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Tesis Doctoral

Role of cognition and neurophysiology in interoceptive dimensions: a multilevel study.

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Introduction

Interoception

The nervous system has been proposed to be the link between body-brain interactions with the conscious experience (Ainley & Tsakiris, 2013). It is responsible for processing sensory signals through interoception (internal surface of the body, viscera), proprioception (skeletal muscles) and exteroception (external surface of the body, in direct contact with the environment) (Freeman & Sherrington, 1907). Interoception, or also called interoceptive awareness, the ability of processing internal bodily stimuli, is particularly important for mental states because body sensations and visceral arousal impact on the emotional experience (Cameron, 2001; Craig, 2002; Damasio, 1994; Dolan, 2002; Jennings, 1992).

From a philosophical perspective, body feelings like pain, hunger and temperature have been considered the basis for the sense of physical self (Sherrington, 1897). For instance, William James proposed that these body feelings are key for self-awareness and emotion (James, 1890) and Sherrington then divided the sensations into senses responsible for vision and hearing, limb position, touch (including pain and temperature) and the viscera, which was called the interoceptive modality (Freeman & Sherrington, 1907).

Although there still are some authors that advocate for a more restrictive definition of interoception, which refers to visceral sensations mainly (Dworkin, 2007), current research suggests that interoception consists of a multi-sensory system. This system includes multimodal integration of sensations, learned associations, memories, and emotions, which together are the subjective representation of the body state, and not only the afferent communication of receptors of the autonomic nervous system (ANS) (Ceunen, Vlaeyen, & Van Diest, 2016). Thus, the ability of the central nervous system (CNS) of processing *internal bodily stimuli*, includes a wide range of phenomenological experiences to ensure homeostasis regulation (Adolphs et al., 2018; A. D. Craig, 2009; Arthur D Craig, 2002;

Wiens, 2005). However, interoception is not determined by whether a sensation is exogenous or endogenous, but it is any sensation that contributes to the perception of body state (Ceunen et al., 2016).

Certainly, interoception involves the senses, and interprets and integrates signals produced moment by moment within the body, generating an internal map of sensations, both consciously and unconsciously (Adolphs et al., 2018). This sensing may be painful or nonpainful (as shown in Table 1); occurs with high or low arousal; outside of conscious awareness (except pain); and generally during homeostatic perturbation.

Table 1. Physiological processes related to interoception (Adolphs et al., 2018)

Nonpainful	Cardiovascular, respiratory, gastrointestinal (oesophageal, gastric, intestinal, colorectal), bladder, hunger, thirst, blood/serum (pH, osmolality, glucose), temperature, vasomotor flush, air hunger, muscle tension, shudder, itch, tickle, genital sensation, sensual touch, fatigue.
Painful	Visceral: kidney stone, pleuritic, angina, pericardial, bowel ischemia, pelvic, sickle crisis. Somatic: abscess/boil, bruising, myalgia, inflammation (systemic/laceration), headache. Skeletal: fractured/bruised bone, stress fracture, inflammatory/mechanical joint pain.

Understanding this bodily phenomenon may be very helpful for *mental health*. Studies so far have shown that people with mental health issues experience a different interoceptive awareness, such issues include for example: mood and anxiety disorders (Krautwurst, Gerlach, & Witthoft, 2016; Paulus & Stein, 2010a); eating disorders (Berner et al., 2018; Frank, 2014; Kerr et al., 2016; Khalsa et al., 2015); drug addiction (Avery et al., 2017; Goldstein et al., 2009; Naqvi & Bechara, 2009; Paulus, Stewart, & Haase, 2013); fibromyalgia (Borg et al., 2018), chronic fatigue syndrome (White, 2004), irritable bowel syndrome (Chey, Kurlander, & Eswaran, 2015), somatoform disorder (Perez, Barsky, Vago, Baslet, & Silbersweig, 2015), functional neurological disorders (Demartini, Ricciardi, Crucianelli, Fotopoulou, & Edwards, 2016; Ricciardi et al., 2016), post-traumatic stress disorder and somatic symptom disorder (Khalsa & Lapidus, 2016), chronic pain (Di Lernia, Serino, & Riva, 2016; Hechler, Endres, & Thorwart, 2016), and panic disorder (Gorman et al., 2001; Pohl et al., 1988).

Even though there is a great increase in knowledge about interoception, the factors that explain its variability are unknow, specially from a multilevel perspective (i.e., behaviorally, neurophysiologically, neuroanatomically and self-reported). As we will explain in the next sections, we are interested in this multilevel perspective of interoceptive awareness to understand the factors that impact on it and thus to be able to contribute with knowledge for general homeostatic processes and mental health field.

Since the design of our study will include different levels of analysis, in the next pages we will explain the main aspects of each one:

- dimensions of interoception (interoceptive awareness from now on) (*sensitivity*, *learning*, *metacognition* and *sensibility*),
- anatomical characteristics and its relevance for mental health,
- cognitive aspects related to interoception,
- its neurophysiological features, and
- the outlines, including the novelty and the main aims of this research.

Dimensions of interoception

Interoceptive awareness

Interoceptive awareness is the experience of perceiving and sensing bodily signals, as a further level of processing (Barttfeld et al., 2013). It refers to the capacity to evaluate the interoceptive performance measured through behaviour. It was firstly used to describe what can be self-reported in a subscale (Garner, Olmstead, & Polivy, 1983), but currently it considers all the characteristics of interoception that are accessible to the consciousness (Adolphs et al., 2018). The conscious experience is measured by report and through some observable signs such as heart rate, respiration rate, pupillary dilation, flushing, nociception, etc. (Adolphs et al., 2018). The classic task to measure sensitivity to visceral activity involves heartbeats detection, where the subjects judge if a visual or auditory signal is synchronous with their heartbeat (Blackwell, 1977). The participant is usually at rest, sitting or lying down, reporting interoceptive sensations such as the timing of heartbeats (Schandry, 1981a).

According to Khalsa et al., (2018) the features of interoceptive awareness are:

- *attention* or observation of internal body sensations,
- *detection*, which is presence or absence of conscious report,
- *magnitude* or perceived intensity,
- *discrimination* or localization of sensations in specific organs differentiating it from other sensations,
- *self-report* or psychometric assessments (questionnaires),
- *accuracy or sensitivity* of correct monitoring,
- *sensibility* or self-perceived tendency to focus on interoceptive stimuli.
- *insight*, which is the metacognitive evaluation of performance,

Sensitivity (accuracy), sensibility and *insight* (metacognition) are the three indices of interoception awareness that we will study in this research, besides a fourth index called *interoceptive learning* that indicates the ability to learn to perceive body sensations. All of these have been widely described in the literature (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015; García-Cordero et al., 2016; Melloni et al., 2013).

a. Interoceptive sensitivity (accuracy)

Interoceptive sensitivity is the perceptual conscious experience, measured by the *heartbeat detection*. It is the accuracy, that is, the correlation between the subjective dial ratings and observed heart rate responses (Khalsa et al., 2015). In other words, it is the *objective performance* in the heartbeat-tracking task (Schandry, 1981).

The heartbeat detection performance can be affected by age, fitness, gender and body fat (Cameron, 2001; Jones, 1994; Yates, Jones, Marie, & Hogben, 1985). People performing as "viscerally aware" tend to be more emotionally expressive and experience more intense emotions (Ferguson & Katkin, 1996).

b. Interoceptive sensibility (self-report)

Interoceptive sensibility is the subjective belief of the own body sensations or signals, which is measured through *self-report scales*, for instance, the body perception questionnaire (BPQ) (Porges, 1993a) or the MAIA (W. E. Mehling et al., 2012). It also may be measured via rated confidence in the own performance accuracy.

c. Insight or metacognitive interoception

Since there is a difference between subjective and objective measures of interoception, a conscious insight can be calculated, which is derived from the correlation between *confidence* and *accuracy* (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015). This dimension is also called *awareness*.

d. Interoceptive learning

After providing the subject with *interoceptive feedback*, which is a period where the subjects listen to their heartbeats with a stethoscope, the difference in accuracy between pre and post is measured, and this is called interoceptive learning (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015).

These four dimensions are characteristics of interoceptive awareness and are the variables that we aim to understand better in relationship to possible impacting factors previously reported in the literature.

Anatomical characteristics of interoception

The *pathways* involved in interoception link autonomic afferents with the central nervous system (CNS) (Craig, 2002; Critchley & Harrison, 2013). Autonomic, neuroendocrine and behavioural processes that maintain the homeostasis of the body receive *afferent inputs* with information about the state of all the tissues of the body (Cannon, 1939). Among the key *afferent processing* regions are brainstem (nucleus of the solitary tract, parabrachial nucleus, periaqueductal gray), subcortical (thalamus, hypothalamus, hippocampus and amygdala) and cortical regions (insula and somatosensory cortices) (Adolphs et al., 2018; Critchley & Harrison, 2013; Khalsa, Rudrauf, Feinstein, & Tranel, 2009). These afferents terminate in the nucleus of the solitary tract (NTS) (vagal and glossopharyngeal afferents, which are parasympathetic) and other fibres end in the lamina I of the spinal and trigeminal dorsal horns (spinothalamocortical) (Craig, 2009; Panneton, 1991). Studies of the functional anatomy of the lamina I spinothalamocortical using neuroimaging techniques, have supported that interoception includes the *whole body* and not only the viscera as it was previously thought (Figure 1) (Craig, Chen, Bandy, & Reiman, 2000). The fibres that end in the lamina I spinothalamocortical convey information of the mechanical, thermal, chemical, metabolic and hormonal status of the skin, muscle, joints, teeth and viscera (Craig, 2009; Panneton, 1991).

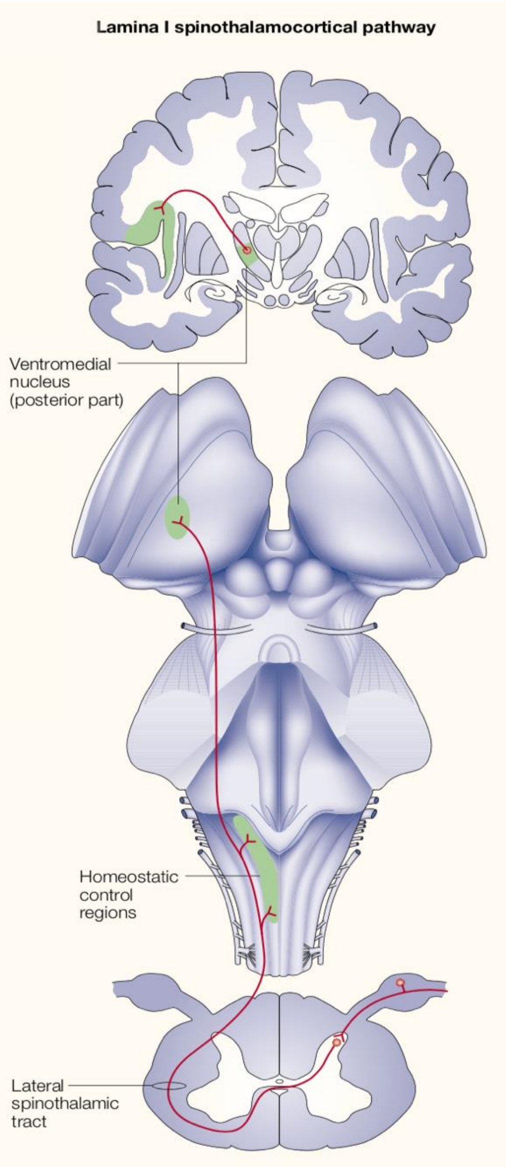

Figure 1. The lamina I spinothalamocortical system drives signals from all tissues of the body, projecting to autonomic and homeostatic centres in the spinal cord and brainstem. The solitary tract (NTS) transmits afferent activity generating a direct thalamocortical representation of the state of the body (how one feels), which is key to process feelings coming from the body. This approach differentiates interoception from pain and temperature, since it suggests that is part of homeostatic processes in the physiology of the whole body (Craig, Chen, Bandy, & Reiman, 2000).

There are different types of neurons in lamina I, each one being selective to specific kinds of receptors, for instance, some are responsive to specific kinds of pain (sharp, burning pain) or specific temperatures (cool, warmth) (Craig, 2003). This is the base for the selective somato-autonomic changes that are made continuously to keep the homeostasis in the system.

The neurons from lamina I project to pre-autonomic sites in the brainstem and generate spino-bulbo-spinal loops for somato autonomic reflexes (Craig, 1995; Sato & Schmidt, 1973). Lamina I and the solitary tract (NTS) connect with the parabrachial nucleus in the brainstem, where the afferent activity is integrated including cardiovascular, respiratory, feeding and fluid homeostasis (Craig, 1995; Saper, 2002). Parabrachial nucleus has projections to the periaqueductal grey, which is the homeostatic motor centre and to the hypothalamus, which is in charge of homeostasis of the diencephalon and drives autonomic, neuroendocrine and behavioural activity (Saper, 2002; Swanson, 2000).

Studies in mammals have shown that afferent information is integrated to maintain homeostasis from parabrachial nucleus and reaches the *anterior cingulate* and *insular cortices* (Krout & Loewy, 2000; Saper, 2002), which include the limbic sensory cortex, control the brainstem homeostatic integration areas responsible for homeostatic behaviour (Johansen, Fields, & Manning, 2001; Yasui, Breder, Safer, & Cechetto, 1991). Specifically, the *anterior insular cortex* and *somatosensory cortex* are key for mediation of perceived body states (Craig, 2009; Craig et al., 2000; Holstege, Bandler, & Saper, 1996). It has been reported an increase in insular activity related to autonomic arousal through visceral stimulation (Aziz, Schnitzler, & Enck, 2000), pain (Peyron et al., 2002), temperature (Craig et al., 2000), and emotional processing (Büchel, Morris, Dolan, & Friston, 1998; Phillips et al., 1998).

Activity is also enhanced in *right insula cortex* by awareness of emotionally potent stimuli (Critchley, Mathias, & Dolan, 2002). *Right anterior insula* has been proposed to mediate somatic and visceral attention, which has been supported by correlations between local grey matter volume and somatic awareness (Porges, 1993b). The *right anterior insular cortex* is involved in the subjective evaluation of oneself, a characteristic exclusively present in humans. This self-evaluation is crucial for emotional regulation, decision making and consciousness (Khalsa et al., 2009).

Therefore, interoception involves all major biological systems in charge of bodily homeostasis (Adolphs et al., 2018), which are important for *somatosensory processing*, *emotional regulation* and *mental health* (Khalsa et al., 2009; Porges, 1993b; Stefanics, Heinzle, Horváth, & Stephan, 2018). The *insula* and *cingulate* are the areas that have been recognised as key for interoceptive awareness, therefore, we will study them in relation to some cognitive domains related to these areas, namely attention, fluid intelligence and executive functions as we will see in the next section.

Interoception and cognition

Attention

Several studies have found that the *anterior insular cortex*, which is key for interoception, also participates in attention processes, particularly in attentional control (Menon & Uddin, 2010). This area is part of the salience network, which is involved in attentional switch from internal processes (interoception) to external events (Uddin, Kinnison, Pessoa, & Anderson, 2014b). Indeed, the *anterior insular cortex* is required for attentional demanding tasks such as the temporal distance task (TD) that measures temporal prediction (Tomasi, Wang, Studentsova, & Volkow, 2015). The *anterior insula* is also associated with focal attention and cognitive control (Nelson et al., 2010). By using resting state functional connectivity MRI, these researchers found that specifically the *ventral* and *dorsal/anterior* regions are involved in task-level control and focal attention, but posterior regions did not.

A meta-analysis of brain activation on studies of emotion, memory, attention and reasoning using neuroimaging techniques, found extensive coactivation of insular subdivisions (Uddin, Kinnison, Pessoa, & Anderson, 2014a). They concluded that *dorsal* and *ventral anterior insula* share coactivation partners with a key brain area for cognitive functions, the *dorsolateral prefrontal cortex*.

These anatomical overlaps between areas involved in interoception and attention may suggest a possible relationship between these functions. To examine the networks that underlie attention and interoception, this is, resting-state networks, a group of researchers studied brain connectivity in melancholia, a psychopathology characterised by problems in concentration, attention, psychomotor disturbance and body perception (Hyett, Breakspear, Friston, Guo, & Parker, 2015). Performing resting-state functional magnetic resonance imaging, they found a reduced effective connectivity in these networks in patients with melancholia in comparison to patients with non-melancholic depression and healthy controls, particularly in the *fronto-parietal attention network* and *anterior insula*. They suggest that this difference may be related to the poor affective quality of internally generated thought in patients with melancholia and a possible interaction of both, attention and interoception, because of the shared brain network.

Another disorder that has a disturbance in sustained attention, autoregulation and self-monitoring is attention-deficit/hyperactivity disorder (ADHD). In a study that used a heartbeat detection task, where participants counted their heartbeat without any external cue (images nor sounds), individuals with ADHD performed significantly worse than controls (Kutscheidt et al., 2019). Therefore, ADHD patients are suggested to be less aware of internal bodily signals, which may be related to problems in self-regulation and monitoring of their own behaviours.

