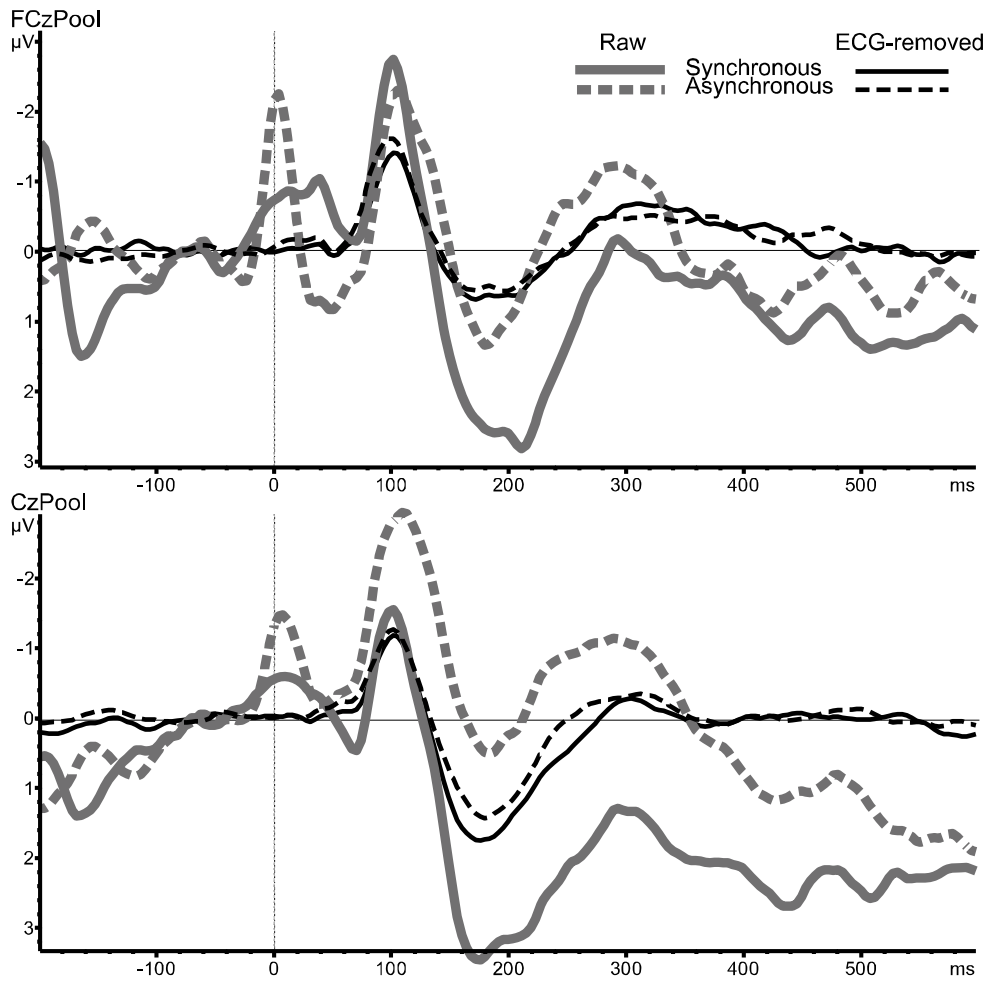


Figure S1. Waveforms of the auditory-evoked ERPs with and without ECG-artifact removal.

The waveforms of ECG-removed data are identical to Figure 2 in the main text. Also note that the R-waves of the ECG occurred at the -200 ms and 0 ms time-points in the synchronous and asynchronous conditions, respectively.

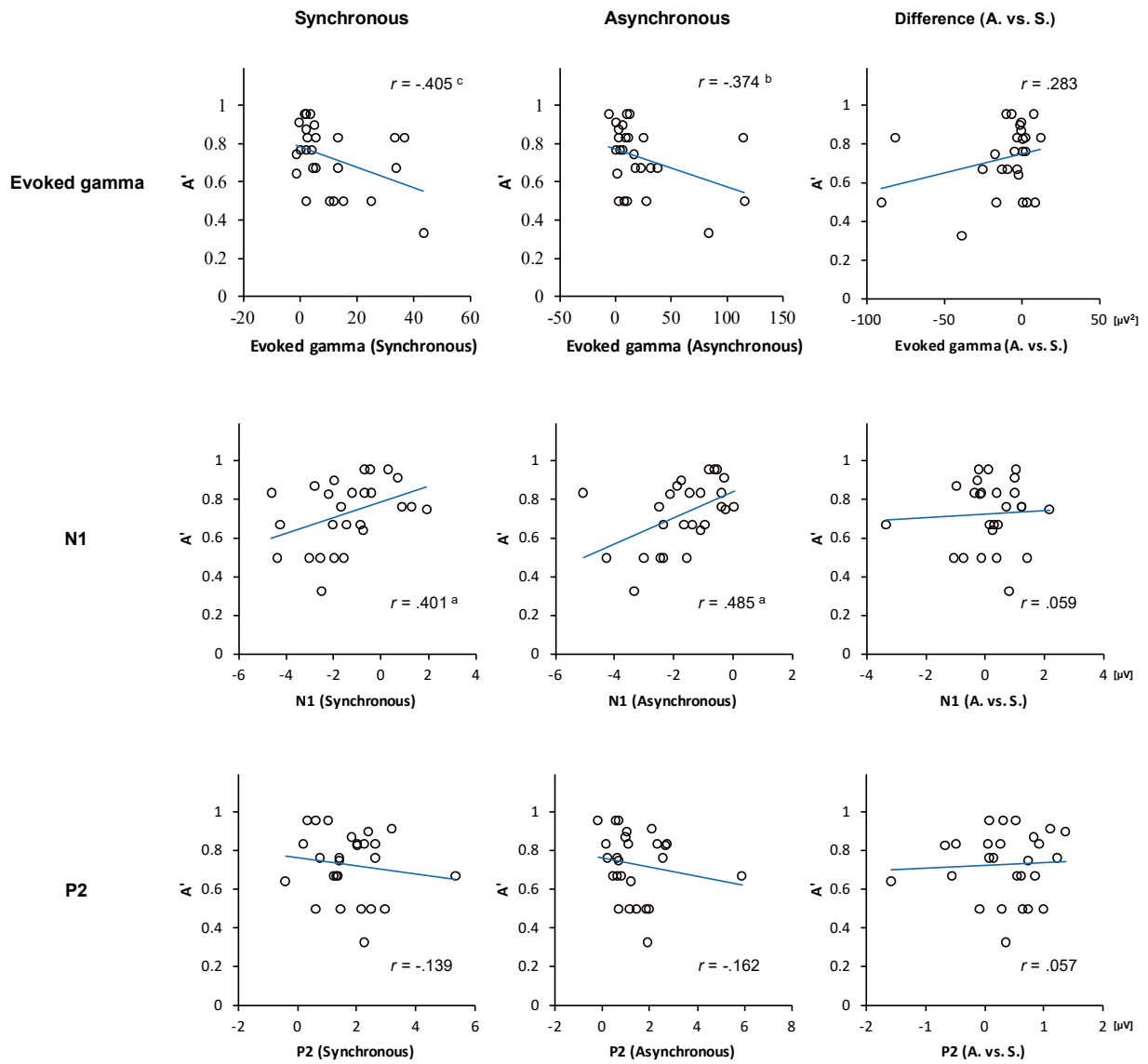


Figure S2. Scatter plots for the correlation analyses shown in Table 2.