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Author for correspondence:
Stefan M. Schulz
e-mail: schulz@psychologie.uni-wuerzburg.de

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Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis

Stefan M. Schulz[1,2]

[1]Department of Psychology I, University of Würzburg, Marcusstrasse 9-11, 97070 Würzburg, Germany
[2]Comprehensive Heart Failure Center Würzburg, University Hospital Würzburg, Straubmühlweg 2a, 97078 Würzburg, Germany

SMS, 0000-0003-0550-2440

Interoception is the ability to perceive one's internal body state including visceral sensations. Heart-focused interoception has received particular attention, in part due to a readily available task for behavioural assessment, but also due to accumulating evidence for a significant role in emotional experience, decision-making and clinical disorders such as anxiety and depression. Improved understanding of the underlying neural correlates is important to promote development of anatomical-functional models and suitable intervention strategies. In the present meta-analysis, nine studies reporting neural activity associated with *interoceptive attentiveness* (i.e. focused attention to a particular interoceptive signal for a given time interval) to one's heartbeat were submitted to a multilevel kernel density analysis. The findings corroborated an extended network associated with heart-focused *interoceptive attentiveness* including the posterior right and left insula, right claustrum, precentral gyrus and medial frontal gyrus. Right-hemispheric dominance emphasizes non-verbal information processing with the posterior insula presumably serving as the major gateway for cardioception. Prefrontal neural activity may reflect both top-down attention deployment and processing of feed-forward cardioceptive information, possibly orchestrated via the claustrum.

This article is part of the themed issue 'Interoception beyond homeostasis: affect, cognition and mental health'.

1. Introduction

Interoception is the ability to perceive the state of one's internal body including the viscera as opposed to exteroception, which is perceiving stimuli of the external environment, and proprioception, which is perceiving posture and position of one's own body parts [1]. This article follows this definition, although it should be noted that others have defined interoception as including both proprio- and viscероception (i.e. sensing one's inner organs) [2].

The idea that central nervous system representations of psychophysiology comprise a basis for emotional feelings and may guide behaviour dates back to the James–Lange theory [3]. While Lange focused on cardiac reactivity James considered any autonomic function as a possible source of emotion. Current neurobiological research has revived this perspective, arguing that emotion may be a kind of interoceptive inference. From that point of view, emotions emerge from active analysis of physiological reactivity [4].

Recently, interoception has been conceptually refined by differentiating dimensions of interoception [5,6]. Firstly, *interoceptive sensibility* may be assessed via self-report of subjective sensitivity to interoceptive signals, specifically targeting self-reported belief in interoceptive aptitude. Examples are the awareness sub-scale of the body perception questionnaire (BPQ) [7] or the multidimensional assessment of interoceptive awareness questionnaire (MAIA) [8], but also average confidence ratings regarding one's interoceptive sensitivity may be used. Secondly, *interoceptive sensitivity* may be operationalized with behavioural tests

of *interoceptive accuracy*, for example with the commonly used *heartbeat detection task* [9]. Maybe the easy implementation but also the possibility to judge individual performance against an absolute and objective reference score obtained from the electrocardiogram has fostered the wide application of this task in empirical research on interoception. Thirdly, *metacognitive awareness*, which may be assessed with ratings of confidence regarding one's objective *interoceptive accuracy*, is considered to provide insight into one's interoceptive aptitude. First evidence suggests that these dimensions are rather independent [6]. Therefore, it appears necessary to consider which of these aspects are relevant in a particular interoceptive task (IT) in order to identify brain correlates specifically associated with these dimensions.

High heart-focused *interoceptive accuracy/sensitivity* has been associated with increased emotional intensity [10], has been shown to support memory [11,12] and adaptive decision-making [13–15], and has predicted increased emotional intensity and reactivity to emotional pictures [16].[1] Furthermore, it has been suggested that mood and anxiety disorders may root in issues related to interoception [17]. This view is supported by accumulating evidence in the domain of anxiety disorders [18] and depression [19,20]. For patients with panic disorder, interoceptive cues may be threatening or confusing. This could explain why high heart-focused *interoceptive accuracy/sensitivity* was associated with impaired intuitive decision-making in these patients [21].

The insula has been suggested as the primary neural correlate of interoception [22]. Peripheral nervous system afferents project contralateral information regarding somatic homeostasis to posterior granular and mid-dysgranular regions of the insula [23] via lamina I and the ventromedial nucleus (sympathetic afferents) and via the nucleus of the solitary tract and the ventromedial thalamic nucleus for sympathetic afferents [22]. At this level, an embodied representation of interoception is expected [24]. The anterior insula is interconnected with prefrontal cortical (e.g. anterior cingulate and orbitofronal cortex) and limbic structures (e.g. amygdala), and has been linked to tasks requiring cognitive control for identifying a signal against a noisy background [25]. Neural activity in the anterior insula may also reflect uncertainty and valence evaluation associated with such tasks [26]. Hence, on an axis from caudal to rostral, interoceptive information is thought to be represented increasingly abstractly, with the anterior agranular insula as a centre for interoceptive awareness [22,25], relating emotional salience and valence to adjacent structures such as the amygdala, anterior cingulate cortex, the orbitofrontal cortex and the ventral striatum [27,28]. Others have differentiated between dorsal and ventral anterior insula, being associated with cognitive and emotional processing, respectively [24].

While much of this knowledge comes from animal research, this view is also supported by research on humans. Meta-analyses of neural activity assessed with magnetic resonance imaging have parcellated the insula into various functional domains, suggesting a particular role of the mid-insula for interoception [29,30]. Concurrently, interoception of respiratory distress, thirst, heartbeat, as well as distension of the oesophagus, stomach, bladder or rectum have been associated with increased insula activation [22,31]. Damage to the insula by contrast hampers interoception [32].

From the view that interoception mediates between the perception of somatic states and domains that are highly relevant for successful coping with the challenges of everyday life, such as intuition, emotion and (decision) behaviour, it follows that improved understanding of the underlying functional anatomy may aid understanding and interventions for a wide array of issues including maladaptive response to somatic cues in panic disorder [21,33], somatoform disorder [34,35], dissociative disorders [36–38] or eating disorders [39,40]. Maladaptive stress reactivity in terms of cognitive and emotional response to issues in processing interoceptive information may contribute to poor somatic health [41].

Despite these interesting perspectives and detailed knowledge about wiring and functional organization of the insula, only a few studies have in fact examined brain activation associated with tasks involving interoception in humans, although functional magnetic resonance imaging (fMRI) serves as a suitable tool with particular advantages regarding spatial resolution and the possibility to locate sub-cortical brain correlates. Therefore, it appears desirable to increase our knowledge about the location of functional correlates of interoception and the potential involvement of adjacent regions.

However, recent findings indicate that the functional specificity of insular subdivisions clearly goes beyond the commonly accepted tripartite division into dorsal anterior, ventral anterior and posterior insula [42]. Another study has examined brain correlates of modality-specific physiological activation [43]. The findings further support the notion that afferent information from different organs is processed in specific subdivisions of the insula, respectively. Considering the high functional heterogeneity of the insula [42], current models could be improved by considering modality-specific brain correlates of interoception. Perhaps, vulnerability with regards to organ-specific information processing could explain comorbidity between somatic disease and psycho-social issues. For example, issues in heart-focused interoception may reveal a neural basis for the high comorbidity between chronic heart failure and affective disorders such as anxiety and depression [44,45].