Finally, an electrophysiological component related to afferent cardiac information, namely, the heart evoked potential (HEP) has brought important insights into the neural dynamics of interoception (Pollatos, Kirsch, & Schandry, 2005a; Schandry, Sparrer, & Weitkunat, 1986). Two studies looking for differentiating what kind of attention was related to interoception, found that the heart evoked potential (HEP) is higher when the attention is focused on internal sensations (interoception) than when is focused on external stimuli (exteroception) (García-Cordero et al., 2017; Petzschner et al., 2019). García-Cordero et al., (2017) found that the highest effect was in the *fronto-parietal area*, which is strongly associated with sustained attention, suggesting that the results were due to a higher cognitive effort. Similarly, Petzchner et al., (2019) proposed that attention plays an important role in interoceptive awareness.

Even though these studies suggest an association between attention and interoception, it is still unclear if interoceptive awareness is dependent on attentional processes and what factors explain this relation.

Fluid intelligence (FI) and Executive functions (EF)

Fluid intelligence is the ability to resolve problems without previous knowledge (Kent, 2017), and executive functions are the cognitive skills aimed to goal achievement (Diamond, 2013b). Both cognitive functions are related to self-monitoring and self-control (Hofmann, Schmeichel, & Baddeley, 2012). Interoception is an explicit self-monitoring function that implies self-regulation, cognitive control and relies on the ability to consciously attend and perceive signals from the own body. In cognitive terms, it depends on executive skills, mainly through inhibitory behavior and resistance to interference, both related to selective attention (Diamond, 2013a). Basically, when we attend to inner body signals it is necessary to inhibit external stimulus. Self-regulatory behavior, for example, emotion regulation or self-control, depend on both, executive functions, and fluid intelligence. Also, these cognitive functions have a positive correlation with social affective capabilities (Amadó, Serrat, & Vallès-Majoral, 2016; Ibanez et al., 2013).

Another argument to support the relation between interoception and fluid intelligence and executive functions is from a neuroanatomical perspective. Interoception has a strong influence from *insular cortex, anterior cingulate* and *sensorimotor areas*, as well as from *prefrontal cortex* (Stern et al., 2017). Fluid intelligence is characterized by an increase in volume in lateral *pre-frontal cortex* (lPFC), *orbitofrontal cortex* (OFC) *hippocampus* (HC), and *cerebellar hemispheres* (Raz et al., 2008). Executive function is related mainly to *dorso-lateral pre-frontal cortex* (dlPFC), *anterior cingulate cortex* (ACC), *somato-motor areas* (SMA), and *insular cortex* (Putkinen & Saarikivi, 2018). These prefrontal areas are implied in interoception, mainly the anterior cingulate cortex and orbital frontal cortex could represent not just a neuroanatomical but functional (behavioural) overlap (Schulz, 2016). Then, we propose that both, *fluid intelligence* and *executive functions* act as cognitive scaffold or pillars for interoceptive awareness, regulating self-monitoring processes and cognitive elaboration about the state of the organism (Figure 2).

Fig 2: Representation of the role of cognitive abilities in interoceptive awareness.

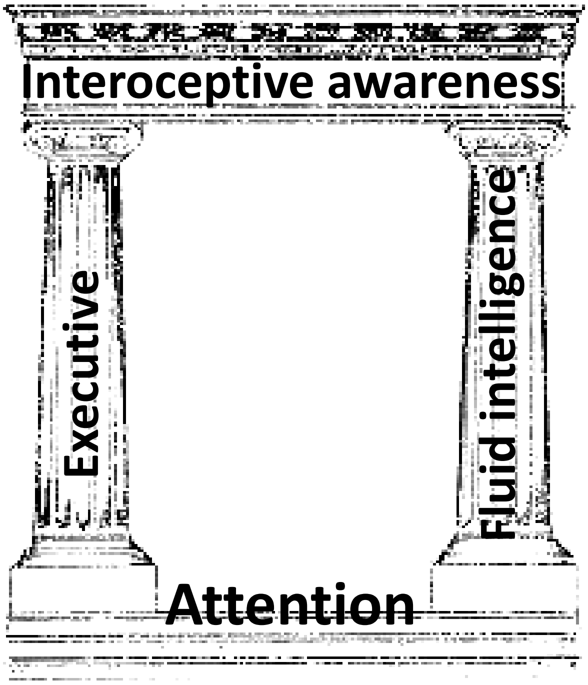

Figure 2. Here, attentional focus is the most basic cognitive resource and the first to be recruited. Fluid intelligence and executive functions act leaning on attention and have a cognitive self-regulatory and self-monitoring role. The interaction of these cognitive abilities allows interoceptive awareness.

Since interoception has been suggested to be closely related to cognitive skills, mainly on attention and self-monitoring or self-evaluative cognitive skills, we propose that these are one of the most relevant variables that impact on interoceptive awareness.

To examine the role of cognition in the four main dimensions of interoceptive awareness *(interoceptive sensitivity, interoceptive learning, metacognitive interoception* and *interoceptive sensibility)* we will use the neurophysiological measures reported in literature so far, namely, heart evoked potential and frequency bands, explained in the next section.

Neurophysiology of interoception

Heart evoked potential and its capacity to measure interoception

The heart evoked potential (HEP) is a cortical activity evoked by the cardiac rhythm (see fig. 3) and is a good technique to know the dynamics of the brain and its visceral afferences in a non-invasive fashion (Montoya, Schandry, & Müller, 1993). Additionally, they suggested that this activity can be a measure of self-monitoring, which depends on executive functions. The HEP is evoked from the R peak which is part of the cardiac complex QRS (i.e., three deflections in an electrocardiogram, the most common electrical activity inside the heart) and represents the highest amplitude of the cycle. HEP lasts between 350 and 550 milliseconds and its topography is in the frontotemporal and frontocentral electrodes.

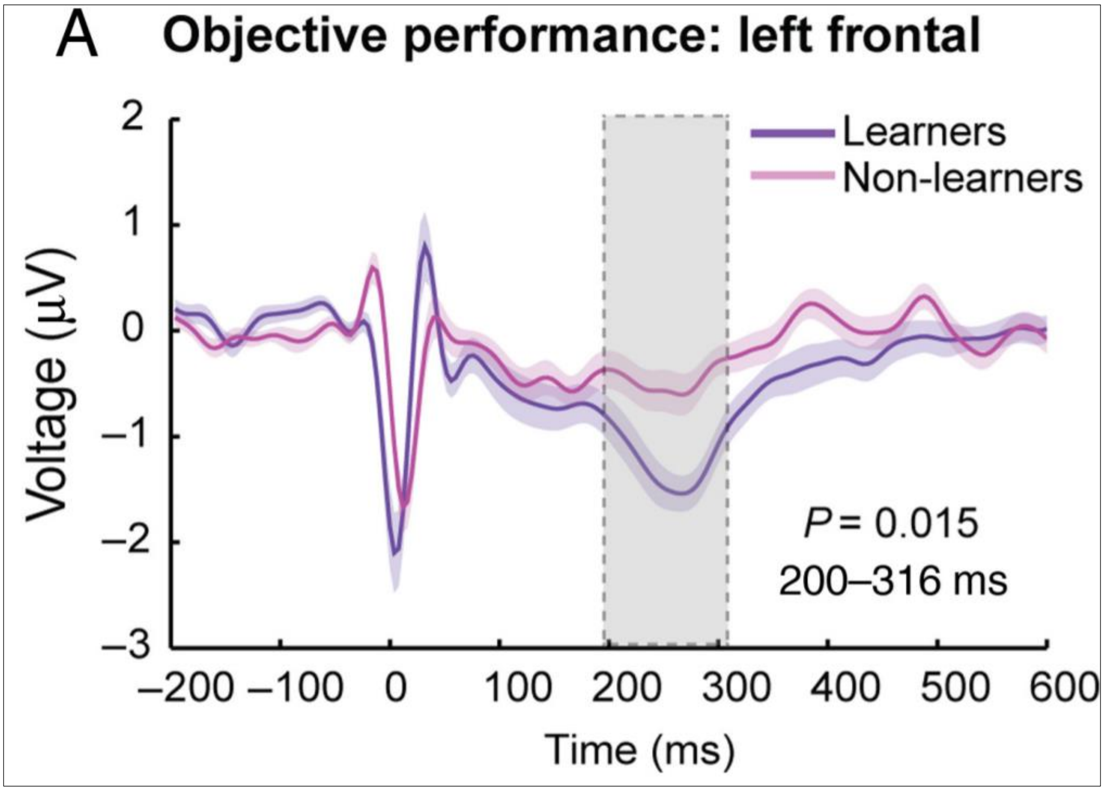

Fig 3: Representation of the heart evoked potential HEP, latency.

Figure 3: this figure represents the heart evoked potential. Time zero corresponds to the actual heartbeat from the subject, and main effects have been observed between 200 to 300 ms. Also, frontal electrodes are the

main topographic characteristics from HEP (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, del Carmen Garcia, et al., 2015).

Similarly, other area associated to HEP is related to high level cognitive functions, namely, frontal cortex, which presents a latency between 300 and 600 milliseconds after the R peak and it is affected by attention and motivation (Schandry & Montoya, 1996).

Electroencephalogram (EEG) and electrocardiogram (ECG) have been registered to observe the HEP during an interoceptive task of cardiac detection, to understand its neural correlates (Pollatos & Schandry, 2004). In this study, the participants were asked to count the number of heartbeats they perceived in a specific timeframe, and they found that the group of participants that had good interoceptive performance had a HEP with a higher amplitude than the group of participants with poor interoceptive performance. A recent study confirms these results, supporting the notion that the HEP increases its amplitude and becomes more negative in people that have better interoceptive skills (Fittipaldi et al., 2020). Interestingly, people that are better at learning interoceptive skills, namely, they improve their interoceptive performance after auditory feedback, show a higher amplitude in the HEP (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015).

The HEP has been reported as an index of conscious perception of somatosensory stimuli (Al et al., 2019). In this study the task consisted of mild electroshocks in the left middle and index fingers of participants, after which, they responded if they perceived the stimulus and where. Some of the trials did not have electroshocks, thus, some of the responses could be "hits" (there was a stimulus, and it was perceived or there was absence of a stimulus and there was not perceived) or "miss" (there was a stimulus and there was not perceived or there was absence of stimulus, but people perceived like it was one). When comparing the responses, they found that the HEP increased in amplitude during the miss responses, being positive, and tended to be negative and decreased during the hit responses.

Since the HEP has been shown to be a reliable and non-invasive technique to measure cortical signal reflecting cardiac activity and related to interoceptive behaviour, we will use it in our study as an electrophysiological measure, aiming to know how important this cortical signal for interoceptive awareness is.

Interoception and frequency bands

Alpha and gamma frequency bands are relevant for our study as they have been linked with cognitive processes that are related to interoceptive awareness, namely, *attention*, fluid intelligence (*cognitive control)* and *executive functions*.

Frequency oscillation in the brain has been related to body cycles as well as body awareness. *Alpha frequency band* (~10 Hz), is an oscillatory electrical brain activity commonly associated with non-REM sleep (Buzsáki, Logothetis, & Singer, 2013). An increase in individual alpha frequency band after physical exercise correlates whit an increase in heart rate for the same period in regards to a baseline condition (Gutmann et al., 2018). Additionally, physical exercise is positive correlated with cognitive performance and in turn, cognitive performance is related to an increase in alpha activity. Then, we can think in a close relation between cognitive performance, bodily signal, and brain processing as an organic and coordinated structure to self-body perception, that is, interoception.

Interoceptive perception has been related to *alpha frequency* in parieto-occipital electrodes. A study found that attending to heartbeat condition exhibited an increase in *alpha frequency band*, concluding that are differences in shifting attention inside (interoception) vs outside (visual perception). Also, a positive correlation between interoceptive accuracy and the percentage of change in alpha power was observed. A possible explanation it is that there is an inhibitory process (reflected in alpha power increase) underlying visceral perception, thus, cortical activity is diminished when visual attention is required (Villena-González et al., 2017). In addition to interoceptive accuracy, interoceptive metacognition has been related to frequency band signatures as well.

Gamma frequency band (~40 Hz) is an oscillatory electrical brain activity commonly associated with attentional performance and waking state (Buzśaki & Wang, 2012). Interoceptive metacognition, the ability to evaluate the own performance from an interoceptive task has a cortical signature reflected in gamma frequency amplitude. In a study, interoceptive skills were evaluated through a heartbeat perception task, which consists of various blocks of interoceptive measures. After every block, participants were asked to respond some metacognitive questions and then self-evaluation was contrasted with their objective performance. People that reported a good performance and objectively had a good accuracy index was categorized as having good metacognitive skills. On the contrary, people that reported bad performance, but they had good accuracy index were categorized as having bad metacognitive skills. Both groups were compared using gamma frequency amplitude as a metacognitive proxy. The results, showed that the group with good metacognitive skills had an increase of amplitude in gamma in comparison to the group with non-good metacognitive skills (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015).

Apart from analysing alpha and gamma frequency bands we have decided, from an exploratory approach, to analyse the predictive value of *beta (13~25) and theta bands (~ 6Hz)*. *Beta* band is related to motor and cognitive skills, frontal beta is mainly related to executive inhibitory functions and attention (Tanaka, Ishii, & Watanabe, 2014). Interoception is a high demanding cognitive behavior and requires both, attentional focus to inner body sensation and inhibition to external stimuli. In the same way, theta frequency band has been related to executive processing (working memory) as well as internal focus, emotional processing, meditation and first stage of sleep (Fingelkurts et al., 2007).

Outline

This thesis consists of four main objectives. Each objective comprises a multilevel approach considering cognitive and neurophysiological variables into a single model (see figure 4). The novelty of this research lies first in the focus on cognition as base for interoceptive awareness and secondly in the multimodal approach integrating neurophysiological, cognitive and behavioural dimensions into a single model to explain interoceptive awareness in its four main dimensions.

Figure 3: General interoceptive awareness predictive model

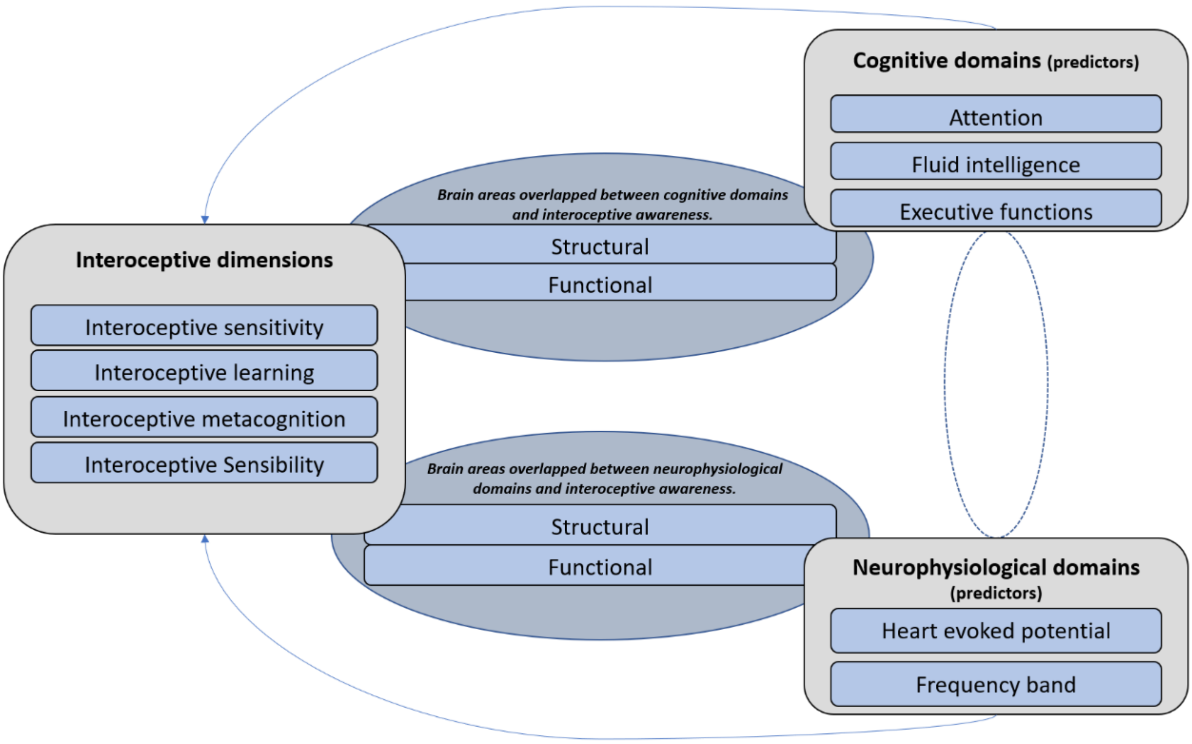

Figure 4. Theoretical representation of interoceptive awareness predictive model. In the left side, the four interoceptive dimensions. Together, these dimensions comprise the interoceptive awareness construct. At the top right-side, cognitive domains: attention, fluid intelligence and executive functions act as predictors of interoception. The most important cognitive function is attention because interoceptive awareness is basically an attentional function. It also requires self-regulation and self-control dimensions, which are cognitively represented by fluid intelligence and executive functions. At the bottom right, neurophysiological domain, which comprises heart evoked potential and frequency band, both correspond to two different approaches. The first is an evoked approach which reflect the neural activity related to the viscera of every heartbeat. The second

approach is an induced neural activity represented by frequency band analysis. This represents the neural correlates from a mental state in an interoceptive awareness period of time. Finally, at the centre of the figure, top and bottom, we propose that some brain areas overlap between interoceptive awareness and both, cognitive and neurophysiological domains through a neuroanatomical overlap help to explain the relation between interoception and the mentioned domains and might be observed trough structural and functional approaches.

