



Research report

Insula mediates heartbeat related effects on visual consciousness

Roy Salomon ^{a,b,c,*}, Roberta Ronchi ^{b,c}, Jonathan Dönz ^{b,c},
 Javier Bello-Ruiz ^{b,c}, Bruno Herbelin ^{b,c}, Nathan Faivre ^{b,c,d},
 Karl Schaller ^{e,f} and Olaf Blanke ^{b,c,e,f}

^a Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan, Israel

^b Laboratory of Cognitive Neuroscience, Ecole Polytechnique Fédérale de Lausanne, Geneva, Switzerland

^c Center for Neuroprosthetics, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Geneva, Switzerland

^d Centre d'Economie de La Sorbonne, CNRS UMR, Paris, France

^e Department of Neurology, University Hospital, Geneva, Switzerland

^f Neurosurgery Division, Department of Clinical Neurosciences, Geneva University Hospitals, Geneva, Switzerland

ARTICLE INFO

Article history:

Received 19 July 2017

Reviewed 31 October 2017

Revised 20 December 2017

Accepted 15 January 2018

Action editor Zoltan Dienes

Published online 31 January 2018

Keywords:

Interoception

Heartbeat

Brain-damaged patients

Anterior insula

Visual awareness

Cardio-visual interaction

ABSTRACT

Interoceptive signals, such as the heartbeat, are processed in a network of brain regions including the insular cortex. Recent studies have shown that such signals modulate perceptual and cognitive processing, and that they impact visual awareness. For example, visual stimuli presented synchronously to the heartbeat take longer to enter visual awareness than the same stimuli presented asynchronously to the heartbeat, and this is reflected in anterior insular activation. This finding demonstrated a link between the processing of interoceptive and exteroceptive signals as well as visual awareness in the insular cortex. The advantage for visual stimuli which are asynchronous to the heartbeat to enter visual consciousness may indicate a role for the anterior insula in the suppression of the sensory consequences of cardiac signals. Here, we present data from the detailed investigation of two patients with insular lesions (as well as four patients with non-insular lesions and healthy age matched controls) indicating that a lesion of the anterior insular cortex, but not of other regions, abolished this cardio-visual suppression effect. The present data provide causal evidence for the role of the anterior insula in the integration of internal interoceptive and external sensory signals for visual awareness.

© 2018 Published by Elsevier Ltd.

1. Introduction

Interoceptive signals convey information regarding the internal physiological states of the body and allow homeostatic control. Despite the importance and the spread of their

sensory effects (Birznieks, Boonstra, & Macefield, 2003, 2012; Ohl, Wohltat, Kliegl, Pollatos, & Engbert, 2016), they typically remain unnoticed and are not accessed consciously (Critchley & Harrison, 2013). Furthermore recent studies have shown that interoceptive (especially cardiac) signals impact

* Corresponding author. Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, 52900, Ramat Gan, Israel.

E-mail address: royesal@gmail.com (R. Salomon).

<https://doi.org/10.1016/j.cortex.2018.01.005>

0010-9452/© 2018 Published by Elsevier Ltd.

emotional (Garfinkel et al., 2014), cognitive (Allen et al., 2016; Dunn et al., 2010)), low-level perceptual (Gray, Rylander, Harrison, Wallin, & Critchley, 2009; Sandman, McCanne, Kaiser, & Diamond, 1977) and self-related processing (Aspell et al., 2013; Babo-Rebelo, Richter, & Tallon-Baudry, 2016; Craig, 2009, 2010; Damasio, 2000; Park & Tallon-Baudry, 2014; Park et al., 2016; Sel, Azevedo, & Tsakiris, 2016; Suzuki, Garfinkel, Critchley, & Seth, 2013). Concerning the self, interoceptive signals such as the heartbeat are thought to provide internally generated signals which have been suggested to provide a fundamental basis for self-representation (Babo-Rebelo, Wolpert, Adam, Hasboun, & Tallon-Baudry, 2016; Craig, 2010; Damasio, 2000; Seth, Suzuki, & Critchley, 2011). Indeed, several recent studies have linked interoceptive processing to self-related thoughts (Babo-Rebelo, Richter, et al., 2016) as well as bodily self-consciousness (Aspell et al., 2013; Park et al., 2016, 2017; Sel et al., 2016; Suzuki et al., 2013).

Earlier work suggested that cardiac activity causes a general suppression of cortical excitability (Koriath & Lindholm, 1986; Lacey & Lacey, 1970; but see; Walker & Sandman, 1982) as well as modulations of sensory and neural processing for auditory, tactile and nociceptive stimuli (Edwards, Inui, Ring, Wang, & Kakigi, 2008; Edwards, Ring, McIntyre, & Carroll, 2001; Edwards, Ring, McIntyre, Winer, & Martin, 2009; Gray et al., 2009; van Elk, Lenggenhager, Heydrich, & Blanke, 2014). This was extended recently in a series of experiments to visual awareness by showing that visual stimuli presented at the frequency of the heartbeat are suppressed from awareness compared to the same stimuli presented asynchronously to the heartbeat (Salomon et al., 2016). Furthermore, in two fMRI experiments this suppression effect was associated with reduced BOLD activity in the anterior insula during synchronous, but not asynchronous, cardio-visual trials. These results provided novel evidence that bilateral anterior insular cortex, central nodes of interoceptive processing (Craig, 2002, 2003; Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004), may modulate the visual sensory consequences of heartbeats, which are known to produce measurable effects on the visual system (Ohl et al., 2016; de Kinkelder et al., 2011). Although recent patient work has related unilateral insula in cardio-visual processing and bodily awareness (i.e., Heydrich and Blanke, 2013; Ronchi et al., 2015), it is not known whether unilateral insula damage may interfere with cardiac suppression of visual awareness. Moreover, while these fMRI data pointed to a role for the anterior insular cortex in cardio-visual interactions for visual consciousness (see also Park & Tallon-Baudry, 2014), they only provided correlational evidence, without demonstrating if this region is necessary for such computations with respect to other parts of the brain. The present study sought to test the causal role of the anterior insula in the processing of cardio-visual signals integration and their role for visual awareness. To this end, we tested a patient with a selective insular lesion, and a group of neurological patients with lesions affecting the posterior insular cortex or other brain regions and adapted previously established psychophysical paradigms to these different patient and control populations.