Altogether, it appears promising for advancing current human functional-anatomical models of interoception to identify brain areas (i) specifically associated with separate modalities such as heart-focused interoception and (ii) to examine closely which particular aspects or dimensions of interoception are reflected in a particular experimental operationalization (i.e. IT).

Therefore, I have performed the first meta-analysis on studies reporting blood-oxygen-level dependent (BOLD) fMRI activation in brain areas associated with the specific modality of heart-focused interoception (i.e. cardioception). In order to optimize conceptual clarity of this approach, I have evaluated characteristics of the interoceptive and respective control tasks based on the model suggested by Garfinkel and co-workers [5,6].

2. Material and methods

(a) Study selection

In order to identify fMRI studies concerned with brain activity related to interoception, a literature search with the search-term '(interoception or cardioception) and (fMRI or fMRT or 'brain activation')' was conducted with no initial restrictions regarding type of publication or time-frame in the following databases (no. of matching entries in parentheses)[2]: WorldCat (520), Web of Science (172), PubMed (135), PsycNet (63), pubPsych (32)

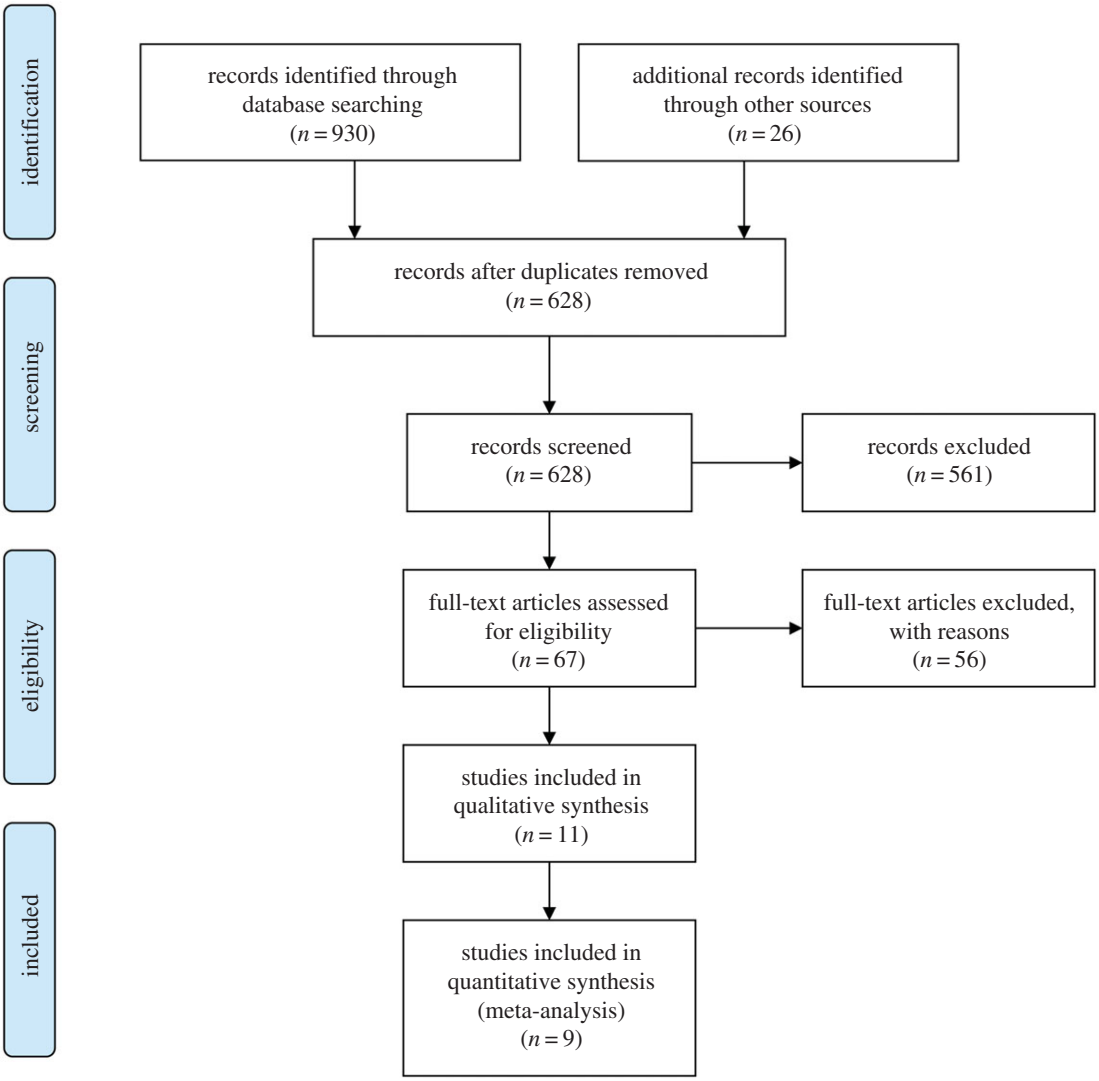

Figure 1. Flow diagram according to PRISMA guidelines [46] depicting the flow of information through the different phases of the literature search for the current meta-analysis. See the text for details regarding reasons for inclusions and exclusions. (Online version in colour.)

and Psyndex (8). The combined list was reduced in line with current guidelines (see figure 1 for a flow diagram according to PRISMA guidelines [46]). After removal of duplicates, studies were identified (i) that reported standard coordinates for neural activity across the entire brain (i.e. excluding studies that focused on limited regions of the brain), (ii) that were associated with performing a heart-focused interoception task (IT) as compared to a control task (CT), (iii) that were assessed via BOLD fMRI contrast of IT > CT. In total, 561 of the 628 screened studies were excluded from the list, when it was evident from the title that they (i) did not report fMRI data, (ii) did not examine human participants, (iii) did not follow an experimental protocol involving an IT or (iv) reported group comparisons only. For the remaining set of 67 studies, full-text articles were considered in detail. In 49 of these articles, the focus was not on brain activation associated with an IT as compared to either baseline or a CT. Only one reported the relevant IT > CT contrast for a single modality other than cardioception, namely respiration monitoring [25], and was therefore omitted from the meta-analysis. In seven studies, the IT was—at least partly—concerned with cardioception and would have allowed computation of an IT > CT contrast, but brain correlates of cardioceptive attentiveness were not reported and the respective data could not be obtained from the authors upon request. Finally, one study opted for execution of a heart-focused IT in the scanner environment [47]. This study was also not included in the current meta-analysis because the IT and CT involved demands that differed strongly from all the other studies.

For the remaining set of nine studies, characteristics of the interoceptive and control tasks were evaluated considering the model introduced by Garfinkel and co-workers [5,6] as described above in order to aid the discussion and interpretation of the results of the meta-analysis as compared to individual studies' findings (see table 1).

Deactivation in response to IT was not scrutinized in the current meta-analysis, because negative BOLD responses were only reported in three studies [50,52,54].

(b) Classification of studies by interoceptive task

All studies included in this meta-analysis have compared neural activity associated with an IT requiring focused attention to sensations from the heart to neural activity associated with a CT requiring attention to exteroceptive stimuli. However, the primary focus of most studies was not this basic comparison. For the current analysis, I ignored further contrasts reported in these articles. With regards to the implementation of both IT and CT, there was considerable variation across studies.

