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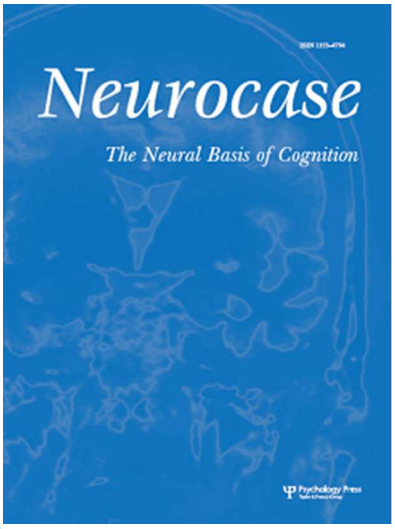

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Unawareness of Bipolar Disorder: The Role of the Cingulate Cortex.

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Unawareness of Bipolar Disorder: The Role of the Cingulate Cortex.

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Abstract

Reduced awareness of illness is a well-known phenomenon that has been understudied in remitted patients with bipolar disorder. In particular, the relationship between reduced awareness and executive dysfunction is an intriguing question that has yet to be resolved. The aim of the current study is to analyze the link between reduced awareness, brain dysfunction and concomitant cognitive-behavioral disturbances from a neurocognitive perspective. In previous studies, we demonstrated a role of the Anterior Cingulate Cortex in the unawareness of distinct pathologies that exhibit overlapping symptoms in the context of overlapping circuit-specific dysfunction.

Given the clinical importance of the results obtained, the present study considers six aware and four unaware remitted bipolar disorder patients. Cingulate functionality was assessed with functional magnetic resonance imaging while patients performed a go/no-go task. Patients were also studied on an overall cognitive tasks battery and with behavioural assessment of mood changes in terms of apathy and disinhibited behavior.

Unaware patients showed fronto-parietal hypo-perfusion with a significant reduction of task-sensitive activity in the bilateral superior and middle frontal gyrus, putamen, insular and anterior cingulate cortices.

Keywords: Remitted Bipolar Disorder patients, awareness deficit, response inhibition, anterior cingulate cortex, fMRI

1. Introduction

A reduction in the awareness of disease[1] in patients with psychiatric disorders is a multifaceted phenomenon that not only impacts the course of the illness and adherence to treatment, with a negative effect on prognosis and rehabilitation efforts (Dell'Osso, Pini, Tundo, Sarno, Musetti et al., 2000), but also increases the risk of violent and suicidal behavior (Yen, Chen, Yen & Ko, 2008). Specifically considering remitted bipolar disorder over a two-year period, impaired awareness of treatment, associated with a high number of hospitalizations, considerably increases the risk of negative clinical outcomes (Yen, Chen, Yen & Ko, 2008). Since it has been found that awareness could be impaired in 60% of Bipolar Disorder patients in remission (Dias, Brisson & Carita, 2008), targeting this aspect might be a promising starting point in order to gain a better understanding of the disease and of the best strategy for engaging patients.

Awareness has been partially associated with intact executive functioning (Amador & David, 2004). Since euthymic patients with Bipolar Disorder (BD-st) present neuropsychological deficits related in particular to executive functions, attention and processing speed (Robinson, Thompson,

[1] A variety of terms have been used to describe reduced awareness in these patients. One among all: "lack of insight". In this article, we will use the term "reduced awareness", which is descriptive and has no theoretical implications.

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Gallagher, Goswami, Young, et al., 2006; Torres, Boudreau & Yatham, 2007), some studies have highlighted the presence of reduced awareness associated with worse performance on executive function tests measuring divided attention, mental flexibility, response inhibition, interference and behavioural conflict resolution, and working memory (Dias, Brissos, Frey & Kapczinski, 2008; Trevisi, Talamo, Bandinelli, Ducci, Kotzalidis et al., 2012). On the other hand, a few studies found no such association when using the Wisconsin Card Sorting Test (WCST) as the target test to assess executive functions and reduced awareness in a population of consecutive Bipolar-I patients (Varga, Magnusson, Flekkøy, Rønneberg & Opjordsmoen , 2006) or bipolar outpatients in remission (Yen, Chen, Yeh, Yen, Ker et al., 2002). Indeed, the WCST has been criticized in that it involves different components of executive functioning (Keefe, 1995; Dimitrov, Granetz, Peterson, Hollnagel, Alexander et al., 1999). The difference in the results could then be due to the multifactorial nature of this test which, in assessing set-shifting abilities, is also highly dependent on memory functions, in that subjects must hold the sorting strategy in their working memory throughout the duration of the task.

We recently demonstrated how a reduction in awareness is related to deficits in metacognitive executive functions i.e., the ability to shift and inhibit a response, self-monitoring and set-shifting (Amanzio et al., 2013). Furthermore, it is interesting to note that patients with Alzheimer's Disease (AD) and the subject with Acquired Brain Injury (ABI) in the case study we recently published showed greater dysfunction of the medial prefrontal cortex (MPF-C: Amodio & Frith, 2006) with an important role played by the dorsal division of the ACC (Amanzio et al., 2011, Palermo, Leotta, Bongioanni & Amanzio, 2013). Interestingly it has been observed that BD-st patients fail to activate areas associated with performance of the Stroop test (for healthy subjects see Goldstein, Volkow, Wang, Fowler & Rajaram, 2001) such as the dorsolateral prefrontal cortex and ACC (Strakowski, Johnson, Delbello, Hamer, Green et al., 2005).

As far as we know, only one study has indirectly explored the association between reduced self-awareness and the cingulate cortex in Bipolar Disorder patients. In particular, Dias et al (2008) analyzed the differences between group awareness in remitted Bipolar patients using the selective attention tests (such as the Trail Making Test A and B, Stroop Colour Test and Stroop Colour-Write Test) for which ACC is known to play an important role (Braver, Barch, Gray, Molfese, & Snyder 2001; Carter, Botvinick, & Cohen, 1999; Casey, Trainor, Orendi, Schubert, Nystrom et al., 1997; Raichle, Fiez, Videen, MacLeod, Pardo et al., 1994). In particular, they reported that unaware BD-st patients showed worse cognitive performance on the Trail Making Test A and B and Stroop Colour Test (in terms of perseveration rates).

To the best of our knowledge, no previous studies have examined awareness of the disease and response-inhibition ability using an event-related fMRI paradigm. With this aim, in this preliminary report, we studied six aware and four unaware remitted patients to investigate whether ACC plays an important role in the phenomenon.

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Methods

2.1 Subjects

The study group included ten right-handed adult outpatients fulfilling DSM-IV-TR criteria for the euthymic phase of Bipolar I disorder. Subjects were enrolled at the Department of Mental Health ASL TO1 and ASL TO2 of Turin. Diagnoses were established using the Structured Clinical Interview for DSM-IV Clinician Version (SCID-I CV: First, Spitzer, Gibbon & Williams, 1996), conducted by two experienced psychiatrists (K.R & G.G). The majority of the subjects had been ill for more than ten years and had at least two previous hypomanic/manic episodes. At the time of evaluation all patients were taking mood-stabilizers (lithium = 715 ± 122.5 mg) as part of a standard clinical regime as prescribed by their psychiatrists. The clinical and demographic variables of these subjects are presented in Table 1 (see section 3.1).