2. Materials and methods

2.1. Participants

As the aim of the present study was to assess the role of the insula for cardio-visual synchrony effects on visual perception, we compared data from a patient with a lesion centered on the anterior insular (Ins) to that of different control participants. In order to test the specificity of the anterior insular region compared to other brain regions in this effect, we compared the performance of the Ins patient with those of a patient with a predominantly posterior insular lesion (PostIns) and a small group of neurosurgical patients with non-insular lesions. To control for possible age effects we also tested age matched, neurologically unimpaired participants. Finally, to assure that the deficit was specific to cardio-visual integration and not a general perceptual deficit we also employed a non-cardiac visual task. All participants gave their written informed consent for participation in the study which was approved by the ethics committee of Canton Genève.

2.2. Insular patient (Ins)

The insular patient was a 43-year-old ambidextrous male, working as a pastry chef. He was admitted to Geneva University Hospital for an epileptic generalized seizure. The computerized tomography (CT) and the magnetic resonance imaging (MRI) scans showed the presence of a right neoplastic lesion affecting the right insula. The tumor invaded both anterior and posterior lobules of the right insula with the exception of the caudal portion of the anterior long insular gyrus, and extended to the postero-medial orbital lobule of the frontal lobe, to the planum polare of the temporal lobe and medially to the capsula extrema, the claustrum and the capsula externa. The patient stated that he had experienced a few short euphoric crises which started few months before the first seizure; no other symptom of the presence of the brain tumour was detected before the seizure. The patient was admitted to the Neurosurgery unit for tumour resection. Following surgery and the diagnosis of an oligoastrocytoma (stage II), the patient was transferred to a neuro-rehabilitation hospital for the presence of a mild left hemiplegia, and was sent back home after the discharge. Fig. 1A shows the MRI of the insular patient acquired three months after the surgery: the damage affected mainly the whole right insular cortex (anterior, posterior, middle parts), with a residual hematoma in the resection cavity.

During the two experimental examinations (see details in 2.2 section), the patient was alert, cooperative, well-oriented in time, space and personal parameters, and fully aware of his medical condition. The neurological exam showed preserved motor, somatosensory and visual-field functions. Visual function as well as the visual cortex and visual pathways from the eyes to the lateral geniculate nucleus and visual cortex were unaffected. The patient was under antiepileptic treatment. This patient also participated in another study regarding cardio-visual stimulation for bodily self-consciousness (Ronchi et al., 2015).

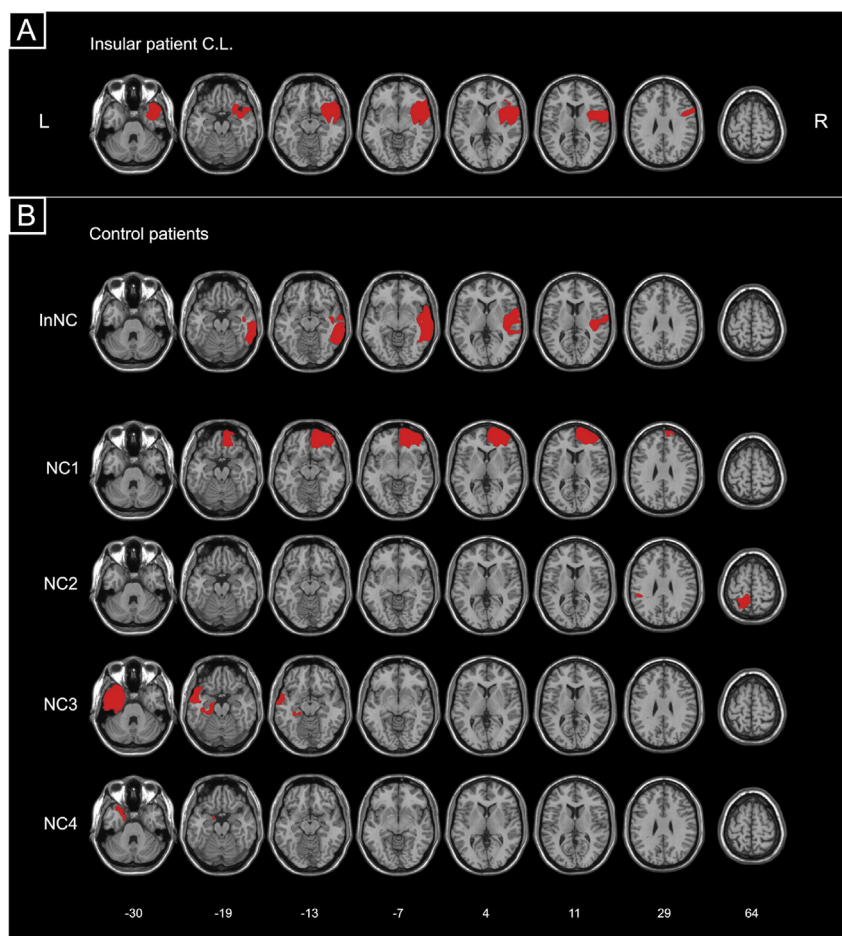


Fig. 1 – Lesion mapping of neurological patient group. Patients' lesions were drawn on a standard MRI template with 1-mm isotropic voxels using the MRicro software (Rorden & Brett, 2000; www.mricro.com). A. Ins patient. B. Neurological control patients with resections not involving the anterior insular cortex.