According to the model introduced by Garfinkel and co-workers [5,6], four studies [20,48,51,52] have assessed *interoceptive*

Table 1. Overview of fMRI study details reporting neural activity associated with interoception. When no laterality is indicated, this means bilateral activation was found to be significant. MDD, major depressive disorder; HC, healthy controls; BII, blood-injection-injury; SP, spider phobia; HP, high-perceiver; LP, low-perceiver; IT, interoception task; CT, control task; TR, fMRI repetition time; B, magnetic field strength of scanner; T, Tesla; FWHM, full width half maximum of fMRI smoothing kernel; BA, Brodmann area. Note that findings listed for contrast IT > CT for studies by Avery and co-workers [19] and Wiebking & Northoff [48] reflect the HC subsample (see the text for details).

index	citation	sample: size (female)	age: *M* (s.d.)	IT	CT	task timing	TR	no. of volumes per IT	B, coil	FWHM	resampled voxel size	hypotheses	brain correlates of significant neural activity in fMRI BOLD contrast IT > CT
1	Avery *et al.* [19]	MDD: 20 (13) HC: 20 (12)	MDD: 36 (9) HC: 33 (7)	focus on intensity of sensations from the heart	count how often the word 'TARGET' on a screen switches to lowercase	9 min run of 10 s randomly alternating IT versus CT and interleaved with null events ($M = 6.7$ s)	2500 ms	approx. 60	3 T, 32-channel head-coil	6 mm	1.75 × 1.75 × 1.75 mm	mid-insula	right dorsal mid-insula
2	Caseras *et al.* [49]	SP: 16 (2) BII: 18 (2) HC: 18 (2)	SP: 21.62 (2.57) BII: 22.78 (2.62) HC: 21.72 (2.80)	attend / press button for each perceived / counted heartbeat	press button for each detected target in series of sounds	20 s of attending followed by 10 s of button pressing, alternated five times with 30 s CT plus 30 s fixation-cross baseline at beginning and end	2000 ms	75	1.5 T, n.a.	5 mm	n.a.	anterior insula, dorsal anterior cingulate	insula, dorsal anterior cingulate (BA 32), supplementary motor cortex (BA 6), thalamus, right superior temporal lobe (BA 22), right somatosensory cortex (BA 3)
3	Critchley *et al.* [50]	17 (9)	n.a.	judge whether tones correspond to heartbeats or are delayed	judge whether one in 10 tones has different pitch	IT and CT trials in randomized order; total duration reflecting individual resting heart rate but less than 15 min	2520 ms	approx. 180	1.5 T, n.a.	12 mm	n.a.	(right anterior) insula, oribitofrontal cortex	inferior parietal lobule/post central gyrus, lateral somatomotor cortex, insula, insula/operculum, inferior frontal gyrus, dorsal anterior cingulate, supplementary motor cortex
4	Kuehn *et al.* [51]	HP: 12 (4) LP: 11 (5)	n.a. but well matched	monitor one's own heartbeat while 60 Hz tones are presented concurrently at random times; 60 Hz tone volume was individually adjusted to make stimuli 'just perceivable'	monitor 60 Hz tones presented at random times in the presence a slow background tone; 60 Hz tone volume was individually adjusted to make stimuli 'just perceivable'	16 trials consisting of 3 s instructions followed by 35 s either IT or CT in pseudo-random order (no condition presented more than twice in a row), followed by rating and 6–7 s pause	2000 ms	140	3 T, 12-channel head-coil	8 mm	n.a.	right anterior insula, right frontal operculum, anterior cingulate cortices, somatomotor areas	frontal operculum and right precentral gyrus (including BA 6), right anterior insula, right parietal operculum (secondary somatosensory cortex), right inferior frontal cortex (BA 44)
5	Pollatos *et al.* [52]	20 (0)	26.8 (3.7)	count number of perceived heartbeats	count number of tones	4 runs filled with 32 s of counting followed by 16 s for reporting by button press	4000 ms	68	1.5 T, n. a.	8 mm	n.a.	(right) insula, (dorsal) cingulate, somatomotor and prefrontal cortex	insula (BA 13), inferior/middle frontal gyrus (BA 10/46), right medial frontal gyrus (BA 6)/dorsal cingulate gyrus (BA 24), right thalamus (ventral), right inferior parietal lobule (40), left middle/inferior temporal gyrus (BA 37)

(*Continued.*)

Table 1. (*Continued.*)

index	citation	sample: size (female)	age: *M* (s.d.)	IT	CT	task timing	TR	no. of volumes per IT	B, coil	FWHM	resampled voxel size	hypotheses	brain correlates of significant neural activity in fMRI BOLD contrast IT > CT
6	Simmons *et al.* [24]	14 (8)	29 (range: 21–43)	perceive any sensation from the heart	count how often an 'O' appears at random intervals	4 runs of 7.5 min filled by 15 s of IT alternating with CT and null events ($M = 6.14$ s)	2000 ms	approx. 170	3 T, 21-channel head-coil	6 mm	$2 \times 2 \times 2$ mm	insula	right mid-insula, left postcentral gyrus, right insula and precentral gyrus, right postcentral gyrus, left precuneus, left middle frontal gyrus, right dorsal insula, right cuneus, right inferior parietal lobule, right inferior frontal gyrus, left precentral gyrus, left postcentral gyrus; (dorsal mid-insula characterized by granular cortex and ventral and anterior to the dorsal insula cluster, in the dysgranular insula)
7	Wiebking *et al.* [20]	MDD: 17 (11) HC: 17 (11)	MDD: 41.88 (12.1) HC: 37.59 (12.84)	count number of perceived heartbeats	count number of tones	4 runs of 9.6 min with 9–13 s of counting followed by 4 s for reporting the counted number (48 repetitions per condition in total)	2000 ms	approx. 264	3 T, 8-channel head-coil	6 mm	$2 \times 2 \times 2$ mm	anterior insula	anterior and mid-insula
8	Wiebking *et al.* [48]	MDD: 16 (11) HC: 30 (11)	MDD: 41.19 (11.78) HC: 33.73 (11.62)	count number of perceived heartbeats	count number of tones	4 runs containing 12 trials per condition (48 repetitions per condition in total), 9–13 s each with IT or CT in pseudo-randomized order	2000 ms	approx. 264	3 T, 8-channel head-coil	5 mm	$2 \times 2 \times 2$ mm	insula	claustrum, medial frontal gyrus (BA 6), left superior frontal gyrus (BA 6), left middle frontal gyrus (BA 6), superior temporal gyrus (BA 22), left cingulate gyrus (BA 24), right inferior parietal lobule (BA 40), left superior temporal gyrus (BA 42)
9	Zaki *et al.* [53]	16 (11)	19.10 (1.72)	press button for each perceived heartbeat (in half of the trials while concurrent repeating tones are present)	press button for each perceived tone (matching the individual participants' heart rate with added 25% variance)	2 runs of 300 s with six 30 s blocks	2000 ms	150	1.5 T, n.a.	6 mm	n.a.	anterior insula	right anterior insula/inferior frontal operculum, dorsomedial prefrontal cortex, medial cingulate, right medial frontal gyrus, hypothalamus

accuracy/sensitivity using minor variants of the *heartbeat detection task* originally coined by Schandry [9]. In these studies' tasks, the participants had to count their heartbeats in given time intervals of variable lengths. Two studies simply required the participants to focus their attention on sensations from the heart [19,24], a task-variant that is not well-determined by the model suggested by Garfinkel and co-workers [5]. I propose the term *attentiveness* as a suitable descriptor for focused attention to a particular interoceptive signal for a given time interval that is to the best of my knowledge unambiguous with regards to the existing literature on interoception. Similar to *interoceptive accuracy/sensitivity*, performance in this task will depend on both top-down resource allocation for conscious registration of relevant events and clarity of bottom-up interoceptive signals against interoceptive background noise, probably mediated by recruitment of strategies like filtering, template matching, and sequence monitoring.