The first aim of this thesis is to study whether *interoceptive sensitivity* (accuracy) is predicted by cognitive and neurophysiological variables. Among the most accessible measures of these factors are attention, heart evoked potential, and alpha frequency band. We anticipate that these three factors explain most variance of interoceptive sensitivity, particularly attention, because of the nature of interoceptive behavior. Neural correlates could play a secondary role reflecting inner focus.

The second aim is to know whether *interoceptive learning* is predicted by cognitive functions, mainly fluid intelligence, executive functions, and neurophysiological factors, theta, beta frequency band and heart evoked potential. We hypothesise that interoceptive learning is predicted by these factors due to their relation with self-monitoring and self-regulatory skills.

The third aim is more exploratory and attempt to address whether *metacognitive interoception* is predicted by cognitive function, mainly attention and fluid intelligence, heart evoked potential, and gamma frequency band. We predict that attention and fluid intelligence play a relevant role in metacognitive interoception as well as gamma frequency band, which has been proposed as a proxy for this behavior.

The fourth objective is to evaluate the role of cognition over *interoceptive sensibility*, mainly fluid intelligence, and executive functions. Due to the assumption of the role of self-monitoring on a self-report measure, we hypothesise that these cognitive skills are involved in self-body perception measure.

Finally, we will explore the possible overlap between interoception and cognitive skills through structural and global functional connectivity.

This thesis is structured in three further sections:

- Chapter 2 presents the methodology and procedure for the entire study.
- Chapter 3 presents results of the cognitive and neurophysiological roles associated with interoceptive sensitivity, interoceptive learning, interoceptive metacognition and interoceptive sensibility.
- Chapter 4 presents the conclusions and discussion for each objective.

Methods

Participants

The sample was recruited from general healthy population and consisted of 80 subjects (46 females, mean age 25.8 and 34 males, mean age 23.9). However, for neuroimage analysis, just 40 participants were recruited. Participants were excluded if they had consumed drugs or alcohol in the last 24 hours; if they had any addiction or consumption antecedents; or if they had a psychiatric or mood disorder diagnosis. All participants were provided with inform consent and only after read, understand and sign the document they were included in the procedure.

Tasks

Tasks consisted of three different measures: behavior, electrophysiology and cognitive (see figure 5).

Figure 5: Interoceptive task

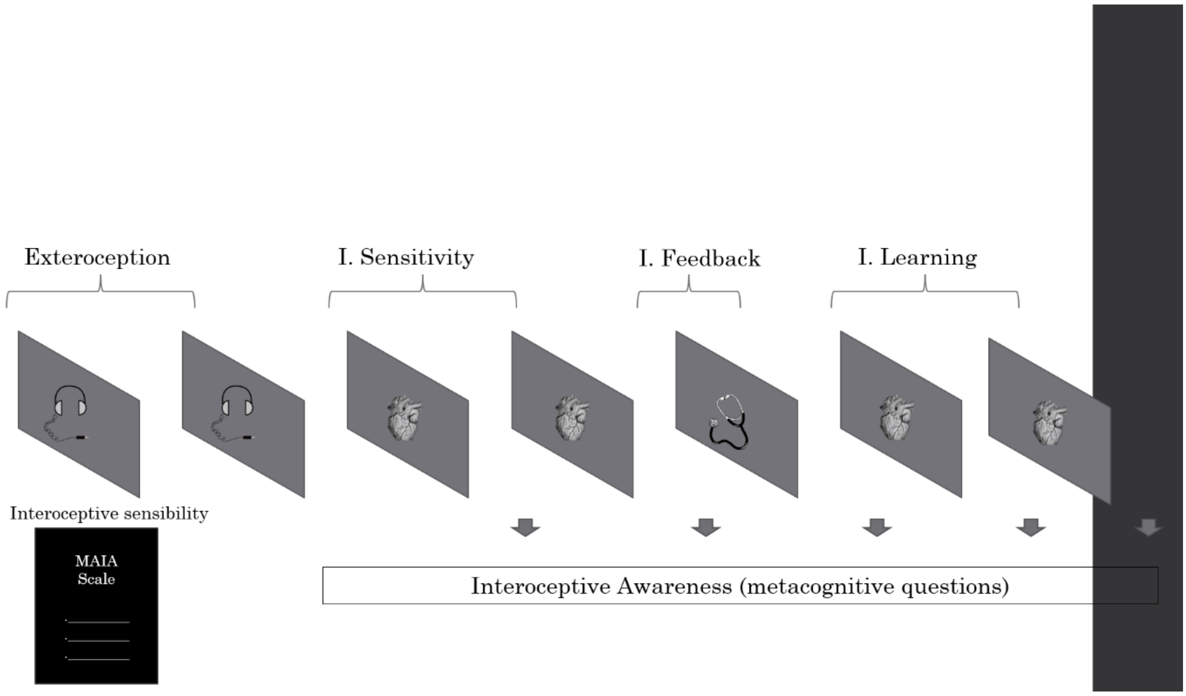

Figure 5. Interoceptive task: block 1, exteroceptive condition; block 2, *interoceptive sensitivity* condition; block 3, interoceptive feedback (stethoscope); block 4, *interoceptive learning*. After interoceptive sensitivity and interoceptive learning conditions, *interoceptive metacognitive* questions were presented. Finally, after the entire session, participants were asked to answer an *interoceptive sensibility* questionnaire.

Behavior

To measure interoceptive behavior in three of its four dimensions (sensitivity [accuracy], learning and metacognitive) we used a previous reported task (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015) that comprises four blocks: the first one is an exteroceptive block in which the participant listened to an audio from a heartbeat through headphones, and then we asked them to tap immediately after each heartbeat. In the second block the participant was asked to perceive and follow their own heartbeats by tapping every time that they perceived one (this block corresponds to *sensitivity interoceptive* measure). The third block corresponds to feedback condition, here, participants were asked to follow their own heartbeat by tapping, but this time, using a stethoscope. Finally, in the fourth block participants were asked to perceive their own heartbeats again (same as block 2) and follow them by tapping (this block correspond to *interoceptive learning* measure). After each block, a metacognitive question was asked regarding the task (this corresponds to the *interoceptive metacognition* measure). The duration of every block was from 2 to 3 minutes. The whole task lasted between 10 to 15 minutes including the metacognitive questions. To measure the fourth interoceptive dimension, this is, *interoceptive sensibility,* the participant was asked to answer a self-report interoceptive scale which took between 3 to 5 minutes.

Electrophysiology

To measure electrophysiology of interoception, we used electroencephalogram (EEG) and electrocardiogram (ECG) during the whole task, across all blocks.

Cognition

Cognitive measures (attention, fluid intelligence and executive functions) were measured in a second session. We used the subtest digits and symbols of the Wechsler Adult

Intelligence Scale III (WAIS-III) to measure attention (Rosas et al., 2014). This subtest has shown to be a good measure of sustained attention (Theiling & Petermann, 2016).

Fluid intelligence was measured trough the subtest Progressive Matrices of the Wechsler Adult Intelligence Scale III (WAIS-III). This subtest has shown to be a good measure of fluid intelligence (Kaufman, 2012; Neisser et al., 1996).

Finally, to measure executive functions, we used the INECO Frontal Screening. This is a fast way to assess executive functions and has been mainly used to assess neurodegenerative disorders (Ihnen, Antivilo, Muñoz-Neira, & Slachevsky, 2013). It measures response inhibition, set shifting, working memory and capacity of abstraction.

Procedure

Brain recording

EEG recordings:

EEG data was obtained using 64 electrodes (Biosemi® ActiveTwo) arranged according to the international 10/20 extended system. Horizontal and vertical eye movements were monitored using four external electrodes. Horizontal EOG was recorded bipolarly from the outer canthi of both eyes and vertical EOG was recorded from above and below of the participant's right eye. Two additional external electrodes were placed on the right and left mastoid to be used for later re-referencing.

ECG recording

Heartbeats were monitored using two electrodes: one placed below the left clavicle and a second one placed below the heart on top of one of the subject's left intercostal muscles. The position of the electrodes was adjusted for each participant, so the QRS wave amplitude was substantially greater than the T wave, to facilitate reading and analysis of the corresponding ECG.

Pre-processing

ERP analyses were conducted using MATLAB R2017b, EEGLAB 13.15.4b and ERPLAB 5.0.0. The data was digitally filtered offline from 0.5 Hz to 30 Hz and down sampled to 250 Hz to remove any unwanted frequency components. Also, trials that contained voltage fluctuations exceeding ± 200 μV were rejected, eye movements and other artefacts as well as trial rejections were removed from further analysis using both visual inspection and Independent Component Analysis (ICA). Continuous EEG data was segmented using a temporal window that began 200 ms prior to the onset of the stimulus and concluded 800 ms after the offset of the stimulus.

Data analysis

The R statistic package (3.3.2) was used for all statistical analysis. The reliability of each test and questionnaire were assessed using the Cronbach's alpha coefficient value with a threshold of 0.7 to be acceptable. The main objective of this study is to find predictors for interception in its four dimensions. We divided our predictors into three models (*body information* (control model), *cognitive* and *neurophysiological*) that are used as factors in a hierarchical regression, considering as dependent variables the four interoceptive measures, i.e., *interoceptive sensitivity*; *interoceptive learning*; *interoceptive metacognition* and *interoceptive sensibility*.

Behavioural analysis

Repeated measure ANOVAs and Tukey HSD post-hoc comparisons were performed to analyse behavioural interoceptive performance. Analyses were conducted in Jamovi (Jamovi project (2018). Jamovi (Version 0.9) [Computer Software]. Retrieved from https://www.jamovi.org).

Heart evoked potential analysis

Heart evoked potential is calculated based on three regions of interest (ROI), considering frontal electrodes grouped in right, central and left ROIs. Time window between

200ms to 300ms post stimulus is considered to average EEG data from the ERP in each ROI. This data is included in posterior hierarchical models.

Frequency band analysis

EEG time-frequency analysis is performed for three regions of interest, same than in evoked potential, ROI right: AF4 AF8 F2 F4 F6 F8; ROI central: Fz AFz Fpz Fp1 Fp2; ROI left: AF3 AF7 F1 F3 F5 F7 electrodes using a short-time window Fast-Fourier Transform (FFT) for frequencies ranging from 1-80 Hz using a window length of 80 seconds and a time step of 4 s. The time-frequency charts were then z-score normalized. Frequency band are defined as follows: theta = 4 – 6 Hz; alpha = 6 – 12 Hz; beta = 12 – 25 Hz and gamma 25 – 45 Hz.

Images acquisition

MRI acquisition and pre-processing steps are reported in accordance with the practical guide from the Organization for Human Brain Mapping (Nichols et al., 2017; Poldrack et al., 2017). Images were obtained from a Siemens 1.5 Tesla MAGNETOM Avanto scanner equipped with a standard head coil (8 channels). For all participants ($N = 40$), we acquired T1-weighted anatomical 3D spin echo sequences parallel to the plane connecting the anterior and posterior commissures, covering the whole brain. The following parameters were used: 144 contiguous axial slices, TR = 1820 ms; TE = 3100 ms; flip angle = 8°; matrix size = 240 x 232; voxel size = $1 \times 1 \times 1$ mm^3, sequence duration = 6.56 minutes.

For functional image we obtained 10-minute resting-state fMRI recordings from 30 participants. Functional spin echo volumes were acquired in sequentially ascending order, parallel to the anterior-posterior commissures, covering the whole brain. The following parameters were used: TR = 3.3 sec; TE = 50 ms; flip angle = 90°; 36 slices, matrix dimension 4 x 64; voxel size in plane RL 3.59mm; AP 3.59mm; slice thickness = 4 mm; number of volumes = 190. Participants were instructed to lay relaxed, keep their eyes closed, and not to think about anything in particular.

Images Data analyses

Structural images: Preprocessing

Images were preprocessed using the Statistical Parametric Mapping 12 software (SPM12; Welcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB (The Mathworks, Natick, MA, USA). Each T1-weighted image was first visually inspected for artifacts. Preprocessing steps were applied as described in the Voxel-Based Morphometry (VBM) pipeline (Ashburner & Friston, 1999). Images were normalized to the same stereotaxic space generated from the complete data set using the DARTEL algorithm, which significantly reduces the imprecision of inter-subject registration. Then, images underwent a tissue segmentation process for separation of WM, GM and non-brain voxels (CSF, skull). Subsequently, they were modulated to correct volume changes by Jacobian determinants. Finally, images were smoothed by convolution with an isotropic Gaussian kernel of 12-mm full-width at half maximum for statistical analyses.

Multiple regressions analyses

Multiple regressions (SPM12 module) were used to investigate the relationship between GM volume and the scores in *sensitivity*, *metacognition*, *attention*, *fluid intelligence*, *executive functions*, and *HEP sensitivity*. Total intracranial volume was included as non-interest covariate. The statistical threshold for statistical analyses was set as p < .001 (uncorrected, extent threshold = 30 voxels) (Alemany et al., 2013; Sedeño et al., 2017).

Resting state fMRI data: Pre-processing

First, we discarded the first three volumes of each subject's resting-state recording to ensure that magnetization achieved a steady state. Images were then pre-processed using the Data Processing Assistant for Resting-State fMRI (DPARSF V2.3) (Chao-Gan & Yu-Feng, 2010) which is an open-access toolbox that generates an automatic pipeline for fMRI analysis. The DPARFS processes the data by recruiting the Statistical Parametric Mapping

(SPM12) and the Resting-State fMRI Data Analysis Toolkit (REST V.1.7). In line with recommendations (Parker & Razlighi, 2019), pre-processing included slice-timing correction (using the middle slice of each volume as the reference scan) and realignment to the first scan of the session to correct head movements (SPM functions). To reduce the effect of motion during image acquisition as well as physiological artifacts (Goto et al., 2016), we controlled six motion parameters, CFS, and WM signals (REST V1.7 toolbox). Motion parameters were estimated during realignment, and CFS and WM masks were derived from the tissue segmentation of each subject's T1 scan in native space with SPM12 (after co-registration of each subject's structural image with the functional image). Then, images were normalized to the MNI space using the echo-planar imaging (EPI) template from SPM (Ashburner & Friston, 1999), smoothed using a 8-mm full-width-at-half-maximum isotropic Gaussian kernel (SPM functions), and band pass filtered between 0.01 and 0.08 Hz. None of the participants showed movements greater than 3 mm ($M = 0.05$, $SD = 0.04$) and/or rotations higher than 3° ($M = 0.05$, $SD = 0.03$).

Functional connectivity analyses

We explored associations between *resting-state functional connectivity* data and scores from *Interoception*, *Cognition* and *Evoked Potential*. First, for each subject, we extracted the mean time course of the BOLD signal in each of the 116 regions of the Automated Anatomical Labelling Atlas (AAL) (Tzourio-Mazoyer et al., 2002), by averaging the signal in all voxels comprising each region. Second, we constructed a connectivity matrix for each subject indicating the strength of association between all pairs of regions (Pearson's correlation coefficient; DPARSF toolbox). Third, we performed a Fisher z-transformation. The resulting FC correlation coefficients between all pairs of regions (AAL atlas) were used to perform Pearson's correlations with the scores of each variable of interest: Interoception; Cognition and HEP. To consider results as significant, the alpha level was set at $p <= 0.001$ (uncorrected).

Organization of predictive model

Hierarchical multiple regression:

Hierarchical multiple regression is a statistical analysis used to know the predictive value from a group of (independent) variables over and above another group of independent variables in regard to a (dependent) variable of interest. It allows to know the amount of variance explained by each independent variable. Variables are entered by steps and organized by theoretical relevance(Petrocelli, 2003; Richardson, Hamra, MaClehose, Cole, & Chu, 2015) .

First, Physiological model (control):

Heart Rate (HR) and Body Mass Index (BMI) were used as control variables due to their unclear relation with interoceptive skills.

Second, Cognitive model:

Attentional skills play a key role into interoceptive tasks, possibly because this task is highly demanding in terms of attentional resources, also *fluid intelligence* was introduced, which is dependent on attention and together work as scaffold for a better performance in very demanding cognitive tasks. Finally, *executive function* was included because it is a function very related with global cognitive performance.

Third, Neurophysiological model:

Event related potential: heart evoked potential (HEP) has been related to interoception since brain activity is evoked by heartbeat specifically by R peak in cardiac signal and has been observed mainly spread in frontal ROIs. For this work, we used Frontal ROIs organised by right, central, and left ROI.

