

F

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex



Single Case Report

The role of the anterior insular cortex in self-monitoring: A novel study protocol with electrical stimulation mapping and functional magnetic resonance imaging



Alba Gomez-Andres ^{a,b}, Toni Cunillera ^{b,c}, Imma Rico ^d, Pablo Naval-Baudin ^e, Angels Camins ^e, Alejandro Fernandez-Coello ^f, Andreu Gabarrós ^f and Antoni Rodriguez-Fornells ^{a,b,c,g,*}

^a Cognition and Brain Plasticity Group [Bellvitge Biomedical Research Institute-IDIBELL], L'Hospitalet de Llobregat, Barcelona, Spain

^b Department of Cognition, Development and Educational Psychology, University of Barcelona, Barcelona, Spain

^c Institute of Neurosciences (UBNeuro), University of Barcelona, Barcelona, Spain

^d Hospital Universitari de Bellvitge (HUB), Neurology Section, Campus Bellvitge, University of Barcelona — IDIBELL, L'Hospitalet de Llobregat (Barcelona), Spain

^e Institut de Diagnòstic per la Imatge, Centre Bellvitge, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat (Barcelona), Spain

^f Hospital Universitari de Bellvitge (HUB), Neurosurgery Section, Campus Bellvitge, University of Barcelona – IDIBELL, L'Hospitalet de Llobregat (Barcelona), Spain

^g Catalan Institution for Research and Advanced Studies, ICREA, Barcelona, Spain

ARTICLE INFO

Article history: Received 22 November 2021 Reviewed 20 April 2022 Revised 18 July 2022 Accepted 5 September 2022 Action editor Robin Morris Published online 4 October 2022

Keywords: Self-awareness Monitoring Anterior insular cortex Intraoperative

ABSTRACT

Becoming aware of one's own states is a fundamental aspect for self-monitoring, allowing us to adjust our beliefs of the world to the changing context. Previous evidence points out to the key role of the anterior insular cortex (aIC) in evaluating the consequences of our own actions, especially whenever an error has occurred. In the present study, we propose a new multimodal protocol combining electrical stimulation mapping (ESM) and functional magnetic resonance imaging (fMRI) to explore the functional role of the aIC for selfmonitoring in patients undergoing awake brain surgery. Our results using a modified version of the Stroop task tackling metacognitive abilities revealed new direct evidence of the involvement of the aIC in monitoring our performance, showing increased difficulties in detecting action-outcome mismatches when stimulating a cortical site located at the most posterior part of the aIC as well as significant BOLD activations at this region during outcome incongruences for self-made actions. Based on these preliminary results, we highlight the importance of assessing the aIC's functioning during tumor resection

Abbreviations: aIC, anterior insular cortex.

^{*} Corresponding author. Cognition and Brain Plasticity Group [Bellvitge Biomedical Research Institute-] IDIBELL, University of Barcelona, Campus de Bellvitge – Pavelló de Govern, 08908 L'Hospitalet de Llobregat (Barcelona), Spain.

E-mail address: arfornells@gmail.com (A. Rodriguez-Fornells).

https://doi.org/10.1016/j.cortex.2022.09.008

^{0010-9452/© 2022} The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Functional magnetic resonance imaging

involving this region to evaluate metacognitive awareness of the self in patients undergoing awake brain surgery. In a similar vein, a better understanding of the aIC's role during self-monitoring may help shed light on action/outcome processing abnormalities reported in several neuropsychiatric disorders such as schizophrenia, anosognosia for hemiplegia or major depression.

© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

For our daily life, it is crucial that we become aware of the consequences of our actions, errors and limitations that force us to adapt our behavior and strategies. In clinical settings, reduced conscious perception of errors has been associated with poor insight of neurological sequelae (O'Keeffe et al., 2004), which may lead to worse functional outcome and poor compliance with rehabilitation (Ownsworth & Clare, 2006). The ability to monitor our actions is mediated by the coordinated activity of several brain regions, including the medial prefrontal cortex (MPFC), especially the anterior cingulate cortex (ACC) and supplementary motor area (SMA), the thalamus and, as we will highlight in this study, the anterior insular cortex (aIC) (Holroyd & Coles, 2002; Ito et al., 2003; Ullsperger & Von Cramon, 2001; Wessel, 2012). Dysfunction of the insular cortex and its interconnected regions are thought to be core features of many psychiatric and neurological disorders (Namkung et al., 2017; Goodkind et al., 2015). In the present study, we propose a new multimodal protocol to explore the functional role of the aIC in selfmonitoring in patients undergoing awake brain surgery for tumor resection.

Described by Reil in 1809, the insula (Latin for 'island') lies folded deep within the lateral sulcus of each hemisphere hidden below parts of the frontal, parietal, and temporal lobes. The insular cortex constitutes an anatomical integration hub which receives direct thalamic and horizontal cortical afferent projections carrying information from all sensory modalities and reciprocally connects to an extensive network of cortical and subcortical brain regions (such as limbic regions, the ACC, orbitofrontal and medial prefrontal cortices) serving sensory, emotional, motivational, and cognitive functions (Gogolla, 2017). Interestingly, a unique feature of the aIC of humans and a few other species (i.e., great apes, elephants, and some cetaceans) is the presence of clusters of large spindle-shaped neurons among the pyramidal neurons in layer 5, called von Economo neurons (Allman et al., 2005; Nimchinsky et al., 1999). While the precise function of these type of cells is not known, functional magnetic resonance imaging (fMRI) studies have shown that these type of neurons are selectively destroyed in disorders characterized by loss of emotional awareness and self-consciousness, such as frontotemporal dementia (Seeley et al., 2006; Sturm et al., 2006), schizophrenia (White et al., 2010) and autism (Minshew & Keller, 2010; Monk et al., 2009), which has led several researchers to postulate their involvement in empathy, self-awareness, and selfmonitoring (Seeley et al., 2007).

Recently, it has been proposed that error awareness can be conceived as a decision process, in which the available evidence from different sources that an error has occurred (i.e., medial prefrontal cortex -MPFC-, autonomic responses, proprioceptive and other sensory inputs) is accumulated until a decision threshold is reached (Steinhauser & Yeung, 2010; Ullsperger et al., 2010; Wess el, Danielmeier & Ullsperger, 2011; Wessel, 2012). It has been proposed that this integration of the different salient signals reflecting a deviation from the predicted outcomes (i.e., prediction errors) may be processed in the insular cortex (Craig & Craig, 2009; Ham et al., 2013), particularly at the aIC, conforming the actual input to the selfmonitoring network signaling the need for cognitive control and behavioral adaptation (Menon & Uddin, 2010). Previous clinical evidence and neuroimaging studies using fMRI provide converging evidence of the role of the aIC in error awareness. It has been reported that the aIC is consistently more activated for errors compared to correct responses (Ham et al., 2013), especially for consciously perceived compared to unperceived errors (Hester et al., 2005; Klein et al., 2007), as well as during negative vs positive informative feedback (Ullsperger & Von Cramon, 2003). Relatedly, the aIC has been found to be involved in self-awareness and self-attribution of actions. For example, in a task where participants were instructed to view self-portrait and pictures of unknown faces, this comparison yielded a greater activation of aIC (Kircher et al., 2000; Sugiura et al., 2000). Moreover, grater activity in the aIC has been found when responding to visual feedback resulting directly from the subject's actions while driving a virtual race car around a track compared to unrelated, random feedback (Farrer & Frith, 2002) as well as reacting to auditory feedback coming from oneself compared to randomly timed feedback during a motor task (Blakemore, Rees & Frith., 1998).

Electrical stimulation mapping (ESM) has been the gold standard technique for identifying essential sensory and motor cortices as well as relevant language areas in patients undergoing tumor resection (Duffau, 2008; Ojemann, 1983; Penfield & Roberts, 2014), also for single-case designs (Rofes et al., 2017; Rojas et al., 2021; Sierpowska et al., 2015). Executive aspects of self-monitoring abilities have been recently explored using ESM, for example, using the Stroop paradigm (Stroop, 1935). Wager et al. (2013) found evidence of the functional role of the ACC in performance monitoring when ESM was applied, and Puglisi et al. (2019) reported that ESM at the subcortical level over white matter sites below the inferior and middle frontal gyri, anterior to the insula and over the putamen, led to impairments in the task performance (i.e., color-word inversion and latency increases). However, the literature concerning the functional mapping of the insular cortex for more complex cognitive functions such as selfmonitoring and error awareness is rather scarce (Erez et al., 2021). In the seminal paper of Penfield and Faulk (1955), ESM of the insula elicit a number of autonomic responses such as gastrointestinal sensations, swallowing, chewing and heart rate increases, highlighting its role for interoception and pointing out to a contribution of this region in the conscious detection of salient events, which capture the subject's attention and awareness in a similar way as errors do (Craig & Craig, 2009; Craig, 2011; see Mazzola et al., 2019 for a review). More recently, Bastin et al. (2016) used intracerebral electroencephalography in a group of epileptic patients during a Stop-signal paradigm; recordings at the aIC showed a rapid increase of electrophysiological activity in this region when an error was committed as well as a feedforward influence from aIC onto ACC and, subsequently, onto the supplementary motor area (SMA), providing direct evidence for a key role of aIC within the saliency-error-monitoring networks.