The exclusion criteria were as follows: less than primary school education; Mini-Mental State Examination performance equal to or less than 27 (Folstein, Folstein, & McHugh, 1975); age over 55 years; previous or concomitant neurological disorder and/or brain organic conditions; history of major head trauma; any comorbid primary Axis I diagnoses; substance abuse or dependence within six months prior to undergoing the neuropsychological evaluation; history of serious mental disorder in first-degree relatives.

2.2 Neuropsychiatric and awareness assessment

All neuropsychiatric and awareness scales were administered by a psychiatrist blind to the results obtained by the patients on the neuropsychological tests. BD-st patients were assessed in the week before the fMRI session using the SCID-I CV (First et al., 1996). This is an effective tool for detecting DSM-IV diagnostic criteria and establishing an accurate and standardized diagnosis in patients aged 18 years and over. It is divided into six self-contained modules (mood episodes, psychotic symptoms, psychotic and mood disorders, substance use disorders and anxiety).

The actual level of symptomatology was assessed using the *Brief Psychiatric Rating Scale 4.0* [BPRS 4.0] (Roncone, Ventura, Impallomeni, Falloon, Morosini et al.,1999; Ventura, Lukoff, Nuechterlein, Liberman, Green et al., 1993). This is a 24-item clinician-rated questionnaire in which, each symptom is rated on a seven-point Likert scale with scores ranging from 1 ("not present") to 7 ("extremely severe"). The purpose of the BPRS 4.0 is to provide the patient's current psychopathological picture expressed both through an overall score, which identifies the severity level, and through the detection of the most significant symptoms at the time of evaluation.

The *Clinical Global Impression scale* [CGI] (Guy, 1976) was used to assess the severity of illness and rate the patient's progress since the last episode of illness (see table 1). This is a three-item observer-rated scale that measures illness severity (CGI Part A), global improvement or change (CGI

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part B) and therapeutic response (CGI part C). The items are rated on a seven-point severity scale. Each component of the CGI is rated separately; the instrument does not yield a global score.

In addition behavioral mood changes were assessed using specific scales.

1) *Apathy Evaluation Scale-Clinician version* [AES-C] (Marin et al., 1991): This is an 18-item clinician-rated questionnaire with scores ranging from 18 to 72. Each item is scored on a four-point scale with descriptors for the clinician version. On this scale, a score of less than or equal to 37.5 has been suggested as the cut-off point for apathetic behaviour.
2) *Hamilton Depression Rating Scale* [HDR-S] (Hamilton, 1960): This is a 21-item clinician-rated questionnaire used to provide an indication of depressive symptomatology. A score of 0-7 is considered to be normal. Scores of 20 or higher indicate moderate, severe, or very severe symptoms, and are usually required for inclusion in a clinical trial.
3) *Young Mania Rating Scale* [YMRS] (Young, Biggs, Ziegler & Meyer, 1978): This is an 11-item clinician-rated scale designed to assess severity of manic symptoms. Scores are based on patient-reported symptoms over the previous 48 hours and clinical observation during the interview. Four of the YMRS items are rated on a scale of 0–8, and the remaining five on a scale of 0–4. A score of ≤12 indicates remission of symptoms. The scale is appropriate for both assessing the baseline severity of manic symptoms and evaluating the response to treatment in patients with bipolar disorder type I and II.

The *Scale to Assess Unawareness of Mental Disorder* [SUMD] (Amador & Strauss, 1990; Amador, Strauss, Yale Endicott & Gorman, 1993) is a semi-structured interview to obtain a detailed assessment of awareness of a wide range of signs and symptoms and their attribution to mental illness. The SUMD consists of: A) three general items (awareness of mental disorder, awareness of the results obtained with treatment, and comprehension of the social consequences of the illness) which only evaluate current and past awareness; B) a checklist of 17 symptoms for each of which current and past awareness and current and past misattribution are rated. On this scale, a score of less than or equal to three has been suggested as the cut-off point for awareness.

The SUMD is the researcher-rated scale most frequently used in a clinical setting in which the health care practitioner and the patient use a structured interview format to explore insight (Jovanovski, Zakzanis, Atia, Campbell & Young, 2007).

2.3 Neuropsychological assessment

The neuropsychological assessment was performed a week before the fMRI session, by neuropsychologists not aware of the patients' scores on the SUMD scale or of their neuropsychiatric profile. The participants were assessed in three sessions each lasting one hour on three different days of the same week.

Intellectual efficiency was measured using the *Wechsler Adult Intelligence Scale Revised* [WAIS-R] (Orsini & Laicardi, 1997; Wechsler, 1981). *Premorbid intellectual efficiency* was measured using the

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Brief Intelligence Test [TIB] (Sartori et al., 1995; Colombo et al., 2002) which is the Italian version of Nelson's *National Adult Reading Test* (1982).

The *cognitive domain* was also analyzed by using an extensive battery assessing memory (*Wechsler Memory Scale*, Subtests 4 and 7: Wechsler, 1945), language (*Verbal Fluency*: Spinnler & Tognoni, 1987), attention and executive functions (*Attentional Matrices* test: Spinnler & Tognoni, 1987; the *Trial Making Test parts A, B*: Reitan & Wolfson, 1994). The *Bells Test* (Gauthier et al., 1989) was used to exclude unilateral visual-attentional neglect.

Dysexecutive syndrome was evaluated by means of tasks designed to reflect situations in daily life: the *Behavioral Assessment of the Dysexecutive syndrome* battery (BADS: Wilson et al., 1996; Amanzio et al., 2013). This battery is composed of six subscales: the Rule Shift Cards [RSC] test; the Action Program [AP] test; the Key Search [KS] test; the Temporal Judgment [TJ] test; the Zoo Map [ZM] test; and the Modified Six Elements [MSE] test [2]. *Perspective-taking abilities* were tested using *Theory of Mind visual stories* (ToM1 and ToM2: Amanzio et al., 2008), while the ability to recognize the mental state of others using the expressions around the eyes, which are key in determining mental states (Adams, Rule, Frankling, Wang, Stevenson et al., 2010), was tested using the *Reading the Mind in the Eyes* task (RME: Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001). The RME is an advanced test of theory of mind. It is widely used to assess individual differences in social cognition and emotion recognition across different groups and cultures.