Avery and co-workers [19] asked participants to rate the intensity of sensations after 50 and 100% of trials. Similarly, Simmons and co-workers [24] asked the participants after 50 and 100% of trials to rate from 1 to 7 how fast their heart had been beating. Kuehn and co-workers [51] asked how well participants were able to solve the task on a scale ranging from 0 to 4. This adds a cognitive component to the tasks and the ratings may be influenced by one's *interoceptive sensibility*, as defined above.

Three studies have used IT that may be considered as in-between *interoceptive attentiveness* and *interoceptive accuracy/sensitivity*. In one study [50], participants were asked to attend to visual or auditory signals which were tied to their individual heartbeats, but either minimally delayed (less than 150 ms, i.e. almost in sync), or more or less out of sync ($\approx$ 500 ms delay). After 10 signals, the participants had to judge whether the signal was in sync or not. From this basic set-up, eight highly similar task variants were derived and applied with the aim of computing a more pure effect of interoception. In another study [54], participants were alerted by a visual cue to attend to their heartbeat for 20 s, followed by a 10 s period where they pressed a button for each detected heartbeat. In a third study [55], participants were asked to tap a button each time they perceived their heartbeat. Despite these variations, all three tasks required tracking of individual heartbeats just as in the four studies assessing *interoceptive accuracy/sensitivity* with the *heartbeat detection task* [20,48,51,52].

To summarize, all studies' IT involved *interoceptive attentiveness* towards sensations from one's heart, which includes attention to individual heartbeats. Three studies involved a mental focus on perceiving and detecting single heartbeats [50,54,55]. Four studies [20,48,51,52] closely matched the *heartbeat detection task* coined by Schandry [9], which is used for assessing *interoceptive accuracy/sensitivity*. However, it is important to note that strictly speaking, none of the contrasts of IT > CT reported in these studies reflected *interoceptive accuracy/sensitivity*, because (i) accuracy was not assessed together with fMRI activation (i.e. outside of the scanner) and (ii) only two studies reported in which of the identified areas brain activity actually correlated with accuracy scores [50,52]. Hence, brain activation identified in this contrast reflects all aspects associated with carrying out the IT as compared to the CT.

(c) The role of control tasks

In fMRI studies, neural activation associated with the effect of interest is identified by subtracting activation that is related to general or unspecific neural processes that might confound the signal of interest, measured during the execution of a CT. Ideally, control and experimental tasks differ in all but the specific effect of interest. fMRI studies investigating neural activity during an IT might primarily want to control for (i) general effects of counting and (ii) neural effects of external cues compared to internal stimuli. Subtracting those confounding effects in subsequent fMRI analysis from neural activity during the IT (contrasting IT > CT) will mirror neural activity that is closely related to the effects of the IT relative to the CT. In the following section, the CTs used in studies submitted to the current meta-analysis have been critically considered in order to identify the potential impact of particular CT characteristics on the outcome.

In the four studies using variants of the *heartbeat detection task* [20,48,51,52], participants had to count (all) tones presented in a given time interval. This interval was of variable length in three of the studies [20,48,52], and had a fixed length of 35 s in one study [51]. In two of these four studies [20,48], the presentation frequency of the tones was adapted to correspond to each participant's heart rate, but onset times of the tones were jittered to avoid synchrony with the actual heartbeat. Avery and co-workers [19] used a visual CT, where participants had to count how often the word 'TARGET' on a screen switched to lowercase in a given time interval. Participants in the study by Simmons and co-workers [24] had to count how often an 'O' appeared randomly in a given time interval. Apart from using a different modality, these tasks were rather similar to the tone counting tasks of the four previously mentioned studies [20,48,51,52].

Interoceptive accuracy/sensitivity as assessed by *heartbeat detection tasks* involves focused attention to a body signal. Hence, performance is confounded with cognitive capacity and ability [21,56]. Both Caseras and co-workers [54] and Zaki and co-workers [55] aimed to minimize effects of this confound by the particular design of their CT, where participants had to press a button for each detected target in a series of external sound events for a given time interval. Zaki and co-workers [55] added a third condition where participants had to count heartbeats during concurrent presentation of sounds, allowing for removal of the additional brain activation related to discriminating exteroceptive signals from noise rather than to interoception *per se* from the contrast of interest. Critchley and co-workers [50] used a similar CT where participants had to evaluate, via button press, whether a series of externally presented tones contained a number of identical tones or whether one of these tones was presented with a different pitch.

Note that in three studies [19,24,51], IT and CT trials closed with rating (see above). As noted above, this adds a cognitive component. However, for the most part associated activation will be cancelled out in the contrast IT > CT because similar brain activation will be induced in both trial types.

Although, task details varied greatly, two main types of CT can be distinguished. While both types of tasks required attention to a series of exteroceptive signals, one set of CT required vigilant attention towards all signals within a given time interval, while another set of CT required identification of rare or singular events within a series of similar other events.

(d) Study samples

The set of studies submitted to the current meta-analysis further varied considerably with regards to the participants. Most of the studies used healthy adult participants with an upper boundary of 43 years; hence, findings may not be valid for older populations. Apart from one study that only included male participants [52], all samples included both sexes (see table 1 for details). One study compared individuals with phobia regarding blood-injection-injury or spiders to healthy controls [54]. In this study, blocks regarding interoception/exteroception were counter-balanced across participants with a 7 min event related phobia symptom provocation task in which phobia-related images where shown. This task may have produced carry-over effects, as increased state anxiety is associated with increased *interoceptive accuracy/sensitivity* [18,57]. However, this task also preceded the CT. Hence, differences between CT and IT should still reflect neural

activity relevant for *interoceptive attentiveness and accuracy/sensitivity*, and for the most part, such carry-over effects will be cancelled out in the contrast of interest (IT > CT).

Several studies compared patients with a clinical diagnosis of major depression (MDD) to healthy participants. It has been shown that *interoceptive accuracy/sensitivity* is increased in patients with moderate depression, but decreased in patients with severe depression when compared with healthy controls [58,59]. For the study by Avery and co-workers [19], the contrast of IT > CT did not show any effects for the MDD subgroup; hence, the available data are rather representative for the subgroup of 20 healthy participants. Note that the respective sample size has been adjusted accordingly in the current analysis (for details see the electronic supplementary material). In the study by Wiebking and co-workers [20], the depressed participants had increased scores (total and all but the awareness subscale) on the BPQ [7] used to assess *interoceptive sensibility*, and they had reduced activation of the insula when performing the IT [20]. I decided to include the data in the current meta-analysis although only findings for the combined sample were reported, because brain areas associated with interoception in healthy participants matched brain areas in depressed individuals, suggesting a quantitative rather than a qualitative difference. For the study by Wiebking & Northoff [48], data from the subgroup of control participants without MDD could be obtained from the authors, hence no data from the MDD subgroup was entered in into the current meta-analysis, and sample size was adjusted accordingly. In one study [51], participants with high cardioceptive accuracy, so-called high-perceivers (HP, see table 1) with an accuracy score of 0.87 and low-perceivers (LP, see table 1) with an accuracy score of 0.54 were identified with the *heartbeat detection task* [9]. Significant findings were only obtained and reported for the HP subgroup. Hence, in the current meta-analysis, only data from the HP sample was included (also see electronic supplementary material).