Both self-awareness and error monitoring abilities are core aspects of metacognition, understood as the cognitive processes that are linked with activation of "thinking about one's own thinking", by which individuals can reflect upon (monitor) their own internal mental states and apply their knowledge to evaluate and regulate (control) their own mental states (Nelson et al., 1999). Clinical findings further support the role of the aIC in self-monitoring/metacognitive processing, as is the case for patients with anosognosia for hemiplegia (AHP), who present unawareness of motor deficits related to hemiplegia and are commonly associated to lesions in insular regions (Karnath et al., 2005; Vocat et al., 2010). Patients suffering from schizophrenia, especially those reporting delusions of control have also been associated to functional and morphological abnormalities in the insular cortex (Crespo-Facorro et al., 2000; Moran et al., 2013; Wylie & Tregellas, 2010).

In the present study, we propose a multimodal protocol for exploring the role of the aIC in error monitoring for self-made actions combining ESM, fMRI and neuropsychological assessment. With this purpose in mind and, due to the inherent difficulty of measuring errors in simple reaction time tasks, mainly due to the small frequency and randomness distribution, we created a situation during which we challenged self-monitoring abilities introducing random feedback informing about the correctness of the response emitted. Based on the exposed above regarding the role of aIC in self-monitoring, our main hypothesis was that ESM applied over the aIC regions would disrupt the ability to correctly detect the incongruences between the patients' action/response and the subsequent feedback appearing on the screen. As feedback correctness was random (50% chance of providing a correct information), we created a situation in which the patient was interrogated about the accuracy of the presented feedback, requiring access to her internal selfmonitoring/metacognitive process. This allowed us to increase the chance of stimulating the insular region while presenting action-outcome incongruences and to obtain a larger number of trials for the evaluation of self-monitoring abilities. Moreover, we expected to find relevant and significant brain activations involving the aIC when introducing

incongruent feedback during the fMRI acquisition at the relevant contrasts. Our results revealed to be quite promising regarding the usefulness of our multimodal approach in studying the implication of the aIC region in self-monitoring and error processing, highlighting the importance of assessing the insular function during tumor resection and functional imaging allowing a better understanding and preservation of the aIC functional role in self-monitoring.

2. Methods

2.1. Clinical case description

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/ exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

MM, a 57-year-old, right-handed woman, Spanish-Catalan bilingual was admitted to the Neurosurgery Department of the Bellvitge Academic Hospital after incidental diagnosis of a left fronto-insular lesion (diffuse astrocytoma, WHO, II) (see Fig. 3A). Due to the lesion location, the patient was selected for the awake mapping multimodal protocol (which includes neuropsychological assessment, fMRI and ESM, in this order) to assess the aIC-related functions. The use of a multimodal protocol allows us to obtain a multidimensional perspective of the patient's state that aided adjusting the surgical procedure to approach tumor recession, benefiting in that way the patient's treatment. The study protocol was accepted by the Ethical Committee of the University Hospital of Bellvitge (reference PR075/19) in accordance with the principles of the Declaration of Helsinki and the participant signed the informed consent for the participation in the study. No part of the study analyses was pre-registered prior to the research being conducted.

2.2. Neuropsychological assessment

A comprehensive neuropsychological assessment was performed at the neurological ward of the University Hospital of Bellvitge both pre- and postoperatively. A specific neuropsychological protocol was employed assessing executive functions such as attention ["Digits -direct-" from Test Barcelona-Revisado (Peña-Casanova, 2005) and "Trail Making Test (TMT) -part A-" (Reitan, 1955)], working memory ["Digits -inverse-" from Test Barcelona-Revisado (Peña-Casanova, 2005), "Letters and Numbers" and "Arithmetic" subtests from the Wechsler Adult Intelligence Scale-IV -WAIS-IV- (Spanish Edition; Wechsler, 2008)], inhibition [Stroop Task (Stroop, 1935)], mental flexibility ["TMT-part B-" (Reitan, 1955)], set shifting abilities [Wisconsin Card Sorting Test - WCST - (Grant & Berg, 1948)] and verbal fluency (semantic and phonological verbal fluency). Moreover, language function was also examined in terms of production and naming [Boston Naming Test-BNTfrom the Boston Diagnostic Aphasia Examination-BDAE-(Goodglass & Kaplan, 2001)] and verbal comprehension [Token Test (De Renzi & Faglioni, 1978)]. Importantly, two tasks tackling more specific insular-related functioning were included namely, the Empathy scale [Interpersonal Reactivity Index -IRI- (Davis, 1983), Spanish version] and the Emotion recognition test [Ekman 60 faces Test (Ekman & Fr iesen, 1976)]. Mood was also assessed using the Hamilton Anxiety Rating Scale-HARS- (Hamilton, 1959) and the Hamilton Depression Rating Scale-HDRS- (Hamilton, 1960).

Standardized tests from the WAIS-IV were interpreted by using Spanish normative data from the WAIS-IV Spanish Edition (Wechsler, 2008). Additionally, Digits, verbal fluencies, TMT (parts A and B), Stroop task, BNT, Token Test were corrected using Neuronorma Spanish normative data and corrected by age and years of education (Peña-Casanova et al., 2009a, 2009b). In both cases, impairment was defined as a scaled score ≤ 6 (see Table 1).

2.3. Electrical stimulation mapping (ESM)

MM underwent awake surgery for tumor removal by the senior neurosurgeon A.G. at the Department of Neurosurgery of

Function (test)	Baseline		Post-surgery		Comments
	R.S.	S.S.	R.S.	S.S.	
Attention and executive function	oning				
A. Attention and verbal WM	•				
Digit span -direct-	6	11	4	6	Significant decrease in attention efficiency.
Digit span -inverse-	6	15	4	10	Slight reduction in verbal WM but preserved.
Letters and Numbers	11	12	5	6	Slower visuomotor processing speed.
Arithmetic	14	12	14	12	
TMT -part A-	30 sec	12	180 sec	2	Slower visuomotor processing speed.
B. Inhibition					Significant reduction in color-word condition
Stroop Test	36	10	7	3	(susceptibility to interference and inhibitory ability).
C. Mental flexibility					Might be influenced by motor/articulatory difficulties. Reduced cognitive flexibility
TMT -part B-	53 sec	14	241 sec	5	neuacea cognate nemonity.
D. Set shifting WCST	55 660		211 500	5	Increased difficulties in set-switching.
Correct responses	84	Preserved	76	Preserved	
Categories achieved	6	Preserved	0	Impaired	
Perseverative errors	9	Preserved	18	Preserved	
Efficient errors	23	Preserved	34	Impaired	
E. Verbal fluency				-	Significant impairment in verbal fluency.
Semantic cue (animals)	21	10	9	4	
Phonological cue ("p")	15	10	6	5	
Language					
A. Production and naming BNT	52/60*	10	45/60**	8	*55/60 with phonological cue, 1 latency. **52/60 with phonological cue, 1 semantic paraphasia, 1 phonemic paraphasia, 5 circumlocutions, 2 switching
B. Verbal comprehension Token Test	36/36	12	32.5/36	8	Slight reduction in verbal comprehension but preserved.
Social cognition					
A. Empathy IRI					More difficulties in <i>Perspective taking</i> and <i>Fantasy</i> items were observed at post-op.
Perspective taking	30	Preserved	13	Impaired	
Fantasy	26	Preserved	13	Impaired	
Empathic concern	34	Preserved	28	Preserved	
Personal concern	19	Preserved	18	Preserved	
B. Emotion recognition					Lower scores were obtained for negative emotions, both
Ekman 60 faces Test Total	36/60	Impaired	38/60	Impaired	during pre-op and post-op, with global scores showing
Anger	0/10	Impaired	8/10	Preserved	an impairment in this test.
Disgust	9/10	Preserved	5/10	Impaired	
Fear	1/10	Impaired	2/10	Impaired	
Happiness	10/10	Preserved	10/10	Preserved	
Sadness	6/10	Preserved	5/10	Impaired	
Surprise	10/10	Preserved	8/10	Preserved	
Mood					
A. Anxiety					
HARS	11	Preserved	14	Preserved	
B. Depression					After surgery, the patient presented a significant
HDRS	3	Preserved	15	Impaired	increase in depressive symptoms.