Frequency band: alpha band has been observed in introspective and mind wandering tasks and is proposed as a neural marker for inner perception. Moreover, since we think that this task is very related to attentional and cognitive resources, we propose that gamma frequency is involved as well. Besides, autonomic visceral activity has been related to theta and beta band and possibly this could be reflected in interoceptive perception.

Fourth, best predictors model:

Finally, to know precisely the best interoceptive predictors, we selected only the significant variables from the models, combining *physiological*, *cognitive* and *neurophysiological* factors.

This organization will be applied to all dependent variables separately. That is, *interoceptive sensitivity*; *interoceptive learning*; *interoceptive metacognition*. For *interoceptive sensibility* will be applied just the control and cognitive model because we do not have enough theoretical support to propose a relation between this self-reported measure neurophysiological activity.

Results

Sample characteristics

Participants

The sample consisted of 80 subjects (46 females, mean age 25.8 and 34 males, mean age 23.9).

Table 1: Descriptive data

	Age	Education	Attention	Fluid Intelligence	Executive functions	Exteroception	Sensitivity	Learning	Metacognition	Sensibility
N	80	80	80	80	80	76	77	77	77	80
Missing	1	1	1	1	1	5	4	4	4	1
Mean	25.0	13.4	63.7	19.0	23.6	0.709	0.475	0.646	0.414	73.0
SD	5.28	1.91	13.4	4.21	3.97	0.126	0.0997	0.107	0.287	20.2
Min	18	10	35	10	17	0.42	0.32	0.41	0.02	32
Max	38	18	87	25	30	0.97	0.77	0.85	1.54	128

Table 1 show descriptive data from participants (age, educational level in years of education); cognitive measures and interoceptive behavior.

Behavioural results

To compare behavioural performance between conditions, repeated measures ANOVA was performed including as factors: exteroception x sensitivity x feedback x learning $F(1, 299) = 168.6, p = <0.001$. Post hoc analysis reveals a significant difference between *interoceptive sensitivity* (M = 0.47, SD = 0.09) and *interoceptive learning* (M = 0.64, SD = 0.10) (p = <0.001) (See figure 5).

Figure 6: Behavior data from interoceptive task

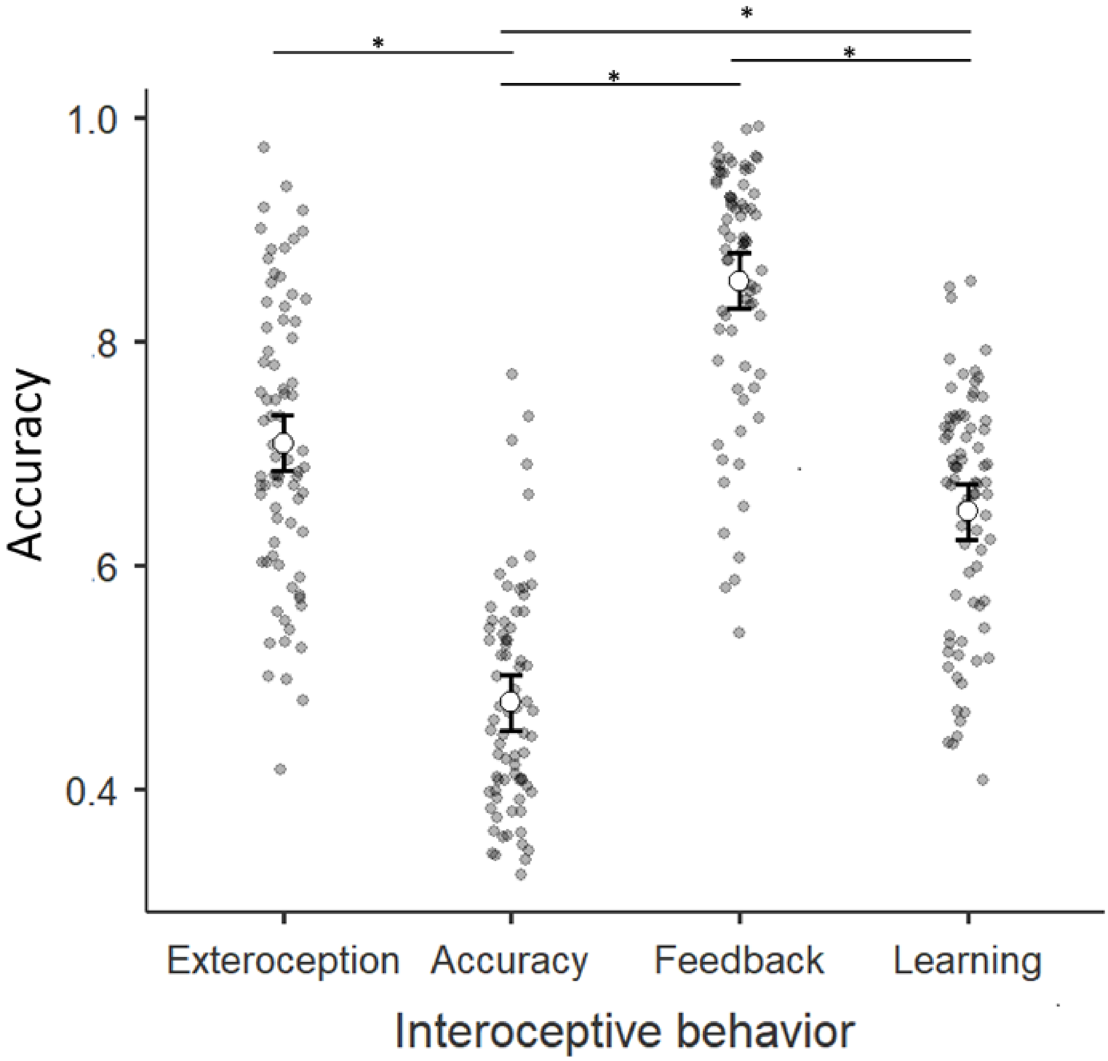

Figure 6. Interoceptive accuracy shows a significant difference regarding *learning* condition, which means that feedback has an effect over interoception. Additionally, the *exteroceptive* condition has a significant difference with *interoceptive* conditions.

Interoceptive predictive models

To know the best predictors for interoceptive behavior the analysis is organized as follow:

First: the analysis is made separately for dependent variables, i.e., interoceptive measures (*sensitivity*, *learning*, *metacognition*, *sensibility*).

Second: we present first cognitive predictors considering as factors *attention*, *fluid intelligence* and *executive functions*, after that, heart evoked potentials are presented as predictors, and finally, frequency band factors are presented as predictors (supplementary data).

Third: We select only the best factors (which means that we chose only significant factors) to perform a final predictive model. In this way, this model could include *cognitive* and *neurophysiological* factors as interoceptive predictors.

Interoceptive sensitivity predictors

Bivariate correlations between interoceptive sensitivity and best predictors.

Best predictors (BP) are organised using the just best factors from previous models, that is, best predictors from cognitive models, HEP models, and frequency band models (see table 2). BP analysed were Attention, Fluid intelligence, HEP at right and central ROI and Alpha band at left ROI, fig. 8 and 9.

Attention (r = .65) show strong correlation with interoceptive sensitivity, while HEP at right and central ROI show a moderate correlation (r = -.59 and -.46 respectively), finally, fluid intelligence (r = 32) and alpha band show a low and weak relation respectively. See Table 02, for a detailed account of correlations and p-value thresholds. See fig. 7.

These results suggest that there is no relation between frequency band and interoceptive sensitivity.

Table 2: correlations for interoceptive sensitivity and best predictors group.

Variable	*M*	*SD*	1	2	3	4	5	6	7
1. Sensitivity	0.48	0.10							
2. IMC	24.19	2.36	.10						
3. HR Sensitivity	72.58	11.29	-.01	.07					
4. Attention	63.46	13.44	.65**	-.09	.05				
5. Fluid Intelligence	18.73	4.28	.32**	-.02	-.03	.24*			
6. Roi right sensitivity	-1.08	1.24	-.59**	-.22	.05	-.28*	-.18		
7. Roi central sensitivity	-1.06	1.59	-.46**	-.18	.07	-.30*	-.24*	.50**	
8. Alpha left sensitivity	0.72	0.81	-.10	.02	.19	.06	-.06	.15	.15

Note: Pearson correlation r and levels of significance. *p<0.1; **p<0.05; ***p<0.001

Figure 7: correlations for interoceptive sensitivity and best predictors group.

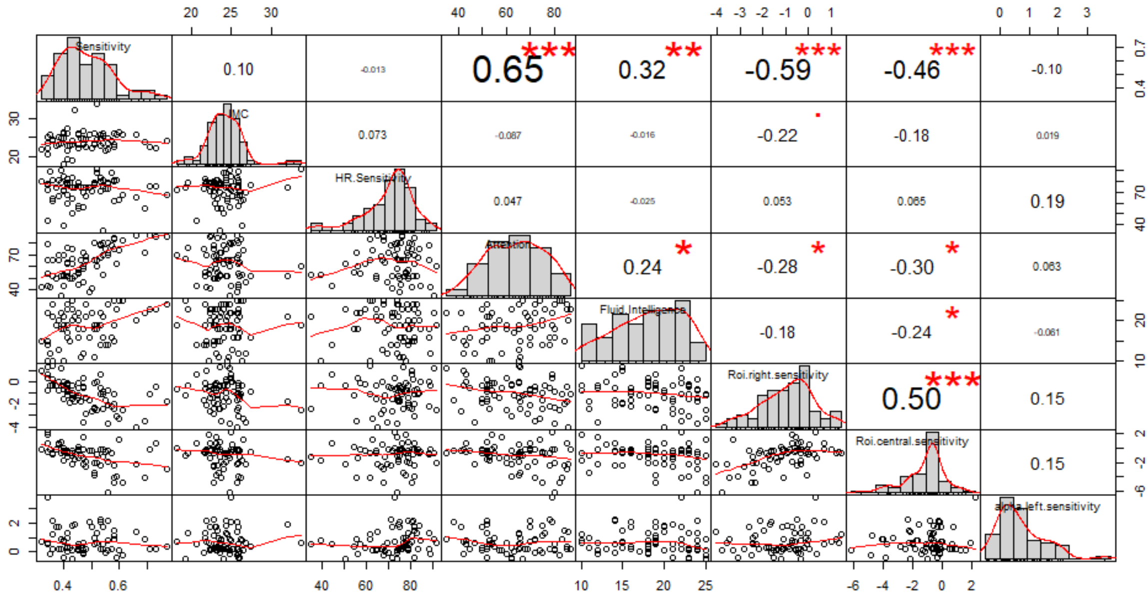

Figure 7. Correlogram represent scatter data dispersion at left side, Pearson correlation at right side and distribution of variables in diagonal.

Figure 8: HEP for sensitivity condition in three frontal regions of interest

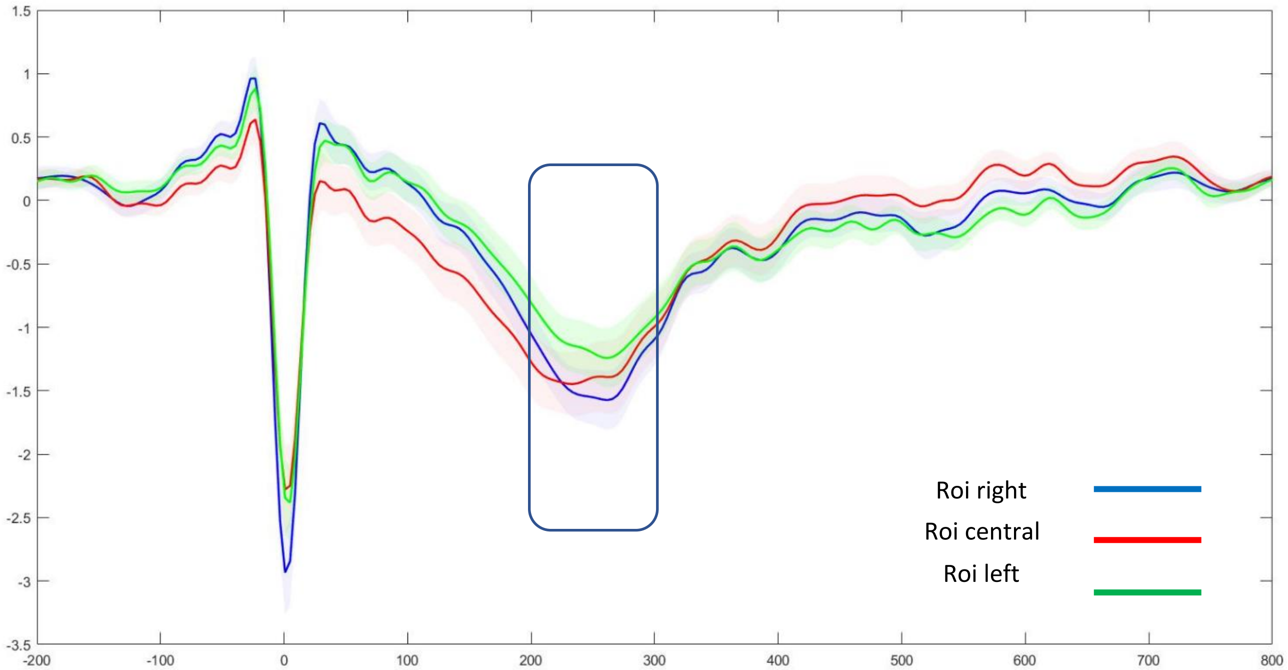

Figure 8. Heart evoked potential, each colour represents a ROI selected for hierarchical model, this time window has been chosen due to its consistent relationship with interoceptive behavior in previous literature.

Figure 9: Frequency band analysis for sensitivity condition in left frontal ROI

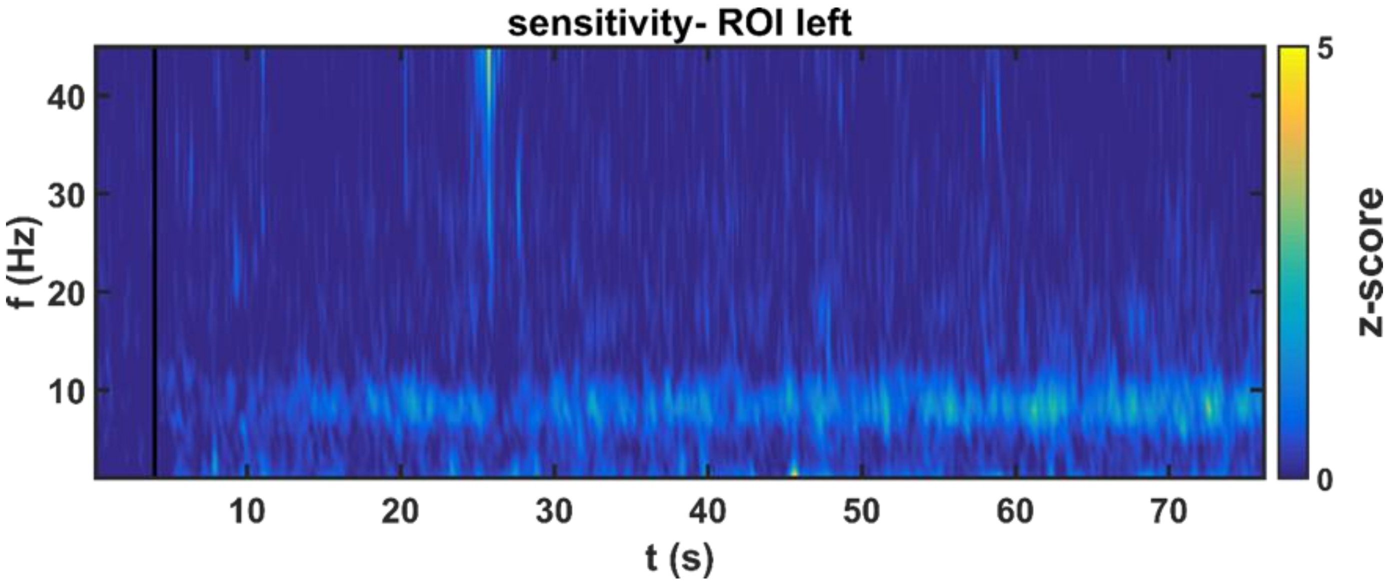

Figure 9. frequency band analysis depicting a long-time window period and important presence of alpha frequency band at left ROI for interoceptive sensitivity.

Hierarchical multiple regression for best factors as interoceptive sensitivity predictors

For hierarchical regression analysis we investigate the ability of neurophysiological evoked activity functions and frequency band (HEP and Alpha band at frontal electrodes in right, central and left ROI for the interoceptive sensitivity period) as well as cognitive (attention and fluid intelligence) to predict interoceptive sensitivity (table xxx). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. Additionally, the correlations amongst the predictor variables (attention, fluid intelligence, and executive functions) included in the study were examined. The variation inflation factor confirmed that the amount of explained variance was not inflated because of correlation between predictors, for attention is (VIF = 1.07), for fluid intelligence (VIF = 1.06) for ROI right: (VIF = 1.41); for ROI central (VIF < 1.43); for alpha band at left ROI (VIF = 1.11). This indicates that multicollinearity was unlikely to be a problem (see Tabachnick and Fidell, 2007).