Metacognition was evaluated using the metacognitive version of the WCST (Koren, Seidman, Goldsmith & Harvey, 2006). The variant to the standard administration is to add two requests: 1) the degree of confidence in the response, expressed on a scale ranging from 0 (random choice) to 100 (absolute certainty); 2) the inclusion or not of the answer in the final score of the test. For each response that is included, the participant receives a monetary bonus if correct or an equal penalty if wrong. In this way both the forced response (input-bound: measure of cognitive functioning efficiency) and the free answer (output-bound: measure of metacognitive knowledge) are obtained. This version of the WCST produces measures in six major areas: (1) free-response output-bound accuracy score; (2) free-choice improvement; (3) global monitoring: (4) monitoring resolution; (5) control sensitivity; (6) monetary gains (Koren et al, 2006).

[2] 1. The RSC subtest assesses the ability to respond correctly to a rule and to shift from the use of one simple rule to another more complex one. 2. The AP examines the ability to solve a closed-ended sequential problem, in which the subject is presented with a set of materials. 3. The KS subtest examines the ability to solve an open-ended problem. 4. The TJ subtest measures cognitive estimation. 5. The ZM subtest assesses planning, sequential behaviour and ability to use feedback in problem solving. 6. The MSE test assesses ability to divide attention, task scheduling, performance monitoring and prospective memory. The rules of the task are placed in front of the subject, in an attempt to reduce demands on verbal working memory.

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2.4 Response inhibition task assessment

Each subject was asked to perform a response inhibition paradigm (go/no-go task, Amanzio et al., 2011 adapted from Braver et al., 2001). They had to respond to 'go' stimuli (the letters 'not-X' with a frequency of 83%) inhibiting the response to infrequent 'no-go' stimuli (the letter 'X' with a frequency of 17%). Every stimulus was shown for 250 ms with a 1000 ms inter-stimulus interval. The two stimulus types (X and non-X) were presented in random order in a continuous series of 232 trials. Subjects had to respond by pressing a button with their right index finger. Only letters from the Italian alphabet were used in order to avoid confounding factors (Amanzio et al., 2011).

The task was presented a first time for familiarization purposes before the fMRI scanning session.

2.5 Functional MRI acquisition and data analysis

The functional MRI assessment was performed at the CCS functional MRI, Koelliker Hospital in Turin. During scanning, each patient performed four runs of the response inhibition task described in the previous paragraph.

Data acquisition was performed on a 1.5 T INTERATM scanner (Philips Medical Systems) with a SENSE high-field, high-resolution (MRIDC) head coil optimized for functional imaging. Functional T2-weighted images were acquired using echo planar sequences, with a repetition time of 2500 ms, echo time of 60 ms and 90° flip angle. The acquisition matrix was 64 x 64 and the field of view was 256 mm. A total of 103 volumes were acquired for each run. Each volume consisted of 16 axial slices, parallel to the anterior–posterior commissure line and covering the whole brain; slice thickness was 6 mm with a 0.5 mm gap. Two scans were added at the beginning of functional scanning and the data discarded to reach steady-state magnetization before acquisition of the experimental data.

In the same session, a set of 3D high-resolution T1-weighted structural images were acquired for each participant. This data set was acquired using a fast field echo sequence, with a repetition time of 25 ms, the shortest echo time and a 30° flip angle. The acquisition matrix was 256 x 256 and the field of view was 256 mm. The set consisted of 160 sagittal contiguous images covering the whole brain. In-plane resolution was 1 x 1 mm and slice thickness was 1 mm (1 x 1 x 1 mm voxels).

A detailed description of both the imaging data pre-analyses and the voxel-wise group analysis procedures is presented elsewhere (Amanzio et al., 2011). Following our specific hypothesis concerning the role of the ACC during the response inhibition task, we computed a random effect Region of Interest [ROI] random effect analysis on this region: we selected a volume of interest encompassing the cingulate zone that has been shown to be specifically activated during tasks that require response selection and willful generation of motor behaviour (Picard & Strick, 1996; Braver et al., 2001). We operationally defined the locations of the volume of interest as y = 6 ± 9 mm [mean ± standard deviation (SD)], and z = 40 ± 9 mm. Within this volume of interest a fixed general linear

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model with separate subject predictors (aware versus unaware subjects) was computed (Amanzio et al., 2011).

Finally, the lateralization was investigated using a in house script (ClassTAL.m Script: D'Agata, 2011).

Functional neuroimaging data of three aware and two unaware subjects were not recorded due to technical problems. Consequently, functional MRI analyses were conducted on three aware and two unaware patients (see table 1, section 3.1).

3. Results

3.1 Evaluation of reduced awareness of deficits and neuropsychiatric-neuropsychological assessment

Tables 1–3 show data for the overall BD-st experimental population and for patients with BD-st divided into two groups according to the presence or absence of awareness. Six patients were classified as 'aware' and four were classified as 'unaware' using the SUMD scale (Amador & Strauss, 1990). The scores obtained by all patients on the YMRS, HDR-S, and AES-C were below the cut-off point, indicating that all the subjects were in a state of remission. The fact that patients with a stable medication regimen for at least four weeks were free from active symptoms was also ascertained by CGI. In particular, during the first neuropsychiatric evaluation, the conditions of the disease before starting treatment were analyzed, while at later stages, when the treatment had started, we evaluated potential improvements. We observed patients' overall clinical status with reduced disease severity (CGI-A), improvement of symptoms (CGI-B) and good therapeutic response (CGI-C).

[Tables 1 around here]

As shown in Table 2, the entire experimental sample had a normal cognitive and intellective level reaching normative scores on all neuropsychological tests, except for performance on Reading the Mind in the Eye task (20.25 ± 5.17).

[Table 2 around here]

As reported in Table 3, the aware group performed better in the go condition, and also exhibited shorter reaction times. In particular, the percentage of omissions in the GO condition was approximately three times higher in unaware BD-st subjects compared to aware patients.

[Table 3 around here]

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3.2 Imaging data

Differences emerged when comparing aware versus unaware patients considering the 'no-go' minus 'go' conditions (see Table 4). Unaware BT-st patients showed reduced task-sensitive activity in the fronto-temporo-parietal-subcortical network which comprises the anterior cingulate and other structures such as the frontal and temporal gyrus, insula, precuneus, caudate and putamen, which are part of an evaluative affective circuit.

Figure 1 shows the ROI activation on a 3D cortex reconstruction and the related activated network. The random effect (region of interest) analysis performed on the cingulate area (y = 6 ± 9 mm, and z = 40 ± 9 mm) using the fixed general linear model revealed a significant difference between groups (aware versus unaware patients), $p < 0.001522$, $t = 3.178$.

[Table 4 and Figure 1 around here]

Finally, the aware group showed more right-lateralized activity than the unaware group in the Inferior, Middle and Superior Frontal gyri, ithe Superior Temporal Gyrus, Precuneus, Supramarginal and Angular Gyri, and in the Cingulate gyrus (for more analysis see the Supplementary Online Material).