R.S.: raw score; S.S.: scalar score; TMT: Trail Making Test; BNT: WCST: Wisconsin Card Sorting Test; Boston Naming Test; IRI: Interpersonal Reactivity Index; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale.

Table 1 – Neuropsychological assessment at baseline and post-surgery.

the University Hospital of Bellvitge. A left frontotemporal craniotomy was performed, and the Sylvian fissure was opened allowing the exposure of the aIC. ESM was performed using an Ojemann cortical stimulator (Radionics, Inc.) under asleep-awake-asleep surgery, following the methodology described previously by Ojemann, Ojemann, Lettich, and Berger (2008) during asleep-awake-asleep surgery and our previous work (Fernández-Coello et al., 2016; Havas et al., 2015; Sierpowska et al., 2013, 2018). The interelectrode distance of the bipolar forceps was 5 mm. The stimulator delivered a biphasic current with a pulse frequency of 60 Hz and a single-pulse phase duration of 1 sec. The duration of each stimulation train was 3 s. The current amplitude was progressively increased by .5 mA, beginning at 1 mA, until the desired responses were observed. During the ESM procedure, the same cortical area was never stimulated twice in succession to avoid seizures, and between each set of 2 stimulations we always performed a control trial without applying electrical current.

Firstly, the primary motor and sensory cortices were mapped. A site was considered positive for motor function when the stimulation elicited involuntary muscle contraction or speech arrest while the patient was counting. On the other hand, the primary sensory cortex was determined by sensory disturbances perceived by the patient upon electric stimulation. Due to the tumor location involving fronto-opercular regions, language mapping was also performed using a home-made simplified version of the picture-naming task, composed by 60 black and white drawings selected from a standard stimuli database (Havas et al., 2015; Snodgrass & Vanderwart, 1980) both in Spanish and Catalan (see the functional map obtained in Fig. 3B and C).

2.3.1. Experimental paradigm: stroop interference task with feedback

Once the aIC was exposed, the experimental paradigm was performed. A modified version of the Stroop task (Stroop, 1935) was designed and implemented both before and after surgery, intraoperatively and during presurgical fMRI (see Fig. 1A and B). The task was adapted for each modality (ESM vs. fMRI) in terms of timing although the same set of stimuli were employed. The Stimulus presentation was controlled with EPrime (Psychology Software Tools Inc., Pittsburgh, PA). In general terms, the task consisted of signaling the color in which a word is printed ignoring the word itself. When the word is a color word printed in a mismatched color ink (i.e., RED printed in blue), an interference effect occurs resulting in a slower, more difficult, and error-prone condition relative to a control condition (i.e., XXXXX printed in blue). The performance cost in the incongruent condition is called the Stroop effect.

The patient was instructed to press a button with either their left or right thumb (see Fig. 1A) whenever the target stimulus was printed in red or blue, respectively, ignoring the word. Additionally, we increased the difficulty of the task by adding a laterality variable which involved placing the target stimulus at the middle-left or middle-right location on the screen, generating either congruent or incongruent trials regarding laterality-correct response. Therefore, 8 different targets were presented based on the word-color and laterality congruence condition (32 trials in total), balanced across the task (4 trials for each word-color and laterality-congruence trial type). After the stimulus presentation (500 msec), the patient had 1000 msec to respond (reaction time-RT). The experimental paradigm is accessible at https://doi.org/10. 34810/data212.

To be able to investigate whether the stimulation of the aIC resulted in a disruption of the ability to self-monitor committed errors, we needed to be able to anticipate the occurrence of the desired event to synchronize it to the electrical stimulation. Because the commission of an error cannot be anticipated, we provided feedback in a random manner [i.e., either positive or negative (green tick or red cross)], which could be either congruent or incongruent with respect to the patient's performance. In 50% of the cases, a positive feedback was provided and distributed equally across the different trial types. Finally, the patient had to say whether she agreed with the feedback she had been given or not. The feedback presentation was synchronized with the electrical stimulation to evaluate the effect of the electrical impulse on performance monitoring. As shown in the trial example in Fig. 2, a cortical site was considered functionally relevant for error/performance monitoring whenever the electrical stimulation resulted in a failure in detecting whether the feedback provided was incongruent with her performance. To do so, the experimenter monitored online the patients' performance via an additional monitor which displayed the correctness or not of the response and the feedback that was given for each trial. The cortical locations of the self-monitoring sites detected during the ESM procedure were transferred to an arbitrary grid (see Fig. 3C).

2.4. fMRI

Patient MM was scanned before surgery in a 1.5 T MRI Philips Igenia system at University Hospital of Bellvitge for presurgical assessment supporting intraoperative neuronavigation. Functional images were acquired in the axial plane using a single-shot T2-weighted gradient-echo EPI sequence with a 3000 msec repetition time (TR), 50 msec echo time (TE) and 90° flip angle (FA). Each volume consisted of 4 mm thick slices with no inter-slice gap; voxel size = $3.59 \times 3.59 \times 4 \text{ mm}^3$; FOV = 230 mm; size of acquisition matrix 64×64 . In addition to the functional images, a high-resolution sagittal T1weighted image (slice thickness = 2 mm; no inter-slice gap; number of slices = 180; TR = 7.8 msec; TE = 3.8 msec; flip angle = 8° ; matrix = 250×250 ; FOV = 250 mm; voxel size = $1 \times 1 \times 2 \text{ mm}^3$) was also acquired.

The Stroop experimental paradigm was adapted during the fMRI acquisition (see Fig. 1B). The stimuli duration were adapted as follows: First, a variable fixation slide –intertrial interval (ITI)– (jittering 1000–4000 msec) was presented followed by the stimulus presentation (500 msec), to which the patient had 1000 msec to respond. A fixation slide –interstimulus interval (ISI)– of 3000 msec was then presented, followed by the feedback (either informative or non-informative, depending on the block), during 1000 msec. Two main conditions were defined: (a) Informative feedback blocks, during which informative feedback was provided in a random manner (i.e., either positive -green tick- or negative





Fig. 1 – Experimental paradigm: Stroop interference task with feedback. (A) Experimental task employed during the electrical stimulation mapping (ESM) procedure. The task always started with a fixation slide (2000 msec). The target stimulus appeared for 500 msec, which varied in terms of the laterality-color congruency and word-color congruency variables (8 trial types in total) The patient was instructed to respond as fast as possible to the ink color ignoring the word by pressing either left (blue) or right (red). After the response, the feedback slide appeared for 1000 msec (either congruent or incongruent with respect to the patient's performance), during which the electrical stimulation was applied signaled by a sound to inform the neurosurgical team. After the feedback + stimulation presentation, the monitoring question was presented. (B) Experimental task employed during the functional magnetic resonance imaging (fMRI) acquisition. Each trial started with a variable fixation slide (1000–4000 msec), followed by the target stimulus presentation (500 msec). Once the patient responded, an ISI of 3000 msec appeared followed by the feedback presentation (1000 msec). During the informative blocks, neutral feedback (grey square) was always presented.

-red cross-, 50% positive/negative) and (b) non-informative feedback blocks, during which neutral feedback was always delivered (i.e., grey square) (see Fig. 1B). A total of 16 blocks were performed (8 Informative and 8 Non-Informative), each one consisting of 24 trials. The total duration of the task was 16 min. As in the task version used during the ESM procedure, the patient was instructed to press a button with either their left or right thumb whenever the target stimulus was printed in red or blue, respectively, ignoring the word and a laterality variable was also included.

In order to examine the brain activity related to congruent vs incongruent vs neutral feedback, we performed an eventrelated design grouping the trials in the following manner: (a) Congruent trials (29 events of interest), trials of the Informative blocks for which a congruent feedback was presented in relation to the participant performance (i.e., correct response followed by correct feedback or erroneous response followed by error feedback), (b) Incongruent trial (15 events of interest), trials corresponding to an incongruent feedback (i.e., correct response followed by error feedback or erroneous response followed by correct feedback) and c) Neutral trials (48 events of interest), corresponding to all trials from the noninformative blocks.

