Aus der Abteilung Neurologie
Max-Planck-Institut für Kognitions- und Neurowissenschaften
Leipzig

DISSERTATION

The psychophysiology of heart-brain-interactions: how active information sampling is modulated across the cardiac cycle

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Stella Kunzendorf

aus München

Datum der Promotion: 26. Juni 2022

Table of contents

Abstract

In English Language

The following text was adapted from the abstract of Kunzendorf et al.[1].

Our interaction with the environment relies on the dynamic relationship between body and brain. Experiments on body-brain coupling investigate how interoceptive signals, conveying information about the internal state of the body, contribute to cognition, perception, and behavior. Thereby, physiological visceral oscillations (e.g., the heartbeat) have been found to modulate mental phenomena: for example, visual perception, oculomotor activity, and memory performance vary across the cardiac cycle. Recent findings show facilitated visual processing of higher-level (behaviorally relevant) stimuli during early cardiac phases (i.e., systole), thus motivating the investigation of modulatory cardiac cycle effects on active (i.e., self-initiated) engagement with visual stimuli. For my doctoral project, I studied the cardiac modulation of *active information sampling* to investigate whether participants implicitly act upon their environment such that relevant information appears during prioritized cardiac phases.

The core of this investigation consists of a psychophysiological experiment on the topic of visual memory. During its encoding period, 47 participants clicked through a set of emotional pictures to memorize them for a subsequent recognition task. Critically, by self-paced key press, participants actively triggered the onset of the next picture, which quickly appeared on-screen for 100 ms. Simultaneous electrocardiography was recorded to analyze the timing of the (self-initiated) stimulus onsets relative to the cardiac cycle. Following a 5-minute break, participants completed the recognition task, in which they were presented with 50% old and 50% new pictures and were asked to indicate for each picture whether or not they had seen it before.

As main result, I find that self-initiated stimulus onsets varied with alternating cardiac phases, showing a significant increase during cardiac systole. However, there was no evidence that memory performance was influenced by the heartbeat. Based on the present findings, I conclude that active information sampling integrates heart-related signals, and thus extend previous results on the association between body-brain interactions and behavior. The interplay of body and brain, which enables us to optimally adapt to changing environments, ensures homeostasis and well-being of our organism. Further investigations of the underlying mechanisms by which interoceptive and behavioral processes interact are necessary for a comprehensive understanding of our health's psychophysiological underpinnings.

In Deutscher Sprache

Der nachfolgende Text wurde in abgeänderter Form dem Abstract von Kunzendorf et al.[1] entnommen.

Unsere Interaktion mit der Umwelt beruht auf dem dynamischen Wechselspiel zwischen Körper und Gehirn. Experimentelle Studien der Körper-Gehirn-Achse erforschen, wie interozeptive Signale, welche Informationen über innere Körperzustände vermitteln, zu Kognition, Wahrnehmung und Verhalten beitragen. Dabei ergab sich, dass physiologische Fluktuationen des Organismus (z.B. der Herzschlag) mentale Prozesse beeinflussen: beispielsweise unterscheiden sich visuelle Wahrnehmung, Okulomotorik und Gedächtnisleistung während verschiedener Phasen des Herzzyklus. Jüngste Ergebnisse zeigen eine erleichterte visuelle Verarbeitung von komplexen (verhaltensrelevanten) Reizen während früher Herzphasen (Systole) und motivieren die Untersuchung von Effekten des Herzzyklus auf aktive (d.h. selbst initiierte) Interaktion mit visuellen Reizen. Über die Zeit meiner Doktorarbeit untersuchte ich die Rolle des Herzschlags für *aktives Information Sampling* (d.h. selbst initiiertes Bereitstellen eines visuellen Reizes), mit der Frage, ob Probanden implizit derart mit ihrer Umwelt interagieren, dass relevante Informationen zu bevorzugten Herzphasen abgefragt werden.

Den Kern dieser Arbeit bildete ein psychophysiologisches Experiment zur Untersuchung des visuellen Gedächtnisses. Hierbei klickten 47 Probanden während der Einprägungsphase durch eine Sammlung emotionaler Bilder, um sich diese für einen anschließenden Wiedererkennungstest einzuprägen. Dabei lösten sie aktiv durch Tastendruck die Präsentation des nächsten Bildes aus, welches unmittelbar darauf für 100 ms auf dem Bildschirm erschien. Die gleichzeitige Messung von Elektrokardiogrammen ermöglichte die zeitliche Analyse der (selbst initiierten) Bildpräsentationen relativ zum Herzzyklus. Nach einer 5-minütigen Pause erfolgte der Wiedererkennungstest, bei welchem 50% alte und 50% neue Bilder präsentiert wurden, und die Probanden für jedes Bild angeben sollten, ob sie es bereits gesehen hatten oder nicht.

Als Hauptergebnis konnte gezeigt werden, dass selbst initiierte Bildpräsentationen mit dem Herzzyklus variieren, wobei ein signifikanter Anstieg in der kardialen Systole erkennbar war. Es wurden keine Hinweise darauf gefunden, dass die Gedächtnisleistung durch den Herzschlag beeinflusst wird. Auf Grundlage der vorliegenden Ergebnisse schlussfolgere ich, dass aktives Information Sampling vom Herz ausgehende Signale integriert und erweitere dadurch bisherige Befunde über die Verbindung von Körper-Gehirn-Interaktionen und Verhalten. Das

Zusammenspiel von Körper und Gehirn, welches eine optimale Anpassung an sich ändernde Umgebungen ermöglicht, sichert die Homöostase und das Wohlbefinden unseres Organismus. Weitere Erforschung der zugrundeliegenden Mechanismen, durch welche interozeptive und Verhaltensprozesse miteinander interagieren, sind notwendig für ein umfangreiches Verständnis der psychophysiologischen Grundlagen menschlicher Gesundheit.

(Übersetzung durch die Autorin)

Synopsis

1. General rationale

An essential question in the neurosciences—and particularly in psychophysiology—is: how are mental phenomena and behavior related to the dynamic relationship between the brain and the rest of the body? Our interaction with varying environments arises from the fine-tuned coupling of our external and internal milieus: exteroceptive (e.g., visual or auditory) sensory input is continuously integrated with bodily (e.g., proprioceptive or interoceptive/viscerosensory) signals[2,3]. The dynamic interplay of mind, brain, and body thereby enables us to optimally react and adjust to environmental changes in support of our bodily integrity and well-being.

Classical experiments have typically investigated how the processing of signals in the external world changes activation in our body and brain, for example by measuring physiological parameters in the autonomic (e.g., heart rate, electrodermal responses) or central nervous system (e.g., blood-oxygen level dependent signals)[4–7]. The inverse direction, that is, how interoceptive signals conveying information about our internal states modulate the processing of the external world[8], has been studied much less frequently (for a review see Critchley & Garfinkel[9]). Afferent feedback loops, targeting subcortical and cortical areas[10–13], constantly inform the brain about our bodily states, primarily to drive internal (autonomic and hormonal) regulation (i.e., homeostasis[14]). There is growing experimental evidence that the influences of our bodily states extend beyond homeostatic control to mental phenomena, such as thoughts, feelings, and memory[9]. Such findings have led to conceptual frameworks of brain-body interactions, which argue (1) that bodily oscillations underlie unified consciousness[15], and (2) that predictions about internal signals (see below) contribute to emotional experience[16]. Measuring processes in the body—and their interactions with the brain—is thus necessary for a comprehensive investigation of the neurobiology of the mind.

How the internal state of the body contributes to mental phenomena can be studied by capitalizing on the oscillatory nature of internal bodily rhythms, such as cardiac, gastric, or respiratory activity[9,17,18]. These natural visceral fluctuations have been linked to phase-related variation in brain activity[17,19], as well as to variation in associated perceptual and cognitive processes[9]. As a prominent internal oscillator, the heart has been the focus of studies on phasic body-to-brain modulations: assessing visual perception in relation to the two cardiac phases, systole and diastole, recent findings show enhanced visual processing of phase-locked systolic compared to diastolic stimuli[19–21], as well as heightened generation of spontaneous eye movements[22] during the phase of systole compared to diastole. Importantly, facilitated visual

perception during cardiac systole has been observed selectively for salient (e.g., threatening) stimuli[23], which suggests a phase-dependent processing benefit specifically for motivational, task- or context-relevant stimuli. In line with evidence that heightened arousal biases stimulus processing, it has been proposed that cardiac interoceptive signaling during systole transmits arousal states to the brain[23]. Systolic modulation of higher-level (behaviorally relevant) visual processing—together with the finding of phase-related spontaneous oculomotor activity—thus suggests a modulatory role of cardiac fluctuations in perceptual behaviors, that is, active (self-initiated) perception of the environment.

Here, I present the study of my doctoral project[1], in which I examined how active engagement with the environment integrates heartbeat-related information. I thereby built on and extended theoretical frameworks of brain-body interactions[15,16] to investigate the role of cardiac phase in modulating self-initiated action towards external stimuli. More specifically, I tested whether participants spontaneously act upon a visual stimulus in a way, which increases the likelihood of receiving and perceiving relevant visual information during a specific cardiac phase. To that aim, I designed and implemented an experimental paradigm, which—in contrast to the prior used externally paced stimulus presentations—allowed for self-induced information sampling of the participants. In the following section (**Part 2**), I describe the conceptual approach to this investigation. **Part 3** provides a detailed account of my methodological approach. In **Part 4**, I highlight the main findings of my study. In **Part 5**, I discuss these findings in context, including their limitations, and propose future investigations and implications.

2. Conceptual approach

2.1. Interoception as multilevel process to support survival, integrity, and well-being

Communication of the internal milieu with the brain, that is, afferent transmission, central processing and representation of signals originating in the viscera has been called *interoception*[24–26], the "sense of the physiological condition of the body"[10]. Interoception encompasses sensing and integrating visceral information across multiple levels: not only does it provide low-level monitoring of physiological parameters (e.g., nutrient and fluid balance, thermoregulation) via afferent feedback loops that engage internal (autonomic, hormonal) homeostatic regulation and allostatic adaptation, it also plays an important role in shaping conscious bodily feelings (e.g., hunger/thirst, cool/warm) that guide motivational behavior and associated emotional experiences[12,25]. Interoception thus is a crucial process to help an organism keep its physiological conditions within a functional range and to engage adaptive behaviors in the face of constant internal and external changes[12,26].

2.2. Interoceptive pathways to the brain

Interoceptive information is communicated to the brain through humoral (involving endocrine and immune) channels, as well as distinct neural pathways linking bodily with brain structures[12,27]. From their peripheral endings (e.g., baro-, or chemoreceptors, nociceptors), visceral afferents transmit interoceptive signals along two major routes—via cranial (e.g., vagus and glossopharyngeal) nerves and the spinal cord (particularly lamina 1 of the spinothalamic tract[10]—to converge in the nucleus of the solitary tract (NTS). From there, these signals are forwarded to other brainstem areas (e.g., parabrachial nucleus, ventrolateral medulla, periaqueductal grey) and the hypothalamus[12]. As part of homeostatic feedback loops, viscerosensory relay across these regions enables adaptive physiological responses via efferent autonomic (sympathetic, parasympathetic) and humoral axes to restore deviation from a desired physiological state, thus ensuring the organism's continuous internal stability[13,27,28]. Importantly, interoceptive channels also connect to a network of subcortical (e.g., visceral sensory thalamus, amygdala) and cortical (e.g., insula, anterior cingulate cortices) areas, which are known to contribute to mental phenomena like cognition, emotion, and perception[12,24,26]. A critical brain structure for viscerosensory processing is the insular cortex (IC), which has extensive functional connections with (pre)frontal, parietal, and limbic regions[16,29]. It has been proposed that interoceptive input converges towards increasingly abstract, higher-order representations accessible to conscious awareness. The hierarchical posterior-to-anterior architecture of IC subregions[16,30] thereby allows an integration of top-down cognitive (e.g., attentional, motivational) processes to support adaptive behavior[9,24,27].

2.3. Theoretical framework of interoceptive predictive coding

The bidirectional dynamics of brain-body interactions have been captured in the theoretical framework of *interoceptive predictive coding*[2,16,31], which applies the *free-energy principle*[32] to interoceptive processes and their relation to consciousness and emotion. Described essentially as "hierarchical prediction machine"[33], the brain makes sense of the plethora of—in this case: bodily—sensations by maintaining internal predictive models to infer their causes based on past experiences[9,27,31]. Interoceptive predictions, generated in hierarchical cortical structures (presumably the IC[2,16]), cascade downwards to be tested against the actual sensory input. A mismatch between the expected and the incoming signal, the prediction error, can be minimized through two types of inferential processes: adjustment of the internal model (via updating the prediction) or of the interoceptive input itself (via autonomic or behavioral responses)—thus constantly optimizing adaptation to environmental changes[9,16,27].

Taken together, in this view, interoception is understood as a dynamic, prediction-driven system, linking generative control of the internal milieu (homeostasis) with the generation of subjective feeling states (i.e., emotions) and adaptive behaviors[16,31]. This overarching theoretical, neuroanatomically plausible, account of interoception can thus provide a framework to interpret and explain the mechanisms by which bodily fluctuations are related to neural fluctuations in the brain; and how they could contribute to cognition, emotion, and behavior.

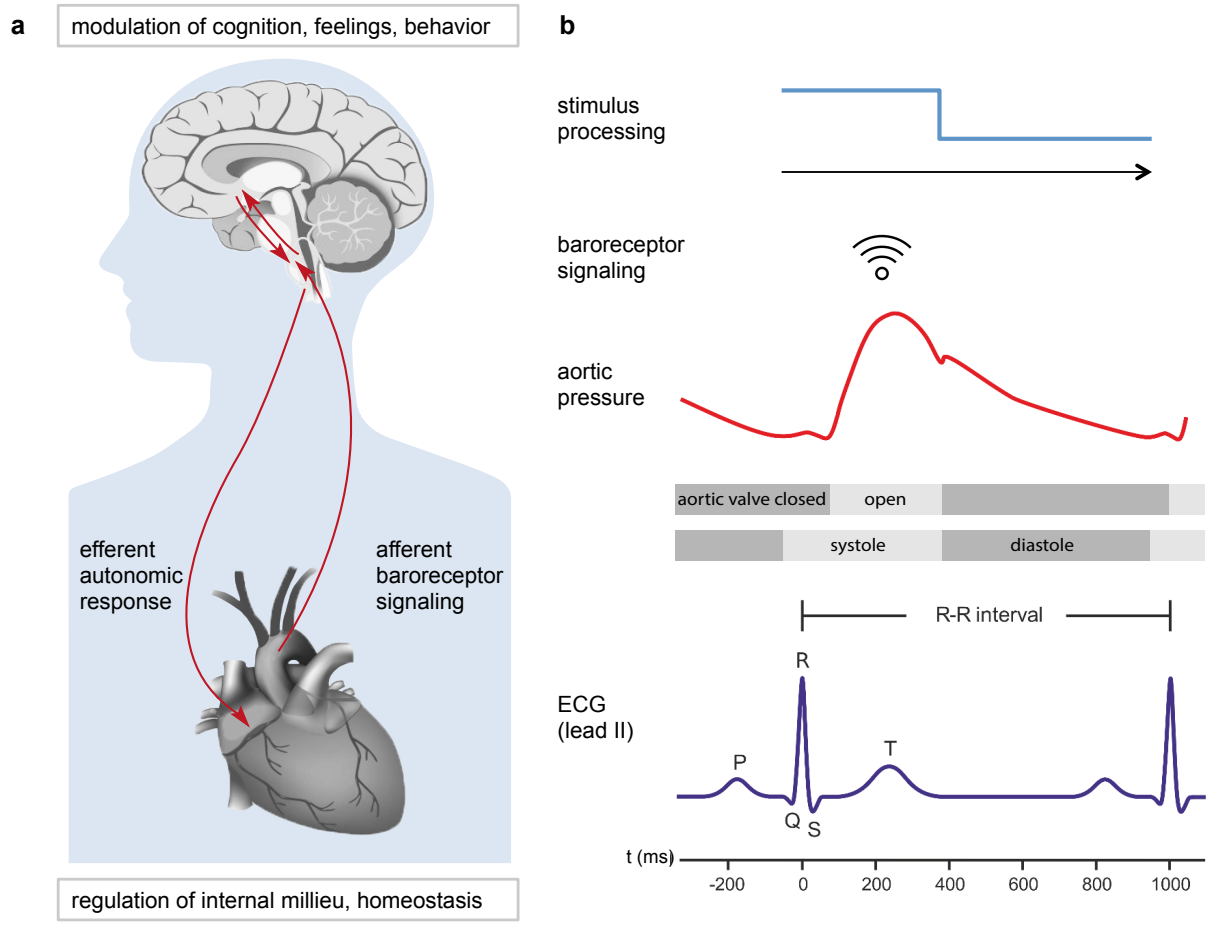

Figure 1 Schematic of heart-brain interactions. (**a**) Interoceptive signaling from the heart to the brain not only ensures adaptive regulation of bodily states via efferent feedback loops (i.e., homeostasis), but also extends to modulate mental processes and behavior. (**b**) Cardiac activity occurs in a repeating cycle of two cardiac phases, systole and diastole. For each cardiac cycle (R-R interval in the electrocardiogram, i.e., ECG, dark blue curve), baroreceptor signals are generated with the systolic upstroke during blood ejection (red curve), following aortic valve opening. During diastole, baroreceptors are largely quiescent. Differences in stimulus processing (light blue curve) in relation to phasic cardiac signaling (systole vs. diastole) have been investigated in cardiac cycle studies. (Figure 1a modified from the original image by Alila Medical Media/Shutterstock[34]).

