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Insular networks for emotional processing and social cognition: Comparison of two case reports with either cortical or subcortical involvement

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ABSTRACT

Introduction: The processing of the emotion of disgust is attributed to the insular cortex (IC), which is also responsible for social emotions and higher-cognitive functions. We distinguish the role of the IC from its connections in regard to these functions through the assessment of emotions and social cognition in a double case report. These subjects were very rare cases that included a focal IC lesion and a subcortical focal stroke affecting the connections of the IC with frontotemporal areas.

Materials & methods: Both patients and a sample of 10 matched controls underwent neuropsychological and affective screening questionnaires, a battery of multimodal basic emotion recognition tests, an emotional inference disambiguation task using social contextual clues, an empathy task and a theory of mind task.

Results: The insular lesion (IL) patient showed no impairments in emotion recognition and social emotions and presented with a pattern of delayed reaction times (RTs) in a subset of both groups of tasks. The subcortical lesion (SL) patient was impaired in multimodal aversive emotion recognition, including disgust, and exhibited delayed RTs and a heterogeneous pattern of impairments in subtasks of empathy and in the contextual inference of emotions.

Conclusions: Our results suggest that IC related networks, and not the IC itself, are related to negative emotional processing and social emotions. We discuss these results with respect to theoretical approaches of insular involvement in emotional and social processing and propose that IC connectivity with frontotemporal and subcortical regions might be relevant for contextual emotional processing and social cognition.

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1. Introduction

The insular cortex (IC) is localized deep in the lateral sulcus and is a brain region considered crucial for body representation and emotional experience. Specifically, the IC is involved in the recognition, experience and imagination of basic emotions (Jabbi et al., 2008; Sprengelmeyer et al., 2010), as well as in social emotions like empathy and moral judgment (Caruana et al., 2011; Decety et al., 2011). The right anterior IC (r-aIC) seems to play an integrative role in coordinating the awareness of body feelings (Craig, 2002), integrating contextual social clues (Amoruso et al., 2011; Ibanez and Manes, 2012), and representing uncertainty (Singer et al., 2009). The functional role of the insula in coordinating emotional and social cognition is supported by the wide array of structural connections of the IC with the orbitofrontal (OFC), dorsolateral prefrontal cortices (DLPFC), anterior cingulate cortex (ACC), medial and lateral temporal lobe structures, ventral striatum and amygdala (Mufson and Mesulam, 1982; Viskontas et al., 2007). In addition, functional connectivity measures during the resting state have identified the aIC as the main functional node related to cognitive, homeostatic and emotional cortico-subcortical networks (Deshpande et al., 2011). Together, these studies highlight the insula as a core region in a broad network integrating emotion and cognition.

The specific function of the IC in negative emotions remains a matter of debate, and there are a number of conflicting studies that still need to be reconciled. Functional magnetic resonance imaging (fMRI) studies in normal subjects show the role of the insula in the perception of aversive emotions (Jabbi et al., 2007; Murphy et al., 2003; Straube and Miltner, 2011), particularly disgust (Brown et al., 2011; Jabbi et al., 2008; Phillips et al., 1997; Reker et al., 2010; Wicker et al., 2003). These results seem compatible with studies in patients with left (Calder et al., 2000) and bilateral (Adolphs et al., 2003) insular damage, who show a deficit in the recognition and experience of disgust. However, in apparent contradiction with these findings, Straube et al. (2010) reported no impairment in disgust recognition and experience in a patient with a right IC stroke. These results have led to the current discussion regarding the specificity of the IC for disgust processing.

This debate among lesion studies has been difficult to resolve mainly because exclusive focal damage to the IC is extremely infrequent in everyday clinical practice because of its anatomical positioning and vascular supply from the middle cerebral artery (MCA) (Cereda et al., 2002). In fact, in all previous studies of IC lesions (Adolphs et al., 2003; Calder et al., 2000; Ibanez et al., 2010b; Manes et al., 1999a, 1999b, 1999c; Straube et al., 2010), the injuries were not fully constrained to the IC. Notably, these injures included extra-insular damage, mainly to the basal ganglia, connecting white matter and structures like the amygdala, the ventral striatum and the claustrum, which also play a role in affective processing networks (Adolphs, 2002; Fernandez-Miranda et al., 2008). Therefore, previous lesion studies cannot rule out the participation of other adjacent areas in negative emotion processing.

On another level, the IC seems to be involved in social emotions and social cognition through interoceptive information and body awareness (Straube and Miltner, 2011). Interoceptive representation has been suggested to modulate motivational behavior (Craig, 2002; Wiens, 2005), empathy (Lamm et al., 2011; Lamm and Singer, 2010), risky decision making (Dunn et al., 2010), and social skills such as the theory of mind (Bird et al., 2010; Keysers and Gazzola, 2007) and intentional action understanding (Brass and Haggard, 2010). Importantly, these are complex social cognition processes that are supported by emotional and body feedback information (Lamm and Singer, 2010). Additionally, several functional connectivity analyses of fMRI data indicate that there is engagement of the IC and cingulate regions in both the dorsal network, which is involved in cognitive control, and the ventral network, which is mostly related to emotional experiences (Cauda et al., 2011; Dosenbach et al., 2007; Kober et al., 2008; Taylor et al., 2009; Touroutoglou et al., 2012). This aIC-ACC network, also known as the *salience network*, is suggested to switch between attentional and resting state modes (Sridharan et al., 2008) and to integrate cognitive, homeostatic and emotional salience information (Deshpande et al., 2011; Medford and Critchley, 2010). Furthermore, a combination of diffusion tensor imaging (DTI) and dissection techniques has revealed that through the external capsule, the IC structurally connects with the adjacent frontal, parietal, and temporal operculae and with the inferior occipitofrontal fascicle running from the PFC to the posterior temporal and occipital cortices (Cerliani et al., 2011; Fernandez-Miranda et al., 2008). Thus, it is intriguing to think that the external capsule and the thin gray matter sheet within it, the claustrum, might be crucial areas connecting IC with a frontotemporal network involved in the integration of basic emotional processing and higher-order social cognition processes (Ibanez and Manes, 2012; Viskontas et al., 2007).

Despite these converging lines evidence suggesting a role of the IC *and related connections* in social emotion and social cognition, the functional significance of this area had yet not been directly tested by means of lesion studies.

The objective of this work is to thoroughly examine the functional role of the IC through the study of two rare focal lesion cases. Our aims are to investigate multimodal emotion recognition (including aversive emotions such as fear and disgust) and social cognition processes such as empathy, contextual social-emotional inference and theory of mind. A key aspect of this investigation is the peculiarity of the lesions studied, which allows us to go beyond previous studies and distinguish the role of the IC per se from that of its connections within the frontotemporal cortical-subcortical network. The first case involves a focal, pure right IC ischemic lesion and the second case involves a right putaminal-white matter hemorrhagic injury, which disrupt the posterior insular connections from the frontotemporal network.

Our unexpected results show that processing of both negative (disgust included) and social emotions is not impaired in focal IC but is affected in the case of a subcortical lesion (SL) disrupting the connection between the insula and frontotemporal regions.

2. Material and methods

2.1. Participants

2.1.1. *Insular lesion (IL) patient*

G.G. is a 52-year-old right-handed woman who had suffered an ischemic IC stroke 18 months before evaluation. Initial symptoms were dysarthria, left hand hemiparesis and left hemianesthesia. This symptomatology was transient and disappeared 3 days after stroke onset with no residual signs at neurological examination despite subjective complaints about the loss of taste and occasional mild pain in her left arm. MRI of the brain showed an ischemic focal lesion comprising the complete right anterior, mid and posterior IC and the internal portion of the posterior part of frontal opercula – a region usually prompted together with aIC in fMRI studies (Cauda et al., 2011; Menon and Uddin, 2010; Sridharan et al., 2008)– with no impairment of subcortical adjacent structures. This was evidenced by normalizing the structural MRI to the standardized space of the Montreal neurological institute atlas (MNI) and using a lesion overlap analysis with SPM8 (Statistical Parametrics Maps, Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm) and MRIcron software (Rorden and Brett, 2000), respectively (Fig. 1A and B). The Estimate&Write module of SPM8 was used for normalization with an affine (linear) transformation and non-linear deformation fields to register the T1 source image to the ICBM/MNI space. Additional overlap with the JHU-Atlas of white matter shows that IL does not involve the external capsule (Fig. 1C) (Bennett et al., 2010; Burzynska et al., 2010).