The fMRI pre-processing and statistical analysis was performed with SPM12 (The Wellcome Trust Centre for Neuroimaging, London, UK). Image pre-processing included

Experimental setting inside the OR



Fig. 2 — Experimental set-up inside the operating room (OR). Once the patient was awakened and the resection reached the insular cortex, the experimental task was performed. A computer screen was placed at the eye-level of the patient, displaying the Stroop modified paradigm. A second computer screen informing the experimenter about the patients' performance and the feedback presented was also available only for the experimenter eyes. The electrical stimulation was cued by a sound informing the neurosurgical team the feedback slide was appearing and therefore the stimulation had to be performed. Once the response and feedback had occurred, the experimenter determined whether the stimulation had impaired or not the patient's monitoring ability. If 3 or more non-consecutive stimulations over the same cortical site resulted in a monitoring impairment, that cortical point was considered to be functionally relevant.

realignment, slice timing, segmentation, normalization and smoothing with an 8 mm gaussian kernel. Unified segmentation (Ashburner & Friston, 2005) with medium regularization was applied. A General Linear Model contrastive analysis was performed. Motion parameters extracted from the realignment were included as regressors of no interest. Statistical parametric maps were obtained for the following contrasts: (a) Congruent vs Neutral, (b) Incongruent vs Neutral and (c) Incongruent vs Congruent feedback. These contrasts are reported at an uncorrected level of p < .01.

Region of interest (ROI) analyses using an uncorrected $\alpha = .05$ with an extent threshold = 20 continuous voxels were performed for the left insular cortex and the ACC (bilateral) based on the WFU Pickatlas toolbox (Maldjian et al., 2003).

3. Results

3.1. Electrical stimulation mapping (ESM)

Functionally, the ESM over the motor and sensory cortices revealed two speech arrest sites (red tags) at the opercular region, and two sensitive points on the somatosensory regions corresponding to the palate (blue tag -1-) and oropharyngeal and nasopharyngeal sensations (blue tag -2-) (see Fig. 3B and C). Surgically, a total resection of the tumor involving the left Broca region was performed, after obtaining no positive functional points at his level neither cortically nor subcortically. Moreover, although two positive sites were encountered (see red tags at Fig. 3B and C), a subtotal resection of the tumor tissue involving the left motor operculum portion was reached in order to decrease the probability of tumor recurrence (Fig. 3A).

Following the cortical ESM, the opening of the sylvian fissure was performed to enable the tumoral resection involving the insular region. Once the aIC was exposed, the ESM was performed. Out of the 32 trials of the experimental task, 10 trials were performed while electrically stimulating the aIC synchronized with the feedback appearance. One functional point for self-monitoring was found at the most posterior part of the aIC (see Fig. 3C). More specifically, 3 nonconsecutive stimulations over the abovementioned cortical site resulted in an inability to correctly state whether the feedback provided was congruent with their actual response. Two of these trials were characterized by erroneous responses followed by the presentation of incongruent feedback (i.e., positive feedback), to which the patient responded 'Yes' during the awareness question revealing her inability to correctly monitor and compare her actual response to the feedback presented. In the case of reaching a third trial for which a monitoring failure was detected while stimulating, a congruent feedback after an error was presented (i.e., negative feedback) followed by an incorrect awareness assertion by the



Fig. 3 – Lesion topography and ESM results. (A) Pre and post-surgical FLAIR acquisitions depicting the tumoral tissue in light yellow and the post-surgical cavity. (B) ESM intraoperative photograph depicting the ESM results at the left fronto-temporal region. In red we see 2 functional motor sites related to speech arrest. In blue, 2 somatosensory points were located corresponding to palate sensations (top) and oropharynx + nasopharynx sensations (bottom). Language-related cortical sites are also depicted for Spanish and Catalan naming impairment. (C) Anatomical map of the cortical surface (top) and insular region (down) depicting positive functional sites (green) and negative sites (grey) for self-monitoring abilities tested with the Stroop experimental paradigm.

patient (i.e., MM responded 'No' to a congruent feedback). A total surgical resection was performed of the tumor tissue involving the aIC boundary with deep inferior fronto-occipital fasciculus (IFOF) boundary.

3.2. fMRI results

3.2.1. Whole brain analysis

The neural networks underlying performance monitoring were assessed by an event-related analysis time-locked to the feedback onset. Results of the whole brain analysis are shown on Fig. 4A. During the Congruent vs Neutral contrast, significant clusters of activations were mainly found at the superior frontal gyrus -SFG-, inferior frontal gyrus -IFG, SMA and ACC (Fig. 4A). When looking at the Incongruence effect (Incongruent vs Neutral feedback contrast), similar regions including the ACC, SMA and IFG were found to be activated. Crucially for the purpose of the current study, the bilateral insular cortex was also found to be significantly engaged during the incongruent feedback (Fig. 4A). Finally, when computing the contrast Incongruent vs Congruent feedback to isolate the incongruence effect, significant clusters were encountered at the ACC, bilateral insular cortices (both anterior and posterior regions), superior temporal gyrus -STG- (bilaterally), and subcortical structures such as the left putamen and right globus pallidus (see Fig. 4A). Patient data accessible at https:// doi.org/10.34810/data212.

3.2.2. ROI analysis

ROI analysis of the left insular cortex for the contrast Incongruent vs Congruent feedback revealed a significant cluster of activation at the left posterior insula (cluster size = 43 voxels, peak t-score = 2.48, $MNI_{XYZ} = -32$, -26, and 16; Fig. 4B).

Moreover, ROI analysis at the ACC also revealed significant clusters of activity mostly left lateralized (left ACC: cluster size = 121 voxels, peak t-score = 2.44, $MNI_{XYZ} = -12$, 46, and 2; right ACC: cluster size = 58 voxels, peak t-score = 2.05, $MNI_{XYZ} = 6$, 38, and 2; Fig. 4B). Patient data accessible at https://doi.org/10.34810/data212.

3.3. Cognitive outcome

Pre-operatively, the patients' neuropsychological profile was within the normal score range in attention and executive functioning, language, semantic knowledge, and social cognition (see Table 1). She did not report any difficulties in motor or sensory abilities. Moreover, the performance in the Stroop experimental paradigm was also within the normal range, obtaining a 100% accuracy on the execution and feedback awareness assessment.

At the post-surgical assessment performed 11 months after the surgery, a significant decline in some cognitive domains was observed (Table 1), most probably due to the resection at the level of the left motor opercular region (see Fig. 3A). A decrease in digit span (direct) and verbal fluency,



Fig. 4 – Functional magnetic resonance imaging results. (A) Whole brain event-related analysis tagged to the feedback onset for the contrasts of interest Congruent vs Neutral, Incongruent vs Neutral and Incongruent vs Congruent feedback. (B) ROI analysis for the contrast Incongruent vs Congruent feedback for the left insular cortex and anterior cingulate cortex (ACC) —bilateral- Results are shown normalized to MNI space at an uncorrected level of *p* < .005.

both for the semantic and phonological cue, was encountered, most probably influenced by the articulatory difficulties. A slower visuomotor processing speed revealed by a significant increase in the time needed to complete the TMT-A and the Letters and Numbers test were observed. Reduced cognitive flexibility assessed with the TMT-B and set-shifting abilities assessed using the WCST, showing a larger number of efficient errors and the impossibility of achieving any category, were also impaired after surgery. Notably, the performance on the Stroop task (standardized version) revealed a large reduction in the number of items completed during the color-word interference condition, pointing out to an increased difficulty in her inhibitory capacity, although it might be influenced by the verbal fluency and dysarthria difficulties the patient presented at post-op after the resection. Language production abilities were preserved, although more difficulties with complex verbal comprehension were recorded.

Social cognition aspects were also assessed, evidencing more difficulties in Perspective taking and Fantasy items of the IRI scale (empathy) after surgery. Moreover, emotion recognition difficulties (Ekman test) were observed both before and after surgery, especially for negative emotions. Importantly, the patient presented a significant increase in depressive symptoms after surgery as revealed by the HDRS.

4. Discussion and clinical relevance

Very few studies addressing self-monitoring and error processing have been performed using ESM during awake brain surgery. Here, we present a new multimodal protocol proposal assessing the functional role of the aIC in performance monitoring for self-made actions. We provide ESM, fMRI and neuropsychological information data for a single patient undergoing awake brain surgery for tumor removal involving the aIC region. For this purpose, we designed a modified version of the Stroop task presenting the patient with either congruent or incongruent feedback with respect to her performance synchronized with the stimulation of the aIC sites exposed.