(e) Details regarding meta-analysis

In order to identify brain regions consistently activated in a given set of fMRI contrasts as extracted from the studies described above, I have employed multilevel kernel density analysis (MKDA) [60,61]. MKDA is similar to other voxel-based methods [62,63] and the activation likelihood estimate method (ALE) [64,65] with one notable exception: the ALE method computes the probability for at least one peak of activation to fall within a particular voxel, based on joint probability across individual peaks. Accordingly, the null hypothesis is that in none of the studies was a particular voxel activated. By contrast, MKDA identifies voxels with density of reported peaks exceeding chance level by computing spatial consistency among reported peaks. Hence, MKDA tests the null hypothesis that spatial distribution of peaks is random.

To conduct MKDA, peak coordinates for the basic contrast identifying neural activity associated with interoception as compared to the CT (i.e. the contrast IT > CT) were extracted from the individuals studies. Next, all peak coordinates (absolute and relative maxima for each cluster) were converted into a common stereotactic system that is Montreal Neurological Institute (MNI) space and these peaks were plotted onto a canonical brain (avg152T1.img; SPM, Wellcome Department of Imaging Neuroscience). Note that MKDA uses a spatial resolution of $2 \times 2 \times 2$ mm per voxel. Each peak was convolved with a 10 mm three-dimensional Gaussian kernel. This reduces potential bias introduced by studies with many close-by peaks, because the peaks will contribute to one overlapping sphere with maximum activity of 1, regardless of the number of contributing peaks, instead of being counted as if they were from independent observations (i.e. studies). Therefore, MKDA is more conservative than common alternative approaches such as ALE. Furthermore, MKDA respects the multilevel aspect of the data by treating peaks as random rather than fixed.

Next, a summary density map representing the observed activation for a specific fMRI contrast by taking a weighted average of the spheres from each study was computed. The respective weighting factors were computed by multiplying the square-root of N (sample size) with 0.75 for fixed-effects versus 1.00 for random-effects analysis [61,66]. Note that all studies used in the current meta-analysis applied random-effects models for second-level analysis. At this stage, a density map was created where each voxel included a weighed proportion of contrasts that activated within 10 mm of that voxel. To generate a comparison model with random spatial organization of voxel-associated density across white and grey matter of the standard brain, a Monte Carlo simulation with 15 000 iterations per analysis was carried out [67]. Significant activation was then identified by comparing density per voxel as derived from the study set to the Monte Carlo simulation (i.e. null hypothesis) to identify voxels with an above-chance number of activation coordinates.

First, MKDA identifies proximate clusters (i.e. inside the 10 mm kernel region) of contiguous voxels according to a 'height-based' threshold. The proportions of contrasts in these voxels exceed the maximum expected over the entire brain by chance. In other words, the chance of making a Type I error at any single voxel is less than or equal to 0.05. Note that this results in family-wise error rate (FWER) correction. Second, MKDA identifies incremental clusters outside the 10 mm of the clusters for the height-based threshold with 'extent-based' thresholds that are FWER-corrected for spatial extent at $p < 0.05$ and meet primary alpha levels of $p < 0.01$ or $p < 0.05$. Basically, this test answers the question how many contiguous voxels would be required until this cluster meets the more stringent criterion of a whole-brain corrected threshold? Next, a combined map of voxels meeting both height- and extent-criterion was computed, and the active voxels were clustered using SPM8 contiguity assessment procedures (spm_clusters.m; Wellcome Department of Imaging Neuroscience).

Finally, anatomical localization of the clusters was identified by converting cluster coordinates into Talairach space and consulting a standard brain atlas [68] via the Talairach Daemon [69,70] set to identify the nearest grey matter. For ease of use, all coordinates are reported in MNI space nonetheless.

3. Results

To reveal neural activity that emerged consistently across studies employing task variants that involved *cardioceptive attentiveness* as defined above, a meta-analysis was conducted including nine studies reporting the BOLD fMRI contrast of interest (IT > CT).

Contiguous clusters of voxels meeting the height-based threshold with proportions of contrasts greater than or equal to 40.11% (632 voxels) at $p < 0.05$ (FWER-corrected), as well as local maxima within these clusters, are reported in table 2.

According to 'extent-based' criteria, incremental clusters (i.e. outside the 10 mm kernel region) of more than 1498 contiguous voxels with proportions of contrasts more than or equal to 16.67% were considered significant at $p < 0.01$ (FWER-corrected, one-tailed), and clusters of more than 402 contiguous voxels with proportions of contrasts more than or equal to 24.74% were considered significant at $p < 0.05$ (FWER-corrected, one-tailed; see tables 3 and 4, for details, respectively).

A functional-anatomical evaluation with the Talairach-Daemon classification system on level 1 (hemisphere), level

Table 2. MNI coordinates (*x*, *y*, *z*), no. of voxels per contiguous cluster, volume in cubic millimetres and *Z*-test statistic (max. proportion of activating studies) peaks and local maxima for sub-clusters identified according to the MKDA 'height-based' threshold, see text for details. Columns for level 1 (hemisphere), level 2 (lobes), and level 3 (sub-lobar structures) of the Talairach-Daemon classification system provide additional details. The respective Brodmann area (BA) has been noted where applicable.

sub-cluster and respective local maxima	*x*	*y*	*z*	voxels	volume (mm^3)	maxStat	level 1	level 2	level 3	BA	range (mm)
1	42	8	2	520	4160	0.73	right cerebrum	sub-lobar	insula	13	1
1a	46	8	0	117	—	0.63	right cerebrum	sub-lobar	insula	13	1
1b	42	2	2	138	—	0.73	right cerebrum	sub-lobar	claustrum	—	1
1c	38	10	4	224	—	0.63	right cerebrum	sub-lobar	insula	13	1
1d	56	2	6	41	—	0.56	right cerebrum	frontal lobe	precentral gyrus	44	1
2	−40	10	0	86	688	0.47	left cerebrum	sub-lobar	insula	13	2
3	52	−22	24	84	672	0.42	right cerebrum	sub-lobar	insula	13	3
4	6	−4	54	2	16	0.50	right cerebrum	frontal lobe	medial frontal gyrus	6	1

2 (lobes) and level 3 (sub-lobar structures) was based on the peak coordinates of identified clusters and sub-clusters and revealed that most significant peaks were located in the right hemisphere in the overall region of the telencephalon (see additional details in tables 2–4).

Figure 2 shows a summary of significant voxels in a representative set of brain slices.

4. Discussion

In this study, I have conducted a meta-analysis (MKDA) in order to identify brain activity associated with an IT as compared to a CT in a set of nine studies reporting BOLD fMRI contrast (IT > CT).

(a) Brain areas associated with heart-focused interoception

As expected, the findings of the current meta-analysis corroborate that neural activation in the insula (bilateral, cluster peak in BA 13) is associated with processing heart-focused *interoceptive attentiveness* probably strongly including aspects of *interoceptive accuracy/sensitivity*. In line with this view, BA 13 has been associated with perceiving visceral information and has been called the interoceptive cortex [22], which has been shown to be activated when participants focus on interoceptive information from various modalities such as temperature, touch, pain, forced respiration and isometric exercise, itching after cutaneous histamine injection, as well as distension of the oesophagus, stomach, bladder or rectum [22,31].