4. Discussion

In this preliminary report, we studied six aware and four unaware remitted BD patients from a neurocognitive perspective, in order to illustrate the link between brain dysfunction and concomitant cognitive-behavioral disturbances (McGlynn & Schacter, 1989; Lezak, Howieson & Loring 2004; Amanzio et al., 2011; Palermo et al., 2013). Considering the small sample size as a first important limitation of the study, we observed that unaware patients obtained scores which were below the cut-off point on the SUMD scale both in the session referring to the past and in that regarding the more recent period. The results on the overall neuropsychological battery underlined the homogeneity of the selected patients in terms of modular and non-modular cognitive functions and intellective functioning. In particular, neither group of patients exhibited impaired performance in the tests, except for the RME. As far as the RME cut-off values were concerned, unaware patients showed deficits at this level compared to aware subjects. Our findings in unaware patients are in line with the meta-analysis performed by Samamè et al. (2012) that considered euthymic bipolar disorder subjects but not the level of awareness. This analysis provided evidence for emotion processing and theory of mind deficits in remitted bipolar patients having a detrimental effect on interpersonal functionality. On the other hand, we did not observe any dysfunction in the ability to make inferences about other people's beliefs in either group of patients (referred to as cognitive ToM). It is important to underline that considering the deficits observed through the RME test and not excluding a possible role of medication, these were not due to neurocognitive dysfunctions since unaware patients reached scores

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above cut-off on the overall neuropsychological battery. Further studies will be necessary in order to confirm this result.

Considering the go/no-go behavioural task, performance by the two groups was consistent with that of Braver's control group (2001). Interestingly, unaware patients made more omission errors than aware patients and healthy controls (unaware=31.5; aware=11.63, and controls=1.1). Our results showed that the functional analysis of areas associated with omission errors previously observed in bipolar disorder subjects (Brooks, Bearden, Hoblyn, Woodard & Ketter, 2010) were the same as the most severely impaired areas we found in the current study comparing unaware and aware patients.

In line with our hypothesis, we observed lower functionality in the dorsal division of the ACC in unaware BD-st subjects when assessed with the response inhibition test during fMRI data acquisition. The results we obtained and the areas we found are in line with our previously published study on patients with Alzheimer's Disease (AD) and underline a reduced functional recruitment of the cingulo-frontal and parieto-temporal regions in patients with reduced awareness (Amanzio et al. 2011). These results underline how the unawareness of distinct pathologies may exhibit overlapping symptoms in the context of overlapping circuit-specific dysfunction (Palermo et al. 2013).

The theoretical framework within which we hypothesize a reduction in awareness is supported by the nature of the executive deficits observed in our BD patients, which suggest a fronto-subcortical dysfunction involving the anterior cingulate and other structures such as the inferior and middle frontal gyri, insula, caudate and putamen, which are part of an evaluative affective circuit that has been described with reference to behavioral inhibition (Pavuluri, Ellis, Wegbreit, Passarotti & Stevens, 2012). This circuit is consistent with the hypofunctional areas we observed in unaware patients in the current study. Meta-analytic findings also support our results, having provided evidence of a trait-related neuropsychological deficit in euthymic bipolar disorder involving the executive metacognitive domain. In particular, the functions that appear to be the most implicated include cognitive flexibility/set-shifting ability as well as dominant response inhibition (Torres, Boudreau & Yatham, 2007). Executive metacognitive functions were previously associated with awareness deficit (Bewick, Raymond, Malia & Bennett, 1995; Keefe, 1995; Fernandez-Duque, Baird & Posner, 2000; Bogod, Mateer., & MacDonald, 2003; Ownsworth, McFarland, & Young, 2002,. O'Keeffe., Dockree, & Robertson, 2004;. Vuilleumier, 2004;.Ownsworth & Fleming, 2005; O'Keeffe, Murray, Coen, Dockree, Bellgrove et al., 2007;.Amanzio et al. 2011; 2013; Palermo et al. 2013).

It is worth emphasizing a possible explanation for unawareness that has never previously been conceptualized in BD-st subjects, which is possibly related to a hypofunctioning of the cingulo-frontal area including the midline anterior cingulate/mesiofrontal areas, as well as the precuneal cortices while performing an fMRI response inhibition task.

To interpret our results, it is important to underline the role of the ACC as part of an attentional monitoring system that is responsible for achieving the highest level of efficiency required by a

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specific task in order to process the information from the other neural substrates with which the ACC communicates (Posner & Raichle, 1994). While the working-memory buffer selection is possible thanks to the interactions with the dorsolateral prefrontal cortex (DLP-C), the intensification of the ability to perceive oneself in relation to others is due to the interaction with the posterior cortices. The latter can be direct or mediated by connection with the prefrontal cortex (Posner & Raichle, 1994). As Devinsky et al. (1995) highlighted, the ACC encompasses Brodmann areas 25, 24, and 33 and it includes the caudal part of area 32. Since the ACC includes modules for emotional, cognitive, motor, and sensory information and integrates inputs from various sources, it is plausible that it plays a role in motivation, evaluation of error, and representations from cognitive and emotional networks (Bush, Luu, & Posner, 2000; Medford & Critchley, 2010; Shackman et al. 2011). The key role of the ACC in the economy of the neural system is also demonstrated by the fact that, thanks to the particular type of activations to which it is subjected, it influences activity in other cerebral areas and controls visceral, endocrine, motor, and cognitive responses (Bush et al., 2000). Interestingly, the dorsal portion of the ACC and the prefrontal cortex collaborate in cognitive tasks that require high levels of mental effort (Bush et al., 2000). The ACC is also cooperatively activated with the anterior insular cortex (AIC), most likely acting as complementary limbic sensory and motor regions that correspondingly produce feeling and motivation (Craig, 2009).

As we observed from performance by unaware patients on RME task, we may hypothesize that the AIC–ACC system is fundamental for creating subjective feelings and coordinating appropriate responses. Indeed, as suggested by Medford & Critchley (2010) feeling states emerge from the raw data of sensory inputs and are integrated through representations in conscious awareness. Since the AIC and ACC are core areas of a “salience network” responsive to a wide range of stimuli, they may be interpreted as being respectively the input and the output of a self-awareness system (Medford & Critchley, 2010) that we found to be more compromised in unaware patients. An fMRI study of self-recognition by Devue and colleagues (2007) supports this hypothesis, finding that specific AIC and ACC regions are key areas for integrative self-related processes. Within this same interpretive framework, Craig (2009), taking into consideration the afferent representation of feelings from the body by the AIC, proposed this as the probable neural substrate for self-awareness, awareness of others, and the environment.

As far as lateralization and awareness are concerned, we found unaware BD-st patients to be more compromised in the right lateralized network compared to aware subjects. This result is comparable with those we found in AD patients (Amanzio et al., 2011). In that case we observed reduced task-sensitive activity in the cingulate cortex and in Brodmann areas 10 and 39 of the right hemisphere in the unaware group. Awareness deficits in AD subjects were previously associated in resting state conditions with decreased perfusion in the lateral right-side frontal inferior (orbital), superior (dorsolateral) (Starkstein, Migliorelli, Teson, Petracca, Chemerinsky et al., 1995) and parietal

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region (Leys, Steinling, Petit, Salomez, Gaudet et al., 1989). Moreover, Vogel et al. (2005) suggested that the right inferior frontal gyrus might be a crucial area for impaired awareness.