2.4. Interoceptive signaling from the heart

Recent developments in refining concepts of interoception (see above) have been substantiated by empirical evidence concerning the coupling of natural rhythmic visceral (mainly: cardiac) activity with neural and mental processes[9]. Through the repeating cycle of the two cardiac phases

(systole, diastole), the heart generates a distinct oscillatory bodily rhythm (**Figure 1**): with every systolic blood ejection and consecutive pressure rises in the arterial system, pressure-sensitive baroreceptors in aorta and carotid sinuses are activated and transmit information about the current state of cardiovascular arousal (i.e., the strength and timing of individual heartbeats) via neural (i.e., vagus and glossopharyngeal) afferents to the NTS (**Figure 1a**), allowing rapid reflexive control of blood pressure and heart rate via efferent sympathetic and parasympathetic responses, respectively (i.e., baroreflex). From brainstem nuclei, cardiac signals are further carried along the neuroaxis to be integrated in cortical structures (particularly the IC, see above), which instantiate higher-level efferent control on cardiovascular physiology[12,35]. Experimental investigation of cardiac influences on cognition and behavior has been carried out (1) by studying stimulus processing in relation to the cardiac cycle (cardiac cycle effects; **Figure 1b**), and (2) by probing behavioral effects through measurements of brain activity (e.g., neural responses to the heartbeat).

2.5. Cardiac influences on stimulus processing—cardiac cycle effects

By presenting stimuli at different phases of the cardiac cycle, so-called *cardiac cycle studies*[36–38] examine processing variations of external stimuli relative to their timing in the cardiac cycle. The evidence from a variety of experimental paradigms, involving perceptual (e.g., stimulus detection) and behavioral (e.g., reaction time) tasks, however, is mixed and the directionality of cardiac influences on sensorimotor processing has remained unclear (see **Table 1** for a detailed summary of cardiac cycle studies).

More specifically, several—particularly earlier—cardiac cycle studies (see **Table 1, 1.**) have shown a general inhibition of stimulus processing during early (i.e., systolic) cardiac phases: attenuated perception (e.g., measured as increased sensory thresholds or prolonged reaction times) were found for the domains of visual[39–42], auditory[36,37,43–48], and somatosensory or pain processing[49–57].

More recent findings have challenged a generic inhibitory systolic influence, by showing facilitated processing during systole (see **Table 1, 2.**), especially for behaviorally or task-relevant visual stimuli. While such facilitating effects were obtained for complex (nonemotional) stimulus constellations in visual masking[21] or visual search tasks[20], studies using valenced stimuli propose an emotional specificity of cardiac-related cognitive influences[23]: cardiac afferent signals have been shown to selectively prioritize the processing of fear and threat, which suggests that afferent signaling conveys bodily arousal states to the brain[19,58,59]. Systole-associated modulation of emotional processing (for a review see Garfinkel & Critchley[23]) has

thus been shown in the context of enhanced intensity ratings[19], improved detection[19], or increased attentional capture of briefly presented fearful faces[59], as well as increased activation of race-associated threat stereotypes[58]. The gating of visual perception by cardiac signals has been also linked to memory processing in the shape of systole-coupled variations in memory encoding and retrieval of nonemotional as well as emotional stimuli[60–63].

2.6. Cardiac influences on brain activity—neural responses to the heartbeat

Behavioral evidence of cardiac-related stimulus processing is complemented by studies investigating neural activation in the central nervous system. Findings of inhibited stimulus processing during systole were linked to reduced sensory (e.g., visual) evoked potentials (EPs) in the electroencephalogram (EEG) for the processing of external systolic compared to diastolic stimuli[54,64]. Moreover, cardiac effects on perception and cognition may be reflected in measurements of neural responses to the heartbeat (i.e., heartbeat evoked potentials, HEPs)[65,66]. Similar to EPs to external stimuli, HEPs are thought to depict transient changes in central neural activity in response to cardiac events and their afferent transmission towards the brain, and are therefore generated in sync with each heartbeat. For example, variation in HEP amplitude was found to predict differences in detection of visual threshold stimuli[67]. Importantly, further experiments are needed to investigate the physiological basis of HEPs, as well as their interplay with external stimulus EPs. Associations between heartbeat-related changes in neural activity and stimulus processing were also shown for blood oxygenation level dependent (BOLD) based neuroimaging (e.g., functional magnetic resonance imaging, fMRI) signals: amygdala activation was increased when electric shock stimuli[68] or fearful faces[19] were presented at systole compared to diastole. These neural findings were suggested to reflect cardiac-associated engagement of threat-mediating neural systems, which might underpin preferential processing of salient (e.g., threatening) stimuli during systole[23]. Taken together, cardiac and associated neural dynamics vary with cognitive and perceptual processes: while particularly recent findings point towards a selective processing benefit for salient visual stimuli, other perceptual processes (e.g., pain perception) have been shown to be attenuated.

2.7. Novel active sampling approach to study heart-brain interactions

It remains unclear to what extent the cardiac effects on perception and cognition translate to more interactive—that is, self-initiated rather than passively presented—forms of stimulus processing. A central feature of previous cardiac cycle studies is that they investigated passive (phase-coupled) stimulus processing, and thus ignored an essential aspect of perception: action. In our daily encounter with varying—and often unpredictable—environments, we typically do

not receive signals in a cardiac-timed manner but rather actively select, attend to, and engage with those of importance for the present context. That is, we naturally interrogate our surrounding by actively sampling relevant information cues[69].

Although scarce, there is evidence that relates the heartbeat to an increased tendency to act, both for somatomotor behavior in the context of firing a virtual[58] or a real[70] gun, as well as for oculomotor[22] behavior. This suggests that systole provides a facilitating time window for spontaneous motor activity. Particularly findings of heightened eye movement generation (i.e., micro-saccades) in early cardiac phases may underlie facilitated visual processing (e.g., visual search) during systole[22], thus pointing towards cardiac-related sensorimotor coupling in the oculomotor domain.

The motor system dynamically orchestrates the incoming stream of sensory data, as it directs the necessary sensors (e.g., eyes, hands, or ears) towards a sensory cue and thereby influences the contextual and temporal structure of perceptual input[71,72]. Based on research of *active sensing*[71] behaviors, during which animals unfold repetitive (e.g., tactile, haptic or visual) movements to accumulate sensory information[71,73], it has been further argued that rhythmic extraction of task-relevant information generates temporal predictions to align fluctuations of attention with the timing of sensory cues and to optimize perceptual processing[74,75]. While these paradigms have primarily highlighted the consequences of active sampling behaviors on processing systems (e.g., increased sensory gain), little is known about the mechanisms that generate intrinsic sampling policies and their impact on self-initiated exploration and collection of sensory data[69]. I here used an active sampling paradigm to integrate the findings of cardiac cycle effects on both (passive) perception and perceptually relevant actions.

2.8. Main research questions

Based on recent evidence of facilitated processing during early phases of the cardiac cycle in visual[19–21,59] and oculomotor[22] domains, I conducted a study[1], which investigated the heartbeat's role for *active information sampling*. Thereby, I tested whether self-initiated action towards a visual stimulus shows periodic variations with alternating phases of the cardiac cycle. In the present self-paced visual sampling paradigm, participants freely decided when to press a key to receive (and perceive) a visual stimulus—thus extending previous accounts of reactive sensorimotor behavior by a self-initiated, proactive processing dimension.

I predicted[1] that facilitated visual perception[20,21]—observed specifically for motivationally salient stimuli[19,59]—as well as heightened oculomotor activity during systole[22] guide active sampling in the shape of a preference to prompt a relevant visual stimulus during

early cardiac phases. More specifically, my first hypothesis was that participants' sampling behavior would be biased towards processing task-relevant stimuli during systole. To address the emotional specificity of cardiac-phase effects[23], stimuli were chosen from a set of standardized and validated affective picture material (EmoPicS[76]), depicting humans in different life situations, which consisted of negative, positive, and neutral content.

Additional stimulus relevance was induced by asking participants to memorize the pictures during sampling (i.e., self-paced encoding) and testing their recognition memory after a delay of several minutes (i.e., recognition). Based on the abovementioned systolic influences on memory formation[61], the second hypothesis connected the cardiac timing of memory probes during encoding to phase-related variations in recognition performance. Specifically, my second hypothesis was that memory performance for pictures encoded at various time points of the cardiac cycle would not be uniformly distributed but differ across the cardiac cycle.

3. Methodological approach

3.1. Open science approach

The present study promotes the mission of transparent and open science[77]. Given the large heterogeneity in the existing cardiac cycle literature (see **Table 1**), the aim of this approach was to increase methodological transparency, to facilitate access to data analysis, and to enable exchange across different labs. It thus fostered reproducibility and replication to maximize accuracy and minimize errors as well as false positives. The hypotheses and the protocol of the present study were pre-registered prior to the data acquisition at the Open Science Framework[78]. The according pre-registration document[79] can be found online (https://osf.io/5z8rx/). In addition, the code of the analyses as well as the data that support the findings of this study were made publicly available[80] on the code-sharing platform GitHub (https://github.com/SKunzendorf/0303_INCASI). Furthermore, an open access pre-print of the manuscript[81] (also in its final version) was published on bioRxiv.

3.2. Sample size and exclusion criteria

A total of 47 (23 female) young, healthy, right-handed adults, ranging in age from 18 to 34 years (M = 25.8 years, SD = 4.31), participated in this study. Prior to the experimental session, participants' health status was assessed by a routine medical history and a health questionnaire, as well as a cardiovascular screening involving resting measurements of blood pressure, heart rate, and examining the electrocardiogram (ECG) for arrhythmias. Current health complaints, impaired (and uncorrected) vision, confirmed history of somatic (e.g., cardiovascular,

neurological) or psychiatric diseases, and regular medication other than oral contraceptives were exclusion criteria. Based on physiological measurements, four participants with diverging cardiovascular parameters were excluded: two participants with resting tachycardia (mean resting heart rates > 100 bpm), parallel to previous studies[19,51,53]; one participant with unusually high resting blood pressure (171/89 mmHg), based on Tukey's criterion[82] of 1.5 times the interquartile range (IQR) above the third quartile (Q3 = 122 mmHg, IQR = 20.5 mmHg); one subject with multiple ventricular extrasystoles (> 10 per minute). The remaining group of 43 subjects reported normal health and showed a mean (*SD*) resting heart rate of 74.0 (9.62) bpm, mean systolic blood pressure of 112 (13.1) mmHg, and a mean diastolic blood pressure of 70.7 (9.54) mmHg. The sample size was chosen based on previous cardiac cycle studies (see **Table 1**): expecting 10% participant exclusions, I aimed for a net sample size of 40 to enter the analyses (see pre-registration[79]). Participants were told that their ECG recording served the general monitoring of physiological changes during the experiment[60] and they provided informed consent before participation. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Psychology at the Humboldt-Universität zu Berlin. [81]

3.3. Experimental procedure

The visual memory experiment consisted of two periods, which were separated by a 5-minute break (for the detailed setup see Kunzendorf et al.[1]): during the encoding (**Figure 2c, 1.**), participants freely clicked through a set of 120 emotional pictures (40 of each valence in randomized order, **Figure 2a**) to memorize them for a later memory test. Critically, by self-paced key press, they actively triggered the immediate onset of the next picture, which briefly appeared on-screen for 100 ms. In the subsequent recognition period (**Figure 2c, 2.**), participants were passively presented with a set of 50% old and 50% new pictures (overall 40 of each valence, random sequence), upon each of which they were asked to enter a recognition response ("old", "new"). Simultaneous registration of the participants' ECG signal through an ActiveTwo AD amplifier (BioSemi, Amsterdam, Netherlands) allowed me to analyze self-initiated picture onsets relative to their cardiac cycle (for electrode positions see **Figure 2b**).

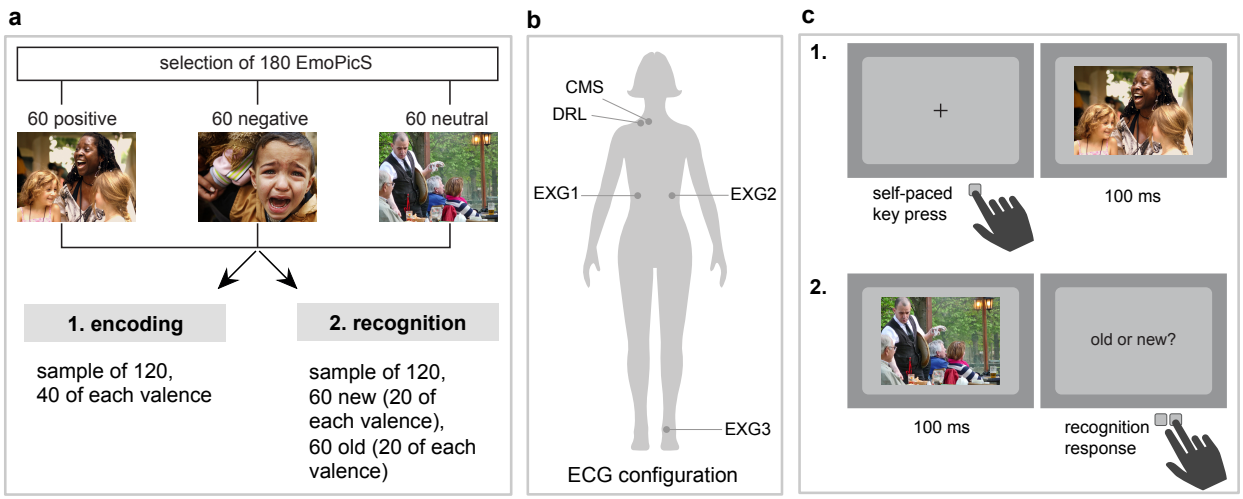

Figure 2 Psychophysiological experiment setup. (**a**) The selected picture set comprised 180 emotional photographs depicting humans in different (positive, negative, neutral) life situations. For every subject, pictures were randomly selected, leading to a random subset of 120 for encoding, as well as a second random subset of 120 (including the 60 yet unused, and 60 old pictures) for the recognition period. (**b**) Three ECG electrodes (EXG1, EXG2, EXG3) were positioned at the right and left lower coastal arch, as well as the left medial ankle (reference electrodes CMS/DRL on the right clavicle). (**c**) Participants performed the behavioral task consisting of two parts (encoding, recognition) while their ECG was being recorded. **1**. During encoding, participants prompted the onset of the next picture via self-paced key press (active sampling task). **2**. In the recognition period, they were asked to indicate for each picture (50% new, 50% old) whether or not they had already seen it during encoding. (Photographs taken from the picture set EmoPicS[76]; icons of Figure 2b[83], 2c[84] modified from the original icons by the Noun Project[85]).