2.3. Neurosurgical control patients (NC)

2.3.1. Posterior insular patient (PostIns)

To assess the specificity of the anterior insula, we examined cardio-visual synchrony effects on a neurosurgical posterior insular patient (PostIns). The patient was a 49-year-old right-handed male, working as a manager. The tumour was discovered because of tinnitus affecting the left ear, followed in time by the presence of partial seizures inducing paraesthesia on the left hemi-body. The surgery was planned for the tumour removal, revealing the presence of an oligoastrocytoma (stage II): the lesion affected the right posterior insula, without involvement of the right anterior insula.

2.3.2. Non insular neurosurgical control patients

We also tested cardio-visual synchrony effects on a small group of four neurosurgical control (NC) patients (2 males; mean age: 36.3 years, SD: 15.5 years), with resection of neoplastic lesions not involving the insular cortex. Fig. 1B shows the lesion locations of the five neurosurgical control (PostIns and NC) patients. Table 1 shows a summary of the demographic and neurological information about the insular

(Ins) and the neurosurgical control (PostIns and NC) patients. All neurosurgical control patients except for NC4 were under pharmacological treatment for epileptic seizures at the moment of testing. All patients underwent neuropsychological testing and were perfectly oriented in time, space, and personal parameters; moreover, they were completely aware about their medical conditions and neurological symptoms, when present. All patients had unimpaired linguistic functions and easily understood the task instructions. The presence of spatial attentional deficits affecting the contralesional hemi-space or hemi-body was assessed using a battery of neuropsychological tasks, when the lesion affected the right hemisphere: neither spatial nor personal neglect was detected. Finally, they were all completely autonomous in daily-life activities.

2.3.3. Neurologically unimpaired healthy controls (HC)

A group of seven neurologically unimpaired healthy controls (HC), age-matched with the insular patient, were recruited for the experiment (2 males; mean age: 45.2 years, SD: 4.4 years). All participants gave their written informed consent for the study's participation.

Table 1 – Demographic and neurological information about neurosurgical patients (insular and NC)

Patient	Sex	Age	Lesion			Neurological deficit
			Hemisphere	Type	Localization	
Ins	M	43	Right	Oligoastrocytoma (stage II)	Anterior and posterior insula, extended to the orbital frontal region and the planum polare of the temporal lobe	-
PostIns	M	48	Right	Oligoastrocytoma (stage II)	Middle and posterior insula, extended to parieto-temporal regions	-
NC1	F	51	Right	Oligoastrocytoma (stage II)	Fronto-polar and fronto-basal region, extended towards the head of the caudate nucleus	-
NC2	M	48	Left	Oligoastrocytoma (stage II)	Parietal lobe affecting the post-central region	+ P (right leg)
NC3	M	26	Left	Dysplasia (type IIIB)	Temporal lobe involving the parahippocampal region	+ V (right quadrantanopia)
NC4	F	20	Left	Astrocytoma (stage I)	Mesial temporal and interpeduncular region	-

InNC: Insular Neurosurgical Control; NC: Neurosurgical Control; M: male, F: female. -/+ : deficit absent/present. P: proprioceptive deficit. V: visual deficit.

2.4. Experimental procedure

Ins, PostIns and NC patients, as well as the HC group, underwent a paradigm of continuous flash suppression (CFS), under cardio-visual stimulation (cardio-visual CFS). CFS is a well-established paradigm based on interocular rivalry, which allows for long-lasting suppression from awareness of visual stimuli (Tsuchiya & Koch, 2005). In the present CFS experiments, participants were shown the visual stimuli through a head-mounted-display. They had to look at a central fixation cross, presented to both eyes, while two different images were projected to each of the two eyes: the visual target, i.e., a yellow octagon (RGB:(255,255,0), visual angle H:4°, V:4°), was presented to the non-dominant eye, and it was suppressed by highly salient dynamic visual patterns flashed to the participants' dominant eye (see Fig. 2). Critically, the masked visual stimulus (i.e., the octagon) was flashed either synchronously (at the same moment) or asynchronously with respect to each participant's heartbeat, measured online by an electrocardiogram (ECG). During the asynchronous trials the octagon flashed at the frequency of either 80% or 120% of the participant's current heartbeat. Participants were required to report whether the stimulus was above or below the fixation cross as soon as they became aware of it, by pressing a button within 20 s of display onset. The experiment included 80 trials, 40 synchronous and 40 asynchronous (for asynchronous stimulation 20 trials were at 120% of the participant's heartbeat and the other 20 were at 80% of their heartbeat). We measured the duration (in seconds) of the target stimulus presentation required for the subject to break suppression and become aware of the stimulus.

To assure that the results of the cardio-visual CFS experiment were not related to generalized deficits in binocular rivalry, we also employed a control experiment using a CFS paradigm involving suppression of upright or inverted bodies (body CFS; see Stein, Sterzer, & Peelen, 2012). Here the participants were exposed to high contrast monochromatic dynamic stimuli masks (Salomon, Lim, Herbelin, Hesselmann, & Blanke, 2013) to the dominant eye while target stimuli (i.e., upright and inverted headless bodies) were presented either above or below the fixation cross (Fig. 2D). The task was to

indicate the location (above/below) of the body as quickly as possible by pressing a button. Due to time constraints with the patients this was only tested in the insular patient and HC.

The whole experimental session (cardio-visual CFS and control CFS) lasted about 1 h. To validate our central finding the insular patient was tested twice: the first testing after 3 months from tumour resection, the second examination after 20 months from the surgery. For more details regarding the methodology of the CFS experiment, see (Salomon et al., 2016).