2.1.2. *SL patient*

N.F. is a 58-year-old right-handed woman who presented with a hemorrhagic stroke that had occurred 12 months before evaluation. Initial symptoms consisted of left sided hemiparesis and hemianesthesia, both of which remained for 4 months and then finally disappeared. At the time of evaluation, she presented with no neurological deficits and only complained about some pain in her left arm, leg and foot. Her brain MRI showed a right subcortical hemorrhage. Lesion normalization to an MNI standardized brain atlas demonstrated engagement of the right putamen and claustrum, as well as white matter belonging to the external capsule (Fig. 1C and D). Additional overlap with the JHU-Atlas of white matter shows the SL compromise of the external capsule (Fig. 1F).

2.1.3. *Control sample*

A group of 10 right-handed women with no history of neurological or psychiatric conditions were evaluated. Demographic data were statistically controlled (see sociodemographic and neuropsychological results below). All participants signed an informed consent before the evaluation, and the study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee.

2.2. *Assessment*

2.2.1. *Neuropsychological and clinical evaluation*

Frontal executive functioning (EF) was evaluated by the administration of the INECO Frontal Screening test (IFS) (Torralva et al., 2009), which assesses eight different domains of EF and has already been used to assess frontal performance in lesioned patients (Roca et al., 2010). The IFS assesses frontal lobe function as an indexed of the following subtasks: Motor Programming, Conflicting Instructions, Verbal Inhibitory Control, Abstraction, Backwards Digit Span, Spatial Working Memory, and Go/No Go. Furthermore, to evaluate mood and affective state, Beck's Depression Inventory (Beck et al., 1996) and State Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) were administered to all participants, respectively.

2.2.2. *Experimental tasks*

2.2.2.1. Emotion recognition. *Emotional morphing*: This facial expression recognition task featured six basic emotions (happiness, surprise, sadness, fear, anger and disgust) taken from the Pictures of Affect Series (Ekman and Friesen, 1976), which had been morphed for each prototype emotion and for a neutral state (Young et al., 1997). This procedure involved taking a variable percentage of the shape and texture differences between the two standard images 0% (neutral) and 100% (full emotion) in 5% steps (500 msec for each image). The 48 morphed facial stimuli were presented on a computer screen (in a random order) for as long as the patient took to respond by pressing the keyboard. Each participant was asked to respond as soon as they recognized the facial expression and then to identify it from a forced-choice list of six options. The accuracy of the emotion recognition and reaction times (RTs) were measured in this task.

Emotional prosody task: The emotional prosody task (Scott et al., 1997) comprises six disyllabic concrete nouns with neutral meaning, which were selected from a larger sample of words used in previous studies (Hurtado et al., 2009; Ibanez et al., 2010a, 2011a, 2011b, 2006). These words were spoken in six different intonations by two speakers (one female and one male) intending to convey emotions of happiness, anger, fear, disgust and sadness, plus a neutral intonation, thereby comprising a total of 72 different stimuli. Patients were presented binaurally with the stimuli and after each presentation, they were asked to respond with a forced-choice list of six emotions according to the one they recognized. Accuracy and reaction times were measured.

2.2.2.2. Contextual inference of emotional states. The Awareness of Social Inference Test (TASIT) is a sensitive test of social perception developed for studies on neuropsychiatry and comprises videotaped vignettes of everyday social interactions (Kipps et al., 2009; McDonald et al., 2006, 2003; Rankin et al., 2009). We considered only part 1, called the Emotion Evaluation Test (EET), which assesses recognition of spontaneous emotional expression (fearful, surprised, sad, angry and disgusted). In the EET, speaker demeanor (voice, facial expression and gesture) together with the social situation indicates the emotional meaning. This task introduces contextual cues (e.g., prosody, facial movement, and gestures) and additional processing demands (e.g., adequate speed of information processing, selective attention, and social reasoning) that are not taxed when viewing static displays. The brief EET comprises a series of 20 short (15–60 sec) videotaped vignettes of trained professional actors interacting in everyday situations. In some scenes, there is only one actor

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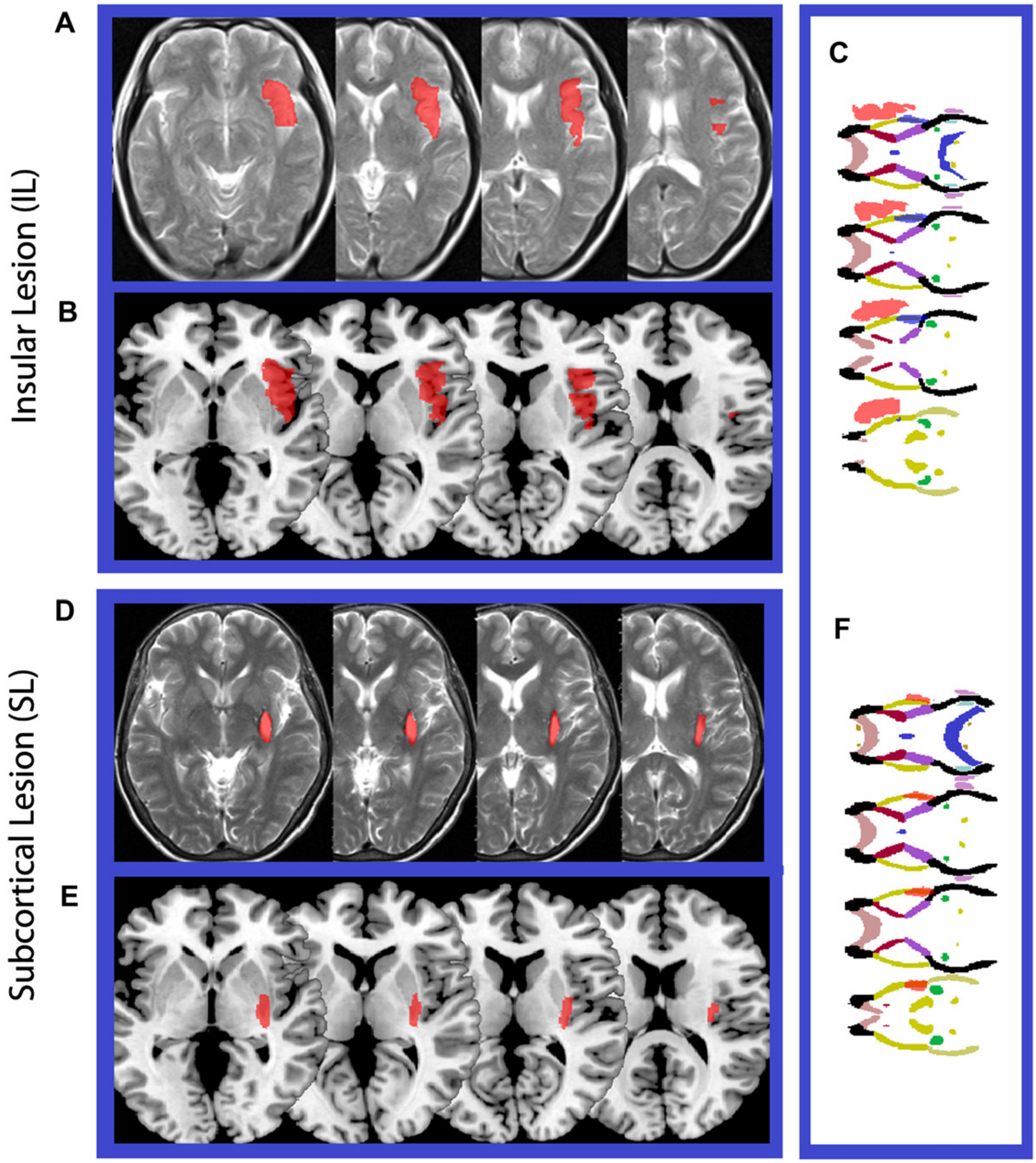

Fig. 1 – Overview of IL and SL MRI images. (A) The IL patient's axial multislice T2-weighted MRI showing the right anterior, mid and posterior IC injury at coordinates z = 4, z = 5, z = 10, and z = 14 from the left to right. (B) Multislice overlap of the IC lesion within a normalized brain from the MNI brain atlas at the same coordinates. (C) Overlap of IL with the JHU-white matter labels atlas showing no engagement of external capsule at the atlas coordinates z = −8, z = −3, z = 2, and z = 7 from the left to right. (D) SL patient's axial multislice T2-weighted MRI showing the right hemorrhagic subcortical injury at coordinates z = 4, z = 5, z = 10 and z = 12 from the left to right. (E) Overlap of the lesion within axial slices at coordinates z = 4, z = 5, z = 10 and z = 14 of a normalized brain. (F) Overlap of SL with the JHU-white matter labels atlas at the atlas coordinates z = −8, z = −3, z = 2, and z = 7 from the left to right.

talking, who is either on the telephone or talking directly to the camera. Other scenes depict two actors and instructions are given to focus on one of them. All scripts are neutral in content and do not lend themselves to any particular emotion. After viewing each scene, the test participant is instructed to choose from a forced-choice list the emotion expressed by the focused actor.