3.4. Circular and binary analyses

In previous cardiac-timing paradigms, stimuli were locked to specific time points (see **Table 1**) that were expected to (most likely) fall into either of the two cardiac phases. In the present, self-paced setting, there were no a-priori experimental restrictions regarding the distribution of picture onsets across the cardiac cycle. This allowed me to post-hoc analyze the association between button presses (leading to immediate picture onset) and the whole (individual) cardiac cycle. The timing of behavioral responses could be related to the participants' cardiac rhythm by extracting the R peaks (demarcating the beginning of the next cardiac cycle) from their ECG signal using the software package Kubios[86] (v2.2; available from http://kubios.uef.fi/[87]). Individual patterns of stimulus onsets (120 per participant) and individual cardiac cycles (i.e., the intervals between two consecutive R peaks) were then compared to analyze the cardiac coupling of (self-initiated) stimulus presentation (**Figure 3a**). In particular, two complementary techniques—circular and binary analyses—were conducted to address the oscillatory (repeating cycle of cardiac events) as well as the binary (two distinct cardiac phases, systole and diastole) nature of the heartbeat, respectively.

Both analytical approaches, applied to the analysis of encoding (hypothesis 1) as well as recognition (hypothesis 2), are described in detail in the paper[1]. The following outline

exemplarily focuses on the analysis of the encoding period, as it underlies the main finding of cardiac-coupled visual sampling and parallels the approach in the recognition period (for more details see the methods described in Kunzendorf et al.[1] and the associated Supporting Information). The analysis code, which was computed in the R Statistical Environment (v3.4.3) with RStudio (v1.0.136)[88], can be accessed on GitHub[80].

Circular analysis. As demonstrated by Ohl et al.[22], circular analysis can be used to detect patterns of phasic coupling between cyclic (here, cardiac) fluctuations and behavioral events. To analyze participants' sampling responses (prompting picture onset) across the cardiac cycle (**Figure 3b**), radian values between 0 and 2π were assigned to each stimulus onset, according to its relative timing within the R-R interval[22,89,90]. Thus, circular distributions of relative stimulus onsets and individual circular means were obtained for each participant. In a subsequent group-level analysis, applying Rayleigh tests, the distribution of participants' average stimulus onsets (i.e., individual circular means) was compared against the uniform circular distribution, which served as null hypothesis[91]. Confidence intervals and significance were calculated through a non-parametrical bootstrapping procedure[22]. While circular statistics can infer circular segments during which the distribution of relative picture onsets differs from a uniform distribution, it does not allow a clear-cut association of a single circular segment with cardiac systole or diastole—particularly in the presence of varying heartbeat lengths (see below), for which the same section of the circular distribution can be associated with different cardiac phases.

Binary analysis. To address the two distinct cardiac phases and to increase comparability with existing cardiac-timing approaches (see **Table 1**), I furthermore ("offline") segmented the cardiac cycle into two time windows (**Figure 3c**), systole and diastole, with the aim to reflect the respective cardiac phase as physiologically correct as possible (based on[92–96]). Although largely ignored in previous cardiac cycle studies, it needs to be noted that systolic phases vary inversely with the heartbeat[94,96–99]: whereas the absolute length of systole decreases in higher heart rates, its relative proportion in the whole cardiac cycle increases (for details see the Supporting Information of Kunzendorf et al.[1]). These inter-individual differences in cardiac phase duration (e.g., arising from different heart rates) emphasize the need to refine cardiac phase analyses. Exploiting the participants' ECG trace as physiological reference signal of their cardiac activity, I did not use global systole and diastole lengths (e.g., determining systole as the 300 ms following an R peak, see **Table 1**) but computed individual cardiac phases. For every participant, the sum of picture onsets in each cardiac phase (i.e., individual systole, diastole) was normalized to the respective phase proportion in the total cardiac cycle. This resulted in participant-specific

systolic and diastolic stimulus onset ratios, which were then compared against each other on the group-level with a two-sided paired t test.

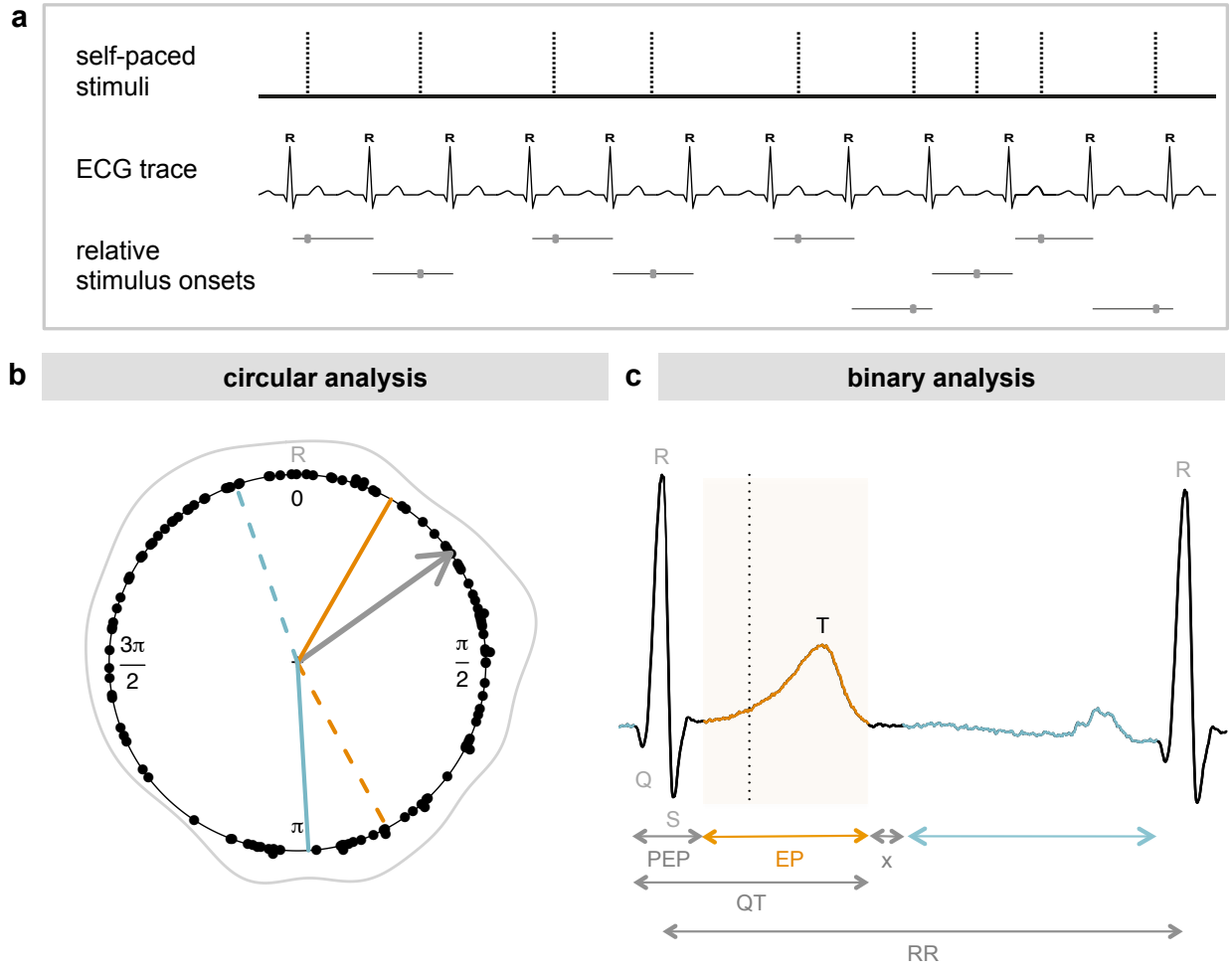

Figure 3 Two complementary analytical approaches (**a**) The sampling behavior (i.e., self-paced stimulus onsets) was analyzed relative to the heartbeat (i.e., ECG). (**b**) In the *circular analysis*, each stimulus onset (black dot) was attributed to a value from 0 to 2 π reflecting its relative timing within the cardiac cycle (R-R interval with length 2 π). For every subject, circular mean (gray arrow) and circular density (gray line) of stimulus onsets were computed. Individual cardiac phases from the binary analysis (see below) are visualized as circular segments (start: solid; end: dashed): systole (orange) and diastole (blue). (**c**) In the *binary analysis*, stimulus onsets (dashed line) were assigned to participant-specific systole (orange) and diastole (blue). Based on a template approach, individual systole (ejection phase, EP) was computed by removing the pre-ejection period (PEP) from the total systolic interval (Q wave onset – T wave end, QT). A 50-ms window after T wave end (x) was inserted to prevent overlap with diastole (for more details see Kunzendorf et al.[1] and the associated Supporting Information**;** Figure 3b, 3c adapted from figure 2 of Kunzendorf et al.[1]).

3.5. Detailed account of individualized cardiac phases

The specifications and (physiological) interpretations of *systole* and *diastole* vary in the previous literature of heart-brain interactions, which contributes to the heterogeneity of empirical results (see **Table 1**). Below, I summarize existing cardiac definitions and compare them to my

approach (for more information on individualized cardiac phases see the Supporting Information of Kunzendorf et al.[1]).

3.5.1. Definitions of systole

In previous cardiac cycle studies, *systolic* stimuli have mostly been presented at fixed time points relative to the R peak (e.g., varying from R+100 ms to R+300 ms), or to the T wave (see **Table 1**). Thus, the definition of systole differs between existing studies or labs.

In my approach, individual systole and diastole lengths were computed in relation to cardio-mechanical events whose critical times could be extracted from the participants' ECG trace. Thereby, I aimed at approximating subject-specific phases of present vs. absent baroreceptor activity. Based on the ECG (**Figure 3c**), the total ventricular systolic phase is described as the time interval between Q wave onset and the T wave end (QT; e.g., Fridericia[99]), and includes two systolic intervals: pre-ejection phase (PEP), that is, depolarization and isovolumetric contraction (no blood outflow), as well as ejection phase (EP, blood outflow into the aorta and pulmonary artery). While some previous studies have used the R peak as diastolic reference (see below, **Table 1**), here, the ECG's R peak was considered as part of total systole as it indicates the depolarization that contracts the ventricles, and thus demarcates the systolic PEP, which prepares the phase of systolic EP. Diastole then refers to the remaining phase of relaxation and filling until the onset of the subsequent QRS complex[92–95]. Since our systolic phase of interest (i.e., baroreceptor activity) is defined by the time course of the pulse pressure wave at each blood ejection[93,100,101], it approximately concurs with the EP, consistent with time estimates showing that systolic pressure waves activate aortic and carotid baroreceptors within as short period of 10 – 15 ms (e.g., R+90 ms) and 40 – 65 ms (e.g., R+140 ms) after aortic valve opening, respectively (see **Table 2**).

Demarcating the total systolic interval, Q waves and T wave ends were detected in the participants ECG based on a template approach. For each participant, the EP was then extracted by removing the PEP from the QT template, using regression equations[96,102] that were formerly applied in clinical cardiology as a "non-invasive" approach to determine systolic time intervals[94]. In the following, the term systole refers to this extracted EP (**Figure 3c**). Thus, individual systole templates (with an individualized systole length per participant) started approximately with the opening of the aortic valve initiating the blood outflow shortly after the R peak[102] and finished with the T wave end, around which the aortic valves close[103]. Of note, the calculated systole may also include a short period before the arrival of baroreceptor signals at central processing sites. However, at what point in the R-R interval this arrival occurs can only be approximated—if

conduction times along afferent pathways are not directly measured—and different values have been reported (see **Table 2**).

Importantly, participants' systoles that were computed with this method strongly overlap with previously used phases of cardio-afferent signaling: first, individual systoles (i.e., EPs)—starting between 53.0 – 82.4 ms (M = 65.1, SD = 6.25) after the R peak and ending between 296 – 375 ms (M = 329, SD = 22.2) after the R peak—closely resemble time intervals of increased baroreceptor activation that were reported or used in previous studies (see **Table 2**). Second, central processing of baroreceptor feedback signals has often been related to the T wave[19,61,63]. As subject-specific systoles comprise the T wave (i.e., end with the T wave end), the central representation of cardio-afferent signals can be considered to be included.

3.5.2. Definitions of diastole

Also the applied definition of diastole differs between existing experimental paradigms: diastole has been either defined by the R peak, indicating the end of diastole (e.g., Garfinkel et al.[61]), but also by other diastolic reference points (usually timed earlier during diastole), reaching from R+350 ms to R+800 ms (see **Table 1**). From a cardio-physiological point of view, such *diastolic* stimuli coincide with different states of the cardiac cycle (e.g., ventricular depolarization vs. relaxation and filling), which might differentially modulate cardiac-related effects, despite the absence of baroreceptor activity at this time.

To avoid noise that might arise from other cardiac processes around the QRS complex, as well as to prevent a cardiac phase overlap, I here restricted the diastolic reference window to the phase of ventricular relaxation and filling (i.e., until the onset of the subsequent QRS complex), and excluded the PEP from the analysis. Consequently, individual diastolic phases (**Figure 3c**), which varied (within-subject) from trial to trial due to beat-to-beat heart rate variability were set to begin after T wave end plus a buffer interval of 50 ms and extended to the onset of the Q wave from the following QRS complex (indicating the start of ventricular depolarization). Beginning between 346 – 425 ms (M = 379, SD = 22.2) after the R peak and ending between 652 – 1101 ms (M = 805, SD = 129) after the R peak, participants' mean diastolic phases thus included the diastolic time points of earlier studies (see **Table 1**).

Taken together, in this analysis[1], I followed the rationale that excluding the PEP as physiologically distinguishable interval of ventricular depolarization and contraction helps to determine—and to distinguish—the two distinct cardiac phases of interest: the systolic phase of blood ejection (activated baroreceptors) and the diastolic phase of ventricular relaxation and filling (quiescent baroreceptors). I conclude that, in line with previous studies, the here computed

systolic intervals include the (central representation of) baroreceptor/cardiac signals. In addition, the diastolic intervals contain the time points at which diastolic stimuli have typically been presented in earlier studies. While consider the present approach more precise than previous methods (e.g., being participant-specific) it allows the comparison of results with the existing literature.

4. Results

In the present study[1], I investigated the association between the cardiac cycle and self-paced visual (information) sampling as well as visual recognition memory for pictures of different emotional valence (for a detailed description and graphical illustration of the present findings see Kunzendorf et al.[1]).

4.1. Visual sampling

My results show that self-initiated action (i.e., key presses) in a visual sampling paradigm is coupled to the heartbeat. In particular, I found that participants were significantly more likely to prompt a picture during early phases of the cardiac cycle (i.e., during systole). The circular analysis showed an accumulation of individual mean picture onsets in early phases of the cardiac cycle (see Kunzendorf et al.[1], **Figure 2a**), supported by Rayleigh tests indicating a nonsignificant trend that the self-initiated picture onsets were unlikely to be uniformly distributed (Rayleigh test statistics $R_0 = 0.26$, $p = .053$). Notably, the same analysis with our preregistered sample size (i.e., the first 40 healthy subjects of $N = 43$; see pre-registration[79]) revealed a significant deviation from the uniform distribution ($R_0 = 0.28$, $p = .039$) that was driven by a significant increase in self-paced key presses in the interval from 0.24 to 0.44π (see Kunzendorf et al.[1], **Figure 2a**), as shown by nonparametric bootstrapping. These results were corroborated by the binary analysis (see Kunzendorf et al.[1], **Figure 2b**), showing a significantly larger ratio of picture onsets in participants' individual systole ($t(42) = 2.76$, $p = .009$, Cohen's $d = 0.42$), compared to diastole (similarly for $n = 40$; $t(39) = 2.70$, $p = .010$, Cohen's $d = 0.43$).