In the Cognitive step of hierarchical multiple regression, we used Heart Rate, Body Mass Index as control and attention with fluid intelligence as predictor. This model was statistically significant, $F(2, 65) = 28.9$; $p < .001$ and explained 44.4% of variance in interoceptive sensitivity. After entry of HEP ROI right and central at Step 3 ($F(2,63) = 12.61$; $p < 0.001$) the total variance explained by the model was 59.1%. The introduction of alpha frequency band at left ROI explained 58.7% of variance in interoceptive sensitivity. In the final adjusted model two out of five predictor variables were statistically significant, with attention ($\beta = 0.50$, $p < .001$) and HEP Roi right ($\beta = 0.37$, $p < .001$) recording a higher Beta value than fluid intelligence ($\beta = 0.11$, $p =.17$), central HEP ($\beta = 0.08$, $p = 0.38$) and alpha band ($\beta = 0.06$, $p < .49$).

In summary, we observe a significant correlation between interoceptive sensitivity and cognitive abilities, specifically attention and fluid intelligence but not with executive functions. Regards to neurophysiological signal, we observe a positive correlation between sensitivity and heart evoked potential at right and central regions o interest, but no relation with alpha frequency band. Once variables are entered into the hierarchical model, just attention and HEP at right roi have significant predictive value.

Table 3: Hierarchical multiple regression for best factors as interoceptive sensitivity predictors

	Control					Cognitive					HEP					Frequency Band				
Predictors	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*
(Intercept)	0.39		0.10 – 0.67		**0.009**	-0.03		-0.27 – 0.21		0.824	0.11		-0.10 – 0.33		0.294	0.11		-0.11 – 0.32		0.326
HR.Sensitivity	-0.00	-0.02	-0.00 – 0.00	-0.26 – 0.22	0.870	-0.00	-0.05	-0.00 – 0.00	-0.23 – 0.13	0.586	-0.00	-0.01	-0.00 – 0.00	-0.16 – 0.14	0.892	-0.00	-0.00	-0.00 – 0.00	-0.16 – 0.15	0.984
IMC	0.00	0.10	-0.01 – 0.01	-0.14 – 0.34	0.409	0.01	0.16	-0.00 – 0.01	-0.02 – 0.34	0.081	0.00	0.05	-0.00 – 0.01	-0.11 – 0.20	0.575	0.00	0.05	-0.00 – 0.01	-0.11 – 0.21	0.545
Attention						0.00	0.62	0.00 – 0.01	0.44 – 0.81	**<0.001**	0.00	0.50	0.00 – 0.00	0.33 – 0.66	**<0.001**	0.00	0.50	0.00 – 0.01	0.34 – 0.67	**<0.001**
Fluid.Intelligence						0.00	0.17	-0.00 – 0.01	-0.01 – 0.35	0.065	0.00	0.11	-0.00 – 0.01	-0.04 – 0.27	0.163	0.00	0.11	-0.00 – 0.01	-0.05 – 0.27	0.173
Roi.right.sensitivity											-0.03	-0.38	-0.05 – -0.02	-0.56 – -0.20	**<0.001**	-0.03	-0.37	-0.04 – -0.02	-0.55 – -0.19	**<0.001**
Roi.central.sensitivity											-0.01	-0.09	-0.02 – 0.01	-0.27 – 0.09	0.343	-0.01	-0.08	-0.02 – 0.01	-0.26 – 0.10	0.387
alpha.left.sensitivity																-0.01	-0.06	-0.03 – 0.01	-0.21 – 0.10	0.492
Observations	70					70					70					70				
R^2 / R^2 adjusted	0.010 / -0.019					0.477 / 0.444					0.626 / 0.591					0.629 / 0.587				

Note: Significant P value are represented in black. This table presents standardized beta values and confidence interval for each variable in each model. This table also presents the results of each step of the hierarchical multiple regression.

Interoceptive learning predictive models.

The analysis for interoceptive learning follows the same logic as the previous analysis for interoceptive sensitivity, that is, first we analyse cognitive factors as predictors, then evoked potential at three frontal ROIs and finally frequency band using the same ROIs used in HEP but considering the entire time window from interoceptive learning.

Bivariate correlations between interoceptive learning and best predictors.

Best predictors (BP) for interoceptive learning were organised using the just best factors from previous models, that is, best predictors from cognitive, HEP amplitude and frequency band models (see table 4 and fig. 10). Best learning Predictors analysed were Attention, HEP at right and central ROI and beta Band at right and central ROI (see fig. 11 and 12).

Attention (r = .27) show a weak correlation with interoceptive learning, while HEP at right and central ROI show a strong and moderate correlation (r = -.53 and -.47 respectively), finally, beta right and central show no significant correlation (r = 0.20 and r = -.01 respectively). See Table 04 for a detailed account of correlations and p-value thresholds.

These results suggest that there is no relation between frequency band and interoceptive learning but attention and HEP amplitude are relevant as possible predictors.

Table 4: Correlation between best predictors and interoceptive learning

Variable	*M*	*SD*	1	2	3	4	5	6	7
1. Learning	0.65	0.11							
2. IMC	24.33	2.35	-.05						
3. HR Learning	73.78	8.42	-.06	.13					
4. Attention	62.69	12.80	.27*	-.16	-.25				
5. Roi right learning	-1.62	1.39	-.53**	-.08	.09	-.30*			
6. Roi central learning	-1.59	1.96	-.47**	.10	.08	-.30*	.35**		
7. beta right learning	0.22	0.27	-.20	.15	.13	-.33*	.22	.08	
8. beta central learning	0.25	0.25	-.01	.26*	.22	-.25	.07	-.03	.81**

Note: Pearson correlation r and levels of significance. *p<0.1; **p<0.05; ***p<0.001

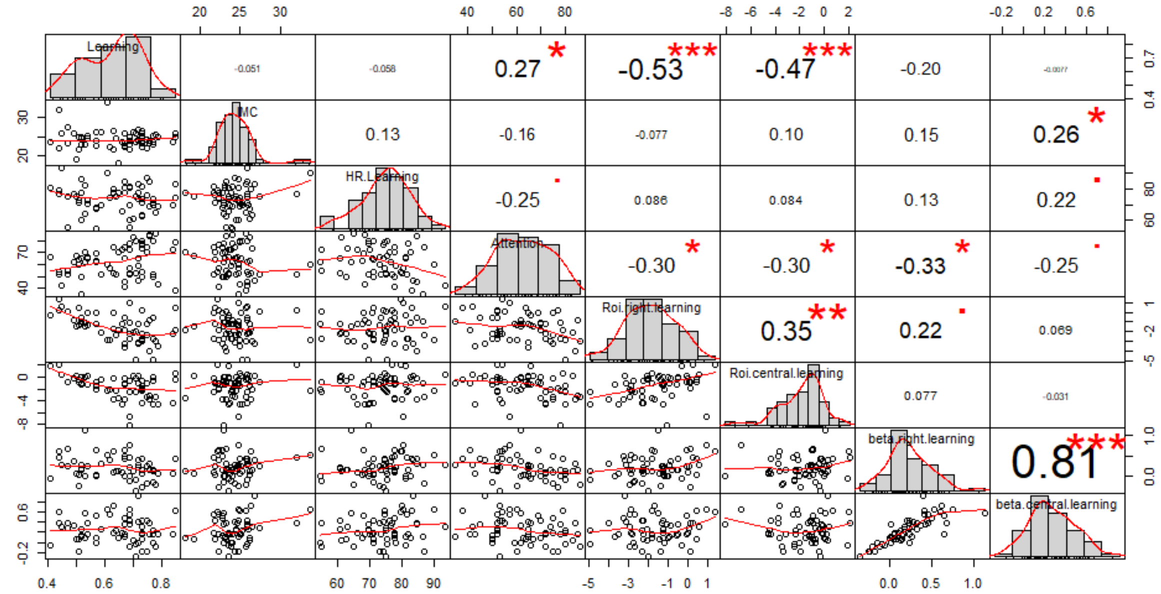

Figure 10: Correlation between best predictors and interoceptive learning

Figure 10. Correlogram represent scatter data dispersion at left side, Pearson correlation at right side and distribution of variables in diagonal.

Figure 11: HEP for learning condition in three frontal regions of interest.

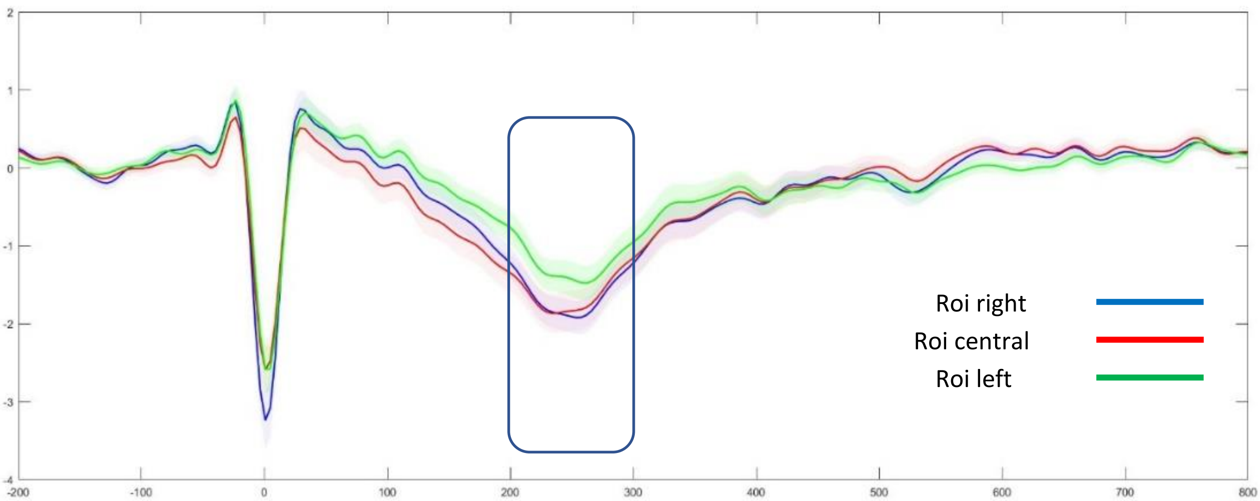

Figure 11. Heart evoked potential, each colour represents a ROI. Rectangle show the time window selected for hierarchical analysis.

Figure 12: Frequency band analysis for learning condition in left frontal ROI

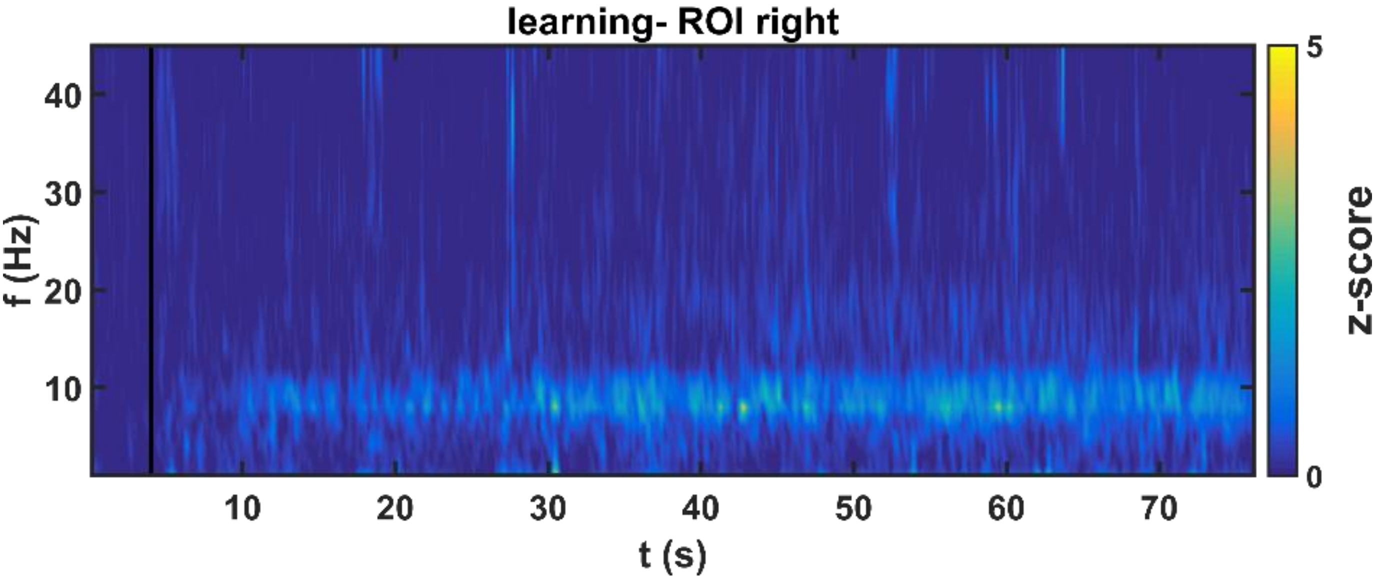

Figure 12. frequency band analysis depicting a long-time window period and important presence of alpha frequency band at right region of interest for interoceptive learning.

Hierarchical multiple regression for best factors as interoceptive learning predictors.

For hierarchical regression analysis we investigate the ability of neurophysiological evoked activity functions and frequency band (HEP and Alpha band at frontal electrodes in right, central and left ROI for the interoceptive learning period) as well as cognitive (attention) to predict interoceptive learning (table 05). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. Additionally, the correlations amongst the predictor variables (attention, HEP right and central, beta band at right and central ROI) included in the study were examined. The variation inflation factor confirmed that the amount of explained variance was not inflated because of correlation between predictors, for attention is (VIF = 1.08), for HEP ROI right: (VIF = 1.23); for ROI central (VIF = 1.21); for beta band right and central the VIF is over 1.6. This indicates that multicollinearity was unlikely to be a problem (see Tabachnick and Fidell, 2007).

We used Heart Rate, Body Mass Index as control variables. At cognitive step of hierarchical multiple regression, was statistically significant when was introduced attention variable, $F(1, 57) = 4.14$; $p = .04$ and explained 7.3% of variance in interoceptive learning. After entry of HEP ROI right and central at Step 3 ($F(2,55) = 13.30$; $p < 0.001$) the total variance explained by the model was 37.5 %. The introduction of beta frequency band at right and central ROI explained a total of 40.4% of variance in interoceptive learning. In the final adjusted model two out of five predictor variables were statistically significant, with HEP right ($\beta = -0.38$, $p = .003$) and HEP central ($\beta = -0.29$, $p = .018$) recording a higher Beta value than attention ($\beta = 0.02$, $p =.84$) right beta band, ($\beta = -0.31$, $p = 0.12$) and beta central ($\beta = 0.29$, $p = .15$).

In summary, interoceptive learning has a significant correlation with attention and heart evoked potential at right and central regions of interest. However, once are entered into the hierarchical model, just HEP show a significant predictive value, neither other cognitive nor other neurophysiological signal are significant in predictive terms into the model.

Table 5: Hierarchical multiple regression for best factors as interoceptive learning predictors.

	Control					**Cognitive**					**HEP**					**Frequency Band**				
Predictors	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*
(Intercept)	0.75		0.37 – 1.13		**<0.001**	0.49		0.04 – 0.94		**0.032**	0.57		0.19 – 0.95		**0.004**	0.65		0.26 – 1.04		**0.002**
HR.Learning	-0.00	-0.05	-0.00 – 0.00	-0.31 – 0.21	0.693	0.00	0.01	-0.00 – 0.00	-0.25 – 0.27	0.934	0.00	0.02	-0.00 – 0.00	-0.20 – 0.24	0.848	-0.00	-0.01	-0.00 – 0.00	-0.23 – 0.21	0.929
IMC	-0.00	-0.04	-0.01 – 0.01	-0.30 – 0.21	0.735	-0.00	-0.01	-0.01 – 0.01	-0.26 – 0.24	0.943	-0.00	-0.05	-0.01 – 0.01	-0.26 – 0.17	0.671	-0.00	-0.08	-0.01 – 0.01	-0.30 – 0.15	0.504
Attention						0.00	0.27	0.00 – 0.00	0.01 – 0.53	**0.046**	0.00	0.05	-0.00 – 0.00	-0.19 – 0.28	0.685	0.00	0.02	-0.00 – 0.00	-0.22 – 0.26	0.848
Roi.right.learning											-0.03	-0.41	-0.05 – -0.01	-0.64 – -0.18	**0.001**	-0.03	-0.38	-0.05 – -0.01	-0.61 – -0.14	**0.003**
Roi.central.learning											-0.02	-0.31	-0.03 – -0.00	-0.54 – -0.08	**0.011**	-0.02	-0.29	-0.03 – -0.00	-0.52 – -0.06	**0.018**
beta.right.learning																-0.13	-0.31	-0.30 – 0.04	-0.69 – 0.08	0.125
beta.central.learning																0.13	0.29	-0.05 – 0.31	-0.10 – 0.68	0.152
Observations	61					61					61					61				
R^2 / R^2 adjusted	0.005 / -0.029					0.073 / 0.024					0.375 / 0.318					0.404 / 0.325				

Note: Significant P value are represented in black. This table presents standardized beta values and confidence interval for each variable in each model. This table also presents the results of each step of the hierarchical multiple regression.