As previously mentioned on introductory paragraphs, ESM is the gold standard technique for locating and identifying essential motor, sensory and other cognitive functions (i.e., language related functions) in patients undergoing awake brain tumor resection (Penfield & Roberts, 1959; Ojemann, 1983), allowing to maximize the extent of the tumor resection and the preservation of functionally relevant brain sites. Among the various cognitive domains ESM is applied, executive functions and more complex cognitive abilities, such as performance monitoring and error awareness, have been less explored due to the inherent complexity of these functions. Here, we explored the functional role of the aIC in performance monitoring for self-made actions by synchronizing the ESM with the presentation of either congruent or incongruent feedback followed by a monitoring assessment as to whether the patient agreed or not with the feedback provided. Our results revealed one relevant point at the most posterior portion of the aIC related to self-monitoring. Specifically, 3 stimulations over the same cortical point of the aIC resulted in an inability to correctly monitor her performance (see Fig. 3B and C). Interestingly, all three trials resulting in a monitoring failure corresponded to erroneous responses, 2/3 when incongruent feedback was presented and 1/3 after congruent feedback.

Previous literature has pointed out the key role of the insula in self-related processing (David, 2012; Sperduti et al., 2011). Together with other brain regions such as the MPFC and the ACC, the insula, particularly the aIC, has been largely found to be involved in self-recognition, self-monitoring and discriminating the self from non-self-sources of sensory input (Blakemore et al., 1998; Farrer & Frith, 2002; Kircher et al., 2000; Sugiura et al., 2000). Self-awareness is an essential component of metacognition, through which we can adjust our beliefs of the world - the modulation of the self-by monitoring and controlling our behavior. For example, patients with frontoinsular stroke, behavioral variant frontotemporal dementia and Alzheimer's disease show a lack of self-awareness, insight, and self-monitoring, which translate into anosognosia and daily behavioral impairments (Shany-Ur et al., 2016; Hebscher et al., 2016; Hebscher & Gilboa, 2016; Rosen et al., 2014; Sunderaraman & Cosentino, 2017), leading to worse functional outcome and poor compliance with rehabilitation (Ownsworth & Clare, 2006). One of the most prominent theories (Blakemore & Frith, 2003; Frith, Blakemore & Wolpert, 2000) claims that self-monitoring in healthy people is based on a comparator process that determines deviations between the predicted and actual consequences of physical or mental actions. When predicted and actual consequences match, the observed outcome is experienced as coming from the self. On the other hand, other authors have proposed that self-monitoring is usually based on a more direct comparison between the intention underlying an action and its observed outcome (Fourneret et al., 2001; Franck et al., 2001; Jeannerod, 1999).

Furthermore, a line of evidence suggests an involvement of the aIC in performance monitoring related to its role in error awareness (Klein et al., 2007; Klein et al., 2013). Direct evidence on the role of the aIC within the error monitoring network has been recently provided (Bast in et al., 2017), showing a broadband increase in neuronal population response at the aIC during erroneous NoGo trials in a group of epileptic patients undergoing intracerebral electroencephalography. Recent models regarding error monitoring suggest the existence of a detection threshold that error signals might need to surpass in order to be detected by our system (Wessel et al., 2011; Steinhauser & Yeung, 2010; Ullsperger et al., 2010; Wessel, 2012). Interestingly, several authors have proposed that these signals provide multimodal information to be integrated in the insula conforming the input to the error monitoring network and reflecting an error-awareness signal (Ham et al., 2013; Klein et al., 2013; Sridharan et al., 2008; Ullsperger et al., 2010).

Consistently with the abovementioned studies, our results support the functional relevance of the aIC in error monitoring/processing indicated by the inability to correctly detect and compare the participants' response/performance to the feedback provided when inducing a virtual lesion on aIC regions, specifically during self-made errors, although caution with this interpretation should be taken due to the reduced number of trials used to evaluate performance monitoring. Hence, these results seem to indicate that the aIC might play a relevant role in monitoring deviances from the predicted action consequences during self-made actions, informing the system than an unexpected outcome/prediction error has occurred. This interpretation fits well with clinical populations showing difficulties in the detection of discrepancies between predicted vs. actual outcomes, such as the case for anosognosia for hemiplegia (AHP) patients, commonly associated to lesions at the aIC region (Karnath et al., 2005; Vocat et al., 2010). Moreover, neuroimaging studies in patients with schizophrenia, who commonly present difficulties in discriminating between self-generated and externally generated sources of sensory stimuli, have consistently reported both structural and functional abnormalities of the insula (Makris et al., 2006; Moran et al., 2013; Palaniyappan et al., 2013; Saze et al., 2007; Takahashi et al., 2004, 2005).

Our event-related fMRI results for the contrasts of interest (Incongruent vs Congruent and Incongruent vs Neutral feedback) support ESM findings by revealing significant clusters of activation at the most posterior portion of the aIC (bilaterally) when the patient was presented with incongruent feedback (Fig. 4A). Importantly, other error-related regions such as the ACC and basal ganglia nuclei such as the putamen (bilaterally) and right globus pallidus were significantly activated during the presentation of incongruent feedback. These regions has been previously related to monitoring and outcome prediction of ongoing events (Botvinick et al., 2001; Mathalon et al., 2003). Several authors suggest that the aIC involvement in selfmonitoring and error awareness may pertain to its role in the salience network (Menon & Uddin, 2010; Seeley et al., 2007), which involves the MPFC, ACC, IFG, amygdala, inferior parietal lobule (IPL), thalamus aIC and other brainstem nuclei (Seeley et al., 2007) and responding to behaviorally relevant events. Functional connectivity analysis of aIC during error awareness confirms its coordinated activity with distant brain regions of the salience network, presumably to amplify the neural salience-signal and motivational properties of the detected error (Deen et al., 2011; Dosenbach et al., 2008). Therefore, it might be the case that when encountering events that deviate from expectations (i.e., prediction errors), as in our case, inserting incongruent feedback, the basal ganglia relays information to the ACC via the thalamus and communicates with the executive control network, signaling the need for increased cognitive control and monitoring (Ham et al., 2013; Kennerley et al., 2006). Interestingly, as previously mentioned on introductory paragraphs, the human insula contains von Economo neurons, whose large axons could provide a neuronal basis for rapid signal communication between aIC and ACC, as well as with other brain networks (Menon et al., 2020).

Several limitations were encountered during this project. On one hand, the limited availability of ESM data might hinder the possible generalization of our findings, therefore more patients must be recruited and tested with this protocol. Moreover, the cognitive decline in the patient's performance at the articulatory level, probably related to the resection at the left motor opercular region, might have influenced her performance on other cognitive domains dependent on verbal articulation outputs. Besides, a sample of healthy individuals could also be recruited to perform the fMRI experimental paradigm favoring the generalization of our results. Therefore, the current protocol should be tested with other similar patients with brain tumors involving the aIC region to properly assess the benefits of this multimodal protocol in evaluating aIC function, allowing for example more strict corrections regarding the significance of the fMRI results.

In conclusion, the present study offers new insight regarding the exploration of the aIC in patients undergoing awake brain surgery to ensure a preservation of the integrity of the self-awareness/monitoring network. We provide novel insight regarding the functional role of the aIC in performance monitoring, following previous findings reporting aIC responses to error trials and incongruent feedback processing (Bastin et al., 2017; Ham et al., 2013). A better understanding of the aIC's role during self-attributed outcomes may help shed light on feedback/error processing abnormalities reported in several neuropsychiatric disorders associated with functional and structural abnormalities of the aIC (Diener et al., 2012; Hatton et al., 2012; Naqvi & Bechara, 2009; Palaniyappan & Liddle, 2012; Shepherd et al., 2012), for example, patients with schizophrenia, AHP, major depression, and/or drug addiction, who show difficulties in self-monitoring as well as an abnormal sense of agency for their thoughts or actions (Vocat & Vuilleumeier, 2010; Eshel & Roiser, 2010; Karnath et al., 2005; Ziauddeen & Murray, 2010).

Funding

This research was supported by the Spanish Ministry of Economy and Competitiveness (PSI2015-69178-P) awarded to ARF and a predoctoral FPI scholarship awarded to A.G-A (BES-2016-078889).

Credit author statement

Alba Gomez-Andres: Conceptualization, Investigation, Formal analysis, Writing - Original Draft, Writing - Review & Editing Toni Cunillera: Conceptualization, Writing - Review & Editing Imma Rico: Investigation, Resources Pablo Naval: Investigation, Resources Angels Camins: Investigation, Resources Alejandro Fernandez-Coello: Investigation, Resources, Writing -Review & Editing Andreu Gabarros: Conceptualization, Resources, Writing - Review & Editing Antoni Rodriguez-Fornells: Conceptualization, Supervision, Writing - Review & Editing.

Data availability

The experimental paradigm and neuroimaging data can be accessible at https://doi.org/10.34810/data212. Legal copyright

restrictions prevent public archiving of the neuropsychological tests employed in this study, which nevertheless can be obtained from the copyright holders in the cited references.

Declaration of competing interest

The authors declare no competing interests.