4.2. Memory performance

Memory performance was only modulated by picture valence, replicating a significant memory benefit for emotional content[104–107], but did not significantly vary as a function of the cardiac phase during which targets were encoded[61]. The circular analysis—testing whether distributions of mean picture onsets during stimulus encoding showed differences for hits (correctly remembered) or misses (erroneously identified as new)—did not indicate a significant deviation from the circular uniform distribution, neither for hits ($R_0 = 0.20$, $p = .21$), nor for misses ($R_0 =$

0.16, p = .36). Furthermore, the binary analysis—employing a general linear mixed model (GLMM) to predict the binary recognition outcome (hit, miss) of memory targets from the cardiac phase during encoding (systole, diastole)—revealed that valenced pictures (negative, positive) were significantly better recognized than neutral pictures (see Kunzendorf et al.[1], **Table 1**). Critically, adding cardiac phase to the model did not significantly improve the model fit (see Kunzendorf et al.[1], **Table 1**), that is, neither phase nor its interaction with picture valence significantly accounted for variation in recognition memory.

5. Cardiac signals as bodily reference—discussion and future implications

5.1. Central integration of intero- and exteroceptive signals

Taken together, the present results demonstrate, to my knowledge for the first time, that self-paced sampling of task-relevant cues shows periodic variations across the cardiac cycle. This implies that the heartbeat, as a bodily signal, contributes to our active engagement with the external world. Building on previous findings of facilitated visual processing during systole, the cardiac coupling of self-initiated actions with a visual stimulus proposes a link between the heartbeat and active perception. The study thus extends the existing literature on the association between heart-brain interactions and behavior on two levels: (1) conceptually, as the present results complement previous cardiac cycle paradigms by the dimension of active sampling and (2) methodologically, as the analyses account for inter-individual differences in cardiac fluctuations (i.e., phase length).

Adding to emerging mind-brain-body frameworks of action and perception[15,16], I hereby propose that we implicitly exploit ongoing visceral (cardiac) oscillations when interacting with external stimuli. Although the physiological pathways underpinning systolic influences on cognition and behavior remain to be fully elucidated, cardiac coupling of external stimulus processing has been attributed to the phasic nature of interoceptive (e.g., baroreceptor) signaling[9]. Transmitted to the brain periodically with each blood ejection, baroreceptor signals (reflecting the current heartbeat's strength and timing) constitute a fine-tuned reference to a crucial property of the bodily state: deviation from normal variation (e.g., drop in arterial pressure) is directly expressed in alternated cardiac signaling, thereby serving as feedback control to counteract environmental challenges (e.g., body position, exercise, or threat). In terms of interoceptive predictive coding, visceral (e.g., cardiac) afferents thus constrain interoceptive predictions and compute interoceptive prediction errors for the maintenance of homeostasis[2,16].

In line with previous cardiac cycle studies, the present findings suggest that interoceptive signals further modulate exteroceptive predictions (i.e., concerning the external world), yet

experimental investigation how the integration of interoceptive and exteroceptive processing is represented centrally remains sparse. Capitalizing on neural responses to heartbeat signals (i.e., HEPs), it has been found that temporal synchronization of exteroceptive (e.g., visual, auditory) and interoceptive (cardiac) signals not only modulates activity in the multimodal integration site IC[108] (see above), but also shapes predictions towards upcoming external cues, as detected in a violation response in HEPs upon stimulus omission—indicating that internal cardiac signals participate to external regularity processing[109]. This suggests that implicit monitoring of internal and external events, and their temporal relation, might generate intrinsic temporal models to drive predictions about future events[109]. Ongoing bodily (cardiac) fluctuations might thus contribute to structured guesses upon the external environment, thereby optimizing sensory processing[109].

At the same time, exteroceptive predictions modulate the processing of interoceptive (cardiac) signals. Critically, modulation of neural cardiac responses (i.e., measured as HEP amplitude) through external predictions concerning upcoming sensory events was found to be specific to the predicted emotional content[110]: expected angry (but not neutral) faces evoked a repetition suppression (i.e., reduced HEP amplitude), suggesting that affective predictions of external emotionally salient information attenuate interoceptive processing. Such emotion specificity was explained in the context of attentional weighting between interoceptive and exteroceptive processing, thereby promoting an attentional shift from internal to external relevant (e.g., threat) information[110,111].

This dynamic interplay between interoceptive and exteroceptive processing implies that exteroceptive predictions towards upcoming (particularly salient) external stimuli integrate interoceptive heartbeat-related information. It could be argued that natural, ongoing cardiac activity generates oscillating phases of predicted (and thus decreased) interoceptive processing, which promotes the allocation of attention towards relevant external stimuli (as shown in selective enhancement of motivationally salient cues during systole). As suggested by the present findings of cardiac-coupled engagement towards relevant external stimuli, interoceptive (cardiac) oscillations might thus serve as a predictable bodily reference upon which interaction with the ever-changing (and often unpredictable) external environment can arise.

5.2. Limitations and future directions

For the interpretation of the current results, a number of limitations should be considered (see also Kunzendorf et al.[1]). First, a better understanding of cardiac influences on active perception could be gained by manipulating the temporal relation between action and stimulus onset. In the

here presented paradigm, stimuli were immediately prompted by the participants' key presses, which does not allow to separate somatomotor, sensory, and cognitive processes. Manipulating this synchronicity through dissociating action initiation (i.e., key presses) from self-initiated action effects (i.e., stimulus onset) could thus allow disentangling the underlying processes. For example, reaction time studies have suggested differential modulation (see **Table 1, 3.**) of motor and (pre-motor) sensory components of the reaction response[112,113]. Future studies could therefore decompose the different processing stages, for example, by keeping the temporal regularity between action and stimulus onset but using fixed delays after key presses. In this way, it could be tested if intrinsic sampling models are adapted and participants learn to shift their key presses to continue perceiving (and receiving) stimuli in preferred (i.e., systolic) cardiac phases. On the other hand, increased motor movements (i.e., key presses) during systole, independent of the delay in stimulus presentation, might point towards other sources of cardiac-coupled key presses, for example due to cardioballistic effects (i.e., bodily vibrations associated with the heart contraction). To rule out a pure motor effect, a control condition could test spontaneous motor actions that are not explicitly coupled to perception of (relevant) sensory input. The hypothesis would be that key presses that do not trigger relevant stimuli would be randomly (i.e., uniformly) distributed across the cardiac cycle.

Second, further investigation is needed to study the role of stimulus predictability in the context of cardiac-coupled visual sampling. Clear temporal relations between action and perceptual processing allow a highly predictable timing of self-initiated action effects (i.e., stimulus onsets). In other words, in the present paradigm, the self-initiated picture onset has a clearly predictable relation to the preceding action: whenever a key is pressed, a picture is simultaneously prompted. This regularity might possibly support the formation of temporal rules upon which predictable phases of cardiac signaling could be integrated. Violating temporal regularities between motor- and sensory processing to intrude such intrinsic sampling rules (e.g., by including omitted trials or unpredictable stimulus delays) could thereby test the role of ongoing cardiac fluctuations in the context of increased sensory uncertainty. It would be expected that decreasing stimulus predictability shifts the attentional focus to external cues to update violated internal sampling models, thereby diminishing the degree to which interoceptive cardiac fluctuations participate to active stimulus processing.

Third, more fine-grained experimental manipulations should not only address temporal aspects of stimulus presentation but also stimulus attributes (e.g., stimulus salience). Based on the observed cardiac-coupled selective enhancement of motivationally salient stimuli[23], the role of stimulus relevance as defining factor could be investigated through further refined stimulus

features. A question would be whether enforced stimulus relevance (e.g., expected monetary gain) strengthens cardiac modulation of visual sampling such that participants increasingly exploit preferred cardiac phases.

Beyond stimulus manipulations on the behavioral level, a crucial future step to investigate interactions of cardiac signals and active stimulus processing would be to measure cardiac-related changes in central neural activity (e.g., through EEG or magnetoencephalography, MEG), as the processing of all studied behavioral components (motor movements, stimulus perception, recognition memory) occurs in the brain. Detection of neural responses to cardiac signals (e.g., HEPs), and their variation with external stimulus processing at different cardiac phases, is needed to extend our understanding of neural mechanisms underlying the central integration of interoceptive and exteroceptive processing. Since the current results are primarily at an observational and behavioral level, measurements of brain activity are essential for a more comprehensive mechanistic understanding of cardiac influences on cognition.

Finally, the present correlational finding does not imply a causal influence of the heartbeat on active sampling, and the functional relevance of this bias remains unclear. While influences of the cardiovascular state on sensorimotor processing emerge subtly with heartbeat-related pressure fluctuations, a sustained shift of the bodily state beyond physiological variability (e.g., under stress) might more pervasively drive cognition and behavior, ultimately aiming at maintaining our physiological integrity and well-being. During heightened arousal, we prioritize relevant information (e.g., threat), whereas other types of stimulus processing (e.g., pain) are attenuated, which is considered beneficial for our survival. An increased heart rate under stressful situations results in relatively increased amounts of systolic signaling (as faster heartbeats occur mainly at the expense of diastole length). It could be argued that the generation of more time intervals of selectively facilitated sensory processing thereby supports what information is preferentially processed. This proposal is supported by evidence from a recent study that associated experimentally raised heart rates[114] with prioritized fear processing across a variety of measures (reaction time, peak velocity, response acceleration, choice uncertainty). Experimental manipulation of the cardiac state (e.g., increasing the heart rate) could thus be used to investigate whether altered cardiac activity modulates the coupling between heartbeat and behavior (e.g., active perception and self-paced action). If cardiac signaling causally influences the generation of sampling movements, raising the heart rate would increase the rate of self-initiated actions during systole. Hence, this approach would help to test the idea that the strength of the coupling between heartbeat and behavior becomes relevant in states of high arousal (e.g., stressful situations). To further address the question regarding the functional relevance of cardiac

contributions to cognition, our group currently conducts an experiment in the context of a virtual reality environment, investigating whether interaction with more naturalistic, emotionally salient stimulus paradigms (e.g., threatening animals) elicits stronger cardiac cycle effects.

In conclusion, the novel finding that cardiac fluctuations modulate how we act upon our environment probes further systematic investigation of the underlying mechanisms by which interoceptive processes—and their central integration—shape human cognition and behavior. A better understanding how the body and its interaction with the brain relates to mental processes and behavior in health may inform our knowledge about pathological mind-brain-body interactions, which underlie mental and physical disorders. Growing evidence highlights the important role of interoceptive processing for our health[27,115]. Altered or dysfunctional interoception, assessed on behavioral as well as neural levels, has been associated with a variety of psychopathological conditions, such as eating disorders including anorexia and obesity[116,117], addiction[118], anxiety disorders and depression[119,120], dissociative syndromes[46], autism spectrum conditions[121], somatoform disorders[122], and functional motor disorders[123]. Furthermore, aberrant interoceptive processing was shown for multiple somatic diseases, including Parkinson's disease[124], focal brain lesions (as present in insular stroke[125]), dementia syndromes (fronto-temporal dementia and Alzheimer's disease[126]), chronic pain[127], multiple sclerosis[128], and hypertension[129]. Altered interoceptive processing across this wide range of psychological and (psycho)somatic conditions might thus provide a handle to further explore the relation of compromised brain- and body-functions in various clinical conditions—for example, regarding the high concurrence of affective disorders (e.g., anxiety, depression) in coronary heart disease[130–132]. Studying the impaired interoceptive processes of these disorders might support the development of novel therapeutic targets and strategies addressing interoceptive deficits. As the way we perceive and engage upon our environments relies on the complex interplay of brain and body, knowledge of the integration of bodily (e.g., cardiac) processes in mental phenomena is essential for a comprehensive understanding and promotion of our psychological and physical well-being.

Appendix

1. Decreased (↓) processing during systole					
Study	**Systolic timing**	**Diastolic timing**	**Stimulus modality**	**Results with respect to the cardiac cycle**	**Number of analyzed subjects (diseases)**
Birren, Cardon, & Phillips, 1963[36]	QRS (end P to onset T), T (onset T to end T), TP (end T to onset P), and P (onset P to end P), reaction time (RT) post-hoc classified into 4 cardiac intervals		auditory	↑ RT (i.e., slower reaction) for stimuli in earlier cardiac phases: slowest during QRS ↓ RT (i.e., faster reaction) for stimuli in later cardiac phases: significantly faster during P than for remaining intervals	56
Réquin & Brouchon, 1964[39]	R+0, 100, 200, … 800 ms		visual (signal detection)	↑ sensory threshold (i.e., ↓ perceptual sensitivity) at R+200 – 400, 600 ms ↓ sensory threshold (i.e., ↑ perceptual sensitivity) at R+100, 500, 800 ms	11
Callaway & Layne, 1964[40]	Q+0, 100, 200, … 900 ms (10 intervals)		visual, auditory (warning)	↑ RT for stimuli in earlier cardiac phases: highest for stimuli at Q+0 (Q+300 ms in patient 2) RT quickens over time course of cardiac cycle	3 (2 pace maker patients)
Saxon, 1970[47]	R (i.e., R-40 to R+40 ms)	P (i.e., R+700 to R+810 ms)	auditory (signal detection)	↑ sensory threshold for stimuli during R ↓ sensory threshold for stimuli during P	4
Lacey & Lacey, 1974[37]	exp. 1 – 3: R (response in systole) exp. 4: R	R+350 ms (response in diastole) R+400 ms	auditory	↓ RT for stimuli later in the cardiac cycle (i.e., response in diastole) slow heart rate (HR) during response associated with fast RT (↑ correlation of HR with RT for diastolic	exp. 1: 40 exp. 2 – 4: 16

				stimuli)	
	exp. 5: button press (within differential reinforcement of low rates (DRL) operant conditioning experiment)			exp. 5: ↑ HR associated with ↑ button presses later in cardiac cycle	exp. 5: 52
Sandman et al., 1977[41]	R, T, P		visual (signal detection)	no main effect of cardiac cycle on stimulus detection ↑ stimulus detection (i.e., ↑ perceptual sensitivity) for stimuli at P (P vs. T, P vs. R) only apparent during fastest stimuli presentation times (6 ms)	26
Lacey & Lacey, 1977[133], Lacey & Lacey, 1978[38]	exp. 1: R-R interval divided into 10 intervals		visual ("ready" stimulus, "go" stimulus)	cardiac cycle-dependent HR changes: ↑ HR deceleration (i.e., ↑ length of concurrent R-R interval) for "go" stimuli presented in early cardiac phases	exp. 1: 66
	exp. 2: self-initiated tachistoscopic exposure (i.e., clock face displaying 12 light-emitting diodes)			cardiac cycle time of self-initiated response modulates R-R interval length: responses early in cardiac cycle associated with ↑ concurrent R-R length responses later in cardiac cycle associated with ↑ subsequent R-R length	exp. 2: 20
Cohen, Lieb, & Rist, 1980[43]	exp. 1: 1/3 of R-R interval	2/3 of R-R interval	auditory	↑ loudness judgments in later cardiac phases (nonsignificant opposite trend for schizophrenic subjects)	28 (14 with schizophrenia)
	exp. 2: 1/6 of R-R, 1/3 of R-R, 1/6 ± 400 ms, 1/3 ± 400 ms			no significant cardiac cycle effects on loudness judgments	34 (17 with schizophrenia)
Rau et al., 1993[55]	R+200 ms (baro-receptor manipulation	100 ms after pressure reversal (2 conditions:	tactile (T reflex)	↓ achilles tendon reflex (i.e., T reflex) for systolic stimuli	12

	via phase-related external suction (PRES), 2 conditions: - PRES: systolic suction/diastolic pressure - control: systolic pressure/diastolic suction)	PRES/control, for details see paper)		effect enhanced by PRES (interaction effect): lowest T reflex during systole+PRES (i.e., during maximum baroreceptor activation)	
Droste et al., 1994[56]	R+200 ms (PRES/control)	100 ms after pressure reversal (PRES/control)	tactile (pain)	↑ pain ratings during diastole+PRES (i.e., during minimum baroreceptor activation) no effect on sensory threshold	28
Dworkin et al., 1994[49]	R+200 ms (PRES/control)	100 ms after pressure reversal (PRES/control)	tactile (T reflex)	↓ T reflex during systole+PRES (exp. 1)	exp. 1: 12
			tactile (pain)	↓ pain ratings during systole+PRES (exp. 2, exp. 3)	exp. 2: 19 (with cardiac ischemia) exp. 3: 116
Edwards et al., 2001[50]	R+5, 100, 200, … 600 ms (7 intervals)		tactile (pain: sural nerve stimulation -> nociceptive flexion reflex, NFR)	↓ NFR response (biceps femoris activity in EMG) at mid cardiac cycle (R+200 – 500 ms, with smallest response at R+300 ms), highest NFR response at R+600 ms	40
Edwards et al., 2002[51]	R+300 ms	R+600 ms	tactile (pain: NFR)	↑ NFR threshold (i.e., ↓ nociception) during systole no influence on intensity ratings	36
Al'Absi et al.,	R+200 ms	R + [(interbeat	tactile (pain: NFR)	↓ NFR response during systole (but not affected by	137 (62 with