2.5. Statistical analyses

In both the cardio-visual and control tasks, accuracy and response time (RT) were recorded. Accuracy was computed as the percentage of trials in which the location of the octagon was correctly reported. The main dependent measure was the duration of the octagon presentation required to break suppression, also called breaking suppression time. Breaking suppression time was defined as the total duration (in seconds) of stimulus presentation when the participant pressed the button to indicate that he had seen the stimulus. The suppression effect was computed as the difference in breaking suppression time in synchronous and asynchronous trials. Only correct trials were analyzed. For each participant, trials in which the RT exceeded 2.5 standard deviations from the participant's mean RT were excluded from analyses (representing a total of 14% of trials). Parametric analyses (t-test) were used to compare the mean accuracy and target presentation duration for synchronous and asynchronous trials. To compare the scores of the Ins patient and the control groups (NC and HC), single case Crawford tests were applied, using the software SINGSLIMS (Crawford & Garthwaite, 2002). For the Ins patient, we further compared individual trial data in the synchronous and asynchronous condition using a one-sample t-test and a permutation test. Effects were also assessed using Bayes factor (BF) tests with default prior scales (<http://www.jneurosci.org/content/36/18/5115.fullRouder> et al., 2009) using JASP (version .7.11). The BF allows assessment of the likelihood of both the null and the alternative hypothesis based on a Bayesian prior. A BF < .33 implies substantial evidence for the null hypothesis, .33 < BF < 3

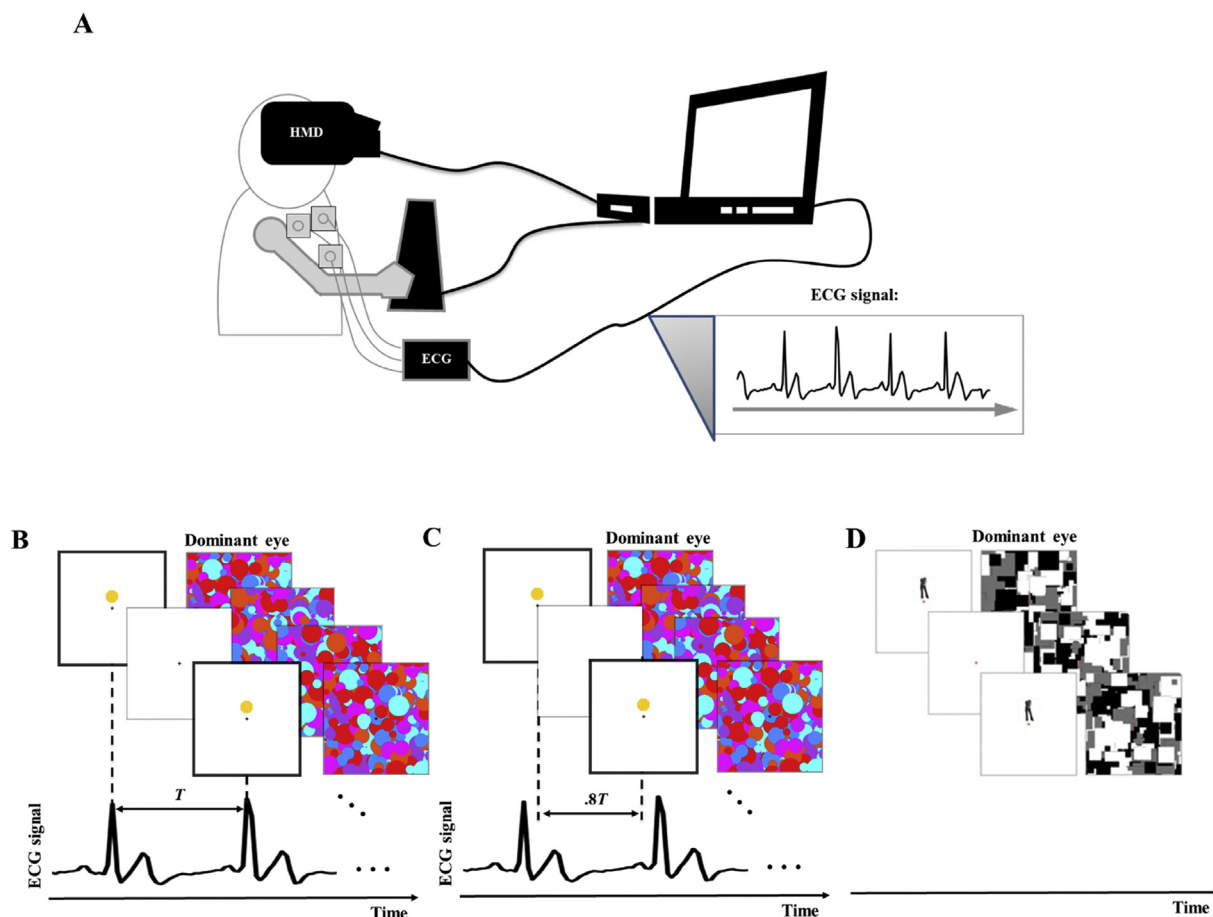


Fig. 2 – Experimental paradigms. A. The participant donned an HMD while heart rate was recorded by ECG. The ECG signal was recorded in real time and was sent to a computer that generated visual stimuli flashing at the frequency of the participant's heartbeat (synchronous trials) or at a modified frequency (asynchronous trials). B & C. Sequence of visual stimuli presented to the participant in the synchronous (B) and asynchronous condition (C). The Mondrian patterns were presented to the dominant eye at a fixed frequency of 10 Hz and the target (yellow octagon) was flashed to the other eye. In synchronous trials (B), the flashes of the target corresponded to the moment of the QRS complex obtained from the ECG signal. The task of the participants was to indicate the position of the target with respect to the fixation cross (above or below). D, CFS control experiment in which Mondrian patterns and target stimuli of an upright or inverted body were presented to assure that the Ins patient was similar to HC in a non-cardiac CFS task.

suggests insensitivity of the data, and $BF > 3$ implies substantial evidence for the alternative hypothesis. We chose the default scaling factor for a Cauchy prior in experiment with the insular patient, considering that it proved acceptable to demonstrate conventional level of substantialevidence for the effect measured in the healthy controls. For visualization the patients' lesions were drawn on a standard MRI template with 1-mm isotropic voxels using the MRICro software (Rorden & Brett, 2000; www.mricro.com).