2.2.2.3. Empathy for pain task (EPT). The EPT evaluates empathy for pain in the context of intentional and accidental harm, as well as control situations. The task consists of the successive presentation of 24 animated situations with two persons (Decety et al., 2011). The three following kinds of situations were depicted: intentional pain in which one person (passive performer) is in a painful situation

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caused intentionally by another (active performer), e.g., stepping purposely on someone's toe (pain caused by other); accidental pain where one person is in a painful situation accidentally caused by another; and control or neutral situations (e.g., one person receiving a flower given by another).

Importantly, the faces of the protagonists were not visible and there was no emotional reaction visible to the participants. We measured the ratings and RTs to *situation comprehension* (e.g., "press the button as soon as you understand the situation"). In addition, we assessed seven questions about the following qualities: the *intentionality*, e.g., the accidental or deliberate nature of the action; the emphatic concern (how sad you feel for the passive performer); the degree of *discomfort* (for the passive performer); the *harmful behavior* (how bad was the purpose of the active performer); the *valence behavior* of the active performer (how much positive emotion he/she felt in performing the action); the *correctness* of the action (moral judgment); and finally *punishment* (how much penalty this action deserves). Each question was answered using a computer-based visual analog scale giving seven different pain ratings by trial. Accuracy, reaction times and rating were measured.

2.2.2.4. Theory of mind. The Mind in the Eyes Test (MET) (Baron-Cohen et al., 1997) assesses the emotional inference of the theory of mind. The MET is a computerized and validated test in which 36 images, showing the region of the face from midway along the nose to just above the eyebrows, are presented. The patient is forced to choose which of four words best describes what the person in the picture is thinking or feeling.

2.2.3. *Procedure*

Patients were first evaluated with a neurological examination by two expert vascular neurologists (L.S. and P.R.), and MRI lesions were analyzed by an expert in clinical neuroimaging (F.M.). Subsequently, patients and subjects were assessed with the battery of multimodal emotion recognition tests, the social cognition tests, and the neuropsychological and affective screening questionnaires.

2.2.4. *Data analysis*

To compare both of the patients' performances with a control sample, we used a modified one-tailed *t*-test (Crawford and Garthwaite, 2002; Crawford et al., 2009, 2011; Crawford and Howell, 1998). This methodology allows the assessment of significance by comparing multiple individual's test scores with norms derived from small samples. This modified test is more robust for non-normal distributions, presents low values of type I error, and has already been reported in recent single case studies (Straube et al., 2010). We also performed inferences for single case significances with software BTD-Cov (Crawford et al., 2011) which included formal educational level as a covariate. Because we are reporting case studies, only values with $p < .05$ were considered statistically significant in all comparisons (e.g., not considering trends as a significant difference). Effect sizes obtained through the same methods are reported as point estimates (z_{ccc} as effect size for the modified *t*-test with covariates analysis) as suggested by a previous study (Crawford et al., 2010). Therefore, results are presented for a simple analysis (no covariates) and followed by the effect size and *p* values for the BTD-Cov (Crawford and Garthwaite, 2012).

3. Results

3.1. *Sociodemographic, clinical and neuropsychological results*

Sociodemographic, clinical and neuropsychological results are provided in Table 1. No significant differences in age ($t = -.50$, $p = .31$) and years of formal education ($t = .69$, $p = .25$) were present between the IL patient and the control sample. No IL patient-control differences were observed in either the neuropsychological EF evaluation (IFS) ($t = .82$, $p = .21$, $z_{ccc} = .56$) or depression (BDI, $t = -.64$, $p = .26$). However, the patient showed a significantly lower score and a trend toward lower anxiety (STAI-S, $t = -2.60$, $p = .01$; STAI-T, $t = -1.63$, $p = .07$).

The age of the SL patient was not different from that of the control sample ($t = 1.03$, $p = .16$), but she had a significantly lower formal education level than the controls ($t = -1.99$,

Table 1 – Demographic and neuropsychological assessment.

	IL						SL						Controls
Sociodemographic data		t	p	Zcc				t	p	Zcc			
Age	51	−.50	.31	−.53			59	1.03	.16	1.08			M = 53.30; SD = 4.34 (44–59)
Formal education[a]	17	.69	.25	.72			7[b]	−1.99	.03	−2.07			M = 14.25; SD = 3.49 (9–18)
		t	p	Zcc	p	Zccc		t	p	Zcc	p	Zccc	
IFS													
Total score	26/30	.82	.21	.86	.18	1.07	29/30[b]	2.23	.02	2.34	.03	2.33	M = 24.2; SD = 2.05 (21–27)
Affective screening													
Depression (BDI)	3	−.64	.26	−.72	.2	−.98	24	1.41	.09	1.48	.07	1.98	M = 9.6; SD = 9.7 (3–33)
Anxiety state (STAI-S)	21[b]	−2.60	.01	−2.74	<.001	−5.28	28	−.49	.31	−.52	.33	.54	M = 29.6; SD = 3.16 (24–32)
Anxiety trait (STAI-T)	28	−1.63	.07	−1.71	.11	−1.55	55	1.46	.09	1.54	.15	1.35	M = 42.2; SD = 8.27 (32–59)

M = Mean; (SD = Standard deviation); and minimum and maximum value for control group.
Zcc, effect size for simple *t*-test; Zccc, effect size of covariate *t*-test.
a In years.
b Significantly different to controls.

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$p = .03$). Between the SL patient and control sample, the SL patient was found to have significantly better performance in EF ($t = 2.23$, $p = .02$, $z_{ccc} = 2.33$). No significant differences were found in either depression (BDI, $t = 1.41$, $p = .09$) or in anxiety (STAI-S, $t = -.49$, $p = .31$; STAI-T, $t = 1.46$, $p = .15$). Due to the differences in the years of formal education, we performed a covariance test (Crawford et al., 2011) to analyze the influence of this variable on the performance of specific emotion and social cognition tests. All results for SL and IL are reported after controlling for educational level and are shown as *t* values with one-tailed significances obtained by this method.

3.2. *Experimental task results*

Tables 2–5 and Figs. 2 and 3 summarize the *main* effects observed in the different tasks when comparing patients against controls. A detailed description of all effects is provided in supplementary data (Table S1).

3.2.1. *Emotional morphing*

The IL patient showed no significant differences from controls in the accuracy recognition of six categories of emotion (happiness, maximum score for both IL patient and controls; anger, $t = .11$, $p = .45$, $z_{ccc} = .09$; fear, $t = .79$, $p = .22$, $z_{ccc} = .98$; sadness, $t = .37$, $p = .35$, $z_{ccc} = -.21$; disgust, $t = -1.16$, $p = .13$, $z_{ccc} = -1.22$; surprise, $t = .00$, $p = .5$, $z_{ccc} = -.1$). However, she performed the task with significantly longer RTs than controls for disgust ($t = 2.20$, $p = .02$, $z_{ccc} = 4.57$), and surprise ($t = -3.92$, $p = .001$, $z_{ccc} = 2.36$). In addition, no significant differences were found in RTs for happiness ($t = .77$, $p = .22$, $z_{ccc} = .44$), anger ($t = .16$, $p = .43$, $z_{ccc} = .57$), fear ($t = 2$, $p = .10$, $z_{ccc} = 1.53$) and sadness ($t = .25$, $p = .40$, $z_{ccc} = .18$).