Cytoarchitectonic examination of the insula allows differentiation of anterior-ventral agranular, middle dysgranular and posterior granular parts. While automated analysis [29] has suggested further subparts of the granular insula (area Ig1 and rostral to it, area Ig2), a more recent study performing manual analysis did not confirm such subdivision [71]. In humans, BA 13 is considered part of the posterior granular insula, comprising a bridge between lateral and medial layers of the brain [72]. This corroborates previous reports associating interoception with posterior and mid-insular regions [24,29].

Predictive coding theory has suggested that pyramidal neurons of the supra-granular layers of the granular insular cortex compute differences between predicted and received sensory signals, and may send the respective prediction-error signal back to deep layers of agranular cortical regions [73]. Other intermixed pyramidal neurons are considered for tuning the gain on predictions and prediction errors dynamically in order to modulate the precision weight associated with a particular prediction error. This weight is supposed to depend on the confidence in descending predictions or the reliability of an incoming sensory signal such as heartbeats. Accordingly, BA 13 may serve as a basic evaluator of cardioceptive input comparing one's internal state to predicted effects of action including attempts for regulating physiological homeostasis. *Cardioceptive accuracy/sensitivity* may therefore correlate with the reliable registration and evaluation of an incoming cardiac afferent signal. Hence, it may be relevant for setting precision weights affecting transmission strength of the respective information and adjusting the priors for subsequent predictions. Organ-specific vulnerability,

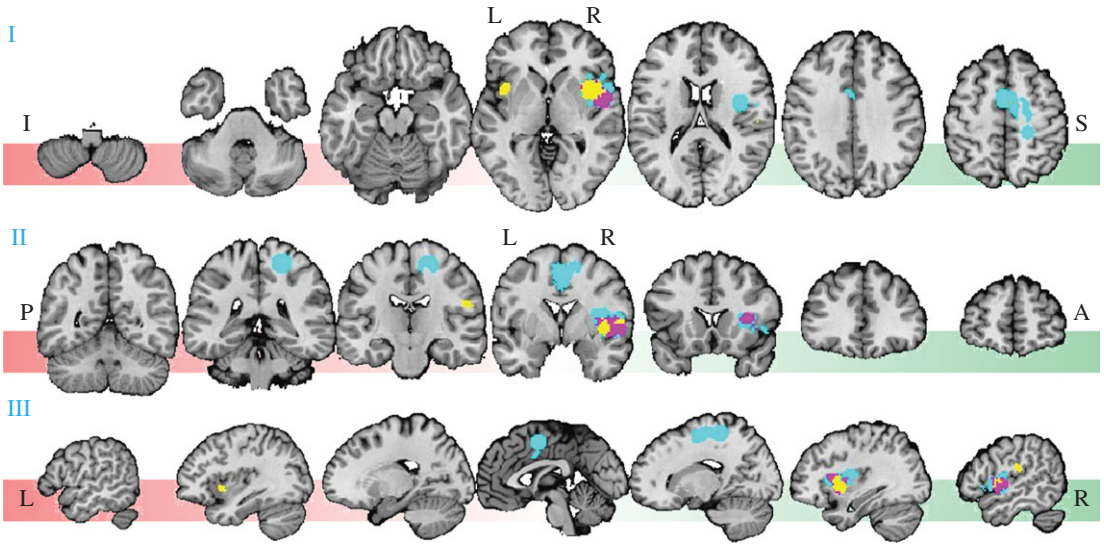

Figure 2. Results of MKDA meta-analysis for neural activity associated with *cardioceptive attentiveness* (I, axial; II, coronal; III, sagittal view). Slices at 18 mm distance were superimposed on the standard SPM8 high resolution anatomical image SPM8_colin27T1_seg.img and show all identified brain areas representatively. Yellow voxels indicate activation meeting the 'height-based' threshold ($p < 0.05$, whole-brain family-wise error (FWER) corrected). Incremental activation outside the 10 mm kernel region (FWER-corrected for spatial extent at $p < 0.05$) is shown in magenta and turquoise with primary alpha levels at $p < 0.01$ and $p < 0.05$, respectively (FWER-corrected, one-tailed). Coordinates mark cluster peaks in MNI space. I, inferior; S, superior; P, posterior, A, anterior; L, left; R, right.

Table 3. MNI coordinates, no. of voxels per contiguous cluster, volume in cubic millimetres and *Z*-test statistic (max. proportion of activating studies) peaks for sub-clusters for incremental clusters (i.e. outside the 10 mm of the clusters reported in table 2) identified according to MKDA 'extent-based' thresholds at a primary alpha level of $p < 0.01$, see text for details. No additional local maxima were found. Columns for level 1 (hemisphere), level 2 (lobes), and level 3 (sub-lobar structures) of the Talairach-Daemon classification system provide additional details. The respective Brodmann area (BA) has been noted where applicable.

sub-cluster	*x*	*y*	*z*	voxels	volume (mm^3)	maxStat	level 1	level 2	level 3	BA	range (mm)
1	50	2	2	522	4176	0.40	right cerebrum	frontal lobe	precentral gyrus	44	0
2	34	16	10	153	1224	0.37	right cerebrum	sub-lobar	claustrum	—	2

Table 4. MNI coordinates, no. of voxels per contiguous cluster, volume in cubic millimetres and *Z*-test statistic (max. proportion of activating studies) peaks for sub-clusters for further incremental clusters (i.e. outside the 10 mm of the clusters reported in table 2, and not included in table 3) identified according to MKDA 'extent-based' thresholds at a primary alpha level of $p < 0.05$, see text for details. No additional local maxima were found. Columns for level 1 (hemisphere), level 2 (lobes), and level 3 (sub-lobar structures) of the Talairach-Daemon classification system provide additional details. The respective Brodmann area (BA) has been noted where applicable.

sub-cluster	*x*	*y*	*z*	voxels	volume (mm^3)	maxStat	level 1	level 2	level 3	BA	range (mm)
1	52	22	2	39	312	0.20	right cerebrum	frontal lobe	precentral gyrus	44	0
2	12	−12	56	1789	14 312	0.39	right cerebrum	frontal lobe	medial frontal gyrus	6	3

for example, in terms of high precision weights could be responsible for the development of affective disorders in patients experiencing cardiac arrhythmia. *Interoceptive attentiveness* may more broadly support optimal resource allocation for the comparison of such information against predictions. This could affect the quality of interoceptive information available for intuition-based decision-making and might affect or even hamper the development of somatic markers, which appears to be an issue in patients with panic disorder [21].