Interoceptive metacognition predictive models.

The analysis for interoceptive metacognition follows the same logic as the previous analysis for interoceptive sensitivity and interoceptive learning that is, firs we analyse cognitive factors as predictors, then evoked potential at three frontal ROIs (right, central and left) after that frequency band using the same ROIs used in HEP but considering the entire time window from interoceptive learning, finally best predictors are selected to analyse the final model.

Bivariate correlations

Best predictors (BP) for interoceptive metacognition were organised using the just best factors from previous models, that is, best predictors from cognitive, HEP amplitude and frequency band models (see table 6 and fig. 13). Best metacognitive Predictors analysed were Attention, alpha Band at left ROI.

Attention (r = -.32), show a weak correlation with interoceptive learning, alpha left shows no significant correlation (r = -0.06). See Table 06, for a detailed account of correlations and p-value thresholds.

These results suggest that there is no relation between frequency band and interoceptive learning but attention are relevant as possible predictors.

Table 6: **Best predictors to interoceptive metacognition**

Variable	*M*	*SD*	1	2	3	4
1. Metacognition	0.41	0.29				
2. IMC	24.14	2.31	.04			
3. HR MC	73.55	8.46	.16	.05		
4. Attention	63.36	13.16	-.32**	-.10	-.05	
5. alpha left MC	0.78	0.73	-.06	-.02	.21	-.03

Note: Pearson correlation r and levels of significance. *p<0.1; **p<0.05; ***p<0.001

Figure 13: **Best predictors to interoceptive metacognition**

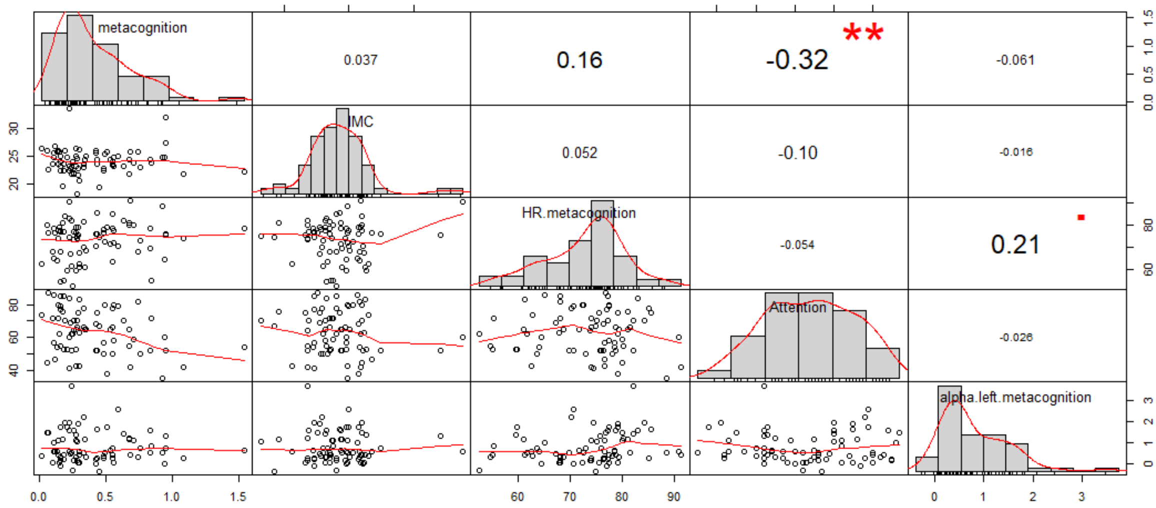

Figure 13. Correlogram represent scatter data dispersion at left side, Pearson correlation at right side and distribution of variables in diagonal.

Hierarchical multiple regression for best factors as interoceptive metacognition predictors.

For hierarchical regression analysis we investigate the ability of neurophysiological activity, specifically frequency band (Alpha band at frontal electrodes in left, ROI for the interoceptive metacognition period) as well as cognitive (attention) to predict interoceptive learning (table 7). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. Additionally, the correlations amongst the predictor variables (attention, and alpha band) included in the study were examined. The variation inflation factor confirmed that the amount of explained variance was not inflated because of correlation between predictors, for attention is (VIF = 1.01),; for alpha band left is (VIF = 1.04). This indicates that multicollinearity was unlikely to be a problem (see Tabachnick and Fidell, 2007).

We used Heart Rate, Body Mass Index as control variables. At cognitive step of hierarchical multiple regression (attention variable), was statistically significant, F (1, 71) = 7.98; p = .006 and explained 12.4% of variance in interoceptive metacognition. After entry of alpha band left (F (1,70) = 0.82; p = .36) the total variance explained by the model was 13.4 %. In the final adjusted model one out of two predictor variables were statistically significant, with attention (β = -0.32, p = .006) recording a higher Beta value than alpha left (β = -0.10, p = .36), this means that the last sept doesn't improve the predictive model.

Table 7: Hierarchical multiple regression for best factors as interoceptive metacognition predictors.

	Control					**Cognitive**					**Frequency Band**				
Predictors	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*
(Intercept)	-0.06		-0.95 – 0.83		0.887	0.51		-0.43 – 1.45		0.286	0.49		-0.45 – 1.44		0.298
HR.metacognition	0.01	0.15	-0.00 – 0.01	-0.07 – 0.38	0.190	0.00	0.14	-0.00 – 0.01	-0.08 – 0.36	0.217	0.01	0.16	-0.00 – 0.01	-0.06 – 0.38	0.163
IMC	0.00	0.03	-0.03 – 0.03	-0.20 – 0.26	0.803	-0.00	-0.00	-0.03 – 0.03	-0.22 – 0.22	0.987	-0.00	-0.00	-0.03 – 0.03	-0.22 – 0.21	0.966
Attention						-0.01	-0.32	-0.01 – -0.00	-0.54 – -0.10	**0.006**	-0.01	-0.32	-0.01 – -0.00	-0.54 – -0.10	**0.006**
alpha.left.metacognition											-0.04	-0.10	-0.13 – 0.05	-0.33 – 0.12	0.367
Observations	75					75					75				
R^2 / R^2 adjusted	0.025 / -0.002					0.124 / 0.087					0.134 / 0.084				

Note: Significant P value are represented in black. This table presents standardized beta values and confidence interval for each variable in each model. This table also presents the results of each step of the hierarchical multiple regression.

In summary, for interoceptive metacognition, just attention show a significant correlation as well as a significant predictive value into the hierarchical model.

Interoceptive sensibility predictors (self-report measure).

Cognitive predictors for interoceptive sensibility.

Bivariate correlations between interoceptive sensibility and cognitive factors

Attention (r = .09), Fluid intelligence (r = .15) and executive functions (r = .02) show non-significant correlation with interoceptive sensibility. See Table 08 and fig. 14 for a detailed account of correlations and p-value thresholds.

These results suggest that cognitive factors have no relation with interoceptive sensibility.

Table 8: Correlation between cognitive predictors and interoceptive sensibility

Variable	*M*	*SD*	1	2	3	4	5
1. Sensibility	73.01	20.19					
2. IMC	24.12	2.29	.09				
3. HR sensibility	72.65	11.62	.01	.06			
4. Attention	63.71	13.43	.09	-.07	-.17		
5. Fluid Intelligence	19.01	4.21	.15	-.03	-.23*	.27*	
6. Executive Functions	23.62	3.97	.02	-.10	-.13	.10	.28*

Note: Pearson correlation r and levels of significance. *p<0.1; **p<0.05; ***p<0.001

Figure 14: Bivariate correlations between interoceptive sensibility and cognitive factors

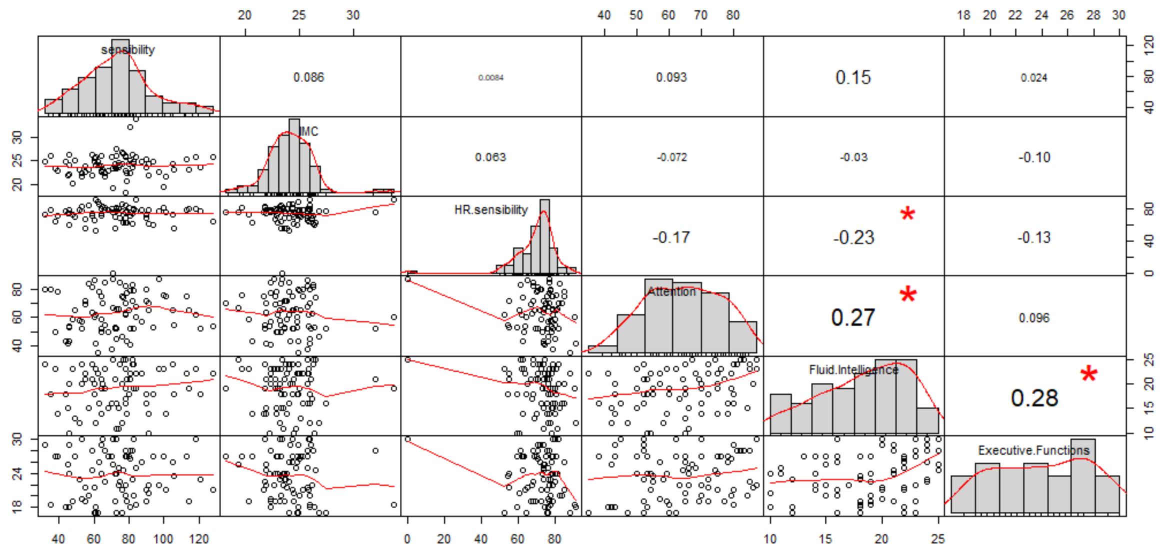

Figure 14. Correlogram represent scatter data dispersion at left side, Pearson correlation at right side and distribution of variables in diagonal.

Hierarchical multiple regression for cognitive factors as interoceptive sensibility predictors.

For hierarchical regression analysis we investigate the ability of cognitive functions (attention, fluid intelligence, and executive functions) to predict interoceptive metacognition (table 9). Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. Additionally, the correlations amongst the predictor variables (attention, fluid intelligence, and executive functions) included in the study were examined. The variation inflation factor confirmed that the amount of explained variance was not inflated because of correlation between predictors, using as criteria a VIF score 1.6, for attention: (VIF = 1.03); for fluid intelligence (VIF = 1.11); for executive functions (VIF = 1.09). This indicates that multicollinearity was unlikely to be a problem (see Tabachnick and Fidell, 2007). No model shows significant predictive value.

In summary, neither cognitive nor neurophysiological factors show a correlation or predictive value for interoceptive sensibility.

Table 9: Hierarchical multiple regression for cognitive factors as interoceptive sensibility predictors.

	Control					Attention					Fluid Intelligence					Executive Functions				
Predictors	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*	*Estimates*	*std. Beta*	*CI*	*standardized CI*	*p*
(Intercept)	54.39		-0.23 – 109.00		0.051	40.95		-21.46 – 103.36		0.195	27.73		-38.31 – 93.78		0.406	28.73		-43.88 – 101.34		0.433
HR.sensibility	0.01	0.00	-0.39 – 0.40	-0.22 – 0.23	0.979	0.04	0.02	-0.36 – 0.44	-0.21 – 0.25	0.859	0.08	0.05	-0.32 – 0.49	-0.18 – 0.28	0.689	0.08	0.05	-0.33 – 0.49	-0.19 – 0.28	0.695
IMC	0.76	0.09	-1.24 – 2.75	-0.14 – 0.31	0.453	0.81	0.09	-1.19 – 2.81	-0.13 – 0.32	0.422	0.81	0.09	-1.18 – 2.81	-0.13 – 0.32	0.420	0.81	0.09	-1.21 – 2.83	-0.13 – 0.32	0.428
Attention						0.16	0.10	-0.19 – 0.50	-0.12 – 0.33	0.376	0.10	0.07	-0.25 – 0.46	-0.16 – 0.30	0.562	0.10	0.07	-0.25 – 0.46	-0.17 – 0.30	0.564
Fluid.Intelligence											0.69	0.14	-0.46 – 1.83	-0.09 – 0.38	0.237	0.70	0.15	-0.50 – 1.89	-0.10 – 0.39	0.248
Executive.Functions																-0.04	-0.01	-1.25 – 1.17	-0.24 – 0.23	0.946
Observations	80					80					80					80				
R^2 / R^2 adjusted	0.007 / -0.018					0.018 / -0.021					0.036 / -0.015					0.036 / -0.029				

Note: Significant P value are represented in black. This table presents standardized beta values and confidence interval for each variable in each model. This table also presents the results of each step of the hierarchical multiple regression.

Neuroimage results

VBM: Multiple regressions results

All our variables of interest showed associations with GM volume. We found significant positive associations between interoception scores and the GM volume in fronto temporo insular areas (fig. 15). Regarding attention, we found positive associations with the insula, and fronto-temporal areas (fig. 16). As for fluid intelligence, there were associations with a wide variety of areas including the insula and across the parietal, temporal, occipital and frontal lobules as well as the anterior cingulate cortex (fig. 17). Finally, HEP sensitivity was mainly negatively associated the insula and temporal areas (fig 18).

The overlap between areas related to interoception, cognition and HEP is represented in figure 19. Here, mainly ParaHippocampal and insular regions reflect this overlap.

Figure 15: Brain volume correlates of interoception.

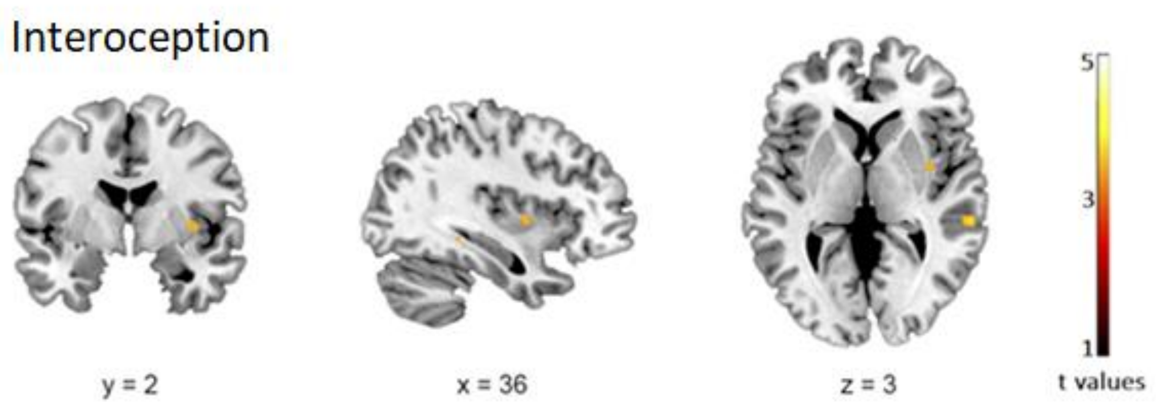

Figure 15. Brain regions significantly associated with interoception, as measured in interoceptive behavioural task ($p < .001$, extent threshold = 30 voxels).

Table 10. Grey matter volume areas positively associated with the **interoception**, controlling for total intracranial volume ($p < .001$, extent threshold = 30 voxels)

Nº Voxels	Peak t-value	MNI Coordinates x	y	z	Brain area (AAL atlas)
147	4,44	46,5	-43,5	24	Angular R
146	3,91	30	-43,5	-4,5	ParaHippocampal R
	3,84	60	-31,5	1,5	Temporal Sup R
120	3,35	52,5	-37,5	-4,5	Temporal Mid R
45	3,52	36	-1,5	3	Insula R

Figure 16: Brain volume correlates of attention.

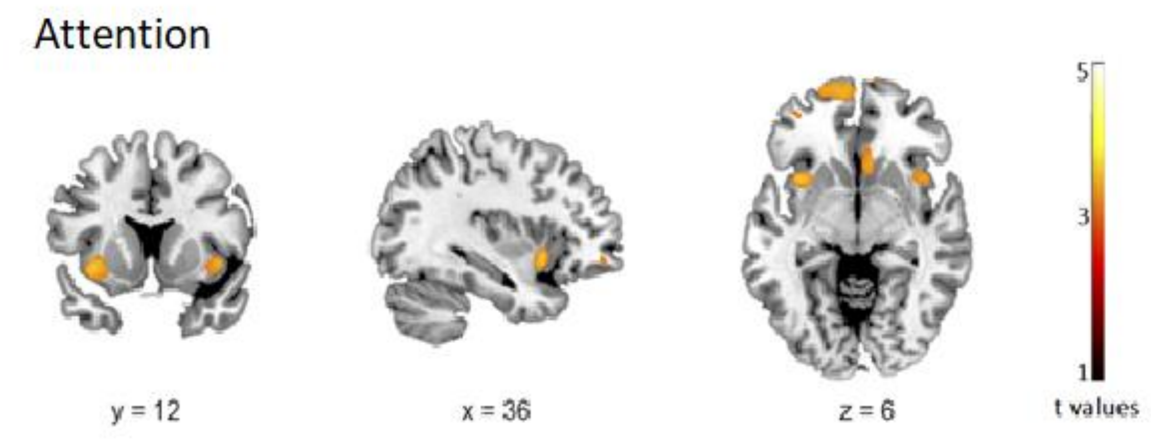

Figure 16. Brain regions significantly associated with attention, measured with digits and symbols from WAIS IV ($p < .001$, extent threshold = 30 voxels).