The pattern observed for patient SL was very similar. Her performance did not differ significantly from controls for any category of emotion recognition (happiness, $t = .00$, $p = .50$; disgust, $t = -1.16$, $p = .13$; fear, $t = -.71$, $p = .24$; anger, $t = .18$, $p = .46$; sadness, $t = 1.00$, $p = .17$; surprise, $t = 1.14$, $p = .14$). However, SL showed significantly longer RTs in comparison to the controls for disgust ($t = -5.32$, $p < .001$, $z_{ccc} = -6$), fear ($t = -4.25$, $p = .001$, $z_{ccc} = -4.46$), anger ($t = -3.52$, $p < .005$, $z_{ccc} = -3.69$), surprise ($t = -3.88$, $p = .001$, $z_{ccc} = -4.07$) and sadness ($t = -5.16$, $p < .001$, $z_{ccc} = -5.41$). In contrast, she exhibited no significant differences in the RTs for happiness ($t = -.02$, $p = .49$, $z_{ccc} = -.02$). See Table 2 and Table S1 in the supplementary data for additional details.

3.2.2. *Emotional prosody task*

In recognizing prosodic signs of disgust, the IL patient scored significantly better than the controls ($t = 3.41$, $p = .005$, $z_{ccc} = 2.41$; see Table 3 for descriptive statistics) and exhibited a trend for better performance for sadness ($t = 1.66$, $p = .06$, $z_{ccc} = 1.94$). No other accuracy differences were observed regarding other emotions (happiness, $t = .64$, $p = .26$, $z_{ccc} = .88$; anger, $t = 1.04$, $p = .16$, $z_{ccc} = .91$; fear, $t = .63$, $p = .27$, $z_{ccc} = .5$; neutral, $t = .33$, $p = .37$, $z_{ccc} = .1$). However, she performed the task with RTs significantly longer than the controls for disgust ($t = -2.43$, $p = .01$, $z_{ccc} = -2.39$) and sadness ($t = -2.04$, $p = .03$, $z_{ccc} = -2.10$), although non-significant RTs for fear ($t = .63$, $p = .27$, $z_{ccc} = .5$), anger ($t = 1.04$, $p = .16$, $z_{ccc} = .91$) and happiness ($t = .64$, $p = .26$, $z_{ccc} = .88$).

As for the SL patient, she exhibited significantly lower accuracy in recognizing disgust ($t = -3.65$, $p = .004$, $z_{ccc} = -3.87$) and longer RTs for the same emotion ($t = 4.85$, $p = .005$, $z_{ccc} = 5.06$), as well as fear ($t = 1.79$, $p = .05$, $z_{ccc} = 1.88$). No other differences were observed (RTs for: happiness, $t = .13$ $p = .09$; disgust, $t = 4.85$, $p = .005$; fear, $t = 1.79$, $p = .05$; anger, $t = .34$, $p = .31$; sadness, $t = .70$, $p = .70$; accuracy for: happiness, $t = .96$, $p = .47$; anger, $t = .07$, $p = .26$; sadness, $t = -.96$, $p = .18$). See Table 3 and Table S1 in supplementary data for additional details.

3.2.3. *TASIT*

Compared to controls, the IL patient performed the task with no significant differences in emotion recognition from contextual paraverbal cues ($t = .42$, $p = .28$, $z_{ccc} = .67$). The analysis of error distribution per category showed a trend for fewer errors by IL for disgust categorization ($t = -1.47$, $p = .09$, $z_{ccc} = -1.59$) and no significant differences for other emotions (fear, $t = 0$, $p = .40$; sadness, $t = .45$, $p = .39$; anger, $t = -.5$, $p = .41$).

On the contrary, the SL patient performed significantly worse than the controls ($t = -2.38$, $p = .03$, $z_{ccc} = -2.5$). Error analysis per category of emotion showed significantly more errors for disgust ($t = 2.62$, $p = .01$, $z_{ccc} = 2.89$), surprise ($t = 2.65$, $p = .01$, $z_{ccc} = 5.07$) and sadness ($t = 2.8$, $p = .01$, $z_{ccc} = 4.42$) in comparison with controls. Remaining emotions were no significant (fear, $t = 0$, $p = .19$; anger, $t = -.5$, $p = .12$). (See Table 4 and Table S1 in the supplementary data for additional details).

3.2.4. *EPT*

The IL patient showed no significant differences in the categorization of pain situations as intentional ($t = 1.16$, $p = .13$, $z_{ccc} = 1.19$) and accidental ($t = 1.57$, $p = .1$, $z_{ccc} = 1.58$), as well as

Table 2 – Emotional morphing (RTs[b]). Facial expression recognition.

	IL						SL						Controls
	RT	t	p	Zcc	p	Zccc	RT	t	p	Zcc	p	Zccc	
Anger	11.56	.16	.43	.16	.32	.57	13.34	−3.52	<.005[a]	−3.69	.01[a]	−3.69	M = 11.19; SD = 2.3 (7.77–14.91)
Sadness	11.28	.25	.40	.27	.43	.18	14.01	−5.16	<.001[a]	−5.41	.05[a]	2.13	M = 10.84; SD = 1.63 (7.58–12.73)
Fear	11.56	2.00	.10	2.10	.10	1.53	13.80	−4.25	.001[a]	−4.46	.02[a]	3.26	M = 8.68; SD = 1.37 (6.95–10.45)
Disgust	11.26	2.20	.02[a]	2.39	.001[a]	4.57	14.34	−5.32	<.001[a]	−5.58	<.001[a]	6.00	M = 8.58; SD = 1.12 (5.83–10.21)
Surprise	11.45	−3.92	.001[a]	−4.37	.03	2.36	12.25	−3.88	.001[a]	−4.07	.04[a]	2.51	M = 8.80; SD = 1.16 (7–10)

M = Mean; (SD = Standard deviation); and minimum and maximum value for control group.
Zcc, effect size for simple t-test; Zccc, effect size of covariate t-test.
a Significant differences from controls.
b Time in seconds.

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Table 3 – Emotional Prosody task. Accuracy and RTs.

	IL						SL						Controls
		t	p	Zcc	p	Zccc		t	p	Zcc	p	Zccc	
Disgust (accuracy)	90%	3.41	.005[a]	3.62	.03[a]	2.41	30%	−3.65	.004[a]	−3.87	.03[a]	−3.23	M = 61%; SD = 8% (50–70%)
Disgust (RT)[b]	3.23	−2.43	.01[a]	−2.54	.03[a]	−2.39	7.95	4.85	.005[a]	5.18	.005[a]	4.55	M = 4.81; SD = .62 (4–5.72)
Sadness (RT)[b]	3.10[a]	−2.04	.03[a]	−2.15	.05[a]	−2.10	5.56	.70	.18	1.10	.29	−1.15	M = 4.93; SD = .85 (4.10–6.98)
Fear (RT)[b]	3.82	−.47	.33	−.45	.44	−.15	5.62[a]	1.79	.05[a]	1.88	.30	.76	M = 4.17; SD = .77 (3.34–5.23)

M = Mean; (SD = Standard deviation); and minimum and maximum value for control group.
Zcc, effect size for simple t-test; Zccc, effect size of covariate t-test.
a Significant differences from controls.
b Time in seconds.