Several of the studies included in the current meta-analysis have found neural activation associated with *cardioceptive attentiveness* in the anterior insula [20,50,54,55]. Only two studies have reported correlations between scores reflecting *interoceptive accuracy/sensitivity* obtained with variants of the above-mentioned *heartbeat detection task* [9], control-task performance as covariate and regions where activity was enhanced by *interoceptive attentiveness* relative to the CT (contrast IT > CT) [50,52]. Strongest relationships

with accuracy were reported for the right anterior insula/opercular cortex ($R = 0.62$, MNI coordinates: 34, 20, 4) and right anterior insula ($R = 0.56$, $p < 0.01$, MNI coordinates: 33, 14, 14) in the two studies, respectively. Further significant correlations with *cardioceptive accuracy/sensitivity* were found in inferior parietal lobule and the medial frontal gyrus extending into the cingulate gyrus in one study with male participants only [52]. If task demands associated with *accuracy* are not needed during *cardioceptive attentiveness*, this could explain why activation in the anterior insula did not reach significance in the current meta-analysis, as *accuracy* was only featured in a subset of studies. However, it is notable that coordinate transformation into Talairach space and search via the Talairach Daemon allocates the above-mentioned coordinates to the claustrum (for further discussion in the context of this area, see below). In addition, it should be considered that both studies also reported correlations of accuracy scores with negative emotion/anxiety, and negative emotion/anxiety also correlated with neural activation in the anterior insula. This is in line with further studies associating activation in the anterior insula with anxiety, worrying about self-aversive events, risk and the anticipation of punishment, disgust, guilt, sadness or fear [29,74–81]. One of the studies in the current meta-analysis included MDD patients [20]. Another one included participants with phobia and exposed them to phobia-related stimuli [54]. Negative emotion may therefore explain anterior insula activation in these studies. Of note, anxiety also has been shown to inflate accuracy scores in the *heartbeat detection task* leading to artificially high *sensitivity* not necessarily rooted in better detection performance [33]. Further studies support the view that the anterior insula is involved in focusing one's attention on detecting salient or deviant external stimuli [82–85]. The IT in two of these studies [54,55] required pressing a button for each detected heartbeat. Another study's IT required judging whether tones corresponded to heartbeats or whether they were delayed. Compared with IT in other studies, these tasks involve monitoring external events. In addition, they may exert particularly high attentional demand. Both could account for higher anterior insula involvement. More studies are required for a comparative analysis that would allow examining whether such task characteristics explain variation in anterior insula recruitment as well as the lack of significant activation in the current meta-analysis. Nevertheless, the findings of our current meta-analysis highlight the robustness of posterior insular activation during *cardioceptive attentiveness* across such variations.

Further neural activation was confirmed in the right claustrum, a small thin and jagged structure located posterior to the insula, projecting back and forth to nearly all cortical regions [86]. Already Brodmann considered the claustrum as a likely extension of cortical layer VI [87] and more recent perspectives suggest the claustrum may comprise a seventh layer of the insular cortex [88]. Cardioception involves focused attention for detecting discrete specific events in an ongoing stream of concurrent noise (i.e. other visceral and body signals). This would also closely match demand characteristics associated with *cardioceptive accuracy*, and matches the suggested role of the claustrum for multimodal coordination of widespread ipsilateral and contralateral cortical regions supporting the experience conscious perception, cognition and action [86] with a particular role in orchestrating regions controlling attention [89]. Although other sources claim that the claustrum may comprise separate unimodal processing regions [90], the widespread connectivity of the area suggests that interoceptive information may be fed forward to many adjacent areas and may thus exert concerted moderating influence on processes performed in higher order cortical regions. It is still under debate whether the claustrum also guides sub-cortical regions such as the basal ganglia, caudate nucleus, putamen and globus pallidus [91]. It is notable that none of the studies in the current meta-analysis had explicit hypotheses regarding the claustrum. One reason may be that it is hard to assess such a thin structure via fMRI specifically (e.g. as a region of interest) but it is to be hoped that increasing magnetic field strength, improved control of movement artefact and, last but not least, fibre tractography will allow detailed examination of the role of this interesting structure for interoception in the near future. This will also improve differentiating the particular roles of the anterior insula versus the claustrum.

Further activation was found in the right medial frontal gyrus (BA 6). This area includes the agranular medial part of the gyrus frontalis superior, lacking the internal granular layer IV. BA 6 has been associated with high-level executive functioning and processes relevant for decision-making [92,93]. Right hemisphere BA 6 is said to be relevant for sequential movements, related error monitoring and control, specifically aiding decisions about equality versus difference. While these functions appear useful for the performance in both IT and CT, task demands of the IT are usually considered to be higher. Therefore, the IT may require stronger activation in BA 6, which would explain activation in the contrast IT > CT. To corroborate this interpretation, it would be interesting to see whether neural activation in BA 6 varies with task difficulty. Yet the two studies aiming for particular control of this issue also found activation in BA 6 [54,55]. This suggests that BA 6 may also be concerned with IT-specific issues.

The right precentral gyrus (BA 44), also known as the pars opercularis of the inferior frontal gyrus borders the insula and is considered relevant for phonological and syntactic processing as well as music perception [94]. Other studies have associated emotional expression, verbal understanding, language accentuation, generating melodies, as well as behaviour monitoring and inhibition [22], in particular selective response suppression in go/no-go tasks [95], with this area. The IT of detecting individual heartbeats shares many characteristics with this functional description, involving decoding of an on-going complex stream of information into relevant versus irrelevant discrete events. As strategies for cardioception vary, it should also be noted that the three studies using a *heartbeat detection task* used tone detection as CT. This may have implicitly led participants to using auditory strategies in the IT. Furthermore, BA 44 activation in the IT > CT contrast may reflect selective suppression of response to events other than the actual heartbeat. Finally, the specific task of identifying heartbeats while scanner noise and vibration distract may reflect processing of whether a signal matches a template or not. Comparing a variety of CT and asking participants about their interoceptive strategies could improve our understanding of this issue.

(b) On hemispheric specialization

With regards to hemispheric specialization, it is noteworthy that the current meta-analysis indicates right-hemispheric dominance for processing heart-related interoceptive information. Although only three of the nine individual fMRI

studies have tentatively suggested right-hemispheric dominance in their hypotheses [50–52], outcomes of several studies already provide evidence for a stronger association of *interoceptive accuracy/sensitivity* with right-insular activation. In the study by Critchley and co-workers [50], accuracy of heartbeat perception correlated with the BOLD response most strongly in the right anterior insula/opercular cortex, but this could also be explained by subjective anxiety symptoms (see above). Caseras and co-workers [54] reported that only right-sided insula activity correlated with *interoceptive accuracy/sensitivity*, while left-sided activity was linked to increased state and trait anxiety as assessed with the Spielberger Trait and State Anxiety Inventory [96]. Kuehn and co-workers [51] found only right-hemispheric activation in participants with high *cardioceptive accuracy*. Further evidence for right-insular dominance for interoception comes from electroencephalography- (EEG-) based dipole source-localization studies [97,98]. EEG studies on the so-called heartbeat-evoked potential also have shown greater amplitudes over right electrode positions for subjects with high *cardioceptive accuracy/sensitivity* [99,100]. Altogether, it is striking that aspects of *accuracy* are quite prominent in these studies.

The right-sided dominance of interoceptive information processing may instead suggest non-verbal information processing which may partly explain why interoception is often described as gut-feeling rather than explicit knowledge. The right-insular cortex has also been considered particularly important for cerebral regulation of cardiac functions [101,102]. For example, after strokes involving the right-insular cortex the risk of cardio-autonomic dysfunction was enhanced [103], and right-sided stroke was associated with reduced heart rate variability [104]. While (rest and digest related) parasympathetic activity is re-represented in the left (or dominant) insula, (distress related) sympathetic activity is re-represented in the right (or non-dominant) hemisphere [22]. A review regarding the role of interoception in anxiety disorders [18] suggests particularly strong links to panic disorder, where hypervigilant processing and biased evaluation of heart-related symptoms is at the core of both psychopathology and therapeutic approaches. Altogether, this opens interesting perspectives on the role of interoception with regards to (chronic) stress, as this affects the balance between parasympathetic and sympathetic nervous system activation. In this regard, it appears promising to focus on laterality and sub-cortical connectivity of neural activation associated with interactions of interoception and different levels of state and trait anxiety.