2005[57]	(3 conditions: PRES/control, no manipulation)	interval/2)-100]+200 ms (PRES/control, no manipulation) ca. R+540 ms (for mean HR of 68bpm)		manipulation conditions PRES/control) ↓ pain ratings in subjects at risk for HTN (only men) ↓ pain ratings in conditions PRES/control vs. no manipulation (i.e., not related to baroreceptor activity) no influences of risk for HTN on NFR threshold	parental history of hypertension, HTN)
McIntyre et al., 2006[134]	R+0, 300, 600 ms (2 conditions: high arousal – mental arithmetic, low arousal – rest)		tactile (pain: NFR)	↓ NFR response at R+300 ms (i.e., systole) during rest condition no cardiac cycle effects during arousal condition	38
Stewart, France, & Suhr, 2006[42]	R+50, 100, 150, … 600 ms (12 intervals)		visual	↑ RT for stimuli at mid cardiac cycle (slower RT at R+150 – 600 ms) ↓ RT for stimuli at late, and very early cardiac phases (faster for R+550 – 600 ms, fastest R+50 – 100 ms) no influence of increased risk for HTN on cardiac cycle effects	93 (normo-tensives at varying risk for HTN: low, normal, high-normal)
Edwards et al., 2008[54]	R+50, 150, 250, … 750 ms (8 intervals, labeled by midpoint), trials sorted post-hoc		tactile (pain)	↓ amplitudes of the N2-P2 pain-related potential at mid (R+250, 350, 450 ms) cardiac cycle (i.e., ↓ cortical processing of nociception during systole) no cardiac cycle effects on pain ratings	10
McIntyre et al., 2008[52]	R+0, 150, 300, 450, 600, 750 ms (6 intervals)		tactile	↑ RT for stimuli at earlier cardiac phases (R+0, 150 ms) ↓ RT for stimuli at later cardiac phases (R+450, 600, 750 ms) no influence of risk for HTN on cardiac cycle effects	113 (at risk for HTN)

Richter et al., 2009[44]	R+230 ms (4 conditions of lower body negative pressure, LBNP)	R+530 ms (4 conditions of LBNP)	auditory (startle -> eye blink reflex, EBR)	↑ EBR response (orbicularis oculi muscle activity in EMG) during diastole ↑ EBR response increased with ↑ LBNP levels (i.e., ↑ unloading of cardiopulmonary baroreceptors) no effect on psychomotor RT no effect on perceived intensity, valence	12
Schulz et al., 2011[45]	R+0, 100, 200, … 400, 500 ms (6 intervals) (2 conditions: control, stress – cold pressor test)		auditory (startle -> EBR)	control: ↓ EBR response at early phases (lowest at R+200, 300 ms) stress: ↓ EBR response even earlier in cardiac cycle (lowest at R+0, 100, 200 ms)	38
Garfinkel et al., 2013[61]	T wave	R peak	visual (emotional words)	↓ encoding memory for words (positive, negative, neutral) during systole cardiac cycle effect decreased in participants with ↑ interoceptive sensitivity	17
Wilkinson, McIntyre, & Edwards, 2013[53]	R+0, 100, 200, … 600 ms (7 intervals)		tactile (pain)	↑ pain threshold mid cycle (higher at R+200, 300 vs. R+100, 500 ms, higher at R+300 vs. R+600 ms) cardiac cycle effect not moderated by tonic blood pressure	49
Schulz et al., 2016[46]	R+0, 100, 200, … 500 ms (6 intervals)		auditory (startle -> EBR)	healthy control: ↓ EBR response in earlier cardiac phases (higher at R+100, 300 vs. R+0, 400 ms) DPD: no cardiac cycle effect on EBR response	45 (22 with depersona-lization-/ derealization disorder, DPD)
Yang, Jennings, &	R+180 ms	R+480 ms	auditory (reaction	↓ RT at diastole, only in conditions, in which RS	49

Friedman 2017[48]	(3 conditions: no accessory stimulus (AS), fearful AS, neutral AS)	(3 conditions)	stimulus, RS) visual (AS)	presented alone (no AS) ↓ RT for AS vs. no AS condition (not influenced by valence, cardiac timing)	
Waselius et al., 2018[135]	R+100 ms	R+500 ms	auditory (conditioned stimulus, CS) tactile (air puff, unconditioned stimulus, US)	exp. 1: ↑ N1 event-related potential (ERP) to systolic CS, but no influence on trace eye blink conditioning	exp. 1: 25 humans
				exp. 2: ↑ hippocampal ERP to systolic CS, ↑ trace eye blink conditioning for diastolic CS (vs. random CS) no differences in conditioning for systolic CS	exp. 2: 25 rabbits

2. Enhanced (↑) processing during systole					
Study	**Systolic timing**	**Diastolic timing**	**Stimulus modality**	**Results with respect to the cardiac cycle**	**Number of analyzed subjects (diseases)**
Konttinen et al., 2003[136]	self-initiated trigger pull			↑ relative number of shots during 10 – 50% of the R-R interval ↓ relative number of shots during 50 – 90% of the R-R interval ↑ performance accuracy for shots early (0 – 50%) and late (70-99%) of the R-R interval	20
Mets, Konttinen, & Lyytinen, 2007[70]	self-initiated trigger pull			↑ relative number of shots during earlier cardiac phases (highest at 10–15% of the R-R interval), ↓ at mid cardiac phases (at 45–60% of the R-R interval)	20

				no influence of cardiac timing on performance accuracy	
Edwards et al., 2009[137]	R+0, 300, 600 ms (3 intervals)		tactile (signal detection)	↓ sensory threshold at R+300 (i.e., ↑ sensibility during systole) vs. R+0, 600 ms	59
Martins et al., 2009[138]	R+0, 150, 300, 450, 600 ms (five intervals) (2 conditions: pain, no-pain)		tactile (pain: NFR, no-pain)	pain condition: highest pain ratings at R+300 ms (lowest at R+0, 600 ms) no-pain condition: highest pain ratings at R+0 ms, linear ↓ along cardiac cycle no cardiac influences on NFR response (no systolic attenuation, see above)	33
Gray et al., 2012[139]	T wave (R+100 – 500 ms)	R peak (R-200 to R+50 ms)	visual (emotional faces: disgust, neutral, happy, sad)	↑ intensity ratings only for disgust faces during systole (associated with activity in periaqueductal grey) ↓ HR changes after disgust happy faces during systole (associated with activity in orbitofrontal cortex)	21
Garfinkel et al., 2014[19]	T wave (R+200 – 550 ms)	R peak (R-350 to R+150 ms)	visual (emotional faces: fear, disgust, neutral, happy)	↑ detection of fearful faces at systole ↑ intensity ratings of fearful faces at systole associated with ↑ amygdala responses to fearful faces at systole vs. diastole	19
Pramme et al., 2014[21]	R+170 ms	R+470 ms	visual (complex, nonemotional)	↑ early visual detection (↑ discrimination of perceptually degraded target from distracting forward-mask) during systole	25
Fiacconi et al., 2016[60]	R+267 ms	R+500 ms	visual (emotional faces: fear)	↑ "old" judgments (i.e., "already seen") during systole, independent of picture status (for old, new faces)	exp. 1: 37
			visual (faces:	↑ "old" judgments (i.e., "already seen") during systole,	exp. 2: 37

			neutral)	independent of picture status (for old, new faces)	
			visual (faces: neutral)	cardiac cycle effects (i.e., ↑ "old") specific to recognition decisions associated with ↑ feeling of familiarity	exp. 2: 34
Ohl et al., 2016[22]	spontaneous microsaccade generation (visual fixation to tiny fixation point)			↑ microsaccade generation during early phases of cardiac cycle (from 0.29 to 0.50π) physiological drift (i.e., retinal image slip) associated with heartbeat (↓ R-500 ms, minimum around R, then ↑)	15
Pramme et al., 2016[20]	R+180 ms	R+480 ms	visual (complex, nonemotional)	↑ visual selection efficiency (i.e., ↓ performance difference for easy vs. difficult selection conditions) during systole (through ↓ interference of highly distracting stimuli)	22
Azevedo et al., 2017[58]	R+200 – 400 ms	R+450 – 800 ms	visual (social scenes: threat, neutral)	↑ racial black-weapon bias (i.e., race-driven misidentification of weapons) for primes (black/white face) presented at systole ↑ racial black-weapon bias (i.e., likelihood to "shoot" unarmed black vs. white individual) during systole no cardiac effects on positive racial (black-athletic) association (i.e., ↑ racial bias during systole only for threat-signaling stimuli)	30
Pfeifer et al., 2017[63]	T wave (R+300 ms)	R peak	visual (face-name pairs: fear, neutral, happy), auditory (feedback signal)	↑ encoding of faces-name pairs (fearful faces) when feedback presented at systole (i.e., ↑ feedback processing) effect only in participants with high interoceptive accuracy	29

				no cardiac effects on memory retrieval	
Azevedo, Badoud, & Tsakiris, 2018[59]	R+300 ms	R+500 ms	visual (emotional faces: fear, neutral, in different spatial ranges: low, broad, high)	↑ attentional engagement (but not disengagement) selectively to low spatial frequency fearful faces during systole no cardiac effects on high, broad spatial frequency cues	34
Galvez-Pol, McConnell, & Kilner, 2018 [140]	R+ 200 – 400 ms	R+ 500 – 700 ms	visual (complex, nonemotional)	↑ saccade generation during systole vs. diastole ↑ subsequent fixation during diastole vs. systole	29

3. Differential cardiac effects on processing components					
Study	**Systolic timing**	**Diastolic timing**	**Stimulus modality**	**Results with respect to the cardiac cycle**	**Number of analyzed subjects (diseases)**
Saari & Pappas, 1976[141]	R-R divided into 9 equal intervals, trials sorted post-hoc		auditory, visual	differential cardiac effects RT components (i.e., pre-motor, motor): - ↑ pre-motor RT in early cardiac phases (↑ in 2nd vs. 4th, 6th, 9th interval) - no cardiac effects on motor RT	8
Edwards et al., 2007[112]	R+0, 300, 600 ms (3 intervals)		tactile , auditory, visual,	differential cardiac effects on RT components (i.e., pre-motor, motor): - ↑ pre-motor RT for (tactile, auditory, visual) stimuli earlier in cardiac cycle (R+0, 300 ms), linear ↓ over time course of cardiac cycle (fastest RT for stimuli at	59 (30 with HTN)

				R+600 ms), varying effect sizes (large: tactile, auditory, medium: visual) - no cardiac effects on motor RT - cardiac effects on total RT only for auditory, tactile RT no differences in RT between normotensives and hypertensives	
McIntyre et al., 2007[142]	R+0, 150, 300, … 750 ms (6 intervals) 2 conditions (legs down, legs up: postural manipulation)		visual (1, 2, 4 - choice RT)	differential cardiac effects on choice RT components (i.e., cognitive – slope, sensorimotor – intercept): - no cardiac effects on cognitive processing (i.e., decision making) RT - ↑ sensorimotor RT for early stimuli (R+0,150 ms), linear ↓ over time course (faster RT for R+450 – 750 ms) of cardiac cycle (i.e., cardiac effects on basic sensory-motor processing) effect sizes for linear trend ↓ with ↑ complexity (lowest for 4-choice) no cardiopulmonary effects found (i.e., during postural manipulation)	36
Gray et al., 2009[68]	T (R+100 – 500 ms)	R (R-100 to R+100 ms)	tactile (electric shock)	differential cardiac effects on neural activity: - ↑ right amygdala activity for shocks at systole vs. diastole - ↑ activity in anterior insula, mid pons for shocks at diastole vs. systole differences in neural activation correlated with inter-	11

				individual differences in heart rate variability) ↓ mean arterial pressure (MAP) increases for shocks at systole	
Schulz et al., 2009[113]	R+230 ms	R+530 ms	auditory (startle -> EBR, different intensities: 85dB, 95dB, 105dB)	differential cardiac effects on RT components (i.e., pre-motor, motor), no influence on total RT: - ↑ evaluative (pre-motor) RT for 85dB stimuli at systole (R+230 ms) - ↓ motor RT for 85dB, 90dB stimuli at systole ↓ EBR response (orbicularis oculi muscle activity in EMG) during systole, only for 105dB stimuli ↓ intensity judgments during systole	25
Martins et al., 2014[62]	R+50, 150, 250, 350, 450, 550 ms (6 intervals, labeled by midpoint), trials sorted post-hoc		visual (numbers, Sternberg memory task)	differential cardiac effects on RT components (i.e., cognitive – slope, sensorimotor – intercept): - ↓ cognitive (retrieval, comparison) RT (i.e., response latency per additional digit) for stimuli early in cardiac cycle (R+50 – 250 ms), ↑ for later stimuli (R+350 – 550 ms) - ↑ sensorimotor RT for early stimuli (R+50 – 250 ms), ↓ for later stimuli (R+350 – 550 ms),	100

4. No variation across the cardiac cycle / conflicting findings					
Study	**Systolic timing**	**Diastolic timing**	**Stimulus modality**	**Results with respect to the cardiac cycle**	**Number of analyzed subjects (diseases)**
Thompson & Botwinick, 1970[143]	R+0, 200, 400, 600 ms (4 intervals)		auditory	no cardiac effects on RT	exp. 1: 18 exp. 2: 31 exp. 3: 22
	during ascending slopes of R, T, P (3 intervals)				exp. 4: 31
Delfini & Campos, 1972[144]	QRS, T, T – P, P (4 intervals), trials sorted post-hoc		auditory (signal detection)	no cardiac effects on perceptual sensitivity and response bias (criterion location)	10
Elliott & Graf, 1972[145]	QRS, T (end QRS to end of T), T – P (end of T to rise of P), P (until onset QRS)		visual (signal detection)	no cardiac effects on perceptual sensitivity	25
Salzman & Jaques, 1976[146]	R, T (R+300 ms), P (R-150 ms)		auditory	no cardiac effects on RT	exp. 1: 20 exp. 2: 20
Jennings & Wood, 1977[147]	R+350 ms	R	auditory	no cardiac effects on RT or speed-accuracy	8
Weisz & Ádám, 1996[148]	R+150 ms	R+600 ms	visual	- ↑ RT for stimuli at systole only for right stimuli and right-hand responses, no cardiac effects for central and left stimuli, and for left-hand responding (lateralization effect) - ↑ RT for stimuli at systole in women with ↓ HR (vs. ↓ RT in women with ↑ HR), no effects for men	38

Table 1 Overview of cardiac cycle studies.