neutral situations ($t = .42$, $p = .34$, $z_{ccc} = .30$), compared to controls. No differences in rating judgments for neutral condition (emphatic concern, $t = .42$, $p = .39$, $z_{ccc} = -.46$; harmful behavior, $t = -7.56$, $p = .33$, $z_{ccc} = -.48$; valence behavior, $t = -1.39$, $p = .27$, $z_{ccc} = -.71$; correctness, $t = 1.89$, $p < .001$, $z_{ccc} = 11.6$; and punishment, $t = -.69$, $p = .35$, $z_{ccc} = -.43$) were observed, neither in accidental pain condition (empathic concern, $t = 1.13$, $p = .09$, $z_{ccc} = 1.63$; discomfort, $t = 1.07$; $p = .09$, $z_{ccc} = 1.62$; harmful behavior, $t = -.67$, $p = .27$, $z_{ccc} = -.7$; valence behavior $t = -.49$, $p = .33$, $z_{ccc} = -.5$; correctness, $t = -1.1$, $p = .19$, $z_{ccc} = -1.03$; punishment, $t = -1.3$, $p = .13$, $z_{ccc} = -1.34$) nor in intentional pain condition (empathic concern, $t = .78$, $p = .13$, $z_{ccc} = 1.33$; discomfort, $t = .96$, $p = .15$, $z_{ccc} = 1.24$; harmful behavior, $t = 2.92$, $p = .22$, $z_{ccc} = .92$; valence behavior $t = .84$, $p = .12$, $z_{ccc} = 1.40$; correctness, $t = .79$, $p = .2$, $z_{ccc} = .99$; punishment, $t = 1.32$, $p = .12$, $z_{ccc} = 1.43$). However, she performed with significantly longer RTs for the intentional pain situation in valence behavior of the active performer ($t = 2.56$, $p = .01$, $z_{ccc} = 2.45$) and, as well as in the punishment judgment ($t = 5.73$, $p < .001$, $z_{ccc} = 6.11$) for the accidental pain situation. Furthermore, she also showed longer RTs for the recognition of neutral situations ($t = 2.43$, $p = .01$, $z_{ccc} = 2.93$). No significant RTs were found in neutral condition (correctness, $t = 2.09$, $p = .07$, $z_{ccc} = 2.33$); in accidental condition (discomfort, $t = 1.58$, $p = .12$, $z_{ccc} = 1.83$; correctness, $t = 2.1$, $p = .06$, $z_{ccc} = 2.38$); and for intentional pain situation (empathic concern, $t = .78$, $p = .13$, $z_{ccc} = 1.33$; discomfort, $t = .96$, $p = .15$, $z_{ccc} = 1.24$; harmful behavior, $t = 2.92$, $p = .22$, $z_{ccc} = .92$; valence behavior $t = .84$, $p = .12$, $z_{ccc} = 1.40$; correctness, $t = .79$, $p = .2$, $z_{ccc} = .99$; punishment, $t = 1.32$, $p = .12$, $z_{ccc} = 1.43$).

On the contrary, the SL patient exhibited a significantly lower accuracy for accidental pain situations ($t = -3.36$, $p < .005$, $z_{ccc} = -3.52$), but she had no impairment in the recognition of either intentional pain (accuracy, $t = -.93$, $p = .18$, $z_{ccc} = -.97$) or neutral situations ($t = .53$, $p = .30$, $z_{ccc} = .44$). She showed significantly higher ratings than controls in empathic concern ($t = 2.6$, $p = .04$, $z_{ccc} = 2.68$), discomfort ($t = 2.93$, $p = .007$, $z_{ccc} = 2.9$), and harmful behavior ($t = 1.99$, $p = .04$, $z_{ccc} = 2.53$) during the accidental pain condition; and in the neutral condition for emphatic concern ($t = 6.55$, $p < .001$, $z_{ccc} = 6.29$), discomfort ($t = 6.68$, $p = .006$, $z_{ccc} = 5.77$), harmful behavior ($t = 5.32$, $p = .01$, $z_{ccc} = 4.69$) and correctness ($t = 10$, $p < .001$, $z_{ccc} = 11.6$). However, she performed with non-significant differences in rating judgments for neutral condition (valence behavior, $t = -2$, $p = .23$, $z_{ccc} = -1.4$; punishment, $t = 3.3$, $p = .16$, $z_{ccc} = 1.93$), nor for accidental pain condition (valence behavior, $t = .88$, $p = .31$, $z_{ccc} = .93$; correctness, $t = 2.6$, $p = .31$, $z_{ccc} = .92$; punishment, $t = -1.9$, $p = .21$, $z_{ccc} = .43$) and neither for intentional pain condition (empathic concern, $t = -1.42$, $p = .24$, $z_{ccc} = -1.34$; discomfort, $t = -.16$, $p = .10$, $z_{ccc} = -2.47$; harmful behavior, $t = .29$, $p = .47$, $z_{ccc} = .09$; valence behavior $t = -1.18$, $p = .14$, $z_{ccc} = -2.05$; punishment, $t = 2.25$, $p = .12$, $z_{ccc} = 2.27$). The SL patient exhibited RTs that were significantly longer than controls for empathic concern ($t = 4.09$, $p < .001$, $z_{ccc} = 6.29$), harmful behavior ($t = 5$, $p < .001$, $z_{ccc} = 5.85$), valence behavior ($t = 3.64$, $p = .007$, $z_{ccc} = 4.34$) and punishment ($t = 4.9$, $p = .004$, $z_{ccc} = 4.87$) in the accidental condition; in the intentional pain condition (initial RT, $t = 3.54$, $p = .03$, $z_{ccc} = 3$; empathic concern, $t = 4.21$, $p = .001$, $z_{ccc} = 6.19$; harmful behavior, $t = 2.89$,

Table 4 – TASIT. General accuracy and errors per emotion. Contextual emotional inference task.

	IL						SL						Controls
	Accuracy	t	p	Zcc	p	Zccc	Accuracy	t	p	Zcc	p	Zccc	
Disgust	0/4	−1.47	.08	−1.58	.09	−1.59	2/4	2.62	.01[a]	2.78	.02	2.89	M = .72; SD = .46 (0–1)
Sadness	1/4	.45	.33	.47	.39	.31	2/4	2.80	.01[a]	2.97	<.01[a]	4.42	M = .81; SD = .40 (0–1)
Surprise	0/4	−.30	.41	−.25	.29	−.62	1/4	2.65	.01[a]	2.81	.01[a]	5.07	M = .1; SD = .32 (0–1)
Correct answers (Total)[b]	18/20	.42	.34	.44	.28	.67	14/20	−2.38	.03[a]	−2.51	.03[a]	−3.81	M = 17.4; SD = 1.35 (16–20)

M = Mean; (SD = Standard deviation); and minimum and maximum value for control group.
Zcc, effect size for simple t-test; Zccc, effect size of covariate t-test.
a Significant differences from controls.
b Time in seconds.

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Table 5 – Empathy for pain test. Pain ratings and RTs.