Open practices

The study in this article earned an Open Data – Protected Access badge for transparent practices. Materials and data for the study are available at https://doi.org/10.34810/data212.

Acknowledgements

The authors would like to thank MM for her collaboration and willingness to participate in this study.

REFERENCES

- Allman, J. M., Watson, K. K., Tetreault, N. A., & Hakeem, A. Y. (2005). Intuition and autism: A possible role for von Economo neurons. Trends in Cognitive Sciences, 9(8), 367–373. https:// doi.org/10.1016/j.tics.2005.06.008
- Ashburner, J., & Friston, K. J. (2005). Unified segmentation. NeuroImage, 26(3), 839–851. https://doi.org/10.1016/ j.neuroimage.2005.02.018
- Bastin, J., Deman, P., David, O., Gueguen, M., Benis, D., Minotti, L., ... Jerbi, K. (2016). Direct recordings from human anterior insula reveal its leading role within the error-monitoring network. *Cerebral Cortex*. https://doi.org/10.1093/cercor/ bhv352. bhv352.
- Blakemore, S. J., & Frith, C. (2003). self-awareness and action. Current Opinion in Neurobiology, 13(2), 219–224. https://doi.org/ 10.1016/s0959-4388(03)00043-6
- Blakemore, S. J., Rees, G., & Frith, C. D. (1998). How do we predict the consequences of our actions? A functional imaging study. *Neuropsychologia*, 36(6), 521–529. https://doi.org/10.1016/s0028-3932(97)00145-0
- Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. Psychological Review, 108(3), 624. https://doi.org/10.1037/0033-295x.108.3.624
- Craig, A. D., & Craig, A. D. (2009). How do you feel-now? The anterior insula and human awareness. Nature Reviews Neuroscience, 10(1). https://doi.org/10.1038/nrn2555
- Crespo-Facorro, B., Kim, J. J., Andreasen, N. C., O'Leary, D. S., Bockholt, H. J., & Magnotta, V. (2000). Insular cortex abnormalities in schizophrenia: A structural magnetic resonance imaging study of first-episode patients. Schizophrenia Research, 46(1), 35–43. https://doi.org/10.1016/ S0920-9964(00)00028-1
- David, N. (2012). New frontiers in the neuroscience of the sense of agency. Frontiers in Human Neuroscience, 6, 161. https://doi.org/ 10.3389/fnhum.2012.00161
- Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of* Personality and Social Psychology, 44(1), 113. https://psycnet.apa. org/doi/10.1037/0022-3514.44.1.113.

- De Renzi, E., & Faglioni, P. (1978). Normative data and screening power of a shortened version of the Token Test. Cortex; *a* Journal Devoted To the Study of the Nervous System and Behavior, 14(1), 41–49. https://doi.org/10.3233/NRE-172244
- Deen, B., Pitskel, N. B., & Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. Cerebral Cortex, 21(7), 1498–1506. https://doi.org/ 10.1093/cercor/bhq186
- Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., & Flor, H. (2012). A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *NeuroImage*, 61(3), 677–685. https://doi.org/10.1016/ j.neuroimage.2012.04.005
- Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of topdown control. Trends in Cognitive Sciences, 12(3), 99–105. https://doi-org.sire.ub.edu/10.1016/j.tics.2008.01.001.
- Duffau, H., Gatignol, P., Mandonnet, E., Capelle, L., & Taillandier, L. (2008). Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. Journal of Neurosurgery, 109(3), 461–471. https:// doi.org/10.3171/jns/2008/109/9/0461
- Ekman, P. (1976). Pictures of facial affect. Consulting psychologists press.
- Erez, Y., Assem, M., Coelho, P., Romero-Garcia, R., Owen, M., McDonald, A., ... Santarius, T. (2021). Intraoperative mapping of executive function using electrocorticography for patients with low-grade gliomas. Acta Neurochirurgica, 163(5), 1299–1309. https://doi.org/10.1007/s00701-020-04646-6
- Eshel, N., & Roiser, J. P. (2010). Reward and punishment processing in depression. Biological Psychiatry, 68(2), 118–124. https://doi.org/10.1016/j.biopsych.2010.01.027
- Farrer, C., & Frith, C. D. (2002). Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. *NeuroImage*, 15(3), 596–603. https://doi.org/10.1006/nimg.2001.1009
- Fernández-Coello, A., Havas, V., Juncadella, M., Sierpowska, J., Rodríguez-Fornells, A., & Gabarrós, A. (2016). Age of language acquisition and cortical language organization in multilingual patients undergoing awake brain mapping. *Journal of Neurosurgery*, 126(6), 1912–1923. https://doi.org/10.3171/ 2016.5.JNS152791
- Fourneret, P., Franck, N., Slachevsky, A., & Jeannerod, M. (2001). self-monitoring in schizophrenia revisited. Neuroreport, 12(6), 1203–1208. https://doi.org/10.1097/00001756-200105080-00030
- Franck, N., Farrer, C., Georgieff, N., Marie-Cardine, M., Daléry, J., d'Amato, T., & Jeannerod, M. (2001). Defective recognition of one's own actions in patients with schizophrenia. The American Journal of Psychiatry, 158(3), 454–459. https://doi.org/ 10.1176/appi.ajp.158.3.454
- Frith, C. D., Blakemore, S. J., & Wolpert, D. M. (2000). Abnormalities in the awareness and control of action. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 355(1404), 1771–1788. https://doi.org/ 10.1098/rstb.2000.0734
- Gogolla, N. (2017). The insular cortex. Current Biology, 27(12), R580-R586. https://doi.org/10.1016/j.cub.2017.05.010
- Goodglass, H., & Kaplan, E. (1983). The assessment of aphasia and related disorders. Philadelphia: Lea & Febiger.
- Goodkind, M. S., Sturm, V. E., Ascher, E. A., Shdo, S. M., Miller, B. L., Rankin, K. P., & Levenson, R. W. (2015). Emotion recognition in frontotemporal dementia and Alzheimer's disease: A new film-based assessment. *Emotion*, 15(4), 416. https://doi.org/10.1037/2Fa0039261
- Grant, D. A., & Berg, E. (1948). A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. *The Journal of Economic*

Perspectives: a Journal of the American Economic Association, 38(4), 404. https://psycnet.apa.org/doi/10.1037/h0059831.

- Hamilton, M. (1959). The assessment of anxiety states by rating. The British Journal of Medical Psychology, 32(1), 50–55. https:// doi.org/10.1111/j.2044-8341.1959.tb00467.x
- Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry, 23(1), 56–62. https:// doi.org/10.1136/jnnp.23.1.56
- Ham, T., Leff, A., de Boissezon, X., Joffe, A., & Sharp, D. J. (2013). Cognitive control and the salience network: An investigation of error processing and effective connectivity. *Journal of Neuroscience*, 33(16), 7091–7098. https://doi.org/10.1523/ 2FJNEUROSCI.4692-12.2013
- Hatton, S. N., Lagopoulos, J., Hermens, D. F., Naismith, S. L., Bennett, M. R., & Hickie, I. B. (2012). Correlating anterior insula gray matter volume changes in young people with clinical and neurocognitive outcomes: An MRI study. BMC Psychiatry, 12(1), 1–10. https://doi.org/10.1186/2F1471-244X-12-45
- Havas, V., Gabarrós, A., Juncadella, M., Rifa-Ros, X., Plans, G., Acebes, J. J., ... Rodríguez-Fornells, A. (2015). Electrical stimulation mapping of nouns and verbs in Broca's area. Brain and Language, 145, 53–63. https://doi.org/10.1016/ j.bandl.2015.04.005
- Hebscher, M., Barkan-Abramski, M., Goldsmith, M., Aharon-Peretz, J., & Gilboa, A. (2016). Memory, decision-making, and the ventromedial prefrontal cortex (vmPFC): The roles of subcallosal and posterior orbitofrontal cortices in monitoring and control processes. *Cerebral Cortex*, 26, 4590–4601. https:// doi.org/10.1093/cercor/bhv220
- Hebscher, M., & Gilboa, A. (2016). A boost of confidence: The role of the ventromedial prefrontal cortex in memory, decisionmaking, and schemas. Neuropsychologia, 90, 46–58. https:// doi.org/10.1016/j.neuropsychologia.2016.05.003
- Hester, R., Foxe, J. J., Molholm, S., Shpaner, M., & Garavan, H. (2005). Neural mechanisms involved in error processing: A comparison of errors made with and without awareness. *NeuroImage*, 27(3), 602–608. https://doi.org/10.1016/ j.neuroImage.2005.04.035
- Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. Psychological Review, 109(4), 679. https://psycnet.apa.org/doi/10.1037/0033-295X.109.4.679.
- Ito, S., Stuphorn, V., Brown, J. W., & Schall, J. D. (2003). Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science*, 302(5642), 120–122. https://doi.org/10.1126/science.1087847
- Jeannerod, M. (1999). The 25th Bartlett Lecture: To act or not to act: Perspectives on the representation of actions. The Quarterly Journal of Experimental Psychology Section A, 52(1), 1–29. https://doi.org/10.1080/2F713755803
- Karnath, H. O., Baier, B., & Nägele, T. (2005). Awareness of the functioning of one's own limbs mediated by the insular cortex? Journal of Neuroscience, 25(31), 7134–7138. https:// doi.org/10.1523/2FJNEUROSCI.1590-05.2005
- Kennerley, S. W., Walton, M. E., Behrens, T. E., Buckley, M. J., & Rushworth, M. F. (2006). Optimal decision making and the anterior cingulate cortex. Nature Neuroscience, 9(7), 940–947. https://doi.org/10.1038/nn1724
- Kircher, T. T., Senior, C., Phillips, M. L., Benson, P. J., Bullmore, E. T., Brammer, M., ... David, A. S. (2000). Towards a functional neuroanatomy of self processing: Effects of faces and words. Cancer Biotherapy & Radiopharmaceuticals, 10(1–2), 133–144. https://doi.org/10.1016/s0926-6410(00) 00036-7
- Klein, T. A., Endrass, T., Kathmann, N., Neumann, J., von Cramon, D. Y., & Ullsperger, M. (2007). Neural correlates of error awareness. *NeuroImage*, 34(4), 1774–1781. https://doi.org/ 10.1016/j.neuroimage.2006.11.014