Time course of afferent heart-brain signaling		
Physiological events	**Estimated time intervals**	**Study**
start of blood ejection from left ventricle into aorta (aortic valve opening)	R+50 – 60 to R+90 ms	Edwards et al., 2001[50]; Kelsey & Guethlein, 1990[149]; Lozano et al., 2007[150]
detectable heartbeat sensation most heartbeat detections	R+100 – 350 ms R+200 – 300 ms	Ring & Brener, 1992[151]; Ring, Liu, & Brener, 1994[152]
arrival of pulse pressure wave at aortic arch -> aortic baroreceptor activation (with systolic upstroke)	R+46 ± 8 ms R+90 – 100 ms (continues for 250 ms) 10 – 15 ms (after aortic valve opening)	Gabriel & Seller, 1970[153]; Seller, 1991[154] Angell James, 1971[100]; Edwards et al., 2001[50]; Edwards et al., 2002[51]; Edwards et al., 2009[137]; Pramme et al., 2016[20]
arrival of pulse pressure wave at carotid sinus -> carotid baroreceptor activation	R+61 ± 13 ms (ca. 16±5 ms after aortic stimulation) R+140 – 150 ms (ca. 50 ms after aortic stimulation, continues for 250 ms) 40 – 65ms (after aortic valve opening)	Gabriel & Seller, 1970[153]; Seller 1991[154] Angell James, 1971[100]; Edwards et al., 2001[50]; Edwards et al., 2002[51]; Edwards et al., 2007[112]; Edwards et al., 2009[137]; Pramme et al., 2016[20]
total interval of baroreceptor activation joint activation of aortic and carotid sites peak aortic and carotid baroreceptor activation (according to peak pulse pressure)	R+90 – 390 ms R+140 – 340 ms R+250 ms 70 – 100 ms after pulse arrival	Edwards et al., 2007[112]; Edwards et al., 2009[137]; Pramme et al., 2016[20] Edwards et al., 2009[137]; Pramme et al., 2016[20] Angell James & Lumley, 1974[155]; Edwards et al., 2002[51]
total conduction time (CT) from baroreceptor stimulation to brainstem -> inhibition of sympathetic activity	150 – 200 ms 180 ms	Dembowsky & Seller, 1995[156]; Edwards et al., 2002[51] Seller, 1991[154]

a. CT along aortic nerve (vagus nerve) and carotid sinus nerve (glossopharyngeal nerve) to nucleus of the solitary tract (NTS) -> signal arrival at NTS	10 – 15 ms R+65 – 70 ms	Dembowsky & Seller, 1995[156]; Edwards et al., 2001[50]; Edwards et al., 2002[51]; Martins et al., 2014[62] Seller, 1991[154]
b. CT from NTS to other brainstem areas (e.g., ncl. ambiguous, right ventrolateral medulla, RVLM)	100 – 150 ms 50 – 60 ms	Dembowsky & Seller, 1995[156]; Edwards et al., 2001[50]; Martins et al., 2014[62] Seller, 1991[154]
c. CT from RVLM to sympathetic preganglionic neurons	30 ms	Dembowsky & Seller, 1995[156]
signal arrival at reticular formation (depending on discharge level of neurons)	R+80 – 240 ms R+ 100 ms	Edwards et al., 2007[112]; Lambertz & Langhorst, 1995[157]; Pramme et al., 2016[20]
effects of peak aortic and carotid baroreceptor activation detectable in brainstem nuclei	R+250 – 350 ms	Edwards et al., 2002[51]; Fiacconi et al., 2016[60]
central processing of baroreceptor signals	R+400 – 800 ms	Fagius & Wallin, 1980[158]; Gray et al., 2007[65]

Table 2 Estimated conduction times of cardiac signals from arterial baroreceptors along afferent pathways.

Referenzliste

1. Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. Active information sampling varies across the cardiac cycle. *Psychophysiology* **56,** e13322 (2019).

2. Barrett, L. F. & Simmons, W. K. Interoceptive predictions in the brain. *Nat. Rev. Neurosci.* **16,** 419–429 (2015).

3. Kleckner, I. R., Zhang, J., Touroutoglou, A., Chanes, L., Xia, C., Simmons, W. K., Quigley, K. S., Dickerson, B. C. & Barrett, L. F. Evidence for a large-scale brain system supporting allostasis and interoception in humans. *Nat. Hum. Behav.* **1,** 0069 (2017).

4. Ulrich-Lai, Y. M. & Herman, J. P. Neural regulation of endocrine and autonomic stress responses. *Nat. Rev. Neurosci.* **10,** 397–409 (2009).

5. Gianaros, P. J. & Wager, T. D. Brain-body pathways linking psychological stress and physical health. *Curr. Dir. Psychol. Sci.* **24,** 313–321 (2015).

6. Fredrikson, M., Furmark, T., Olsson, M. T., Fischer, H., Andersson, J. & Långström, B. Functional neuroanatomical correlates of electrodermal activity: a positron emission tomographic study. *Psychophysiology* **35,** 179–185 (1998).

7. Critchley, H. D. Psychophysiology of neural, cognitive and affective integration: fMRI and autonomic indicants. *Int. J. Psychophysiol.* **73,** 88–94 (2009).

8. Critchley, H. D., Eccles, J. & Garfinkel, S. N. Interaction between cognition, emotion, and the autonomic nervous system. *Handb. Clin. Neurol.* **117,** 59–77 (2013).

9. Critchley, H. D. & Garfinkel, S. N. The influence of physiological signals on cognition. *Curr. Opin. Behav. Sci.* **19,** 13–18 (2018).

10. Craig, A. D. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* **3,** 655–666 (2002).

11. Mayer, E. A. Gut feelings: the emerging biology of gut–brain communication. *Nat. Rev. Neurosci.* **12,** 453–466 (2011).

12. Critchley, H. D. & Harrison, N. A. Visceral influences on brain and behavior. *Neuron* **77,** 624–638 (2013).

13. Saper, C. B. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu. Rev. Neurosci.* **25,** 433–469 (2002).

14. Cannon, W. B. Organization for physiological homeostasis. *Physiol. Rev.* **9,** 399–431 (1929).

15. Park, H.-D. & Tallon-Baudry, C. The neural subjective frame: from bodily signals to perceptual consciousness. *Philos. Trans. R. Soc. B Biol. Sci.* **369,** (2014).

16. Seth, A. K. Interoceptive inference, emotion, and the embodied self. *Trends Cogn. Sci.* **17,** 565–573 (2013).

17. Richter, C. G., Babo-Rebelo, M., Schwartz, D. & Tallon-Baudry, C. Phase-amplitude coupling at the organism level: the amplitude of spontaneous alpha rhythm fluctuations varies with the phase of the infra-slow gastric basal rhythm. *Neuroimage* **146,** 951–958 (2017).

18. Zelano, C., Jiang, H., Zhou, G., Arora, N., Schuele, S., Rosenow, J. & Gottfried, J. A. Nasal respiration entrains human limbic oscillations and modulates cognitive function. *J. Neurosci.* **36,** 12448–12467 (2016).

19. Garfinkel, S. N., Minati, L., Gray, M. A., Seth, A. K., Dolan, R. J. & Critchley, H. D. Fear from the heart: sensitivity to fear stimuli depends on individual heartbeats. *J. Neurosci.* **34,** 6573–6582 (2014).

20. Pramme, L., Larra, M. F., Schächinger, H. & Frings, C. Cardiac cycle time effects on selection efficiency in vision. *Psychophysiology* **53,** 1702–1711 (2016).

21. Pramme, L., Larra, M. F., Schächinger, H. & Frings, C. Cardiac cycle time effects on mask inhibition. *Biol. Psychol.* **100,** 115–121 (2014).

22. Ohl, S., Wohltat, C., Kliegl, R., Pollatos, O. & Engbert, R. Microsaccades are coupled to heartbeat. *J. Neurosci.* **36,** 1237–1241 (2016).

23. Garfinkel, S. N. & Critchley, H. D. Threat and the body: how the heart supports fear processing. *Trends Cogn. Sci.* **20,** 34–46 (2016).

24. Critchley, H. D. & Garfinkel, S. N. Interoception and emotion. *Curr. Opin. Psychol.* **17,** 7–14 (2017).

25. Tsakiris, M. & Critchley, H. Interoception beyond homeostasis: affect, cognition and

mental health. *Philos. Trans. R. Soc. B Biol. Sci.* **371,** (2016).

26. Strigo, I. A. & Craig, A. D. (Bud). Interoception, homeostatic emotions and sympathovagal balance. *Philos. Trans. R. Soc. B Biol. Sci.* **371,** (2016).

27. Quadt, L., Critchley, H. D. & Garfinkel, S. N. The neurobiology of interoception in health and disease. *Ann. N. Y. Acad. Sci.* **1428,** 112–128 (2018).

28. Corcoran, A. W. & Hohwy, J. in *The interoceptive mind: from homeostasis to awareness.* (eds. Tsakiris, M. & De Preester, H.) **1,** 272–292 (Oxford University Press, 2018).

29. Deen, B., Pitskel, N. B. & Pelphrey, K. A. Three systems of insular functional connectivity identified with cluster analysis. *Cereb. Cortex* **21,** 1498–1506 (2011).

30. Craig, A. D. (Bud). How do you feel — now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* **10,** 59–70 (2009).

31. Seth, A. K. & Friston, K. J. Active interoceptive inference and the emotional brain. *Philos. Trans. R. Soc. B Biol. Sci.* **371,** (2016).

32. Friston, K. The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* **11,** 127–138 (2010).

33. Clark, A. Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav. Brain Sci.* **36,** 181–204 (2013).

34. Alila Medical Media. 'Regulation of blood pressure by autonomic reflex' graphic. at https://www.shutterstock.com/de/image-vector/regulation-blood-pressure-by-autonomic-reflex-97755605?src=pQTrmnOiTgH1QYNznaBl8w-1-0 (accessed: 17th June 2019).

35. Gianaros, P. J., Onyewuenyi, I. C., Sheu, L. K., Christie, I. C. & Critchley, H. D. Brain systems for baroreflex suppression during stress in humans. *Hum. Brain Mapp.* **33,** 1700–1716 (2012).

36. Birren, J. E., Cardon, P. V. & Phillips, S. L. Reaction time as a function of the cardiac cycle in young adults. *Science* **140,** 195–196 (1963).

37. Lacey, B. C. & Lacey, J. I. in *Cardiovascular psychophysiology: current issues in response mechanisms, biofeedback and methodology.*. (eds. Obrist, P. A., Black, A. H., Brener, J. & DiCara, L. V.) 538–564 (Aldine Transaction, 1974). at http://psycnet.apa.org/record/2007-11499-026 (accessed: 17th June 2019).

38. Lacey, B. C. & Lacey, J. I. Two-way communication between the heart and the brain. Significance of time within the cardiac cycle. *Am. Psychol.* **33,** 99–113 (1978).

39. Réquin, J. & Brouchon, M. Mise en évidence chez l' homme d'une fluctuation des seuils perceptifs visuels dans la période cardiaque. [Demonstration in man of a fluctuation of visual perceptive thresholds in the cardiac period]. *C. R. Seances Soc. Biol. Fil.* **158,** 1891–1894 (1964).

40. Callaway, E. & Layne, R. S. Interaction between the visual evoked response and two spontaneous biological rhythms: the EEG alpha cycle and the cardiac arousal cycle. *Ann. N. Y. Acad. Sci.* **112,** 421–431 (1964).

41. Sandman, C. A., McCanne, T. R., Kaiser, D. N. & Diamond, B. Heart rate and cardiac phase influences on visual perception. *J. Comp. Physiol. Psychol.* **91,** 189–202 (1977).

42. Stewart, J. C., France, C. R. & Suhr, J. A. The effect of cardiac cycle phase on reaction time among individuals at varying risk for hypertension. *J. Psychophysiol.* **20,** 1–8 (2006).

43. Cohen, R., Lieb, H. & Rist, F. Loudness judgments, evoked potentials, and reaction time to acoustic stimuli early and late in the cardiac cycle in chronic schizophrenics. *Psychiatry Res.* **3,** 23–29 (1980).

44. Richter, S., Schulz, A., Port, J., Blumenthal, T. D. & Schächinger, H. Cardiopulmonary baroreceptors affect reflexive startle eye blink. *Physiol. Behav.* **98,** 587–593 (2009).

45. Schulz, A., Plein, D. E., Richter, S., Blumenthal, T. D. & Schächinger, H. Cold pressor stress affects cardiac attenuation of startle. *Int. J. Psychophysiol.* **79,** 385–391 (2011).

46. Schulz, A., Matthey, J. H., Vögele, C., Schaan, V., Schächinger, H., Adler, J., Beutel, M. E. & Michal, M. Cardiac modulation of startle is altered in depersonalization-/derealization disorder: evidence for impaired brainstem representation of baro-afferent neural traffic. *Psychiatry Res.* **240,** 4–10 (2016).

47. Saxon, S. A. Detection of near threshold signals during four phases of cardiac cycle. *Ala. J. Med. Sci.* **7,** 427–430 (1970).

48. Yang, X., Jennings, J. R. & Friedman, B. H. Exteroceptive stimuli override interoceptive state in reaction time control. *Psychophysiology* **54,** 1940–1950 (2017).

49. Dworkin, B. R., Elbert, T., Rau, H., Birbaumer, N., Pauli, P., Droste, C. & Brunia, C. H.

Central effects of baroreceptor activation in humans: attenuation of skeletal reflexes and pain perception. *Proc. Natl. Acad. Sci. U. S. A.* **91,** 6329–6333 (1994).

50. Edwards, L., Ring, C., McIntyre, D. & Carroll, D. Modulation of the human nociceptive flexion reflex across the cardiac cycle. *Psychophysiology* **38,** 712–718 (2001).

51. Edwards, L., McIntyre, D., Carroll, D., Ring, C. & Martin, U. The human nociceptive flexion reflex threshold is higher during systole than diastole. *Psychophysiology* **39,** 678–681 (2002).

52. McIntyre, D., Ring, C., Edwards, L. & Carroll, D. Simple reaction time as a function of the phase of the cardiac cycle in young adults at risk for hypertension. *Psychophysiology* **45,** 333–336 (2008).

53. Wilkinson, M., McIntyre, D. & Edwards, L. Electrocutaneous pain thresholds are higher during systole than diastole. *Biol. Psychol.* **94,** 71–73 (2013).

54. Edwards, L., Inui, K., Ring, C., Wang, X. & Kakigi, R. Pain-related evoked potentials are modulated across the cardiac cycle. *Pain* **137,** 488–494 (2008).

55. Rau, H., Brody, S., Brunia, C. H., Damen, E. P. & Elbert, T. Activation of carotid baroreceptors inhibits spinal reflexes in man. *Electroencephalogr. Clin. Neurophysiol.* **89,** 328–334 (1993).

56. Droste, C., Kardos, A., Brody, S., Greenlee, M. W., Roskamm, H. & Rau, H. Baroreceptor stimulation: pain perception and sensory thresholds. *Biol. Psychol.* **37,** 101–113 (1994).

57. Al'Absi, M., France, C. R., Ring, C., France, J., Harju, A., McIntyre, D. & Wittmers, L. E. Nociception and baroreceptor stimulation in hypertension-prone men and women. *Psychophysiology* **42,** 83–91 (2005).

58. Azevedo, R. T., Garfinkel, S. N., Critchley, H. D. & Tsakiris, M. Cardiac afferent activity modulates the expression of racial stereotypes. *Nat. Commun.* **8,** 13854 (2017).

59. Azevedo, R. T., Badoud, D. & Tsakiris, M. Afferent cardiac signals modulate attentional engagement to low spatial frequency fearful faces. *Cortex* **104,** 232–240 (2018).

60. Fiacconi, C. M., Peter, E. L., Owais, S. & Köhler, S. Knowing by heart: visceral feedback shapes recognition memory judgments. *J. Exp. Psychol. Gen.* **145,** 559–572 (2016).

61. Garfinkel, S. N., Barrett, A. B., Minati, L., Dolan, R. J., Seth, A. K. & Critchley, H. D.

What the heart forgets: cardiac timing influences memory for words and is modulated by metacognition and interoceptive sensitivity. *Psychophysiology* **50,** 505–512 (2013).

62. Martins, A. Q., McIntyre, D. & Ring, C. Effects of baroreceptor stimulation on performance of the Sternberg short-term memory task: a cardiac cycle time study. *Biol. Psychol.* **103,** 262–266 (2014).