	IL						SL						Controls
		t	p	Zcc	p	Zccc		t	p	Zcc	p	Zccc	
Accidental condition													
(Pain rating)$^{+}$Accuracy	100%	1.57	.07	1.65	.10	1.58	54.5%*	−3.36	**.004**	−3.52	.06	−3.08	M = 85.5; SD = 8.78 (72.72–100)
Empathic	3.18	1.13	.14	.82	.09	1.63	8.24*	2.61	**.01**	2.78	.04	2.68	M = −.57; SD = 3.16 (−5.73/3.64)
Discomfort	2.55	1.07	.15	1.18	.09	1.62	7.97*	2.93	**.007**	3.18	**.03**	2.9	M = −.40; SD = 2.63 (−5/2.97)
Harmful behavior	−5.73	−.67	.26	−.67	.27	−.70	2.12*	1.99	**.03**	2.17	**.04**	2.53	M = −3.82; SD = 2.73 (−8.21/.18)
(RTs) $^{\#}$Initial	2.13	−1.04	.16	−1.09	.19	−1.03	7.81*	4.71	**.01**	4.11	**.01**	4.04	M = 3.32; SD = 1.09 (2.13–4.82)
Emphatic	3.19	−.84	.21	−.87	.22	−.89	9.41*	4.09	**<.001**	5.40	**<.001**	6.29	M = 4.06; SD = .99 (2.76–5.59)
Harmful behavior	2.59	−.78	.22	−.81	.26	−.72	6.88*	5.01	**.001**	5.68	**.001**	5.85	M = 3.13; SD = .66 (2.31–4.22)
Valence behavior	3.30	−.5	.31	−.52	.32	−.51	8.87*	3.64	**.002**	3.85	**.007**	4.34	M = 3.97; SD = 1.27 (2.01–6.56)
Punishment	7.23*	5.73	<.001*	6.01	<.001*	6.11	6.55*	4.90	**.004**	5.01	**.004**	4.87	M = 2.72; SD = .75 (1.77/3.6)
Intentional condition													
(Pain rating)$^{+}$Correctness	7.42	.79	.22	.82	.20	.99	6.67*	2.60	**<.001**	.41	.48	.06	M = 5.9; SD = 1.84 (2.18–7.90)
(RTs) $^{\#}$Initial	2.76	−.57	.28	−.60	.35	−.42	7.1*	3.54	**<.005**	3.49	**.03**	3.02	M = 3.4; SD = 1.06 (1.86–5.2)
Emphatic	4.94	.33	.37	.34	.44	.15	10.7*	4.21	**.001**	4.57	**.001**	6.19	M = 4.46; SD = 1.38 (1.94–6.31)
Discomfort	2.13	−1.25	.12	−1.31	.12	−1.39	8.19*	6.15	**<.001**	12.5	**<.001**	7.07	M = 3.18; SD = .8 (1.62–4.65)
Harmful behavior	2.96	−.48	.31	−.51	.28	−.66	6.43*	2.89	**.01**	2.89	**.01**	3.89	M = 3.48; SD = 1.02 (2.25–5.42)
Valence behavior	7.4*	2.56	**.01**	2.64	**.02**	2.45	8.55*	3.34	**.003**	3.65	**.006**	4.43	M = 4.38; SD = 1.15 (3.10/6.98)
Correctness	1.90	−.99	.17	−1.04	.20	−.98	**5.08**	3.35	**.005**	3.31	**.02**	3.21	M = 2.66; SD = .73 (1.31–3.57)
Punishment	2.72	−.38	.35	−.40	.35	−.42	**5.94**	3.50	**.004**	3.52	**.01**	4.04	M = 3.05; SD = .82 (1.79–4.18)
Neutral Condition													
(Pain rating)$^{+}$Emphatic	−8.33	−.63	.27	−.66	.34	−.46	1.78*	6.55	**<.001**	6.55	**<.001**	6.29	M = −7.4; SD = 1.4 (−8.33/−4.78)
Discomfort	−8.33	−.74	.34	−.75	.31	−.48	2.00*	6.68	**.006**	6.99	**.009**	5.77	M = −7.3; SD = 1.33 (−8.33/−4.67)
Harmful behavior	−8.33	−7.56	.33	−.66	.28	−.50	2.33*	5.32	**.01**	5.60	**.02**	4.69	M = −7.2; SD = 1.7 (−8.33/−3.33)
Correctness	−8.33	−.76	.23	−.79	.28	−.66	1.89*	10	**<.001**	11.5	**<.001**	11.6	M = −7.67; SD = .83 (−8.33/−6)
(RTs) $^{\#}$Initial	9.96*	2.43	**.01**	2.56	**.01**	2.93	4.91*	.23	.41	.24	.41	−.32	M = 4.38; SD = 2.18 (2.2/9.36)
Emphatic	3.44	−.71	.24	−.75	.29	−.63	15.71	5.28	**.001**	6.02	**.001**	6.02	M = 4.80; SD = 1.81 (2.62–8.54)
Discomfort	2.68	.08	.46	.09	.36	.39	4.90	3.52	**.004**	3.50	**.03**	2.99	M = 2.62; SD = .65 (1.64–3.47)
Harmful behavior	2.17	−.30	.38	−.32	.45	−.12	5.43	5.15	**.003**	5.20	**.003**	4.95	M = 2.36; SD = .59 (1.38–3.36)
Valence behavior	2.81	−.69	.25	−.72	.28	−.67	9.53	3.93	**.007**	4.07	**.007**	4.37	M = 3.83; SD = 1.4 (2.24–7.12)
Punishment	3.24	1.17	.13	1.22	.49	−.02	5.65	4.51	**<.001**	4.62	**.004**	4.85	M = 2.37; SD = .71 (1.52–3.7)

M = Mean; (SD = Standard deviation); and minimum and maximum value for control group.
Zcc, effect size for simple t-test; Zccc, effect size of covariate t-test.
Significant p values in bold.
* for significant results; # for RTs; + for pain rating.

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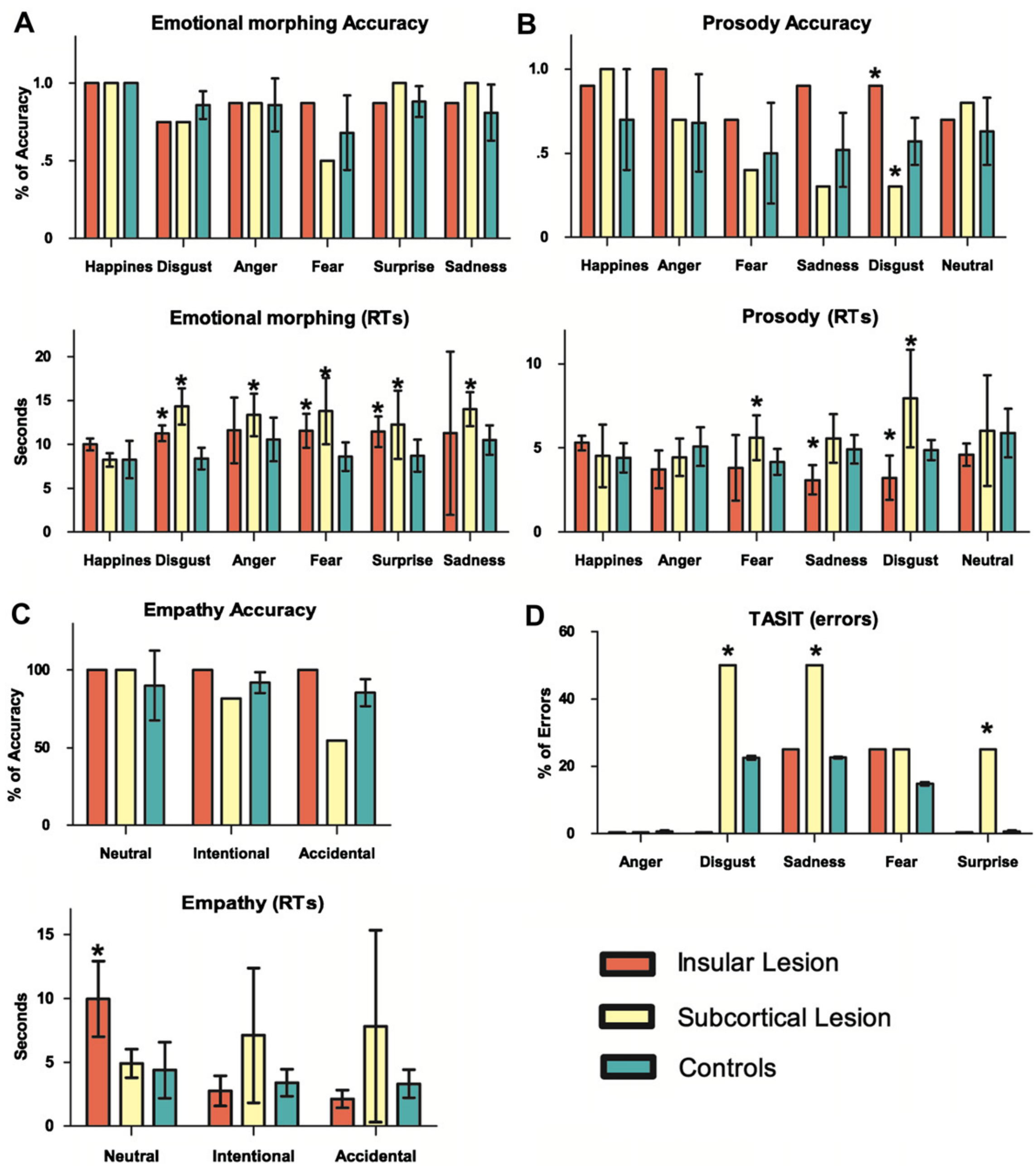

Fig. 2 – Performance of the IL and SL patients and controls in emotion and social cognition tasks. (A) Emotional morphing task, accuracy and RTs. (B) Emotional prosody task (Accuracy). (C) EPT (categorization accuracy and RTs). (D) TASIT (% of errors). *, significant differences ($p < .05$).

$p = .01$, $z_{ccc} = 3.89$; correctness, $t = 3.35$, $p = .02$, $z_{ccc} = 3.21$; and valence behavior $t = 3.34$, $p = .006$, $z_{ccc} = 4.43$) as well as for the neutral condition in empathic concern ($t = 5.28$, $p = .001$, $z_{ccc} = 6$), discomfort ($t = 3.52$, $p = .03$, $z_{ccc} = 2.99$), harmful behavior ($t = 5.15$, $p = .003$, $z_{ccc} = 4.95$), valence behavior ($t = 3.93$, $p = .007$, $z_{ccc} = 4.37$) and punishment ($t = 4.51$, $p = .004$, $z_{ccc} = 4.85$). She performed with no significantly different RTs for correctness in neutral condition ($t = 2.09$, $p = .07$, $z_{ccc} = 2.33$), and discomfort ($t = 1.58$, $p = .12$, $z_{ccc} = 1.83$) and correctness ($t = 2.1$, $p = .06$, $z_{ccc} = 2.83$) in accidental pain situation. See Table 5 and Table S1 in the supplementary data for additional details.