Table 11. Grey matter volume areas positively associated with attention scores, controlling for total intracranial volume ($p < .001$, extent threshold = 30 voxels)

Nº Voxels	Peak t-value	MNI Coordinates x	y	z	Brain area (AAL atlas)
3207	4,98	-6	57	-16,5	Rectus L
	4,84	-18	55,5	-18	Frontal Mid Orb L
	4,43	24	58,5	-18	Frontal Mid Orb R
130	4,26	-15	-91,5	16,5	Occipital mid L

275	4,00	-36	12	-6	Insula L
163	3,79	40,5	13,5	-3	Insula R
195	3,77	1,5	60	7,5	Frontal Sup Medial R
272	3,74	9	22,5	-7,5	Cingulum Ant R
125	3,67	57	-18	-18	Temporal Mid R
	3,66	69	-9	-19,5	Temporal Mid R
104	3,59	-37,5	49,5	-7,5	Frontal Mid Orb L
130	3,58	-40,5	49,5	-15	Frontal Mid Orb L

Figure 17: Brain volume correlates of fluid intelligence.

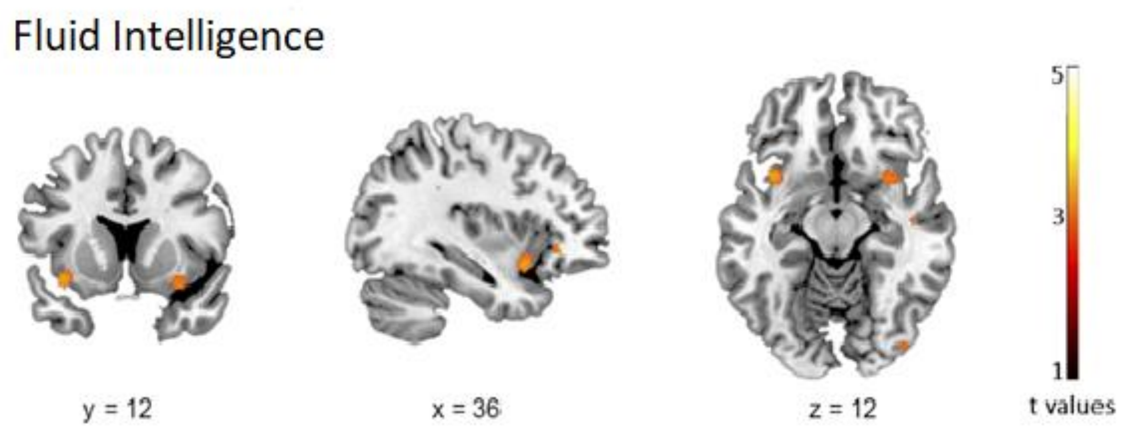

Figure 17. Brain regions significantly associated with fluid intelligence, as measured with matrix from WAIS IV ($p < .001$, extent threshold = 30 voxels).

Table 12. Grey matter volume areas positively associated with fluid intelligence scores, controlling for total intracranial volume ($p < .001$, extent threshold = 30 voxels)

Nº Voxels	Peak t-value	MNI Coordinates x	y	z	Brain area (AAL atlas)
2718	6,39	66	-30	3	Temporal Sup R
	4,14	49,5	-22,5	1,5	Temporal Sup R
	3,96	55,5	-36	22,5	Parietal Sup R
67	4,44	-25,5	-48	43,5	SupraMarginal R
683	4,38	-10,5	-51	13,5	Precuneus L

	3,79	-12	-66	28,5	Cuneus L
	3,49	-21	-64,5	13,5	Frontal Sup L
200	4,11	-16,5	34,5	40,5	Frontal Sup L
42	4,04	-36	33	-4,5	Frontal Inf Orb L
161	3,94	34,5	4,5	12	Insula R
144	3,94	-36	12	-12	Insula L
174	3,92	-19,5	52,5	12	Frontal Sup L
130	3,87	40,5	-87	-4,5	Occipital Inf R
	3,66	33	-93	-1,5	Occipital Inf R
105	3,66	9	52,5	15	Frontal Sup Medial R
122	3,60	31,5	10,5	-13,5	Frontal Sup R
233	3,59	-3	24	-6	Olfactory L
	3,42	-3	30	1,5	Cingulum Ant L
33	3,49	19,5	4,5	-15	Amygdala R

Figure 18: Brain volume correlates of HEP.

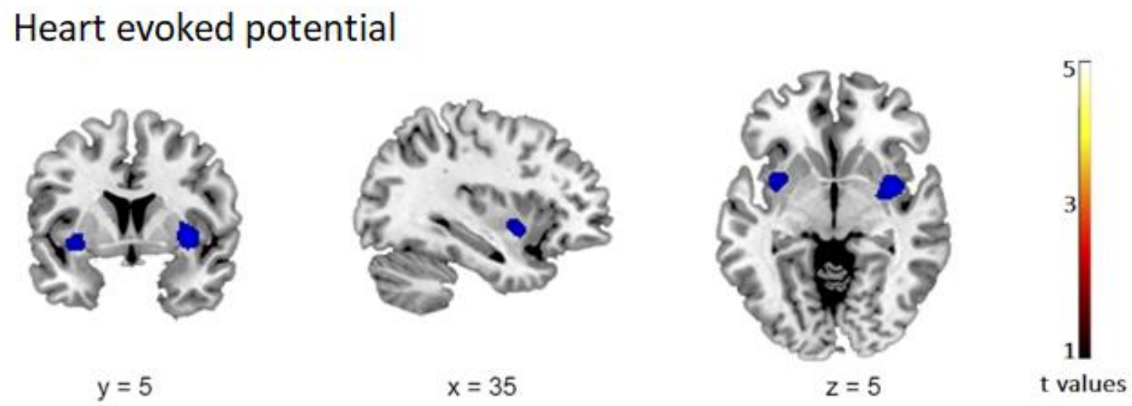

Figure 18. Brain regions significantly associated with HEP sensitivity, measured via EEG during an interoceptive task ($p < .001$, extent threshold = 30 voxels).

Table 13. Grey matter volume areas negatively associated with HEP scores, controlling for total intracranial volume ($p < .001$, extent threshold = 30 voxels)

Nº Voxels	Peak	MNI Coordinates	Brain area (AAL atlas)

	t-value	x	y	z	
886	5,28	34,5	0	3	Putamen R
454	4,53	36	-33	-12	ParaHippocampal R
	3,40	27	-42	-9	Fusiform R
456	4,46	51	-76,5	4,5	Temporal Mid R
	3,75	43,5	-72	16,5	Temporal Mid R
139	4,29	-16,5	-37,5	6	Hippocampus L
269	4,01	-34,5	4,5	-4,5	Insula L
39	3,86	54	-72	-10,5	Temporal Inf R

Figure 19: brain structural region overlaps between interoception, HEP, and cognitive domains.

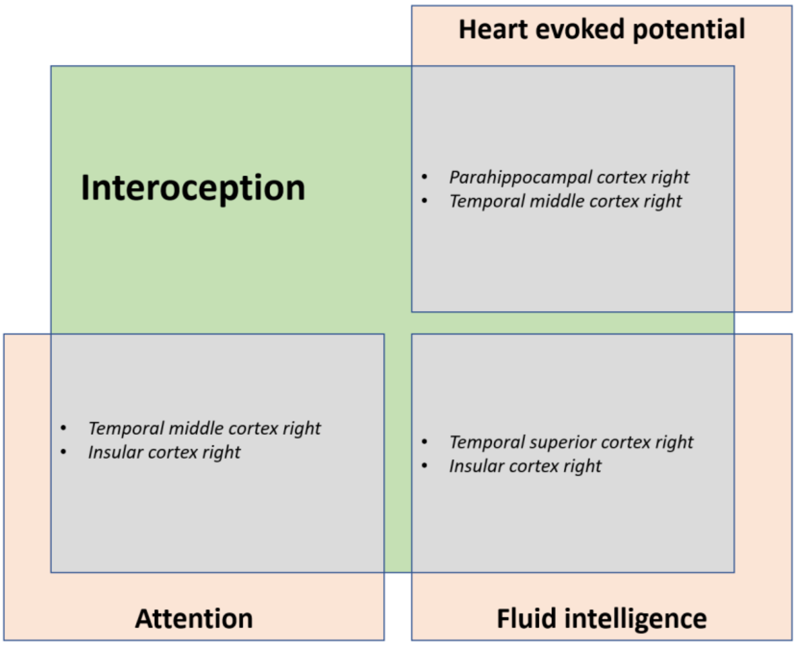

Figure 19. represent the brain structural regions overlapping between interoception and HEP, Attention & fluid intelligence.

Functional connectivity results

We found significant association between Interoception, Cognition (attention, fluid intelligence) & HEP with functional connectivity among key areas with cognition and integration of information.

Briefly, interoception scores were associated with increased functional connectivity within a wide network comprising frontal, orbital, thalamic and temporal regions (fig 20). Cognition (attention, Fluid intelligence) is associated with increased functional connectivity mainly between the frontal, temporal poles and motor areas (fig 21). Lastly, HEP is associated with the functional connectivity of a more circumscribed set of areas, mainly comprising frontal, hippocampal and amygdala (fig 22).

Specific overlap between functional connectivity from interoceptive awareness and attention, fluid intelligence and heart evoked potential is represented in figure 23.

Figure 20: Functional connectivity of interoception.

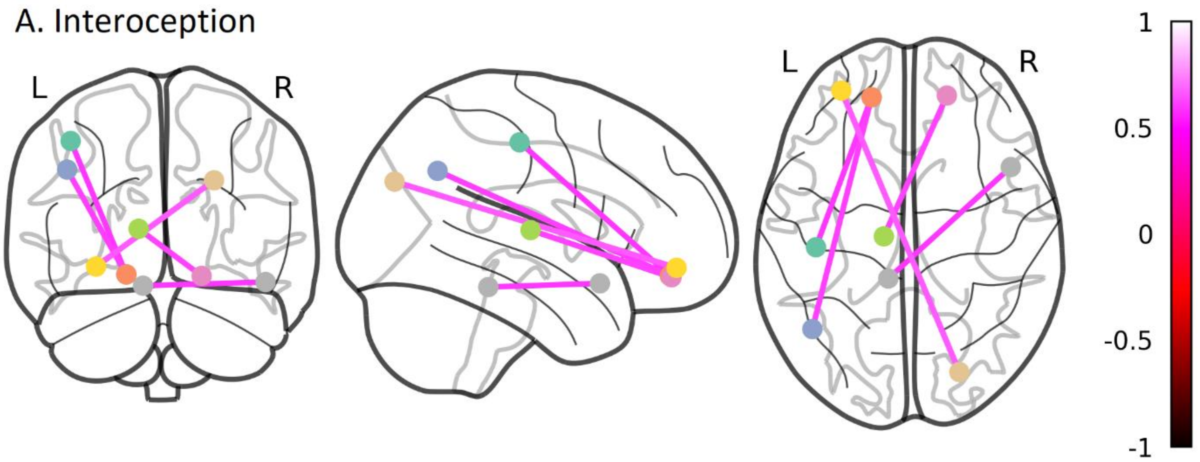

Figure 20. Correlation between resting-state functional connectivity and **A.** Interoceptive behavior. The figure above shows pair of areas with a threshold of p<0.001.

Table 14. Functional connectivity associated with Interoception.

Interoception		
Regions	**Parson's r**	***p*-value**
Frontal Sup Orb L - Postcentral L	0.59	<.001
Frontal Sup Orb L - Angular L	0.61	<.001
Frontal Sup Orb R - Thalamus L	0.62	<.001
Frontal Mid Orb L - Occipital Sup R	0.66	<.001
Temporal Pole Sup R - Cerebellum L	0.77	<.001

Figure 21: Functional connectivity of cognition.

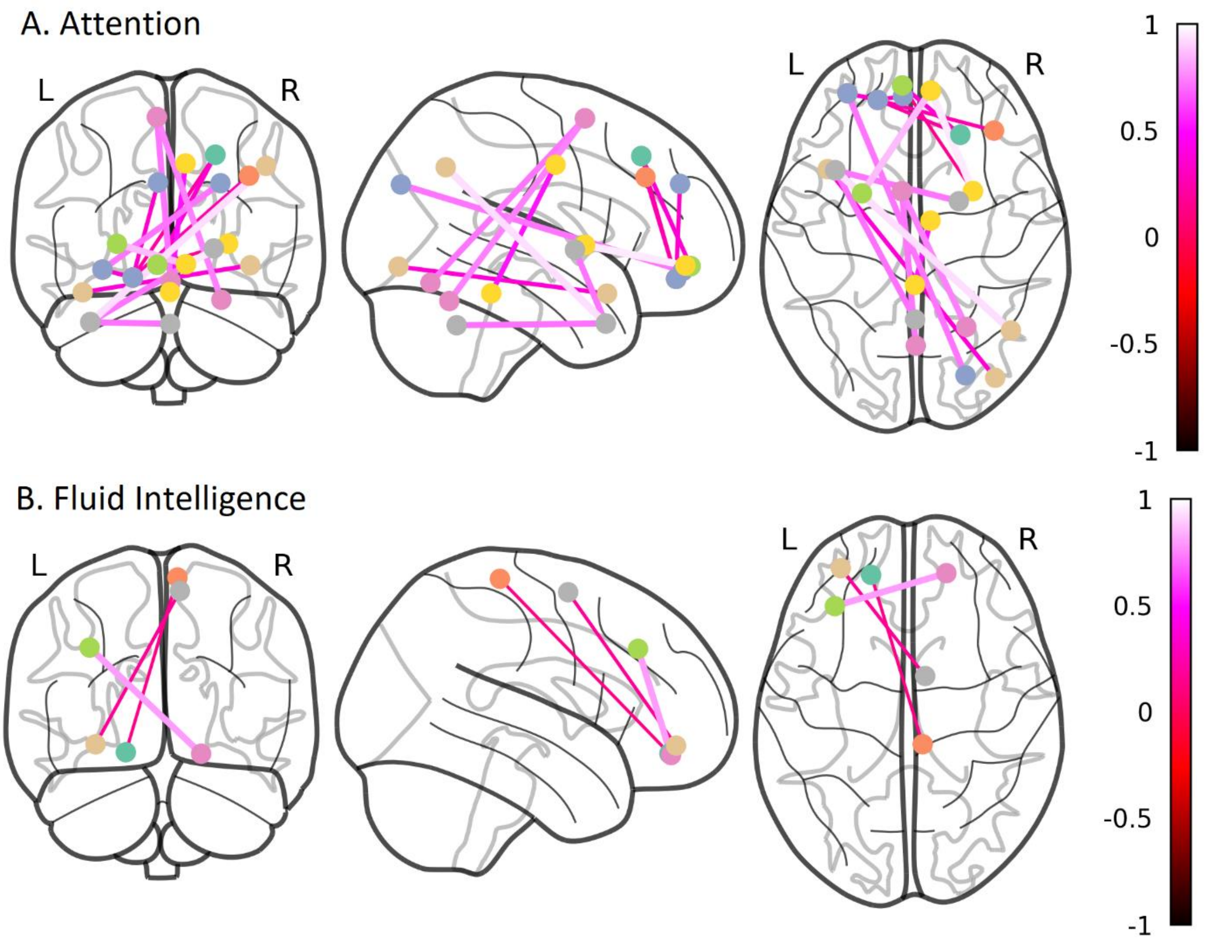

Figure 21. Correlation between resting-state functional connectivity and **A.** Attention, **B.** Fluid intelligence. The figure above shows pair of areas with a threshold of p<0.001.

Table 15. Functional connectivity associated with Interoception and Metacognition

Attention		
Regions	**Parson's r**	***p*-value**
Frontal Sup R - Frontal Sup Orb L	0.64	<.001
Frontal Sup R - Frontal Med Orb L	0.62	<.001
Frontal Sup Orb L - Frontal Mid R	0.63	<.001
Frontal Sup Orb L - Frontal Mid Orb L	0.62	<.001
Frontal Sup Orb L - Frontal Sup Medial L	0.62	<.001
Frontal Mid Orb L - Occipital Sup R	0.60	<.001
Supp Motor Area L - Cerebelum R	0.60	<.001
Supp Motor Area L - Vermis	0.60	<.001
Frontal Med Orb L - Putamen R	0.65	<.001
Frontal Med Orb R - Putamen L	0.59	<.001
Frontal Med Orb R - Putamen R	0.73	<.001
Cingulum Mid R - Vermis	0.61	<.001
Occipital Inf R - Temporal Pole Sup L	0.62	<.001
Angular R - Temporal Pole Mid L	0.59	<.001
Pallidum R - Temporal Pole Mid L	0.60	<.001
Temporal Pole Mid L - Vermis	0.60	<.001

Fluid intelligence		
Regions	**Parson's r**	***p*-value**
Frontal Sup Orb L - Paracentral Lobule R	0.66	<.001
Frontal Sup Orb R - Frontal Mid L	0.59	<.001
Frontal Mid Orb L - Supp Motor Area R	0.64	<.001

Figure 22: Functional connectivity of HEP.