3. Results

3.1. Cardio-visual CFS

As reported previously, in HC accuracy scores showed no significant difference between the synchronous (mean = 89.1%, SD = 10.1) and asynchronous (mean = 89.6%,

SD = 9.1) conditions ($t(6) = -.6, p = .28$). The duration of target presentation required to break suppression was significantly larger in the synchronous (mean = 3.75 sec, SD = 1.1) than the asynchronous (mean = 3.5 sec, SD = .9) conditions ($t(6) = 2.83, p = .02, BF = 3.38$, one tailed based on previous findings (Salomon et al., 2016)): therefore, in HC visual stimuli synchronized with the heartbeat took more time to break suppression than asynchronous cardio-visual ones. Analysis using permutation testing revealed similar results (see [supplementary materials](#)).

This was similar in the NC group. Accuracy scores were on average 94.6% (SD = 7.6) for synchronous and 95.2% (SD = 6.9) for asynchronous trials: no difference between conditions was found ($t(3) = -.4, p = .68$). The duration of target presentation required to break suppression was numerically larger in the synchronous (mean = 3.83 sec, SD = .7) than the asynchronous (mean = 3.57 sec, SD = .42) condition, but was not statistically significant ($t(3) = 1.3, p = .13, BF = .78$).

Performance differed for the Ins patient. Thus, during the first session, the Ins patient's accuracy in the cardio-visual CFS experiment was lower for both the synchronous (66.6%) and the asynchronous condition (72.7%); the duration of target presentation required to break suppression (i.e., breaking suppression time) was 3.95 sec in the synchronous and 4.6 sec in the asynchronous condition. During the second session, the Ins patient's accuracy was 88.8% in the synchronous and 84.2% in the asynchronous condition; the breaking suppression time was 4.65 sec in the synchronous and 5.5 sec in the asynchronous condition. The control PostIns patient's accuracy in the cardio-visual CFS experiment was in the normal range with 98.2% correct in the synchronous and 94.7% correct in the asynchronous condition; the breaking suppression time was 4.4 sec in the synchronous and 4.09 sec in the asynchronous condition.

Single case Crawford analyses (Crawford & Garthwaite, 2002) and Bayesian one sample t-tests were performed to compare the data of insular patients with the control groups. We found that the suppression effect (i.e., breaking suppression times during synchronous and asynchronous trials) differed significantly between the Ins patient and HC, both in the first ($t = -3.8, p = .005$ Crawford test, $BF = 552.2$, one tailed based on previous findings) and in the second ($t = -2.5, p < .05$ Crawford test, $BF = 46.88$) testing session (Fig. 3). On the contrary, the PostIns patient showed a suppression effect comparable to HC, since no significant difference was found ($t = -.046, p = .96$ Crawford test, $BF = .43$, two tailed). Likewise, comparing suppression effects between NC vs. HC participants revealed no significant difference ($t(9) = -.2, p = .81, BF = .49$). Thus, HC and neurosurgical patients without insular lesion (NC) were not significantly different in the magnitude of cardio-visual synchrony effect on visual awareness (i.e., a relative suppression of awareness); we

note, however, that the BF (.49) indicates only twice as much evidence for the H0 (no difference between groups) which is considered inconclusive. Importantly, this comparison was confirmed using statistics for single cases, comparing the performance of each patient in the NC group to the average score of the HC (all $p > .35$, Crawford test, all $BF < 3$). Only one NC patient (NC3) had a significantly higher score ($t = 2.6, p = .03$, Crawford test, $BF = 39$) than HC, but this effect was in the opposite direction (i.e., larger suppression effects than HC) compared to the results of the patient with insular damage. The difference in the suppression effect between the Ins patient and NC was significant for the first testing session ($t = -2.49, p = .02$ Crawford test, $BF = 9.39$, one tailed) and approached significance in the second testing session ($t = -1.7, p = .09$, Crawford test, $BF = 4.79$ one tailed). The performance of the PostIns patient was comparable to the mean score of the NC group ($t = -.7, p = .4$, Crawford test, $BF = .49$). Analysis using permutation testing revealed similar results (see [supplementary materials](#)).

Finally, we tested the significance of the synchrony suppression effect in the Ins patient's results by using a permutation test in which we shuffled the labels of the trials between the synchronous and asynchronous conditions and then computed the difference between the means of two halves of the vector to create a null distribution. This was repeated 10,000 times and compared to the real difference found between the synchronous and asynchronous in the Ins patient's data using a one sample t-test. The results indicated that the effect was not significant neither in the first testing session ($t = -.31, p = .75$) nor in the second session ($t = -.4, p = .68$). Thus, while the Ins patient's results showed a numerical inversion with respect to those of NC and HC (i.e., more time for asynchronous stimuli to break suppression), this difference was not significant in either session.

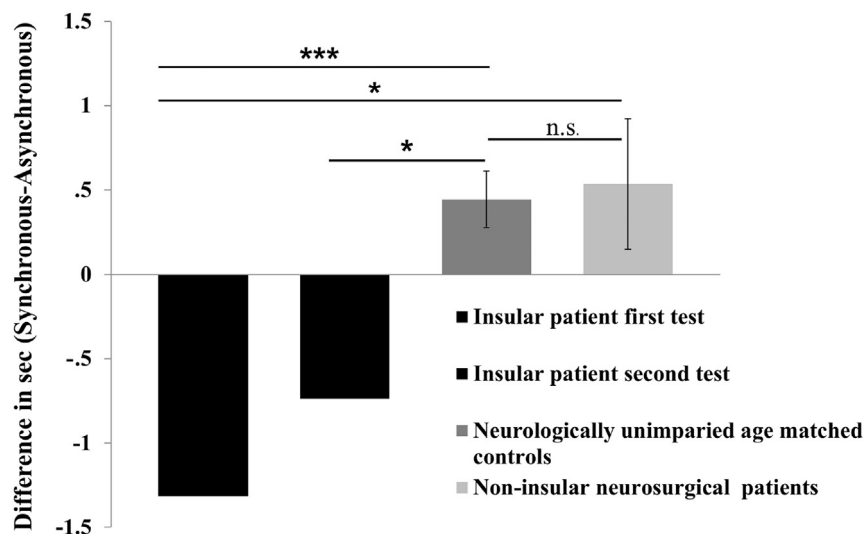


Fig. 3 – Performance on Cardiac CFS task by group. Time in seconds required to break suppression (synchronous-asynchronous conditions). Both NC and HC showed the cardio-visual suppression effect (longer time to break suppression when stimuli are presented synchronously to the heartbeat), which was significantly larger than zero in the HC group. Conversely, the anterior insular patient showed no such suppression effect in neither the first testing nor the second testing sessions. Error Bars denote SEM. * $p < .05$, *** $p < .01$.