63. Pfeifer, G., Garfinkel, S. N., Gould van Praag, C. D., Sahota, K., Betka, S. & Critchley, H. D. Feedback from the heart: emotional learning and memory is controlled by cardiac cycle, interoceptive accuracy and personality. *Biol. Psychol.* **126,** 19–29 (2017).

64. Walker, B. B. & Sandman, C. A. Visual evoked potentials change as heart rate and carotid pressure change. *Psychophysiology* **19,** 520–527 (1982).

65. Gray, M. A., Taggart, P., Sutton, P. M., Groves, D., Holdright, D. R., Bradbury, D., Brull, D. & Critchley, H. D. A cortical potential reflecting cardiac function. *Proc. Natl. Acad. Sci.* **104,** 6818–6823 (2007).

66. Schandry, R. & Montoya, P. Event-related brain potentials and the processing of cardiac activity. *Biol. Psychol.* **42,** 75–85 (1996).

67. Park, H.-D., Correia, S., Ducorps, A. & Tallon-Baudry, C. Spontaneous fluctuations in neural responses to heartbeats predict visual detection. *Nat. Neurosci.* **17,** 612–618 (2014).

68. Gray, M. A., Rylander, K., Harrison, N. A., Wallin, B. G. & Critchley, H. D. Following one's heart: cardiac rhythms gate central initiation of sympathetic reflexes. *J. Neurosci.* **29,** 1817–1825 (2009).

69. Gottlieb, J. & Oudeyer, P.-Y. Towards a neuroscience of active sampling and curiosity. *Nat. Rev. Neurosci.* **19,** 758–770 (2018).

70. Mets, T., Konttinen, N. & Lyytinen, H. Shot placement within cardiac cycle in junior elite rifle shooters. *Psychol. Sport Exerc.* **8,** 169–177 (2007).

71. Morillon, B., Schroeder, C. E. & Wyart, V. Motor contributions to the temporal precision of auditory attention. *Nat. Commun.* **5,** 5255 (2014).

72. Morillon, B., Hackett, T. A., Kajikawa, Y. & Schroeder, C. E. Predictive motor control of sensory dynamics in auditory active sensing. *Curr. Opin. Neurobiol.* **31,** 230–238 (2015).

73. Schroeder, C. E., Wilson, D. A., Radman, T., Scharfman, H. & Lakatos, P. Dynamics of

active sensing and perceptual selection. *Curr. Opin. Neurobiol.* **20,** 172–176 (2010).

74. Rohenkohl, G., Cravo, A. M., Wyart, V. & Nobre, A. C. Temporal expectation improves the quality of sensory information. *J. Neurosci.* **32,** 8424–8428 (2012).

75. Morillon, B. & Baillet, S. Motor origin of temporal predictions in auditory attention. *Proc. Natl. Acad. Sci.* **114,** E8913–E8921 (2017).

76. Wessa, M., Kanske, P., Neumeister, P., Bode, K., Heissler, J. & Schönfelder, S. EmoPics: subjektive und psychophysiologische Evaluationen neuen Bildmaterials für die klinisch-bio-psychologische Forschung. [Subjective and psycholophysiological evaluation of a new picture set for clinical biopsychological reserch]. *Z. Klin. Psychol. Psychother.* **1,** S11–S77 (2010).

77. Open Science Collaboration. Estimating the reproducibility of psychological science. *Science* **349,** aac4716–aac4716 (2015).

78. Foster, E. D. & Deardorff, A. Open Science Framework (OSF). *J. Med. Libr. Assoc.* **105,** 203–206 (2017).

79. Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. The influence of cardiac signals on perception and behaviour (INCASI). (2017). at https://osf.io/5z8rx/ (accessed: 17th June 2019).

80. Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. SKunzendorf/0303_INCASI. (2018). at https://github.com/SKunzendorf/0303_INCASI (accessed: 17th June 2019).

81. Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. Active vision varies across the cardiac cycle. *bioRxiv* 283838 (2018). at http://biorxiv.org/content/early/2018/03/18/283838.abstract (accessed: 17th June 2019).

82. Tukey, J. W. *Exploratory data analysis*. (Addison Wesley, 1977).

83. Bohdan Burmich. 'Female' icon. at https://thenounproject.com/term/female/2213228/ (accessed: 17th June 2019).

84. Stefan Kovac. 'pointing' icon. at https://thenounproject.com/term/pointing/162367/ (accessed: 17th June 2019).

85. The Noun Project - icons for everything. at https://thenounproject.com/ (accessed: 17th

June 2019).

86. Tarvainen, M. P., Niskanen, J.-P., Lipponen, J. A., Ranta-aho, P. O. & Karjalainen, P. A. Kubios HRV – Heart rate variability analysis software. *Comput. Methods Programs Biomed.* **113,** 210–220 (2014).

87. Kubios - Heart rate variability (HRV) analysis software for scientific research and professional use. at https://www.kubios.com/ (accessed: 17th June 2019).

88. RStudio Team. RStudio: integrated development environment for R. (2016). at http://www.rstudio.com/ (accessed: 17th June 2019).

89. Pikovsky, A., Rosenblum, M. & Kurths, J. *Synchronization: a universal concept in nonlinear sciences*. (Cambridge University Press, 2001). at http://www.fulviofrisone.com/attachments/article/412/synchronization an universal concept in nonlinear sciences.pdf (accessed: 17th June 2019).

90. Schäfer, G., Rosenblum, M. G., Kurths, J. & Abel, H. H. Heartbeat synchronized with ventilation. *Nature* **392,** 239–240 (1998).

91. Pewsey, A., Neuhäuser, M. & Ruxton, G. D. *Circular statistics in R*. (Oxford University Press, 2013). at https://global.oup.com/academic/product/circular-statistics-in-r-9780199671137?cc=de&lang=en& (accessed: 17th June 2019).

92. Boudoulas, H., Rittgers, S. E., Lewis, R. P., Leier, C. V & Weissler, A. M. Changes in diastolic time with various pharmacologic agents: implication for myocardial perfusion. *Circulation* **60,** 164–169 (1979).

93. Levick, J. R. *An introduction to cardiovascular physiology*. (Hodder Education Publishers, 2010).

94. Lewis, R. P., Rittogers, S. E., Froester, W. F. & Boudoulas, H. A critical review of the systolic time intervals. *Circulation* **56,** 146–158 (1977).

95. Pappano, A. J. & Wier, W. G. *Cardiovascular physiology*. (Elsevier/Mosby, 2013). at https://www.sciencedirect.com/book/9780323086974/cardiovascular-physiology (accessed: 17th June 2019).

96. Weissler, A. M., Harris, W. S. & Schoenfeld, C. D. Systolic time intervals in heart failure in man. *Circulation* **37,** 149–159 (1968).

97. Lombard, W. P. & Cope, O. M. The duration of the systole of the left ventricle of man. *Am. J. Physiol. Content* **77,** 263–295 (1926).

98. Wallace, A. G., Mitchell, J. H., Skinner, N. S. & Sarnoff, S. J. Duration of the phases of left ventricular systole. *Circ. Res.* **12,** 611–619 (1963).

99. Fridericia, L. S. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. *Ann. Noninvasive Electrocardiol.* **8,** 343–351 (2003).

100. Angell James, J. E. The effects of altering mean pressure, pulse pressure and pulse frequency on the impulse activity in baroreceptor fibres from the aortic arch and right subclavian artery in the rabbit. *J. Physiol.* **214,** 65–88 (1971).

101. Coleridge, H. M., Coleridge, J. C., Poore, E. R., Roberts, A. M. & Schultz, H. D. Aortic wall properties and baroreceptor behaviour at normal arterial pressure and in acute hypertensive resetting in dogs. *J. Physiol.* **350,** 309–326 (1984).

102. Weissler, A. M., Harris, W. S. & Schoenfeld, C. D. Bedside technics for the evaluation of ventricular function in man. *Am. J. Cardiol.* **23,** 577–583 (1969).

103. Gill, H. & Hoffmann, A. The timing of onset of mechanical systole and diastole in reference to the QRS-T complex: a study to determine performance criteria for a non-invasive diastolic timed vibration massage system in treatment of potentially unstable cardiac disorders. *Cardiovasc. Eng.* **10,** 235–245 (2010).

104. Hamann, S. Cognitive and neural mechanisms of emotional memory. *Trends Cogn. Sci.* **5,** 394–400 (2001).

105. Kensinger, E. A. Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *J. Neurosci.* **26,** 2564–2570 (2006).

106. Kensinger, E. A. & Corkin, S. Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words? *Mem. Cognit.* **31,** 1169–1180 (2003).

107. LaBar, K. S. & Cabeza, R. Cognitive neuroscience of emotional memory. *Nat. Rev. Neurosci.* **7,** 54–64 (2006).

108. Salomon, R., Ronchi, R., Dönz, J., Bello-Ruiz, J., Herbelin, B., Martet, R., Faivre, N.,

Schaller, K. & Blanke, O. The insula mediates access to awareness of visual stimuli presented synchronously to the heartbeat. *J. Neurosci.* **36,** 5115–5127 (2016).

109. Pfeiffer, C. & De Lucia, M. Cardio-audio synchronization drives neural surprise response. *Sci. Rep.* **7,** 14842 (2017).

110. Gentsch, A., Sel, A., Marshall, A. C. & Schütz-Bosbach, S. Affective interoceptive inference: evidence from heart-beat evoked brain potentials. *Hum. Brain Mapp.* **40,** 20–33 (2019).

111. Marshall, A. C., Gentsch, A., Schröder, L. & Schütz-Bosbach, S. Cardiac interoceptive learning is modulated by emotional valence perceived from facial expressions. *Soc. Cogn. Affect. Neurosci.* **13,** 677–686 (2018).

112. Edwards, L., Ring, C., McIntyre, D., Carroll, D. & Martin, U. Psychomotor speed in hypertension: effects of reaction time components, stimulus modality, and phase of the cardiac cycle. *Psychophysiology* **44,** 459–468 (2007).

113. Schulz, A., Reichert, C. F., Richter, S., Lass-Hennemann, J., Blumenthal, T. D. & Schächinger, H. Cardiac modulation of startle: effects on eye blink and higher cognitive processing. *Brain Cogn.* **71,** 265–271 (2009).

114. Pezzulo, G., Iodice, P., Barca, L., Chausse, P., Monceau, S. & Mermillod, M. Increased heart rate after exercise facilitates the processing of fearful but not disgusted faces. *Sci. Rep.* **8,** 398 (2018).

115. Farb, N., Kerr, C., Mehling, W. E. & Pollatos, O., eds. *Interoception, contemplative practice, and health*. (Frontiers Media, 2017). at http://www.frontiersin.org/books/Interoception_Contemplative_Practice_and_Health/1116 (accessed: 17th June 2019).

116. Herbert, B. M. & Pollatos, O. Attenuated interoceptive sensitivity in overweight and obese individuals. *Eat. Behav.* **15,** 445–448 (2014).

117. Pollatos, O., Kurz, A.-L., Albrecht, J., Schreder, T., Kleemann, A. M., Schöpf, V., Kopietz, R., Wiesmann, M. & Schandry, R. Reduced perception of bodily signals in anorexia nervosa. *Eat. Behav.* **9,** 381–388 (2008).

118. Verdejo-Garcia, A., Clark, L. & Dunn, B. D. The role of interoception in addiction: a critical review. *Neurosci. Biobehav. Rev.* **36,** 1857–1869 (2012).

119. Paulus, M. P. & Stein, M. B. Interoception in anxiety and depression. *Brain Struct. Funct.* **214,** 451–463 (2010).

120. Stern, E. R. Neural circuitry of interoception: new insights into anxiety and obsessive-compulsive disorders. *Curr. Treat. Options Psychiatry* **1,** 235–247 (2014).

121. Garfinkel, S. N., Tiley, C., O'Keeffe, S., Harrison, N. A., Seth, A. K. & Critchley, H. D. Discrepancies between dimensions of interoception in autism: implications for emotion and anxiety. *Biol. Psychol.* **114,** 117–126 (2016).

122. Schaefer, M., Egloff, B. & Witthöft, M. Is interoceptive awareness really altered in somatoform disorders? Testing competing theories with two paradigms of heartbeat perception. *J. Abnorm. Psychol.* **121,** 719–724 (2012).

123. Ricciardi, L., Demartini, B., Crucianelli, L., Krahé, C., Edwards, M. J. & Fotopoulou, A. Interoceptive awareness in patients with functional neurological symptoms. *Biol. Psychol.* **113,** 68–74 (2016).

124. Ricciardi, L., Ferrazzano, G., Demartini, B., Morgante, F., Erro, R., Ganos, C., Bhatia, K. P., Berardelli, A. & Edwards, M. Know thyself: exploring interoceptive sensitivity in Parkinson's disease. *J. Neurol. Sci.* **364,** 110–115 (2016).

125. Couto, B., Adolfi, F., Sedeño, L., Salles, A., Canales-Johnson, A., Alvarez-Abut, P., Garcia-Cordero, I., Pietto, M., Bekinschtein, T., Sigman, M., Manes, F. & Ibanez, A. Disentangling interoception: insights from focal strokes affecting the perception of external and internal milieus. *Front. Psychol.* **6,** 503 (2015).

126. García-Cordero, I., Sedeño, L., de la Fuente, L., Slachevsky, A., Forno, G., Klein, F., Lillo, P., Ferrari, J., Rodriguez, C., Bustin, J., Torralva, T., Baez, S., Yoris, A., Esteves, S., Melloni, M., Salamone, P., Huepe, D., Manes, F., García, A. M. & Ibañez, A. Feeling, learning from and being aware of inner states: interoceptive dimensions in neurodegeneration and stroke. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **371,** 20160006 (2016).

127. Di Lernia, D., Serino, S. & Riva, G. Pain in the body. Altered interoception in chronic pain conditions: a systematic review. *Neurosci. Biobehav. Rev.* **71,** 328–341 (2016).

128. Salamone, P. C., Esteves, S., Sinay, V. J., García-Cordero, I., Abrevaya, S., Couto, B., Adolfi, F., Martorell, M., Petroni, A., Yoris, A., Torquati, K., Alifano, F., Legaz, A.,

Cassará, F. P., Bruno, D., Kemp, A. H., Herrera, E., García, A. M., Ibáñez, A. & Sedeño, L. Altered neural signatures of interoception in multiple sclerosis. *Hum. Brain Mapp.* **39,** 4743–4754 (2018).

129. Yoris, A., Abrevaya, S., Esteves, S., Salamone, P., Lori, N., Martorell, M., Legaz, A., Alifano, F., Petroni, A., Sánchez, R., Sedeño, L., García, A. M. & Ibáñez, A. Multilevel convergence of interoceptive impairments in hypertension: new evidence of disrupted body-brain interactions. *Hum. Brain Mapp.* **39,** 1563–1581 (2018).

130. Schulz, S. M. Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **371,** 20160018 (2016).

131. Watkins, L. L., Koch, G. G., Sherwood, A., Blumenthal, J. A., Davidson, J. R. T., O'Connor, C. & Sketch, M. H. Association of anxiety and depression with all-cause mortality in individuals with coronary heart disease. *J. Am. Heart Assoc.* **2,** e000068 (2013).

132. Lichtman, J. H., Bigger, J. T., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lespérance, F., Mark, D. B., Sheps, D. S., Taylor, C. B. & Froelicher, E. S. Depression and coronary heart disease. *Circulation* **118,** 1768–1775 (2008).

133. Lacey, B. C. & Lacey, J. I. Change in heart period: a function of sensorimotor event timing within the cardiac cycle. *Physiol. Psychol.* **5,** 383–393 (1977).

134. McIntyre, D., Edwards, L., Ring, C., Parvin, B. & Carroll, D. Systolic inhibition of nociceptive responding is moderated by arousal. *Psychophysiology* **43,** 314–319 (2006).

135. Waselius, T., Wikgren, J., Halkola, H., Penttonen, M. & Nokia, M. S. Learning by heart: cardiac cycle reveals an effective time window for learning. *J. Neurophysiol.* **120,** 830–838 (2018).

136. Konttinen, N., Mets, T., Lyytinen, H. & Paananen, M. Timing of triggering in relation to the cardiac cycle in nonelite rifle shooters. *Res. Q. Exerc. Sport* **74,** 395–400 (2003).