3.2.5. *Theory of mind*

In recognizing mental states and feelings in another person's eyes (MET task), both the IL and SL patients performed the task with no significant differences compared with the controls ($t = .42$, $p = .34$, $z_{ccc} = -.12$ and $t = -.13$, $p = .45$, $z_{ccc} = -.13$, respectively, see Table S1 in supplementary data for descriptive statistics).

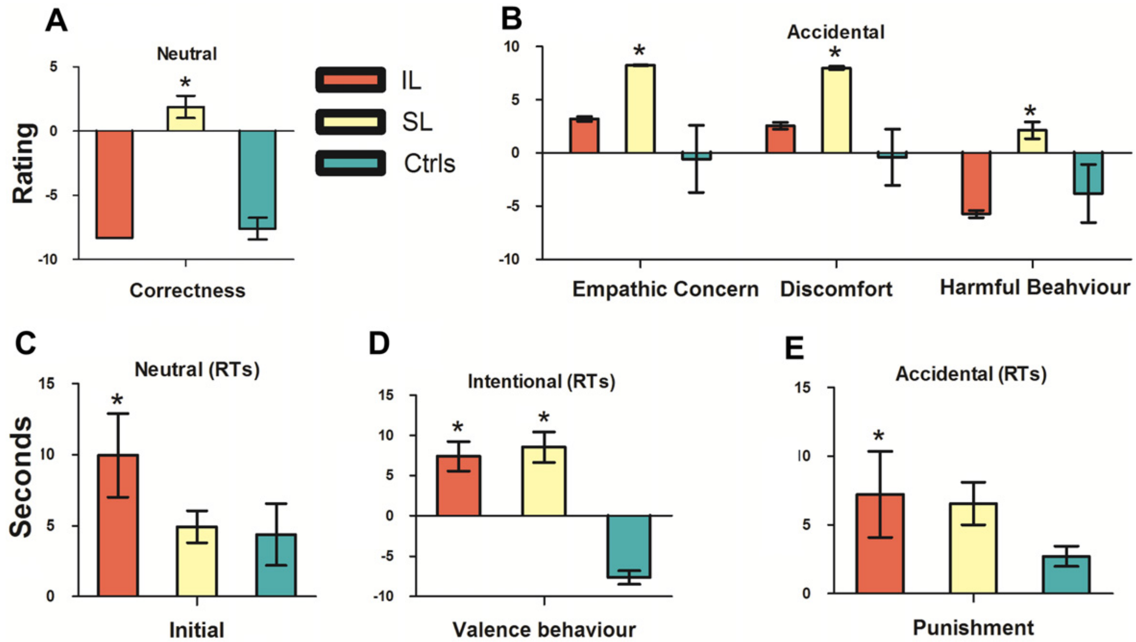

Fig. 3 – Empathy for pain subtasks (significant effects). (A) Judgment ratings about the correctness of neutral situations. (B) Judgment ratings about empathic concern, discomfort and harmful behavior of neutral situations. (C) Initial responses (RTS to situation comprehension) during neutral situations. (D) Reaction times to questions about valence behaviors during intentional situations. (E) Reaction times to questions about punishment during accidental situations. *, significant differences ($p < .05$).

4. Discussion

This study investigated the role of the right IC and the right insular-frontotemporal networks in emotional processing, which included disgust and negative emotions, as well as social cognition tasks. The most important finding of our study is that both the recognition of emotions (including disgust and other negative emotions) and social cognition (contextual inference of emotions, empathy, theory of mind and moral judgments) were unimpaired in a patient with an ischemic lesion limited within the IC. Our conclusion is supported by converging lines of evidence from independent experiments that probed distinct modalities and levels of emotional recognition and social cognition, which included prosody, words, morphed expressions and real life video-clips.

The only consistent difference observed in the IL patient compared with the control group was a general trend toward slower responses in the facial emotional morphing task. In this task, response time is indicative of the intensity of the emotion (because longer times indicate that the morph has evolved closer to the target emotion) and may be indicative of a relatively higher threshold for emotional recognition. Another alternative is that the IL patient may have adopted a conservative strategy of responding only at a higher threshold of the decision signal (Wickelgren, 1977). At this stage of our research, we cannot distinguish between these alternatives; however, two observations make the latter more likely. First, evidence from other tests that used non-morphed stimuli did not reveal any trace of impaired recognition. Second, the effect was not sensitive to the emotion (there is more variability in RT with emotion in the control group than for the patient), thereby suggesting that it is not intrinsically related to the stimulus properties but is a strategic response policy instead. Regardless of this interpretation, we emphasize that performance, which was the main variable investigated here, was completely unimpaired. Furthermore, the IL patient outperformed the controls in the prosody test and in recognition of disgust (the emotion for which the IC has been proposed to serve a fundamental role) by responding much more accurately (90%, while the controls performed within a 30–70% range) and with faster responses. Although at some extent unexpected, this result would be explained by the patient use of explicit compensatory strategies. In addition, enhanced neuroplasticity and a successfully functional remapping of the fronto-insular-temporal network after IC stroke would allow for the correct disgust recognition.

The performance of the IL patient in a broad variety of empathy and social inference tasks was virtually indistinguishable from the group of controls. Hence, both the perception of emotion primitives from facial and prosody information and the extraction of emotions from complex multimodal setups are unimpaired in a patient with a lesion in the IC.

We investigated performance in the same battery of tests in a patient with a lesion in the right putamen and claustrum, as well as in the white matter belonging to the external capsule. Among other functions, these areas play a role in insular-frontotemporal connectivity (Adolphs, 2002; Fernandez-Miranda et al., 2008; Mufson and Mesulam, 1982; Viskontas et al., 2007). Compared to the IL patient and the controls, SL showed evidence of emotion recognition impairment, which mainly occurred for disgust and multimodal stimuli. In contrast to the IL patient, the SL patient had lower (although not significant) performance in the facial recognition of anger and slower response times that were more pronouncedly for sadness, disgust and fear. In regard to emotion recognition from prosody, the scores of SL were below IL for all emotional categories (except neutral) and were significantly below the controls for disgust. Patient SL also made a high number of errors in the inference of sadness and disgust in the videos of real life situations. Overall, we observed a consistent impairment of performance specific to negative emotions, which mainly included disgust, sadness and fear. Patient SL also showed several instances of impairment in an empathy test, while patient IL showed no impairment.

Although it was not completely unexpected in this study to find deficits in the SL patient for emotional and social cognition tasks, it was very surprising to find an IL patient with a restricted IL and preserved subcortical connections who was unimpaired in emotion and social cognition tasks. What is the potential cause of these differences in these patients? Based on these two neuroanatomical lesion models, we tentatively propose that frontotemporal *connections* of the IC are a critical hub for emotion recognition and social cognition. This conclusion is derived from the two following observations: first, the right IC per se might not be uniquely and directly involved in basic emotion recognition and social cognition; second, a patient with a lesion compromising subcortical tracts underlying the surface of the IC displays impairments in performance that have been typically assigned to the IC (Adolphs et al., 2003; Bar-On et al., 2003; Calder et al., 2000; see review: Ibanez et al., 2010b).

Understanding the atypical contribution of focal ILs is essential in interpreting the results of previous extended lesion studies of emotion and social cognition following stroke. For instance, the case reported by Calder et al. (2000) on disgust demonstrated neural damage of the posterior part of the anterior insula, posterior insula, internal capsule, putamen and globus pallidus. Patient B reported in a study by Adolphs et al. (2003) examining emotional processing presented with complete damage of both amygdala, hippocampi, as well as adjacent perirhinal, entorhinal, and parahippocampal cortices (greater on the right than on the left). There was also bilateral destruction of temporal neocortical in Brodman's areas (BA) 38 and BA 20/21 and most of BA 37 on the right. In addition, complete bilateral damage to the basal forebrain nuclei and extensive damage to the anterior insula were present. Moreover, parts of the ventromedial frontal cortices and of the ACC were damaged. Finally, in all three subjects reported by Reuven Bar-On et al. (2003) who showed social and emotional impairments the IC was damaged. There was also extensive damage to the superior and inferior parietal lobules, which include the somatosensory (SI, SII) cortices. In two of the subjects, the damage extended to the right DLPFC and included the right pre-central gyrus; however, the cortex anterior to this region was spared. There was also damage to the superior temporal gyrus. In one subject, the lesion included the right IC and inferior parietal lobule.