We believe the above-mentioned findings will be useful for clinicians in both the diagnostic and the treatment processes. The neuropsychological assessment of unawareness deficits can definitely enable better and earlier differential diagnosis. Moreover, the measurement of this clinical variable may improve adherence to pharmacological treatment by patients who are more likely to refuse treatment when they do not understand its purpose and usefulness. This could improve the course of recovery.

In conclusion, it should be pointed out that, whereas all the cognitive tests except for the RME failed to detect the cognitive deficits that characterize the unaware sample, the fMRI go/no-go task did allow us to describe the compromised underlying brain network. Indeed, these findings also have implications in considering the ACC as a clinically important imaging biomarker even though the neuropsychological assessment appeared to be normal.

5. Acknowledgments

All the patients read the information sheet setting for their rights and signed the informed consent for the use of their personal data for scientific purposes and research. The study was previously approved by the Ethics Committee of the University of Turin.

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References

Adams, R. B., Rule, N. O., Franklin, R. G., Wang, E., Stevenson, M. T., Yoshikawa, S., Nomura, M., Sato, W., Kveraga, K., & Ambady, N. (2010). Cross-cultural reading the mind in the eyes: an fMRI investigation. J Cogn Neurosci, 22(1), 97-108 doi:10.1162/jocn.2009.21187

Agnew, S. K. & Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: a review of the literature and a proposed model. Aging and Mental Health, 2, 9-15

Amador, X. F. & David, A. S. (2004). Insight and psychosis: Awareness of deficits in Schizophrenia and related disorders (2nd eds). Oxford: Oxford University Press.

Amador, X. F. & Strauss, D. H. (1990). The Scale to Assess Unawareness of Mental Disorder (SUMD). New York: New York State Psychiatric Institute, Columbia University.

Amador, X. F., Strauss, D. H., Yale, S. A., Flaum, M. M., Endicott, J., & Gorman, J. M. (1993). Assessment of insight in psychosis. Am J Psychiatry, 150(6), 873-9

Amanzio, M., Geminiani, G., Leotta, D., & Cappa, S. (2008). Metaphor comprehension in Alzheimer's disease: novelty matters. Brain Lang, 107(1), 1-10 doi:10.1016/j.bandl.2007.08.003

Amanzio, M., Monteverdi, S., Giordano, A., Soliveri, P., Filippi, P., & Geminiani, G. (2010). Impaired awareness of movement disorders in Parkinson's disease. Brain Cogn, 72(3), 337-46 doi:10.1016/j.bandc.2009.10.011

Amanzio, M., Torta, D. M., Sacco, K., Cauda, F., D'Agata, F., Duca, S., Leotta, D., Palermo, S., & Geminiani, G. C. (2011). Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex. Brain, 134(Pt 4), 1061-76 doi:10.1093/brain/awr020

Amanzio, M., Vase, L., Leotta, D., Miceli, R., Palermo, S., & Geminiani, G. (2013). Impaired awareness of deficits in Alzheimer's disease: the role of everyday executive dysfunction. J Int Neuropsychol Soc, 19(1), 63-72 doi:10.1017/S1355617712000896

Amodio, D. M. & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci, 7(4), 268-77 doi:10.1038/nrn1884

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry, 42(2), 241-51

Beck, A. T., Baruch, E., Balter, J. M., Steer, R. A., & Warman, D. M. (2004). A new instrument for measuring insight: the Beck Cognitive Insight Scale. Schizophr Res, 68(2-3), 319-29 doi:10.1016/S0920-9964(03)00189-0

For Peer Review Only

Bewick, K. C., Raymond, M. J., Malia, K. B., & Bennett, T. L. (1995). Metacognition as the ultimate executive: Techniques and tasks to facilitate executive functions. NeuroRehabilitation, 5, 367-75

Blumberg, H. P., Stern, E., Martinez, D., Ricketts, S., de Asis, J., White, T., Epstein, J., McBride, P. A., Eidelberg, D., Kocsis, J. H., & Silbersweig, D. A. (2000). Increased anterior cingulate and caudate activity in bipolar mania. Biol Psychiatry, 48(11), 1045-52

Bogod, N. M., Mateer, C. A., & MacDonald, S. W. (2003). Self-awareness after traumatic brain injury: a comparison of measures and their relationship to executive functions. J Int Neuropsychol Soc, 9(3), 450-8 doi:10.1017/S1355617703930104

Braver, T. S., Barch, D. M., Gray, J. R., Molfese, D. L., & Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb Cortex, 11(9), 825-36

Brooks, J. O., Bearden, C. E., Hoblyn, J. C., Woodard, S. A., & Ketter, T. A. (2010). Prefrontal and paralimbic metabolic dysregulation related to sustained attention in euthymic older adults with bipolar disorder. Bipolar Disord, 12(8), 866-74 doi:10.1111/j.1399-5618.2010.00881.x

Burdick, K. E., Endick, C. J., & Goldberg, J. F. (2005). Assessing cognitive deficits in bipolar disorder: are self-reports valid? Psychiatry Res, 136(1), 43-50 doi:10.1016/j.psychres.2004.12.009

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci, 4(6), 215-22

Carter, C. S., Botvinick, M. M., & Cohen, J. D. (1999). The contribution of the anterior cingulate cortex to executive processes in cognition. Rev Neurosci, 10(1), 49-57

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., Castellanos, F. X., Haxby, J. V., Noll, D. C., Cohen, J. D., Forman, S. D., Dahl, R. E., & Rapoport, J. L. (1997). A Developmental Functional MRI Study of Prefrontal Activation during Performance of a Go-No-Go Task. J Cogn Neurosci, 9(6), 835-47 doi:10.1162/jocn.1997.9.6.835

Colombo, L., Sartori, G., & Brivio, C. (2002). Stima del quoziente intellettivo tramite l'applicazione del TIB (test breve di intelligenza). Giornale Italiano di Psicologia, 3, 613-37

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci, 10(1), 59-70 doi:10.1038/nrn2555

D'Agata, F (2011). ClassTAL. Nature Precedings. <http://dx.doi.org/10.1038/npre.2011.6142.2>

Dell'Osso, L., Pini, S., Tundo, A., Sarno, N., Musetti, L., & Cassano, G. B. (2000). Clinical characteristics of mania, mixed mania, and bipolar depression with psychotic features. Compr Psychiatry, 41(4), 242-7 doi:10.1053/comp.2000.7432

For Peer Review Only

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. Brain, 118 (Pt 1), 279-306

Devue, C., Collette, F., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., & Brédart, S. (2007). Here I am: the cortical correlates of visual self-recognition. Brain Res, 1143, 169-82 doi:10.1016/j.brainres.2007.01.055