3.2. Body CFS (control task)

In HC, the accuracy was 100% in the upright and 99.6% in the inverted body conditions. The duration of target presentation required to break suppression was 2.11 sec in the upright and 2.12 sec in the inverted condition ($t(6) = -.04, p = .96$). The Ins patient's accuracy was 80% in the upright and 82.5% in the inverted body conditions. The duration of target presentation required to break suppression was 4.5s in the upright and 4.6 sec in the inverted condition. Unlike the cardio-visual CFS task, the Ins patient did not differ from HC group in the body control CFS task ($t = -.6, p = .52$, Crawford test, $BF = 1.07$).

4. Discussion

This study provides neuropsychological evidence for the causal role of the anterior insular cortex in integrating interoceptive (cardiac) and exteroceptive (visual) information for visual awareness. First, our previous behavioral finding of cardio-visual suppression for visual stimuli presented synchronously to the heartbeat (Salomon et al., 2016) was replicated in a new group of healthy participants. Furthermore, based on our fMRI results linking this effect to the bilateral anterior insular cortex we found that a patient with unilateral focal damage including the right anterior insula did not show this suppression effect in two testing sessions separated by 17 months. Control patients with lesions to other cortical regions including frontal, parietal and temporal regions showed normal cardio-visual suppression, that was absent in the present patient with right anterior insula damage. Further comparison between this patient and a patient with selective damage affecting the posterior insula (PostIns) supports our finding that the anterior insula may have a key role in mediating intero-exteroceptive integrative processes that impact visual awareness. Finally, we show additional evidence that this deficit is specific to cardio-visual integration as damage to the right anterior insula was not found to alter his performance in a CFS task that was not related to heartbeat timing.

Taken together these results are the first demonstration of a causal role for the anterior insular cortex in the integration of interoceptive and exteroceptive signals, and suppression of synchronous cardio-visual stimuli from visual awareness. We have previously suggested that suppressing the sensory consequences related to interoceptive signals may allow reducing the impact of self-generated signals such as heartbeats on perception. Indeed suppression of sensory events linked to self-generated motor actions (Shergill et al., 2013; Van Elk, Salomon, Kannape, & Blanke, 2014; Volkmann, Riggs, & Moore, 1980; Weiss, Herwig, & Schütz-Bosbach, 2011) thought to be based on predictive mechanisms (efference copy) is well documented. The present findings show that not just sensory processing, but processing related to the integration of interoceptive-exteroceptive signals is also mediated by the anterior insular and that such processes further impact visual awareness for visual stimuli presented at particular timings of the heartbeat cycle. We note that the same insular patient has been previously shown to have abnormal subjective effects on self-consciousness based on cardio-visual

stimulation (Ronchi et al., 2015), suggesting a role of the anterior insula not just in visual, but also self-awareness.

While the current study has found evidence for deficient cardio-visual suppression following a lesion of the anterior insula several limitations must be considered. First, one must take into consideration that lesions are never fully circumscribed to a single neuroanatomical region. Thus, while the Ins patient's lesions were generally localized to the anterior portion of the insular cortex, other proximal regions were also affected (see methods, Fig. 1 and Table 1). Furthermore, due to the rarity of localized anterior insular lesions only one such subject was tested here as well as a limited number of neurological and healthy control subjects. Therefore, the abnormal cardio-visual suppression effect should be confirmed in additional neuropsychological studies to verify the specific role of the anterior insula in cardio-visual suppression. However, the deficient performance of the insular patient provides converging evidence from previous fMRI studies showing the involvement of this region in cardio-visual integration (Salomon et al., 2016; Blefari et al., 2017).

Recent accounts have suggested that the anterior insular cortex may be involved in predictive processing of interoceptive signals (Barrett & Simmons, 2015; Seth, 2013; Seth et al., 2011). Such putative predictive models may enable interoceptive inference in which comparisons between predicted interoceptive states and afferent sensory interoceptive signals indicate unexpected changes in the internal states of the organism (interoceptive prediction error). This mechanism has also been suggested to underlie the phenomena of attenuation of the sensory consequences due to interoceptive processes such as cardiac activity (Salomon et al., 2016; van Elk, Lenggenhager, et al., 2014). Indeed, the insular cortex is well suited for such a role as it is an important cortical afferent relay for interoceptive information and awareness (Craig, 2003; Critchley & Harrison, 2013; Khalsa, Rudrauf, Feinstein, & Tranel, 2009) and has been proposed as a site for multimodal and interoceptive predictive processing (Karnath & Baier, 2010; Preusschoff, Quartz, & Bossaerts, 2008; Seth, 2013; Seth et al., 2011; Wiebking et al., 2014). Lesions to the anterior insular cortex are known to impair emotional processing (Hogeveen, Bird, Chau, Krueger, & Grafman, 2016), and interoceptive awareness (Grossi et al., 2014; but see; Khalsa et al., 2009), as well as learning of negatively valenced events (Palminteri et al., 2012). The present data extend these data and provide converging evidence in line with previous neuroimaging data using fMRI (Salomon et al., 2016) EEG (van Elk, Lenggenhager, et al., 2014) and intracranial electroencephalography (Park et al., 2017), attesting to the role of the anterior insular cortex as a multimodal convergence zone between interoceptive and exteroceptive signals modulating the sensory consequences of interoceptive activity on perception, emotion and cognition.