- Klein, T. A., Ullsperger, M., & Danielmeier, C. (2013). Error awareness and the insula: Links to neurological and psychiatric diseases. Frontiers in Human Neuroscience, 7, 14. https://doi.org/10.3389/fnhum.2013.00014
- Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophrenia Research, 83(2–3), 155–171. https://doi-org.sire.ub.edu/10.1016/j.schres.2005.11. 020.
- Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*, 19(3), 1233–1239. https://doi.org/10.1016/s1053-8119(03)00169-1
- Mathalon, D. H., Whitfield, S. L., & Ford, J. M. (2003). Anatomy of an error: ERP and fMRI. Biological Psychology, 64(1-2), 119–141. https://doi.org/10.1016/S0301-0511(03)00105-4
- Mazzola, L., Mauguiere, F., & Isnard, J. (2019). Functional mapping of the human insula: Data from electrical stimulations. *Revue Neurologique*, 175(3), 150–156.
- Menon, V., Gallardo, G., Pinsk, M. A., Nguyen, V. D., Li, J. R., Cai, W., & Wassermann, D. (2020). Microstructural organization of human insula is linked to its macrofunctional circuitry and predicts cognitive control. *eLife*, 9, Article e53470. https://doi.org/10.7554/eLife.53470
- Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. Brain Structure & Function, 214(5–6), 655–667. https://doi.org/10.1007/ s00429-010-0262-0
- Minshew, N. J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: Functional brain imaging studies. Current Opinion in Neurology, 23(2), 124–130. https://doi.org/ 10.1097/WCO.0b013e32833782d4
- Monk, C. S., Peltier, S. J., Wiggins, J. L., Weng, S. J., Carrasco, M., Risi, S., & Lord, C. (2009). Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *NeuroImage*, 47(2), 764–772. https://doi.org/10.1016/j.neuroimage.2009.04.069
- Moran, L. V., Tagamets, M. A., Sampath, H., O'Donnell, A., Stein, E. A., Kochunov, P., & Hong, L. E. (2013). Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. Biological Psychiatry, 74(6), 467–474. https:// doi.org/10.1016/j.biopsych.2013.02.029
- Namkung, H., Kim, S. H., & Sawa, A. (2017). The insula: An underestimated brain area in clinical neuroscience, psychiatry, and neurology. Trends in Neurosciences, 40(4), 200–207. https://doi.org/10.1016/j.tins.2017.02.002
- Naqvi, N. H., & Bechara, A. (2009). The hidden island of addiction: The insula. Trends in Neurosciences, 32(1), 56–67. https:// doi.org/10.1016/j.tins.2008.09.009
- Nelson, T. O., Stuart, R. B., Howard, C., & Crowley, M. (1999).
 Metacognition and clinical psychology: A preliminary framework for research and practice. Clinical Psychology & Psychotherapy: An International Journal of Theory & Practice, 6(2), 73–79. https://doi.org/10.1002/(SICI)1099-0879(199905)6:2% 3C73::aICD-CPP187%3E3.0.CO;2-7
- Nimchinsky, E. A., Gilissen, E., Allman, J. M., Perl, D. P., Erwin, J. M., & Hof, P. R. (1999). A neuronal morphologic type unique to humans and great apes. Proceedings of the National Academy of Sciences, 96(9), 5268–5273. https://doi.org/10.1073/ pnas.96.9.5268
- O'Keeffe, F. M., Dockree, P. M., & Robertson, I. H. (2004). Poor insight in traumatic brain injury mediated by impaired error processing?: Evidence from electrodermal activity. Cognitive Brain Research, 22(1), 101–112. https://doi.org/10.1016/ j.cogbrainres.2004.07.012
- Ojemann, G. A. (1983). Brain organization for language from the perspective of electrical stimulation mapping. Behavioral and

Brain Sciences, 6(2), 189–206. https://psycnet.apa.org/doi/10. 1017/S0140525X00015491.

- Ownsworth, T., & Clare, L. (2006). The association between awareness deficits and rehabilitation outcome following acquired brain injury. *Clinical Psychology Review*, 26(6), 783–795. https://doi.org/10.1016/j.cpr.2006.05.003
- Palaniyappan, L., & Liddle, P. F. (2012). Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. Journal of Psychiatry & Neuroscience. https://doi.org/10.1503/jpn.100176
- Palaniyappan, L., Simmonite, M., White, T. P., Liddle, E. B., & Liddle, P. F. (2013). Neural primacy of the salience processing system in schizophrenia. Neuron, 79(4), 814–828. https:// doi.org/10.1016/j.neuron.2013.06.027
- Peña-Casanova, J. (2005). Programa integrado de exploración neuropsicológica: TRB: Test Barcelona Revisado. Elsevier España.
- Peña-Casanova, J., Quinones-Ubeda, S., Gramunt-Fombuena, N., Quintana-Aparicio, M., Aguilar, M., Badenes, D., ... NEURONORMA Study Team. (2009a). Spanish multicenter normative studies (NEURONORMA project): Norms for verbal fluency tests. Archives of Clinical Neuropsychology, 24(4), 395–411. https://doi.org/10.1093/arclin/acp042
- Peña-Casanova, J., Quiñones-Úbeda, S., Quintana-Aparicio, M., Aguilar, M., Badenes, D., Molinuevo, J. L., ... Blesa, R. (2009b). Spanish multicenter normative studies (NEURONORMA project): Norms for verbal span, visuospatial span, letter and number sequencing, trail making test, and symbol digit modalities test. Archives of Clinical Neuropsychology, 24(4), 321–341. https://doi.org/10.1093/arclin/acp038
- Penfield, W., & Faulk, M. E., Jr. (1955). The insula: Further observations on its function. Brain: a Journal of Neurology, 78(4), 445–470. https://doi.org/10.1093/brain/78.4.445
- Penfield, W., & Roberts, L. (2014). Speech and brain mechanisms. Princeton University Press.
- Puglisi, G., Howells, H., Sciortino, T., Leonetti, A., Rossi, M., Conti Nibali, M., ... Bello, L. (2019). Frontal pathways in cognitive control: Direct evidence from intraoperative stimulation and diffusion tractography. Brain: a Journal of Neurology, 142(8), 2451–2465. https://doi.org/10.1093/brain/awz178
- Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. Journal of Consulting Psychology, 19(5), 393. https://doi.org/10.1037/h0044509
- Rofes, A., Spena, G., Talacchi, A., Santini, B., Miozzo, A., & Miceli, G. (2017). Mapping nouns and finite verbs in left hemisphere tumors: A direct electrical stimulation study. *Neurocase*, 23(2), 105–113. https://doi.org/10.1080/ 13554794.2017.1307418
- Rojas, P. H., Sivaraju, A., Quraishi, I. H., Vanderlind, M., Rofes, A., Połczynska-Bletsos, M. M., ... Benjamin, C. F. (2021). Electrical cortical stimulation can impair production of the alphabet without impairing counting. Epilepsy & Behavior Reports, 15, Article 100433. https://doi.org/10.1016/j.ebr.2021.100433
- Rosen, H. J., Alcantar, O., Zakrzewski, J., Shimamura, A. P., Neuhaus, J., & Miller, B. L. (2014). Metacognition in the behavioral variant of frontotemporal dementia and Alzheimer's disease. *Neuropsychology*, 28(3), 436. https:// doi.org/10.1037/neu0000012
- Saze, T., Hirao, K., Namiki, C., Fukuyama, H., Hayashi, T., & Murai, T. (2007). Insular volume reduction in schizophrenia. European Archives of Psychiatry and Clinical Neuroscience, 257(8), 473–479. https://doi-org.sire.ub.edu/10.1007/s00406-007-0750-2.
- Seeley, W. W., Allman, J. M., Carlin, D. A., Crawford, R. K., Macedo, M. N., Greicius, M. D., ... Miller, B. L. (2007). Divergent social functioning in behavioral variant frontotemporal dementia and Alzheimer disease: Reciprocal networks and neuronal evolution. Alzheimer Disease and Associated Disorders, 21(4), S50–S57. https://doi.org/10.1097/wad.0b013e31815c0f14