These extended lesions around the IC are not unexpected. Arterial contributions to the IC exclusively originate from the MCA, especially from its superior segment (Varnavas and Grand, 1999). However, in addition to the IC, the insular arteries also supply the extreme capsule, the claustrum and external capsule, as well as larger insular arteries extending branches to the medial surfaces of the frontal, temporal, and parietal opercula (Ture et al., 2000). Thus, encountering an isolated, focal IC infarction following MCA stroke is markedly unusual. For example, out of 4800 consecutive first ever acute stroke patients, only four were found to have a truly isolated infarction of the IC (Cereda et al., 2002). In this sense, one could question the extent to which emotion and social cognition changes described by various studies of patients with MCA territory stroke involving the insula are really the result of lesions to this area (considering the extensive MCA territory).

These results suggest that the neighboring regions of the IC possess a broad mesh connecting the IC to other systems and that these connected areas are the sine-qua-non structures for the recognition of negative emotions and not the IC itself. Although controversial, this conclusion has also progressively evolved in other cortical systems. For instance, the posterior inferior frontal gyrus (IFG) has been considered a critical area for language production since the early studies of the French surgeon, Pierre Paul Broca. However, recent high resolution MRIs of the preserved brains of Broca's two historic patients demonstrated that both lesions extended significantly into medial regions of the brain, in addition to the surface lesions observed by Broca (Dronkers et al., 2007). Subsequent studies have confirmed the relevance of white matter lesions by showing that IFG lesions produce *transient* aphasia and that this symptom only persists if the *white matter* and IC are also affected (Ackermann and Riecker, 2010; Dronkers, 1996; Mandonnet et al., 2007; Naeser et al., 1989; Vassal et al., 2010). Our conclusions parallel these observations, and we suggest that subcortical tracts convey the inputs for affective and cognitive information to the IC and provide an important link between this and other nodes of the social-emotion network. Along this line, much of the previous evidence describing impaired disgust recognition, empathy and social emotions in IC lesions [e.g., (Adolphs et al., 2003; Bar-On et al., 2003; Berthier et al., 1988; Calder et al., 2000)] may be partially explained by concurrent damage of its connections with the basal ganglia and frontotemporal regions.

Our conclusions are also consistent with converging lines of evidence characterizing the IC as a cortical hub linking external and internal information processing (Craig, 2010a; Ibanez et al., 2010b; Ibanez and Manes, 2012; Lamm and Singer, 2010). This phenomenon has been shown by anatomical dissection and *in vivo* cortical stimulation in humans and primates, respectively (Caruana et al., 2011; Fernandez-Miranda et al., 2008), as well as by lesion studies (for a Review see, Ibanez et al., 2010b) and a wealth of recent evidence from fMRI connectivity analysis (Cauda et al., 2011; Deen et al., 2011; Deshpande et al., 2011; Kober et al., 2008; Seeley et al., 2007; Sridharan et al., 2008). Several structural and functional networks link IC with structures related to body awareness, such as the gustatory (frontal operculum) and olfactory (piriform cortex), visual, somatosensory (SC) and vestibular regions (Piwnica-Worms et al., 2010). Nevertheless, other cortices also engaged in higher-level cognitive functions including the ventrolateral prefrontal cortex (vlPFC), ACC, superior orbital sulcus (SOS), medial temporal lobe and temporal pole (Craig, 2002; Mufson and Mesulam, 1982). The disruption of some of these latter connections that allow IC participation in higher-cognitive (Dosenbach et al., 2007; Seeley et al., 2007) and social tasks (Lamm and Singer, 2010) might explain why the SL patient presented with impairments in emotional and social cognition tasks. Having such a central (in a graph-theoretical sense) role in the network of cortical function, it is not surprising that lesions affecting IC connectivity compromise the proper functioning of the entire network (Albert et al., 2000). In the same line, imbalanced communication between fronto-insular-temporal nodes in SL patient (due to the white matter infarction) would produce aberrant information processing and related behavioral deficits. However, as external capsule conveys multiple different white matter fiber tracts, current analysis cannot completely rule out the presence of additional disconnected areas in SL accounting for behavioral profile.

Body-signal modulation of emotional processing in the IC has been suggested to be instantiated through interoception (Craig, 2010b; Lamm and Singer, 2010; Wiens, 2005). Although the IC contribution to interoception has been confirmed (Critchley et al., 2004), different pathways of interoceptive awareness reaching the somatosensory cortex and ACC have also been demonstrated (Khalsa et al., 2009). Thus, other structures beyond the insula that account for interoceptive processing might also be implicated in its modulation of emotion recognition (Wiens, 2005). Therefore, we suggest that the delayed response pattern in the insular patient may be related to the compensatory activation of these extra-insular pathways of interoception, which actually allow her to accurately recognize emotion but are not as fast as through insular interoceptive modulation.

Furthermore, although the right aIC has been proposed as the core area for the awareness of the emotional state of the body (Bechara and Naqvi, 2004; Craig, 2002; Critchley et al., 2004), our results demonstrate preserved emotion recognition in the right aIC after stroke. Reviews of interoceptive and higher-order cognitive functions of the IC suggest that right aIC engages in the awareness of homeostatic emotions and body feelings (Brass and Haggard, 2010; Craig, 2002, 2010b; Deshpande et al., 2011; Ibanez et al., 2010b). However, lesion studies of the IC do not show conclusive evidence supporting the lateralization of specific emotion recognition in this region (Straube et al., 2010). In this way, the absence of impairments in the right IL patient of this study may be accounted for by the fact that emotion recognition engages several areas beyond the IC (Adolphs, 2002; Adolphs et al., 2000), including the basal ganglia and ACC. In addition, compensatory function of the left insula by post-lesion plasticity changes has also been implicated (see Straube et al., 2010) and might have successfully remapped the functionality of IL patients' fronto-insular-temporal networks. Further single case analyses of focal lesions and other convergent evidence are still needed to answer the question of IC lateralization in emotion recognition.

Our conclusions are based on focal lesion models that lead us to make inferences on function through the performance analysis of patients. With this approach, we intend to overcome the caveats of previous reports that share the limitation of studying patients with extended lesions involving neighboring structures (i.e., basal ganglia, amygdala, and frontal-parietal-temporal opercula; Adolphs, 2002; Calder et al., 2000), most of which are engaged to some extent in affective and social cognition processing networks (Adolphs, 2002; Adolphs et al., 2002, 2000; Calder et al., 2000; Kipps et al., 2009; Kober et al., 2008; Phillips et al., 1997). Therefore, this study provides neuroanatomical and behavioral evidence supporting that integrity of frontotemporal brain networks is required for intact social cognition and emotional processing.

As far as we know, this is the first study to compare the consequences of damage to the IC and its connections on emotion recognition and social cognition, while controlling for the extent of damage. Thus, our findings contribute to clarifying two currently discussed ideas about the role of the IC on emotion and social cognition. First, our results account for the two dimensions of emotion and social performance in the insula and subcortical structures. Furthermore, our findings are in accordance with the proposal of multiple pathways for interoception, whereby conserved extra-insular interoceptive pathways in the IL patient may allow her to take advantage of the body-signal modulation of her own effective emotion recognition networks. Second, because social emotions involve several areas including the IC (Decety et al., 2011), we suggest that these social processes, such as empathy and social context inference of emotions, also depend on the IC connections with subcortical structures and connections between other brain regions such as temporal and frontal regions running along the insula, as was demonstrated by the SL patient. Therefore, as emotion processing requires the integrity of fronto-insular-temporal networks, not only the connected nodes, but also the underlying connections between these regions need to be preserved for its proper functioning.

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Conflict of interest

None to declare.

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Supplementary data

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