137. Edwards, L., Ring, C., McIntyre, D., Winer, J. B. & Martin, U. Sensory detection thresholds are modulated across the cardiac cycle: evidence that cutaneous sensibility is greatest for systolic stimulation. *Psychophysiology* **46,** 252–256 (2009).

138. Martins, A. Q., Ring, C., McIntyre, D., Edwards, L. & Martin, U. Effects of unpredictable

stimulation on pain and nociception across the cardiac cycle. *Pain* **147,** 84–90 (2009).

139. Gray, M. A., Beacher, F. D., Minati, L., Nagai, Y., Kemp, A. H., Harrison, N. A. & Critchley, H. D. Emotional appraisal is influenced by cardiac afferent information. *Emotion* **12,** 180–191 (2012).

140. Galvez-Pol, A., McConnell, R. & Kilner, J. Voluntary visual search is modulated by the cardiac cycle. *bioRxiv* 405902 (2018). at http://biorxiv.org/content/early/2018/09/03/405902.abstract (accessed: 17th June 2019).

141. Saari, M. J. & Pappas, B. A. Cardiac cycle phase and movement and reaction times. *Percept. Mot. Skills* **42,** 767–770 (1976).

142. McIntyre, D., Ring, C., Hamer, M. & Carroll, D. Effects of arterial and cardiopulmonary baroreceptor activation on simple and choice reaction times. *Psychophysiology* **44,** 874–879 (2007).

143. Thompson, L. W. & Botwinick, J. Stimulation in different phases of the cardiac cycle and reaction time. *Psychophysiology* **7,** 57–65 (1970).

144. Delfini, L. F. & Campos, J. J. Signal Detection and the 'cardiac arousal cycle'. *Psychophysiology* **9,** 484–491 (1972).

145. Elliott, R. & Graf, V. Visual sensitivity as a function of phase of cardiac cycle. *Psychophysiology* **9,** 357–361 (1972).

146. Salzman, L. F. & Jaques, N. Heart rate and cardiac cycle effects on reaction time. *Percept. Mot. Skills* **42,** 1315–1321 (1976).

147. Jennings, J. R. & Wood, C. C. Cardiac cycle time effects on performance, phasic cardiac responses, and their intercorrelation in choice reaction time. *Psychophysiology* **14,** 297–307 (1977).

148. Weisz, J. & Ádám, G. The influence of cardiac phase on reaction time depending on heart period length and on stimulus and response laterality. *Psychobiology* **24,** 169–175 (1996).

149. Kelsey, R. M. & Guethlein, W. An evaluation of the ensemble averaged impedance cardiogram. *Psychophysiology* **27,** 24–33 (1990).

150. Lozano, D. L., Norman, G., Knox, D., Wood, B. L., Miller, B. D., Emery, C. F. & Berntson, G. G. Where to B in dZ/dt. *Psychophysiology* **44,** 113–119 (2007).

151. Ring, C. & Brener, J. The temporal locations of heartbeat sensations. *Psychophysiology* **29,** 535–545 (1992).

152. Ring, C., Liu, X. & Brener, J. Cardiac stimulus intensity and heartbeat detection: effect of tilt-induced changes in stroke volume. *Psychophysiology* **31,** 553–564 (1994).

153. Gabriel, M. & Seller, H. Interaction of baroreceptor afferents from carotid sinus and aorta at the nucleus tractus solitarii. *Pflugers Arch.* **318,** 7–20 (1970).

154. Seller, H. in *Baroreceptor reflexes: integrative functions and clinical aspects.* (eds. Persson, P. B. & Kirchheim, H. R.) 45–74 (Springer, 1991). doi:10.1007/978-3-642-76366-3_3

155. Angell James, J. E. & Lumley, J. S. The effects of carotid endarterectomy on the mechanical properties of the carotid sinus and carotid sinus nerve activity in atherosclerotic patients. *Br. J. Surg.* **61,** 805–810 (1974).

156. Dembowsky, K. & Seller, H. in *From the heart to the brain: the psychophysiology of circulation–brain interaction.* (eds. Vaitl, D. & Schandry, R.) 35–60 (Peter Lang, 1995).

157. Lambertz, M. & Langhorst, P. Cardiac rhythmic patterns in neuronal activity are related to the firing rate of the neurons: I. brainstem reticular neurons of dogs. *J. Auton. Nerv. Syst.* **51,** 153–163 (1995).

158. Fagius, J. & Wallin, B. G. Sympathetic reflex latencies and conduction velocities in normal man. *J. Neurol. Sci.* **47,** 433–448 (1980).

Eidesstattliche Versicherung

„Ich, Stella Kunzendorf, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „*The psychophysiology of heart-brain-interactions: how active information sampling is modulated across the cardiac cycle*“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

_____ _____

Datum Unterschrift

Ausführliche Anteilserklärung

Publikation:

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. Active information sampling varies across the cardiac cycle. *Psychophysiology* **56,** e13322 (2019).

Beitrag im Einzelnen:

In der vorliegenden Arbeit wurde der Zusammenhang zwischen aktivem *Information Sampling* und dem Herzzyklus mittels eines psychophysiologischen Studiendesigns untersucht. Mein Arbeitsanteil daran war wie folgt:

- Die Hypothesen sowie das experimentelle Design der vorliegenden Studie wurden in Zusammenarbeit mit den Ko-Autoren von mir anteilig entwickelt.
- Die online zugängliche Präregistrierung der Studie (mitsamt Hypothesen und Studienprotokoll) wurde komplett von mir verfasst und vor Beginn der Datenerhebung auf *Open Science Framework* hochgeladen (https://osf.io/5z8rx/).
- Ich war größtenteils an der Planung der praktischen Umsetzung des Experiments beteiligt, d.h., ich verfasste zu größten Anteilen den Ethikantrag, stellte größtenteils das visuelle Stimulusmaterial zusammen und half anteilig bei der Implementierung der Experimentskripte (programmiert durch Ko-Autor Sven Ohl) mittels PsychToolbox. Ich bereitete größtenteils alle notwendigen Schritte für die experimentelle Durchführung vor, d.h. Verfassung der Probandeninformation und -aufklärung, Implementierung des *Heartbeat Perception Tasks* und Organisation des Versuchsablaufs. Darüber hinaus implementierte ich komplett eigenständig die EKG-Messung mithilfe des ActiveTwo AD Amplifiers im EEG-Labor der Berlin School of Mind und Brain.
- Ich führte komplett die zur Testung des Studiendesigns notwendigen Pilotstudien durch. Zudem war ich komplett zuständig für die praktische Durchführung der Studie, d.h., Probandenrekrutierung, Probandenaufklärung, sowie Datenerhebung erfolgten komplett in meiner Eigenarbeit.
- Die Aufarbeitung der Primärdaten mittels EEGLAB (Matlab) und Kubios (http://kubios.uef.fi/) erfolgte, nach Rücksprache mit den Ko-Autoren, komplett durch mich.
- Ich führte größtenteils die statistische Datenauswertung und Programmierung der Auswertungsskripte durch, d.h., in regelmäßiger Absprache und unterstützt durch meine Ko-

Autoren entwarf ich die zweigleisige (zirkuläre und binäre) Herangehensweise zur Untersuchung des Probandenverhaltens (1. *Encoding*, 2. *Recognition*) in Bezug auf deren Herzzyklus. Der Ansatz zur probandenspezifischen Individualisierung der Herzphasen (d.h. automatisierte Detektion der individuellen Systole auf Basis des EKGs) im Rahmen eines *Cardiac Cycle*-Studiendesigns wurde, literaturbasiert, komplett durch mich eingeführt und umgesetzt. Mit Ausnahme des *Bootstrapping*-Ansatzes der zirkulären Analyse, welcher (wie in der Publikation beschrieben) aus einer früheren Studie von Ohl et al. angepasst wurde, programmierte ich die Skripte komplett selbst in R/RStudio.

- Ich führte die aus den Analysen entstehende graphische Aufarbeitung der Methoden und Ergebnisse (d.h. die Konzeption und Erstellung aller Abbildungen und Tabellen der Publikation) mit Feedback der Ko-Autoren aber komplett eigenständig durch.
- Für die *Open Access*-Veröffentlichung der Auswertungsskripte auf GitHub (https://github.com/SKunzendorf/0303_INCASI) (überprüft durch die Ko-Autoren) sowie des Pre-prints auf bioRxiv (http://biorxiv.org/content/early/2018/03/18/283838.abstract) war ich komplett selbst zuständig.
- Als Erstautorin der Publikation führte ich komplett eigenständig eine ausführliche Recherche zur bisherigen Studienlage durch und schrieb zu größten Anteilen das Manuskript, d.h., ich verfasste den Text, welcher im Anschluss von meinen Ko-Autoren überarbeitet wurde. Den Review Prozess bearbeitete ich größtenteils selbst.
- Ich erstellte den Manteltext samt aller Abbildungen und Tabellen komplett eigenständig.

_____

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

_____

Unterschrift des Doktoranden/der Doktorandin

Auszug aus der Journal Summary List (ISI Web of Knowledge[SM])

Im Fachbereich Psychophysiologie („*Biological Psychology*“) ist das Journal *„Psychophysiology“* im Jahr 2017 an dritter Stelle von 14 der nach Impact Factor sortierten Journale (Rangfolge siehe unten) gelistet. Das Journal verfügt über einen Impact Factor von 3.118 und einem Eigenfaktor von 0.012340. Damit gehört das Journal nach Charité-Vorgaben zu den „*Topjournals*“.

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE, SSCI

Selected Categories: **“PSYCHOLOGY, BIOLOGICAL”** Selected Category Scheme: WoS

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	BEHAVIORAL AND BRAIN SCIENCES	8,900	15.071	0.010130
2	EVOLUTION AND HUMAN BEHAVIOR	4,043	3.623	0.006730
3	PSYCHOPHYSIOLOGY	13,301	3.118	0.012340
4	BIOLOGICAL PSYCHOLOGY	9,081	2.891	0.013510
5	INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY	7,496	2.868	0.010950
6	PHYSIOLOGY & BEHAVIOR	20,530	2.517	0.021730
7	EXPERIMENTAL AND CLINICAL PSYCHOPHARMACOLOGY	2,454	2.354	0.003290
8	JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR	3,035	2.010	0.001790
9	JOURNAL OF EXPERIMENTAL PSYCHOLOGY-ANIMAL LEARNING AND COGNITION	2,061	1.861	0.001380
10	BEHAVIOURAL PROCESSES	4,337	1.555	0.006980
11	LEARNING & BEHAVIOR	814	1.434	0.001220
12	Integrative Psychological and Behavioral Science	484	1.295	0.000760
13	JOURNAL OF PSYCHOPHYSIOLOGY	679	0.917	0.000440
14	LEARNING AND MOTIVATION	786	0.660	0.000580

Quelle: **ISI Web of Knowledge[SM]**, (https://intranet.charite.de/medbib/zugangsdaten_fuer_zeitschriften/; Stand: 13. März 2019)

Publikation

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. Active information sampling varies across the cardiac cycle. *Psychophysiology* **56,** e13322 (2019). https://doi.org/10.1111/psyp.13322

Open Access Preprint auf bioRxiv: https://www.biorxiv.org/content/10.1101/283838v2

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Zeitschriftenbeiträge (2)

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. Active information sampling varies across the cardiac cycle. *Psychophysiology* **56,** e13322 (2019). Impact Factor (2017): 3.118

Babayan, A., Erbey, M., Kumral, D., Reinelt, J. D., Reiter, A. M. F., Röbbig, J., Schaare, H. L., Uhlig, M., Anwander, A., Bazin, P.-L., Horstmann, A., Lampe, L., Nikulin, V. V., Okon-Singer, H., Preusser, S., Pampel, A., Rohr, C. S., Sacher, J., Thöne-Otto, A., Trapp, S., Nierhaus, T., Altmann, D., Arelin, K., Blöchl, M., Bongartz, E., Breig, P., Cesnaite, E., Chen, S., Cozatl, R., Czerwonatis, S., Dambrauskaite, G., Dreyer, M., Enders, J., Engelhardt, M., Fischer, M. M., Forschack, N., Golchert, J., Golz, L., Guran, C. A., Hedrich, S., Hentschel, N., Hoffmann, D. I., Huntenburg, J. M., Jost, R., Kosatschek, A., Kunzendorf, S., Lammers, H., Lauckner, M. E., Mahjoory, K., Kanaan, A. S., Mendes, N., Menger, R., Morino, E., Näthe, K., Neubauer, J., Noyan, H., Oligschläger, S., Panczyszyn-Trzewik, P., Poehlchen, D., Putzke, N., Roski, S., Schaller, M.-C., Schieferbein, A., Schlaak, B., Schmidt, R., Gorgolewski, K. J., Schmidt, H. M., Schrimpf, A., Stasch, S., Voss, M., Wiedemann, A., Margulies, D. S., Gaebler, M. & Villringer, A. A mind-brain-body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults. *Sci. Data* **6,** 180308 (2019).
Impact Factor (2017): 5.305

Posterpräsentationen auf Konferenzen (4)

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. Active information sampling varies across the cardiac cycle. Presented at: *Jährliche Konferenz der Neurologie, MPI CBS, Leipzig* (2018).

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. The influence of cardiac signals on visual sampling and memory performance. Presented at: *European Conference of Visual Perception, Berlin* (2017).

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. The influence of cardiac signals on visual sampling and memory performance. Presented at: *Summer School „The Social Brain: Embodiment & Culture"; Aegina, Greece; Organisatoren UCL, London, und BSMB, Berlin* (2017).

Kunzendorf, S., Klotzsche, F., Akbal, M., Villringer, A., Ohl, S. & Gaebler, M. The influence of cardiac signals on visual sampling and memory performance. Presented at: *Mind-Brain-Body Symposium, BSMB, Berlin* (2017).

Danksagung

Ich möchte mich hier bei meinem Betreuer Dr. Michael Gaebler bedanken, der mich für die psychophysiologische Wissenschaft begeistern konnte, für die geteilte Neugier und die zahlreichen anregenden Gespräche, seine fortwährend herzlich offene und tatkräftige Unterstützung, sowie sein Vertrauen und den Freiraum für Eigeninitiative und das Ausprobieren neuer Ansätze und Ideen.

Ganz besonders danken möchte ich auch Prof. Dr. Arno Villringer, für sein bereicherndes Hinterfragen, seinen Weitblick und seine umfassende Förderung, Dr. Sven Ohl, für seine wertvollen Beiträge und Denkanstöße zur methodischen Herangehensweise, Dr. Birol Taskin für seine hilfreichen Inputs zur Herzphysiologie und deren graphischer Veranschaulichung, sowie Felix Klotzsche, für das gemeinsame Durchstehen vieler praktischer technischer Knobeleien und seine hilfsbereite, aufmunternde Gesellschaft während der gesamten Zeit meiner Arbeit.

Darüber hinaus gilt mein Dank den Mitgliedern des MindBrainBody Instituts—Esra Al, Deniz Kumral, Miray Erbey, Mert Akbal, Ahmed Khalil, Johanna Grosse Rueschkamp, Fivos Iliopoulos, Firat Sansal, Simon Hofmann, Lina Schaare, Anahit Babayan, Janis Reinelt und Mauricio Martins. Dank ihnen habe ich erfahren, wie viel Freude es bereitet, in regem Austausch, durch das Einbringen unterschiedlicher Interessen und Blickwinkel und in achtsamem Miteinander wissenschaftlich zu arbeiten. Ich schätze es zutiefst während dieser intensiven Zeit Teil eines solch vielfältigen, dynamischen Teams gewesen zu sein, das mich auf dem Weg zur Fertigstellung meiner Arbeit von vielen Seiten bereichert hat.

Zuletzt möchte ich meinen Freunden und meiner Familie danken, meinen Eltern, meiner Schwester und insbesondere meiner Patentante, für ihre Unterstützung mit Herz und Kopf und ihre stets ermutigenden Worte, meinen eigenen Weg zu gehen.