(c) Tasks and methods

As reviewed above, considerable variation exists in the study set with regards to task characteristics as well as measurement and analysis features. It may be argued that this heterogeneity hampers the meta-analysis. However, it may also be considered a particular strength of a meta-analysis to reveal which areas are consistently activated across the IT > CT contrasts obtained from individual studies. Interpretation of the current findings should therefore consider such characteristics. Consistently, the studies' IT required *cardioceptive attentiveness* involving focused attention to one's heartbeat for a given time interval and/or *cardioceptive accuracy/sensitivity* involving exact counting of perceived heartbeats in a given time interval, and the CT required focused attention to discrete (external) tones uncorrelated to one's heartbeat. It should be noted that variation in the design of CTs lead to variable degrees of control of attentional demand characteristics in the IT > CT contrast. Most studies' CTs simply required attention to target stimuli. Other studies' CTs also involved discrimination of rare targets against a series of concurrent tones. Brain activation identified in the current meta-analysis may therefore reflect aspects of attentional demand characteristics not controlled by the particular CTs of individual studies.

Summarizing table 1 provides further information for correct interpretation of the current findings. First of all, it is notable, that several studies failed to provide all details necessary for precise replication of both study protocol and analysis. The number of volumes per task had to be estimated in five studies, coil-type was not reported in four studies, and resampled voxel size was only reported in four studies. Second, it should be noted that smoothing kernel varied greatly from 5 to 12 mm full width at half maximum (FWHM). Kernel size can have profound effects on outcomes, and an FWHM of at least 8 mm has been suggested as optimal for group inference [105]. In the current meta-analysis, one could roughly conclude that findings of studies with larger smoothing kernel may be overrepresented while studies with smaller kernel may be underrepresented. In the current meta-analysis, a kernel of 6 mm FWHM was used most often. Replication may benefit from choosing similar kernel size. With regards to field strength, the study set is well balanced with four studies using a 1.5 Tesla scanner, and four studies using a 3 Tesla scanner; 3 Tesla can be considered to be the current gold standard for psychological fMRI experiments, because lower field strength leads to reduced detection power whereas higher field strength involves increasing issues due to movement artefacts. Henceforth, the 3 Tesla studies could be weighted in more strongly when interpreting the results of the current meta-analysis.

When considering further task details, it is important to note that variation in measurement and task features or sample characteristics is unfortunately confounded in any pair of studies one might compare. The limited available data also renders statistical comparison of sub-sets of studies rather questionable as they would comprise three or four studies at the most, and variations other than the feature of interest would not be well balanced across the compared study sets. Hence, it would be impossible to evaluate the basis for differences in brain activity identified in such a comparison.

Considering that the MKDA approach relies on location of cluster peaks and sample size to compute meta-analysis further underlines that the results most likely reflect large commonalities between studies rather than being affected by subtle detail.

(d) Limitations and recommendations

The number of available BOLD fMRI studies with human participants on interoception is rather limited. Almost all of these studies have applied IT concerned with cardioception. Therefore, comparative meta-analysis of neural activation associated with different target organs is currently not possible. Studies investigating interoception of target organs other than the heart also deviate in many procedural aspects. Therefore, stringent comparison is rendered rather futile due to confounders. In addition, IT and CT are not always conceptually clear with regards to which aspects of interoception are

examined. In this regard, the recently introduced model by Garfinkel and co-workers [5,6] may provide a valuable tool. The current findings can also not differentiate more general from heart-specific aspects of interoceptive information processing. To improve upon this situation, it would be helpful if studies would at least uniformly report findings of whole-brain analysis regarding the basic contrast IT > CT. A comparative meta-analysis across a variety of tasks with the unique commonality of particular target organs might solve these issues, when more studies become available.

With regard to the subset of studies using versions of the *heartbeat detection task* [9], it is important to note that none of these studies has assessed *interoceptive accuracy/sensitivity* directly in the scanner. Therefore, results of the current meta-analysis instead reflect all aspects involved in cardioception rather than the aspect of *accuracy/sensitivity* alone. Of note, neural activity correlated with *interoceptive accuracy/sensitivity* assessed outside the scanner only in some of the brain areas identified in the contrast IT > CT (see above). Yet a recent study has developed a task for assessing *interoceptive accuracy/sensitivity* in the scanner. The authors found similar significant neural activity to the current meta-analysis including the right middle frontal gyrus, right inferior frontal operculum, bilateral insular cortices, left inferior frontal triangular gyrus, left superior middle frontal gyrus and bilateral inferior parietal gyri [47]. Cluster peak coordinates particularly pointed out the posterior right insula (BA 13) and the left claustrum. Connectivity analysis in this study further highlighted involvement of prefrontal areas. These findings suggest that brain areas associated with assessing heart-focused *interoceptive accuracy/sensitivity* largely overlap with brain areas relevant for *cardioceptive attentiveness* as identified in the current meta-analysis. Future reviews and meta-analyses would however greatly profit if all studies assessing specific aspects of interoception would report correlations between brain areas identified in the basic contrast IT > CT.

Owing to the limited availability of data, it is currently also not possible to consider whether neural activation truly reflects enhanced information processing or inhibition. To this end, it would be helpful if more studies reported data on deactivation related to interoception. Together with appropriate baselines, as for example introduced by Critchley and co-workers [50], this could help to systematically approach this issue.

Finally, the great variation in candidate regions and hypotheses in the current set of studies is remarkable. This underlines the need for further refinement of functional-anatomical models underlying interoception. A meta-analysis is one approach for identifying particularly important structures by revealing the most consistently active areas across variations of task details, samples and experiments. However, the current approach ignores a huge amount of information that could be exploited if original raw data were shared, for example, in open databases available online (e.g. www.openfMRI.org or www.nitric.org).

5. Conclusion and outlook

Findings of the current meta-analysis on nine studies reporting BOLD fMRI contrast regarding *cardioceptive attentiveness* (i.e. focused attention to one's heartbeat for a given time interval) and/or *cardioceptive accuracy* (i.e. exact counting of perceived heartbeats in a given time interval) as compared to a CT corroborate and extend established models of interoceptive processing [22]. The MKDA meta-analysis has revealed a complex network involving the posterior (granular) insula (BA 13), the claustrum, as well as temporal and frontal areas, highlighting right-hemispheric dominance of cardioception. This may reflect non-verbal information processing involving sequence monitoring and features of acoustic event detection that may be applied to identification of individual heartbeats. Notably, the claustrum has not been considered in individual studies but emerged as an important brain area in the meta-analysis, possibly orchestrating top-down attention deployment and processing of feed-forward cardioceptive information related to prefrontal neural activity. Although some of the individual studies have emphasized the role of the anterior insula [20,50,54,55], the current findings suggest that this area may rather be concerned with evaluative aspects of interoception and probably negative or anxious emotion. Further research is required on different targets organs (e.g. stomach or bladder) and specific aspects of interoception such as *interoceptive sensibility* and *metacognitive awareness* in order to further improve our understanding of the neural correlates of interoception.

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Endnote

[1]Please note that the original authors may have used deviating terminology and sometimes have used the same labels with deviating definitions. The terminology in the current manuscript has been unified in accord with the definitions of Garfinkel and co-workers [5,6].
[2]The reference list is available upon request from the corresponding author.

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