Acknowledgments

O.B. is supported by the Bertarelli Foundation, the Swiss National Science Foundation, and the European Science Foundation. R.S. was supported by the National Center of

Competence in Research, NCCR “SYNAPSY—The Synaptic Bases of Mental Diseases” financed by the Swiss National Science Foundation (no. 51AU40_125759) & an Israel Science Foundation grant. (1169/17). N.F. is an École Polytechnique Fédérale de Lausanne Fellow co-funded by a Marie Skłodowska-Curie fellowship and was also supported by the European Union Human Brain Project.

Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.cortex.2018.01.005>.

REFERENCES

- Allen, M., Frank, D., Schwarzkopf, D. S., Fardo, F., Winston, J. S., Hauser, T. U., et al. (2016). Unexpected arousal modulates the influence of sensory noise on confidence. *eLife*, 5. <https://doi.org/10.7554/eLife.18103>.
- Aspell, J. E., Heydrich, L., Marillier, G., Lavanchy, T., Herbelin, B., & Blanke, O. (2013). Turning body and self inside out: visualized heartbeats alter bodily self-consciousness and tactile perception. *Psychological science*, 24(12), 2445–2453.
- Babo-Rebelo, M., Richter, C. G., & Tallon-Baudry, C. (2016). Neural responses to heartbeats in the default network encode the self in spontaneous thoughts. *The Journal of Neuroscience*, 36(30), 7829–7840.
- Babo-Rebelo, M., Wolpert, N., Adam, C., Hasboun, D., & Tallon-Baudry, C. (2016). Is the cardiac monitoring function related to the self in both the default network and right anterior insula? *Philosophical Transactions of the Royal Society B*, 371(1708), 20160004.
- Barrett, L. F., & Simmons, W. K. (2015). Interoceptive predictions in the brain. *Nature Reviews Neuroscience*, 16(7), 419.
- Birznieks, I., Boonstra, T. W., & Macefield, V. G. (2012). Modulation of human muscle spindle discharge by arterial pulsations—functional effects and consequences. *Plos One*, 7(4), e35091.
- Blefari, M. L., Martuzzi, R., Salomon, R., Bello-Ruiz, J., Herbelin, B., Serino, A., et al. (2017). Bilateral Rolandic operculum processing underlying heartbeat awareness reflects changes in bodily self-consciousness. *European Journal of Neuroscience*, 45(10), 1300–1312.
- Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, 3(8), 655–666.
- Craig, A. (2003). Interoception: The sense of the physiological condition of the body. *Current Opinion in Neurobiology*, 13(4), 500–505.
- Craig, A. (2009). How do you feel—now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, 10(1), 59.
- Craig, A. D. (2010). The sentient self. *Brain structure and function*, 214(5), 563–577.
- Crawford, J. R., & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia*, 40(8), 1196–1208.
- Critchley, H., & Harrison, N. (2013). Visceral influences on brain and behavior. *Neuron*, 77(4), 624–638.
- Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7(2), 189–195.
- Damasio, A. (2000). *The feeling of what happens: Body and emotion in the making of consciousness*: Harvest Books.
- Dunn, B. D., Galton, H. C., Morgan, R., Evans, D., Oliver, C., Meyer, M., et al. (2010). Listening to your heart how interoception shapes emotion experience and intuitive decision making. *Psychological Science*, 21(12), 1835–1844.
- Edwards, L., Inui, K., Ring, C., Wang, X., & Kakigi, R. (2008). Pain-related evoked potentials are modulated across the cardiac cycle. *Pain*, 137(3), 488–494.
- Edwards, L., Ring, C., McIntyre, D., & Carroll, D. (2001). Modulation of the human nociceptive flexion reflex across the cardiac cycle. *Psychophysiology*, 38(04), 712–718.
- Edwards, L., Ring, C., McIntyre, D., Winer, J. B., & Martin, U. (2009). Sensory detection thresholds are modulated across the cardiac cycle: Evidence that cutaneous sensibility is greatest for systolic stimulation. *Psychophysiology*, 46(2), 252–256.
- van Elk, M., Lenggenhager, B., Heydrich, L., & Blanke, O. (2014). Suppression of the auditory N1-component for heartbeat-related sounds reflects interoceptive predictive coding. *Biological Psychology*, 99, 172–182.
- Garfinkel, S. N., Minati, L., Gray, M. A., Seth, A. K., Dolan, R. J., & Critchley, H. D. (2014). Fear from the heart: Sensitivity to fear stimuli depends on individual heartbeats. *The Journal of Neuroscience*, 34(19), 6573–6582.
- Gray, M. A., Rylander, K., Harrison, N. A., Wallin, B. G., & Critchley, H. D. (2009). Following one's heart: Cardiac rhythms gate central initiation of sympathetic reflexes. *The Journal of Neuroscience*, 29(6), 1817–1825.
- Grossi, D., Di Vita, A., Palermo, L., Sabatini, U., Trojano, L., & Guariglia, C. (2014). The brain network for self-feeling: A symptom-lesion mapping study. *Neuropsychologia*, 63, 92–98.
- Heydrich, L., & Blanke, O. (2013). Distinct illusory own-body perceptions caused by damage to posterior insula and extrastriate cortex. *Brain*, 136(3), 790–803.
- Hogeveen, J., Bird, G., Chau, A., Krueger, F., & Grafman, J. (2016). Acquired alexithymia following damage to the anterior insula. *Neuropsychologia*, 82, 142–148.
- Karnath, H.-O., & Baier, B. (2010). Right insula for our sense of limb ownership and self-awareness of actions. *Brain Structure and Function*, 214(5–6), 411–417.
- Khalsa, S. S., Rudrauf, D., Feinstein, J. S., & Tranel, D. (2009). The pathways of interoceptive awareness. *Nature Neuroscience*, 12(12), 1494–1496.
- de Kinkelder, R., Kalkman, J., Faber, D. J., Schraa, O., Kok, P. H., Verbraak, F. D., et al. (2011). Heartbeat-induced axial motion artifacts in optical coherence tomography measurements of the retina. *Investigative Ophthalmology and Visual Science*, 52(6), 3908–3913.
- Koriath, J. J., & Lindholm, E. (1986). Cardiac-related cortical inhibition during a fixed foreperiod reaction time task. *International Journal of Psychophysiology*, 4(3), 183–195.
- Lacey, J. I., & Lacey, B. C. (1970). Some autonomic-central nervous system interrelationships. *Physiological Correlates of Emotion*, 205–227.
- Ohl, S., Wohltat, C., Kliegl, R., Pollatos, O., & Engbert, R. (2016). Microsaccades are coupled to heartbeat. *The Journal of Neuroscience*, 36(4), 1237–1241.
- Palminteri, S., Justo, D., Jauffret, C., Pavlicek, B., Dauta, A., Delmaire, C., et al. (2012). Critical roles for anterior insula and dorsal striatum in punishment-based avoidance learning. *Neuron*, 76(5), 998–1009. <https://doi.org/10.1016/j.neuron.2012.10.017>.
- Park, H.-D., Bernasconi, F., Bello-Ruiz, J., Pfeiffer, C., Salomon, R., & Blanke, O. (2016). Transient modulations of neural responses to heartbeats covary with bodily self-consciousness. *The Journal of Neuroscience*, 36(32), 8453–8460.
- Park, H.-D., Bernasconi, F., Salomon, R., Tallon-Baudry, C., Spinelli, L., Seeck, M., ... Blanke, O. (n.d.). Neural Sources and Underlying Mechanisms of Neural Responses to Heartbeats, and their Role in Bodily Self-consciousness: An Intracranial