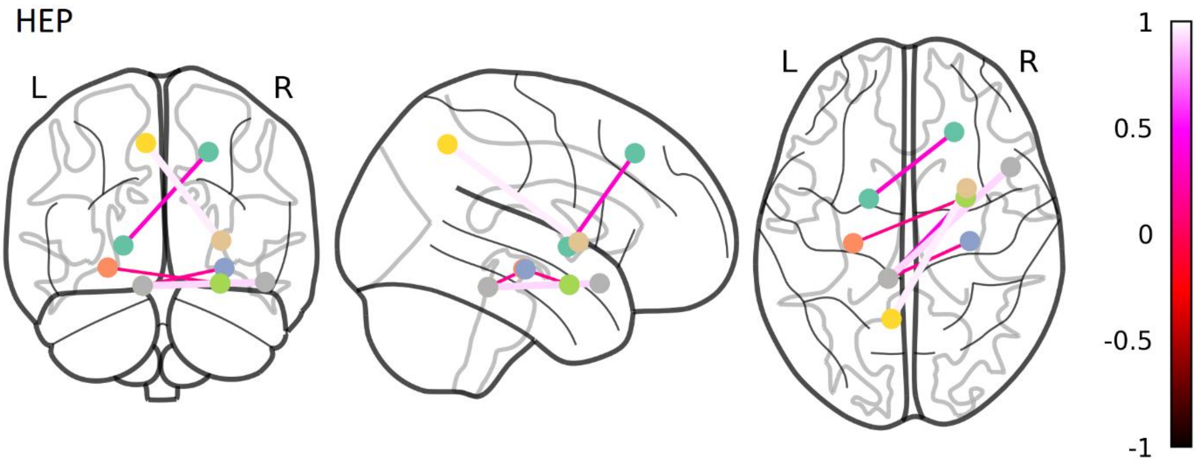

*Figure 22***.** Correlation between resting-state functional connectivity and Heart evoked potential. The figure above shows pair of areas with a threshold of p<0.001.

Table 16. Functional connectivity associated with Interoception and Metacognition

HEP		
Regions	**Parson's r**	***p*-value**
Frontal Sup R - Pallidum L	0.63	<.001
Hippocampus L - Amygdala R	0.67	<.001
Hippocampus R - Cerebelum L	0.66	<.001
Amygdala R - Cerebelum 3 L	0.63	<.001
Precuneus L - Putamen R	0.59	<.001
Temporal Pole Sup R - Cerebelum L	0.60	<.001

Figure 23: Brain functional connectivity overlap between interoception, HEP and cognitive domains.

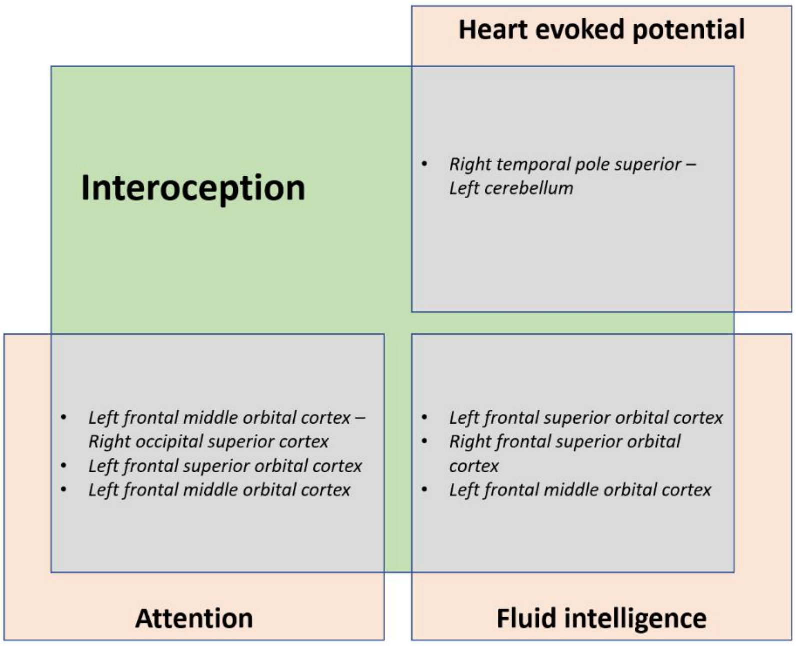

Figure 23 represent the brain functional regions overlapping between interoception and HEP, Attention & fluid intelligence.

Discussion

This work provides, for the first time, a multilevel approach to examine the proposed relationship between *interoceptive awareness* (in its dimensions: sensitivity, learning, metacognition, sensibility), *cognitive domains* (attention, fluid intelligence and executive functions) and *neurophysiological signatures* (heart evoked potential and frequency band), considering neuro anatomical and functional brain correlates as an explanatory bridge among them.

The first aim of this thesis was to study the relationship among *interoceptive sensitivity* (accuracy) and cognitive (attention, fluid intelligence and executive functions) and neurophysiological variables (frontal heart evoked potential and alpha frequency band). We anticipated that of these factors, attention (due to its importance for interoceptive behavior) and frontal evoked potential (important in reflecting inner focus) will explain variability the most. By doing an interoceptive task during EEG recording and subsequent cognitive evaluation, our data showed, as expected, involvement of cognition, mainly *attention* and *fluid intelligence* as predictors of interoceptive sensitivity. Additionally, neurophysiology throughout the *heart evoked potential lateralized at right frontal electrodes* predicted interoceptive sensitivity.

Our second aim was to examine the relationship between *interoceptive learning*, cognitive functions (mainly fluid intelligence and executive functions), and neurophysiological factors, namely, theta, beta frequency band and heart evoked potential. We hypothesised *that interoceptive learning* is predicted by these factors due to the need of self-monitoring and self-regulatory cognitive skills, and to neural signatures related to these abilities. By doing an interoceptive learning task, our data showed that only *heart evoked potential in frontal right and fronto central regions of interest* (ROI) play a predictive role in interoceptive learning.

The third aim was - because the scarce literature about it - more exploratory and attempted to study *metacognitive interoception,* this consists in a self-evaluation regards own performance in an interoceptive task, and its relationship with cognitive function. We predicted that attention and fluid intelligence play a relevant role in predicting metacognitive interoception, as well as gamma frequency band, which has been proposed as a proxy for this behavior. By asking metacognitive questions during an interoceptive task, our results showed that only *attention* predicts metacognitive interoception.

Our fourth objective was to know the role of cognition over *interoceptive sensibility* (self-report), mainly fluid intelligence and executive functions. Due to the role of self-monitoring on a self-report measure, we hypothesised that these cognitive skills are predictors of this self-body perception measure. However, our study of interoceptive sensibility measured trough a self-reported scale, showed that none of the proposed variables predicted interoceptive sensibility.

Finally, we explored the possible overlap between interoception, cognitive skills and neurophysiological correlates through *structural* and *global functional connectivity*. Structural findings (volume) showed that interoception, attention and fluid intelligence share the *insular right cortex*. Functional analysis showed that interoception, attention and fluid intelligence share the *frontal orbital cortex*.

Interoceptive Sensitivity

Interoceptive sensitivity, is the most common interoceptive measure and corresponds to an accuracy measure. It has been associated to socio-cognitive (Dunn et al., 2010; Fukushima, Terasawa, & Umeda, 2011; Grynberg & Pollatos, 2015), affective (Dunn et al., 2010; Garfinkel & Critchley, 2013; Gentsch, Sel, Marshall, & Schütz-Bosbach, 2019) and cognitive processes (Brener & Ring, 2016; Gentsch et al., 2019; W. Mehling, 2016; Tsakiris & Critchley, 2016; Uddin et al., 2014b).

The data from our first hierarchical model support the idea that cognitive functions are crucial for interoceptive sensitivity, based on that attention and fluid intelligence together conform the basis to the awareness about inner states, helping to elaborate a compressible understanding of our global state and being alert about any dysregulation of homeostatic state (Tsakiris & Critchley, 2016). Our cognitive model indicates that interoceptive sensitivity is predicted by *attention* and *fluid intelligence* mainly, confirming the hypothesis that *attentional* function is the most relevant. Attention is key in the task itself, but it has also been previously found to have some important brain hubs that are important in interoception, such as the insulate cortex, anterior cingulate cortex, and orbital frontal areas (Albert et al., 2016; Chambers & Heinen, 2010; Colby, 1991; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Klabunde et al., 2019). Additionally, fluid intelligence, which is related to self-monitoring, it is the second variable that most contributes significantly to this model and is characterized by an increase in volume to common interoceptive areas as lateral *pre-frontal cortex* (lPFC), *orbitofrontal cortex* (OFC) *hippocampus* (HC), and *cerebellar hemispheres* (Raz et al., 2008).

Regarding the second hierarchical model, we tested the predictive value of HEP for interoceptive sensitivity, evaluating frontal electrodes. As we expected, and according to the literature, we found that this *evoked potential* represents a strong neural correlate of cardiac interoception. Additionally, its negative deflection has been related to inner attentional focus, which is more negative in subjects with best interoceptive skills (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015). Whereas central and frontal regions have been reported mainly (Canales-Johnson, Silva, Huepe, Rivera-Rei, Noreika, Del Carmen Garcia, et al., 2015; Montoya et al., 1993),we used frontal electrodes divided into right, central and left ROIS, and we found that *right* and *central* regions of interest predicted the highest *sensitivity variance*, which could reflect a possible lateralized neural synchronization.

In the third model, we analysed frequency bands related to inner attentional focus, mind wandering and interoception (alpha) (Compton, Gearinger, & Wild, 2019; Villena-González et al., 2017), cognitive attentional performance (gamma) (Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2005), and executive functional behavior (beta and theta bands) (Sauseng, Klimesch, Schabus, & Doppelmayr, 2005). With the idea of analysing the neural correlates of a mental state during the task, we analysed an extended time window, considering the duration of the entire interoceptive block. Our data show that a*lpha band* in frontal left electrodes, predicts variance the most, over other frequency bands, and it is the only one that explains interoceptive variance significantly.

The fourth model combines a selection of the best predictors from the previous models, in this way, cognitive (attention, fluid intelligence) and neurophysiological (HEP and alpha frequency band) were selected. So far, *attention* plays a key role predicting this interoceptive measure and *HEP in right electrodes* contributes to the model in the second place. However, the rest of variables do not explain variance significantly. This is interesting, because all of these factors are relevant in their own domains, for example, fluid intelligence is important in the cognitive model, but it loses significance in this multilevel model. Only attention keeps being relevant together with heart evoked potential.

Interoceptive Learning

In our first learning model (cognitive model), we suggested that only attention would play a crucial role in interoceptive learning, which means that self-monitoring and self-regulatory skills (executive functions and fluid intelligence) are recruited only for visceral perception the first time, when the experience is new and there is conscious demand. Our data confirm that that once people learn to perceive their own heartbeat only *attention* is needed.

In the second model, *heart evoked potential*, both *right and central* ROIs are predict interoceptive learning, interestingly, neural correlates shows a more distributed effect for this dimension than other interoceptive dimensions.

In the third model about frequency bands, just *beta band* shows a relevant role in interoceptive learning. This frequency band has been related to cognitive processes involved in go-no-go tasks, like inhibition and attention (Rossiter, Davis, Clark, Boudrias, & Ward, 2014; Wu et al., 2019). This could reflect attentional and inhibitory demands for interoceptive learning.

The fourth model, integrative model which combines attentional, HEP and beta band contribution, shows that just *HEP* is a relevant factor. This mean that once people learn how to perceive their inner body, only neural correlates related to heart beat signal predict interoceptive learning, none cognitive nor frequency band.

Since interoception is related to homeostatic processes and contributes to organism and mental wellbeing, the possibility to train interoceptive behavior may be an enormous contribution to health and wellbeing. Many studies have reported that interoception is severely altered in various health conditions, for example, mood disorders (Eggart, Lange, Binser, Queri, & Müller-Oerlinghausen, 2019; Furman, Waugh, Bhattacharjee, Thompson, & Gotlib, 2013), anxiety (Krautwurst et al., 2016), eating disorders (Jenkinson, Taylor, & Laws, 2018), and addictive behavior (Ibañez, Vicencio, Quintanilla, & Maldonado, 2019). In some cases, such as in anxiety, interoception is characterized by an abnormal increase in heart perception, while in other cases, such as mood disorders, a lack of visceral perception has been reported (Eggart et al., 2019; Paulus & Stein, 2010b; Pollatos, Traut-Mattausch, & Schandry, 2009). As the relevance of cognitive aspects in our data, like attention, it is possible to think that interoception is a behavior susceptible to be trained trough cognitive abilities and moreover, it could be used as an important component of therapy for different health issues.

Interoceptive metacognition

In the first model we evaluated the role of cognitive abilities, namely, attention, fluid intelligence and executive functions on interoceptive metacognition, expecting to find a main effect of self-monitoring (fluid intelligence). However, we found that *attention* was the most important variable for metacognition. This result could reflect that perception of bodily states does not depend totally on self-regulatory processes but mainly on attentional and likely inhibitory capabilities.

Lastly, in the integrative model, which included alpha frequency band as predictor, again showed that *attentional* skills had the most relevant role. This could indicate that cognition, specifically *attention* explain interoceptive metacognitive processes, more than neural activity.

Interoceptive metacognition is a critical function to evaluate our own interoceptive capabilities, which is key in self-awareness. Here cognitive components mainly related to attention and self-monitoring are crucial factors. In this sense, interoceptive metacognition is relevant for example for the decisions that we make to keep our organism in balance.

Interoceptive Sensibility

This is the most exploratory study in this project. The relevance of this study is to understand if *self-belief* in regard to bodily state is related to *cognitive signatures*. Beliefs about body changes, measured trough interoceptive sensibility scales, have been associated to emotion regulation (Willem et al., 2019) and anxiety (Melzig, Michalowski, Holtz, & Hamm, 2008), and both have an important cognitive component related to self-regulation, inhibition, and attentional focus (Scheibe & Blanchard-Fields, 2009). However, cognitive signature shows no effect on interoceptive sensibility which means that even when cognitive aspects have been strongly related with emotions, it seems that body changes do not require attention nor self – monitoring skills. Future studies could explore other cognitive aspects, such as memory for example.

Neuroanatomical and functional correlates of interoception and their association with heart evoked potential and cognition.

Structural correlates

Brain structures related to interoception measured trough morphometry are anterior insula, operculum region, orbitofrontal cortex and medial cerebellar gray matter (Critchley et al., 2004). Our data show that, *right angular gyrus,* related to cognitive functions as language, number processing, attention, and theory of mind; *right ParaHippocampal region,* related to cognitive-social skills, specifically helping to understand social paralinguistic context; *right temporal superior cortex*, related to social conceptualization; *right middle temporal cortex*, related to auditory functions and social anxiety; and *right insula*, related to visceral perception and integration of sensorial stimulus; have an increase in gray matter volume related to interoceptive awareness. In summary, all of these regions previously related to cognitive and social skills, in our brain morphometric analysis are related to interoceptive awareness. These founding support our idea that there is a dependency between cognitive capabilities and interoceptive awareness.

Additionally, we found a qualitative morphometric overlap between interoception and HEP in ParaHippocampal and temporal middle cortex, interoception and attention in temporal middle cortex and right insular cortex. Finally, an overlap between interoception and fluid intelligence at temporal superior cortex and right insular cortex.

Functional correlates

Functional connectivity from a resting state period, covariates with interoception, measured trough whole brain analysis shows an important effect between *orbitofrontal areas* and, *thalamic*, *postcentral* and *cerebellum* regions. Orbital regions have been related to control and regulatory behavior, mainly in social and cognitive contexts but also have been proposed as an interoceptive centre, very close with insular and cingulate cortices. Thalamic cortical network has been associated with consciousness and motivated behavior and is an important pathway to communicate afferent signal from the body to the brain cortex.

Conclusions, limitations, and future directions

Our study was able to confirm and understand better the relationship between cognitive and neurophysiological variables and interoception, which will allow us to study this thoroughly through experimental designs, which was our main limitation. In the future, it would be very valuable to test our models using an experimental design, for example in a sample of subjects with interoceptive difficulties such as in the case of Attention Deficit and Hyperactivity Disorder (ADHD) and compare them with healthy controls.

Another limitation of our study is that neuroimaging measures were not taken from the entire sample, moreover, they were taken from a resting state, not from an interoceptive active task. However, our sample was large enough to be confident in our results, and we could shed light about the role of relevant variables in interoception from hierarchical models.

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