- Seeley, W. W., Carlin, D. A., Allman, J. M., Macedo, M. N., Bush, C., Miller, B. L., & DeArmond, S. J. (2006). Early frontotemporal dementia targets neurons unique to apes and humans. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 60(6), 660–667. https://doi.org/10.1002/ana.21055
- Shany-Ur, T., Lin, N., Rosen, H. J., Sollberger, M., Miller, B. L., & Rankin, K. P. (2014). self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention. Brain: a Journal of Neurology, 137(8), 2368–2381. https://doi.org/10.1093/brain/awu161
- Shepherd, A. M., Matheson, S. L., Laurens, K. R., Carr, V. J., & Green, M. J. (2012). Systematic meta-analysis of insula volume in schizophrenia. Biological Psychiatry, 72(9), 775–784. https:// doi.org/10.1016/j.biopsych.2012.04.020
- Sierpowska, J., Fernandez-Coello, A., Gomez-Andres, A., Camins, À., Castaner, S., Juncadella, M., ... Rodriguez-Fornells, A. (2018). Involvement of the middle frontal gyrus in language switching as revealed by electrical stimulation mapping and functional magnetic resonance imaging in bilingual brain tumor patients. Cortex; a Journal Devoted To the Study of the Nervous System and Behavior, 99, 78–92. https:// doi.org/10.1016/j.cortex.2017.10.017
- Sierpowska, J., Gabarrós, A., Fernandez-Coello, A., Camins, À., Castañer, S., Juncadella, M., ... Rodríguez-Fornells, A. (2015). Morphological derivation overflow as a result of disruption of the left frontal aslant white matter tract. Brain and Language, 142, 54–64. https://doi.org/10.1016/j.bandl.2015.01.005
- Sierpowska, J., Gabarrós, A., Ripollés, P., Juncadella, M., Castañer, S., Camins, Á., ... Rodríguez-Fornells, A. (2013). Intraoperative electrical stimulation of language switching in two bilingual patients. *Neuropsychologia*, 51(13), 2882–2892. https://doi.org/10.1016/j.neuropsychologia.2013.09.003
- Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. Journal of Experimental Psychology: Human Learning and Memory, 6(2), 174. https:// psycnet.apa.org/doi/10.1037/0278-7393.6.2.174.
- Sperduti, M., Delaveau, P., Fossati, P., & Nadel, J. (2011). Different brain structures related to self-and external-agency attribution: A brief review and meta-analysis. Brain Structure & Function, 216(2), 151–157. https://doi.org/10.1007/s00429-010-0298-1
- Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between centralexecutive and default-mode networks. Proceedings of the National Academy of Sciences, 105(34), 12569–12574. https:// doi.org/10.1073/pnas.0800005105Ullspeger
- Steinhauser, M., & Yeung, N. (2010). Decision processes in human performance monitoring. Journal of Neuroscience, 30(46), 15643–15653. https://doi.org/10.1523/jneurosci.1899-10.2010
- Stroop, J. R. (1935). Studies of interference in serial verbal reactions. Journal of Experimental Psychology, 18(6), 643. https:// psycnet.apa.org/doi/10.1037/h0054651.
- Sturm, V. E., Rosen, H. J., Allison, S., Miller, B. L., & Levenson, R. W. (2006). self-conscious emotion deficits in frontotemporal lobar degeneration. Brain: a Journal of Neurology, 129(9), 2508–2516. https://doi.org/10.1093/brain/awl145
- Sugiura, M., Kawashima, R., Nakamura, K., Okada, K., Kato, T., Nakamura, A., ... Fukuda, H. (2000). Passive and active recognition of one's own face. NeuroImage, 11(1), 36–48. https://doi.org/10.1006/nimg.1999.0519

- Sunderaraman, P., & Cosentino, S. (2017). Integrating the constructs of anosognosia and metacognition: A review of recent findings in dementia. Current Neurology and Neuroscience Reports, 17(3), 27. https://doi.org/10.1007/s11910-017-0734-1
- Takahashi, T., Suzuki, M., Hagino, H., Zhou, S. Y., Kawasaki, Y., Nohara, S., Nakamura, K., Yamashita, I., Seto, H., & Kurachi, M. (2004). Bilateral volume reduction of the insular cortex in patients with schizophrenia: A volumetric MRI study. Psychiatry Research, 132(2), 187–196. https://doi.org/ 10.1016/j.pscychresns.2004.11.002
- Takahashi, T., Suzuki, M., Zhou, S. Y., Hagino, H., Tanino, R., Kawasaki, Y., Nohara, S., Yamashita, I., Seto, H., & Kurachi, M. (2005). Volumetric MRI study of the short and long insular cortices in schizophrenia spectrum disorders. Psychiatry Research, 138(3), 209–220. https://doi.org/10.1016/ j.pscychresns.2005.02.004
- Ullsperger, M., Harsay, H. A., Wessel, J. R., & Ridderinkhof, K. R. (2010). Conscious perception of errors and its relation to the anterior insula. Brain Structure & Function, 214(5), 629–643. https://doi.org/10.1007/s00429-010-0261-1
- Ullsperger, M., & Von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. NeuroImage, 14(6), 1387–1401. https://doi.org/10.1006/ nimg.2001.0935
- Ullsperger, M., & Von Cramon, D. Y. (2003). Error monitoring using external feedback: Specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional magnetic resonance imaging. *Journal of Neuroscience*, 23(10), 4308–4314. https://doi.org/10.1523/ jneurosci.23-10-04308.2003
- Vocat, R., Staub, F., Stroppini, T., & Vuilleumier, P. (2010). Anosognosia for hemiplegia: A clinical-anatomical prospective study. Brain: a Journal of Neurology, 133(12), 3578–3597. https://doi.org/10.1093/brain/awq297
- Wager, M., Du Boisgueheneuc, F., Pluchon, C., Bouyer, C., Stal, V., Bataille, B., ... Gil, R. (2013). Intraoperative monitoring of an aspect of executive functions: Administration of the Stroop test in 9 adult patients during awake surgery for resection of frontal glioma. Operative Neurosurgery, 72(2), ons169–ons181. https://doi.org/10.1227/NEU.0b013e31827bf1d6
- Wechsler, D. (2008). Escala de Inteligencia de Wechsler Para Adultos-IV (WAIS-IV): Manual de Aplicación y Corrección. Madrid: TEA.
- Wessel, J. R. (2012). Error awareness and the error-related negativity: Evaluating the first decade of evidence. Frontiers in Human Neuroscience, 6, 88. https://doi.org/10.3389/ fnhum.2012.00088
- Wessel, J. R., Danielmeier, C., & Ullsperger, M. (2011). Error awareness revisited: Accumulation of multimodal evidence from central and autonomic nervous systems. *Journal of Cognitive Neuroscience*, 23(10), 3021–3036. https://doi.org/ 10.1162/jocn.2011.21635
- White, T. P., Joseph, V., Francis, S. T., & Liddle, P. F. (2010). Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. Schizophrenia Research, 123(2–3), 105–115. https://doi.org/10.1016/j.schres.2010.07.020
- Wylie, K. P., & Tregellas, J. R. (2010). The role of the insula in schizophrenia. Schizophrenia Research, 123(2–3), 93–104. https://doi.org/10.1016/j.schres.2010.08.027
- Ziauddeen, H., & Murray, G. K. (2010). The relevance of reward pathways for schizophrenia. Current Opinion in Psychiatry, 23(2), 91–96. https://doi.org/10.1097/YCO.0b013e328336661b