Dias, V. V., Brissos, S., & Carita, A. I. (2008). Clinical and neurocognitive correlates of insight in patients with bipolar I disorder in remission. Acta Psychiatr Scand, 117(1), 28-34 doi:10.1111/j.1600-0447.2007.01110.x

Dias, V. V., Brissos, S., Frey, B. N., & Kapczinski, F. (2008). Insight, quality of life and cognitive functioning in euthymic patients with bipolar disorder. J Affect Disord, 110(1-2), 75-83 doi:10.1016/j.jad.2008.01.010

Dimitrov, M., Granetz, J., Peterson, M., Hollnagel, C., Alexander, G., & Grafman, J. (1999). Associative learning impairments in patients with frontal lobe damage. Brain Cogn, 41(2), 213-30 doi:10.1006/brcg.1999.1121

Dubovsky, S. (2008). Euthymia: it depends on how you define it. Journal Watch Psychiatry,

Fernandez-Duque, D., Baird, J. A., & Posner, M. I. (2000). Awareness and metacognition. Conscious Cogn, 9(2 Pt 1), 324-6 doi:10.1006/ccog.2000.0449

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1996). Structured <clinical Interview for DSM-IV Axis I Disorder: Clinician Version. Washington, D.C.: American Psychiatric Press, Inc.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12(3), 189-98

Gauthier, L., Dehaut, F., & Joannette, Y. (1989). The Bells Test: a quantitative and qualitative test for visual neglect. International Journal of Clinical Neuropsychology, 11, 49-54

Goldstein, R. Z., Volkow, N. D., Wang, G. J., Fowler, J. S., & Rajaram, S. (2001). Addiction changes orbitofrontal gyrus function: involvement in response inhibition. Neuroreport, 12(11), 2595-9

Guy, W. (1976). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse and Mental Health Administration.

Hamilton, M. (1960). A rating scale for depression. J Neurol Neurosurg Psychiatry, 23, 56-62

For Peer Review Only

Jovanovski, D., Zakzanis, K. K., Atia, M., Campbell, Z., & Young, D. A. (2007). A comparison between a researcher-rated and a self-report method of insight assessment in chronic schizophrenia revisited: a replication study using the SUMD and SAIQ. J Nerv Ment Dis, 195(2), 165-9 doi:10.1097/01.nmd.0000253765.05357.c7

Keefe, R. S. (1995). The contribution of neuropsychology to psychiatry. Am J Psychiatry, 152(1), 6-15

Koren, D., Seidman, L. J., Goldsmith, M., & Harvey, P. D. (2006). Real-world cognitive--and metacognitive--dysfunction in schizophrenia: a new approach for measuring (and remediating) more "right stuff". Schizophr Bull, 32(2), 310-26 doi:10.1093/schbul/sbj035

Koren, D., Seidman, L. J., Poyurovsky, M., Goldsmith, M., Viksman, P., Zichel, S., & Klein, E. (2004). The neuropsychological basis of insight in first-episode schizophrenia: a pilot metacognitive study. Schizophr Res, 70(2-3), 195-202 doi:10.1016/j.schres.2004.02.004

Leys, D., Steinling, M., Petit, H., Salomez, J. L., Gaudet, Y., Ovelacq, E., & Vergnes, R. (1989). [Alzheimer's disease: study by single photon emission tomography (Hm PAO Tc99m)]. Rev Neurol (Paris), 145(6-7), 443-50

Lezak, M. D. (2004). Neuropsychological Assessment. (4 th ed.): Oxford University Press.

Lysaker, P. H., Carcione, A., Dimaggio, G., Johannesen, J. K., Nicolò, G., Procacci, M., & Semerari, A. (2005). Metacognition amidst narratives of self and illness in schizophrenia: associations with neurocognition, symptoms, insight and quality of life. Acta Psychiatr Scand, 112(1), 64-71 doi:10.1111/j.1600-0447.2005.00514.x

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res, 38(2), 143-62

McGlynn, S. M. & Schacter, D. L. (1989). Unawareness of deficits in neuropsychological syndromes. J Clin Exp Neuropsychol, 11(2), 143-205 doi:10.1080/01688638908400882

Medford, N. & Critchley, H. D. (2010). Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct Funct, 214(5-6), 535-49 doi:10.1007/s00429-010-0265-x

Nelson, H. E. (1982). The National Adult Reading Test (NART):Test manual. Windsor: NFER-Nelson Publishing.

O'Keeffe, F. M., Murray, B., Coen, R. F., Dockree, P. M., Bellgrove, M. A., Garavan, H., Lynch, T., & Robertson, I. H. (2007). Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. Brain, 130(Pt 3), 753-64 doi:10.1093/brain/awl367

For Peer Review Only

O'Keeffe, F. M., Murray, B., Coen, R. F., Dockree, P. M., Bellgrove, M. A., Garavan, H., Lynch, T., & Robertson, I. H. (2007). Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. Brain, 130(Pt 3), 753-64 doi:10.1093/brain/awl367

Orsini, A. & Laicardi, C. (1997). WAIS-R. Contributo alla taratura italiana. Firenze: Giunti Organizzazioni Speciali.

Ownsworth, T. L., McFarland, K., & Young, R. M. (2002). The investigation of factors underlying deficits in self-awareness and self-regulation. Brain Inj, 16(4), 291-309 doi:10.1080/02699050110103986

Ownsworth, T. & Fleming, J. (2005). The relative importance of metacognitive skills, emotional status, and executive function in psychosocial adjustment following acquired brain injury. J Head Trauma Rehabil, 20(4), 315-32

Ownsworth, T., Fleming, J., Strong, J., Radel, M., Chan, W., & Clare, L. (2007). Awareness typologies, long-term emotional adjustment and psychosocial outcomes following acquired brain injury. Neuropsychol Rehabil, 17(2), 129-50 doi:10.1080/09602010600615506

Ownsworth, T. L., Turpin, M., Andrew, B., & Fleming, J. (2008). Participant perspectives on an individualised self-awareness intervention following stroke: a qualitative case study. Neuropsychol Rehabil, 18(5-6), 692-712 doi:10.1080/09602010701595136

Palermo, S., Leotta, D., Bongioanni, M. R., & Amanzio, M. (2013). Unawareness of deficits in ischemic injury: Role of the cingulate cortex. Neurocase, doi:10.1080/13554794.2013.826686

Pavuluri, M. N., Ellis, J. A., Wegbreit, E., Passarotti, A. M., & Stevens, M. C. (2012). Pharmacotherapy impacts functional connectivity among affective circuits during response inhibition in pediatric mania. Behav Brain Res, 226(2), 493-503 doi:10.1016/j.bbr.2011.10.003

Picard, N. & Strick, P. L. (1996). Motor areas of the medial wall: a review of their location and functional activation. Cereb Cortex, 6(3), 342-53

Posner, M. I. & Reichle, M. E. (1994). Images of Mind. New York: Scientific American Library.

Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A. M., Pardo, J. V., Fox, P. T., & Petersen, S. E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex, 4(1), 8-26

Reitan, R. M. & Wolfson, D. (1994). A selective and critical review of neuropsychological deficits and the frontal lobes. Neuropsychol Rev, 4(3), 161-98

For Peer Review Only

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., & Moore, P. B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord, 93(1-3), 105-15 doi:10.1016/j.jad.2006.02.016

Roncone, R., Ventura, J., Impallomeni, M., Falloon, I. R., Morosini, P. L., Chiaravalle, E., & Casacchia, M. (1999). Reliability of an Italian standardized and expanded Brief Psychiatric Rating Scale (BPRS 4.0) in raters with high vs. low clinical experience. Acta Psychiatr Scand, 100(3), 229-36

Samamé, C., Martino, D. J., & Strejilevich, S. A. (2012). Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. Acta Psychiatr Scand, 125(4), 266-80 doi:10.1111/j.1600-0447.2011.01808.x

Sartori, G., Colombo, L., Vallar, G., Rusconi, M. L., & Pinarello, A. (1995). T.I.B. Test di Intelligenza Breve per la valutazione del quoziente intellettivo attuale e premorboso. Professione di Psicologo Giornale dell'Ordine degli Psicologi, 4, 1-24

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat Rev Neurosci, 12(3), 154-67 doi:10.1038/nrn2994

Shamay-Tsoory, S., Harari, H., Szepsenwol, O., & Levkovitz, Y. (2009). Neuropsychological evidence of impaired cognitive empathy in euthymic bipolar disorder. J Neuropsychiatry Clin Neurosci, 21(1), 59-67 doi:10.1176/appi.neuropsych.21.1.59

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. J Cogn Neurosci, 15(3), 324-37 doi:10.1162/089892903321593063

Spinnler, H. & Tognoni, G. (1987). Standardizzazione italiana e taratura di test neuropsicologici. Italian Journal of Neurological sciences, 6,

Spreen, O. & Strauss, E. (1998). A compendium of neuropsychological tests: administration, norms and commentary. (2nd ed.). New York.

Starkstein, S. E., Migliorelli, R., Tesón, A., Petracca, G., Chemerinsky, E., Manes, F., & Leiguarda, R. (1995). Prevalence and clinical correlates of pathological affective display in Alzheimer's disease. J Neurol Neurosurg Psychiatry, 59(1), 55-60

Stoll, A. L., Renshaw, P. F., Yurgelun-Todd, D. A., & Cohen, B. M. (2000). Neuroimaging in bipolar disorder: what have we learned? Biol Psychiatry, 48(6), 505-17

For Peer Review Only

Strakowski, S. M., Adler, C. M., Holland, S. K., Mills, N. P., DelBello, M. P., & Eliassen, J. C. (2005). Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. Am J Psychiatry, 162(9), 1697-705 doi:10.1176/appi.ajp.162.9.1697

Torres, I. J., Boudreau, V. G., & Yatham, L. N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand Suppl, (434), 17-26 doi:10.1111/j.1600-0447.2007.01055.x

Trevisi, M., Talamo, A., Bandinelli, P. L., Ducci, G., Kotzalidis, G. D., Santucci, C., Manfredi, G., Girardi, N., & Tatarelli, R. (2012). Insight and awareness as related to psychopathology and cognition. Psychopathology, 45(4), 235-43 doi:10.1159/000329998

Varga, M., Magnusson, A., Flekkøy, K., Rønneberg, U., & Opjordsmoen, S. (2006). Insight, symptoms and neurocognition in bipolar I patients. J Affect Disord, 91(1), 1-9 doi:10.1016/j.jad.2005.09.002

Ventura, J., Lukoff, D., Nuechterlein, K. H., Liberman, R. P., Green, m., & Shaner, A. (1993). Appendix 1: Brief Psychiatric Rating Scale (BPRS) Expanded Version (4.09 scales, anchor points and administration manual. International Journal of Methods in Psychiatric Research, 3, 227-43

Vuilleumier, P. (2004). Anosognosia: the neurology of beliefs and uncertainties. Cortex, 40(1), 9-17

Wechsler, D. (1945). Wechsler memory scale. San Antonio, TX: Psychological Corporation.

Wechsler, D. (1981). WAIS-R. Scala d'intelligenza Wechsler per Adulti - Riveduta. Tr. Ital (1997). Firenze: Giunti Organizzazioni Speciali.

Wilson, B. A., Alderman, N., Burguess, P. W., Emslie, H., & Evans, J. J. (1996). Behavioural Assessment of the Dysexecutive Syndrome. Bury St Edmunds: Thames Valley Test Company.

Yen, C. F., Chen, C. S., Yeh, M. L., Yen, J. Y., Ker, J. H., & Yang, S. J. (2002). Comparison of insight in patients with schizophrenia and bipolar disorder in remission. J Nerv Ment Dis, 190(12), 847-9 doi:10.1097/01.NMD.0000034519.08746.91

Yen, C. F., Chen, C. S., Yen, J. Y., & Ko, C. H. (2008). The predictive effect of insight on adverse clinical outcomes in bipolar I disorder: a two-year prospective study. J Affect Disord, 108(1-2), 121-7 doi:10.1016/j.jad.2007.10.004

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry, 133, 429-35

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Table 1. Demographic and neuropsychiatric assessment for the overall sample and for the aware and unaware groups.

	Total BD Sample (N=10)	Aware BD Sample (N=6)	Unaware BD Sample (N=4)	fMRI aware sample (N=3)	fMRI unaware sample (N=2)	Cut-off
Gender (M/F)	6/4	3/3	3/1	1/2	1/1	
Age (years)	46.90 (±12)	44.3 (±11.2)	50.8 (±12.1)	40	40	
Schooling (years)	12.40 (±3.1)	14.16 (±2.71)	9.75 (±2.06)	13	13	
Onset (years)	11.45 (±9.61)	7.92 (±7.34)	16.75 (±12.47)	3.16 ± 4.19	6	
Litio (mg)	715 (±122.5)	716.7 (±132.9)	712.5 (±143.6)	833.36	675	
SUMD (past section)	3.2 (±2.64)	1.5 (±1.5)	5.75 (±1.79)	1	6	≤ 3
SUMD (contemporary section)	3.3 (±2.53)	1.5 (±1.5)	5.75 (±1.3)	1.33	6	≤ 3
BPRS [168]	29.15 (±9.16)	29.33 (±2.42)	35.5 (±5.03)	32	41	
YMRS [60]	4.8 (±4.77)	2.67 (±1.97)	9.25 (±5.80)	5	14	≤ 12
HDR-S [67]	5.24 (±2.64)	5.17 (±2.73)	6 (±2.74)	10	9	≤ 7
AES-C [72]	45.49 (±13.94)	53 (±2.83)	43 (±3.61)	55	38	≥ 37.5
CGI_A [7]	2.44 (±0.76)	2.83 (±0.41)	2.25 (±0.43)	3	2	≤ 3
CGI_B [7]	2.5 (±0.87)	3	2.25 (±0.5)	3	3	≤ 3
CGI_C [16]	1.25 (±0.6)	1	2	1	2	≤ 3

Maximum scores for each test are shown in square brackets. For the BPRS, YMRS, HDR-S and CGI, higher scores indicate more severe symptoms. In the case of the AES-C, lower scores indicate more severe symptoms. Wherever there is a normative value, the cut-off scores are given in the statistical normal direction; the values refer to the normative data for healthy controls matched for age and education. Cells in light gray represent abnormal values. Cells in black indicate the absence of a normative cut-off for that assessment tool.