- EEG Study. *Cerebral Cortex*, 1–14. <https://doi.org/10.1093/cercor/bhx136>.
- Park, H.-D., & Tallon-Baudry, C. (2014). The neural subjective frame: From bodily signals to perceptual consciousness. *Philosophical Transactions of the Royal Society B*, 369(1641), 20130208.
- Preuschhoff, K., Quartz, S. R., & Bossaerts, P. (2008). Human insula activation reflects risk prediction errors as well as risk. *The Journal of Neuroscience*, 28(11), 2745–2752.
- Ronchi, R., Bello-Ruiz, J., Lukowska, M., Herbelin, B., Cabrilo, I., Schaller, K., & Blanke, O. (2015). Right insular damage decreases heartbeat awareness and alters cardio-visual effects on bodily self-consciousness. *Neuropsychologia*, 70, 11–20.
- Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, 12(4), 191–200.
- Salomon, R., Lim, M., Herbelin, B., Hesselmann, G., & Blanke, O. (2013). Posing for awareness: Proprioception modulates access to visual consciousness in a continuous flash suppression task. *Journal of Vision*, 13(7). <https://doi.org/10.1167/13.7.2>.
- Salomon, R., Ronchi, R., Dönz, J., Bello-Ruiz, J., Herbelin, B., Martet, R., et al. (2016). The insula mediates access to awareness of visual stimuli presented synchronously to the heartbeat. *The Journal of Neuroscience*, 36(18), 5115–5127.
- Sandman, C. A., McCanne, T. R., Kaiser, D. N., & Diamond, B. (1977). Heart rate and cardiac phase influences on visual perception. *Journal of Comparative and Physiological Psychology*, 91(1), 189.
- Sel, A., Azevedo, R. T., & Tsakiris, M. (2016). Heartfelt self: Cardio-visual integration affects self-face recognition and interoceptive cortical processing. *Cerebral Cortex*. <https://doi.org/10.1093/cercor/bhw296>.
- Seth, A. K. (2013). Interoceptive inference, emotion, and the embodied self. *Trends in Cognitive Sciences*, 17(11), 565–573.
- Seth, A. K., Suzuki, K., & Critchley, H. D. (2011). An interoceptive predictive coding model of conscious presence. *Frontiers in Psychology*, 2.
- Shergill, S. S., White, T. P., Joyce, D. W., Bays, P. M., Wolpert, D. M., & Frith, C. D. (2013). Modulation of somatosensory processing by action. *Neuroimage*, 70, 356–362.
- Stein, T., Sterzer, P., & Peelen, M. V. (2012). Privileged detection of conspecifics: Evidence from inversion effects during continuous flash suppression. *Cognition*, 125(1), 64–79. <https://doi.org/10.1016/j.cognition.2012.06.005>.
- Suzuki, K., Garfinkel, S. N., Critchley, H. D., & Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia*, 51(13), 2909–2917.
- Tsuchiya, N., & Koch, C. (2005). Continuous flash suppression reduces negative afterimages. *Nature Neuroscience*, 8(8), 1096–1101. <https://doi.org/10.1038/nn1500>.
- Van Elk, M., Salomon, R., Kannape, O., & Blanke, O. (2014). Suppression of the N1 auditory evoked potential for sounds generated by the upper and lower limbs. *Biological Psychology*, 102, 108–117.
- Volkman, F. C., Riggs, L. A., & Moore, R. K. (1980). Eyeblinks and visual suppression. *Science*, 207(4433), 900–902.
- Walker, B. B., & Sandman, C. A. (1982). *Visual evoked potentials change as heart rate and carotid pressure change*.
- Weiss, C., Herwig, A., & Schütz-Bosbach, S. (2011). The self in action effects: Selective attenuation of self-generated sounds. *Cognition*, 121(2), 207–218. <https://doi.org/10.1016/j.cognition.2011.06.011>.
- Wiebking, C., Duncan, N. W., Tiret, B., Hayes, D. J., Marjańska, M., Doyon, J., et al. (2014). GABA in the insula—a predictor of the neural response to interoceptive awareness. *Neuroimage*, 86, 10–18.