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Table 2. Neuropsychological evaluation for the overall sample and for the aware and unaware groups.

	Total BD Sample (N=10)	Aware BD Sample (N=6)	Unaware BD Sample (N=4)	Cut-off
ATTENTIONAL MATRICES [60]	46.675 (±6.56)	47.79 (±7.16)	42.5 (±3.75)	≥ 31
TMT A [500]	31.08 (±12.42)	30.96 (±13.33)	31.25 (±10.89)	≤ 94
TMT B [500]	62.11 (±42)	70.67 (±30.59)	49.25 (±52.26)	≤ 283
TMT B-A	39.73 (±40.35)	39.21 (±21.97)	18 (±55.46)	≤ 187
BELL TEST [35]	34.4 (±0.70)	34.5 (±0.76)	34.25 (±0.43)	≥ 32
VERBAL FLUENCY_ SEMANTIC	21.05 (±5.03)	21.29 (±6.03)	20.69(±2.93)	≥ 7.25
VERBAL FLUENCY_ PHONETIC	29.04 (±5.61)	30.52 (±5.079	26.825 (±5.65)	≥ 17.35
Wechsler memory_4 [22]	9.5 (±2.89)	11.25 (±1.96)	6.875 (±2.07)	
Wechsler memory_7 [22,5]	16.75 (±2.54)	18.25 (±1.76)	14.5 (±1.27)	
TOM_1 [4]	4	4	4	≥ 3
comprehension	3.9 (±0.3)	4	3.75 (±0.5)	
Memory	4	4	4	
TOM_2 [4]	3.75 (±0.51)	3.833 (±0.37)	3.625 (±0.65)	≥ 3
comprehension	4	4	4	
memory	4	4	4	
RME	20.25 (±5.17)	24.25 (±2.05)	16.25 (±4.15)	≥ 21
TIB_IQ TOT	112.054 (±3.71)	114.228 (±2.68)	108.793 (±2.43)	90-110
TIB_IQ VERBAL	110.258 (±3.90)	112.487 (±2.19)	106.915 (±3.48)	90-110
TIB_IQ PERFORMANCE	111.959 (±4.22)	112.693 (±4.72)	110.86 (±3.01)	90-110
WAIS-R IQ_TOT	73.5 (±48.05)	108.5 (±14.58)	94.5 (±8.96)	90-110
WAIS-R IQ VERBAL	74.5 (±48.60)	110 (±14.24)	95.75 (±8.50)	90-110
WAIS-R IQ PERFORMANCE	74.21 (±47.03)	105.83 (±13.91)	94 (±8.22)	90-110
BADS Total Score [24]	10.57 (±7.04)	18 (±2.64)	14.25 (±2.77)	≥ 13
RSC	1.64 (±1.54)	2.33 (±1.25)	2.25 (±1.48)	
AP	3 (±1.93)	4.17 (±0.37)	4.25 (±4.33)	
KS	1.43 (±3.99)	2.17 (±1.34)	1.75 (±0.83)	
TJ	1.5 (±1.12)	2.33 (±0.47)	1.75 (±0.83)	
ZM	1.57 (±1.29)	2.33 (±0.75)	2 (±1.22)	
MSE	1.43 (±1.16)	1.83 (±0.69)	2.25 (±0.83)	
WCST %	43.3 (±0.30)	64.3 (±0.15)	55.1 (±0.10)	≥ 37.1
WCST_ERRORS %	28.1 (±0.22)	35.7 (±0.15)	44.9 (±0.10)	
WCST_PERS ERRORS %	18.9 (±0.14)	25.7 (±0.11)	27.5 (±0.04)	≤ 42.7
CONFIDENCE	42.92 (±32.89)	67.01 (±19.57)	49.70 (±21.28)	
ACCURACY	0.00814 (±0.01)	0.01094 (±0.001)	0.012063 (±0.01)	
FREE CHOICE IMPROVEMENT	-0.42482 (±0.29)	-0.63223 (±0.15)	-0.53853 (±0.10)	
GLOBAL MONITORING	-12.214 (±11.41)	-16.667 (±3.86)	-17.75 (±14.96)	
MONITORING RESOLUTION	0.21205 (±0.23)	0.3125 (±0.26)	0.27244 (±0.14)	
CONTROL SENSITIVITY	0.26751 (±0.43)	0.40545 (±0.53)	0.32813 (±0.36)	
MONETARY GAIN	2.4 (±1.17)	3.83 (±1.98)	2.65 (±1.30)	

Maximum scores for each test are shown in square brackets. Wherever there is a normative value, the cut-off scores are given in the statistical normal direction; the values refer to the normative data for healthy controls matched for age and education. Cells in light gray represent abnormal values. Cells in black indicate the absence of a normative cut-off for that assessment tool.

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Table 3. Go/no-go response inhibition test. Results expressed for aware and unaware patients and taking normative data into consideration.

	aware BD patients	unaware BD patients
Response Inhibition Task GO:		
% TARGET	88.37 (±0.003)	83.59
Reaction Time (ms)	241.86 (± 76.673)	322.13
% ERRORS	11.63 (±0.0006)	31.5 (±15.75)
Response Inhibition Task NO-GO:		
% TARGET	84.16 (±0.007)	85
% ERRORS	15.83 (±0.003)	15

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Table 4. Functional MRI results for the 'no-go' minus 'go' conditions, in the comparison between aware (n = 3) minus unaware (n = 2) patients.

Area	Voxels	L/R%	Brodmann area
Middle Frontal Gyrus	18272	42/58%	BA 10
Superior Frontal Gyrus	17656	44/56%	BA 10
Inferior Frontal Gyrus	11207	47/53%	BA 9
Insular	9538	65/35%	BA 21 - 38
Superior Temporal Gyrus	9260	39/61%	BA 38
Pre-Cuneus	8167	23/77%	BA 31
Supramarginal Gyrus	8072	15/85%	BA 2
Caudate Body	6894	42/58%	-
Putamen	6647	62/38%	-
Angular Gyrus	4869	39/61%	BA 40
Cingulate Gyrus	4600	49/51%	BA 32 - 24
Middle Temporal Gyrus	1538	12/88%	BA 21- 39

The table indicates cortical areas showing significant activity (using False Discovery Rate significant threshold $q<0.05$) at cluster level of differential activations (aware – unaware patient group).

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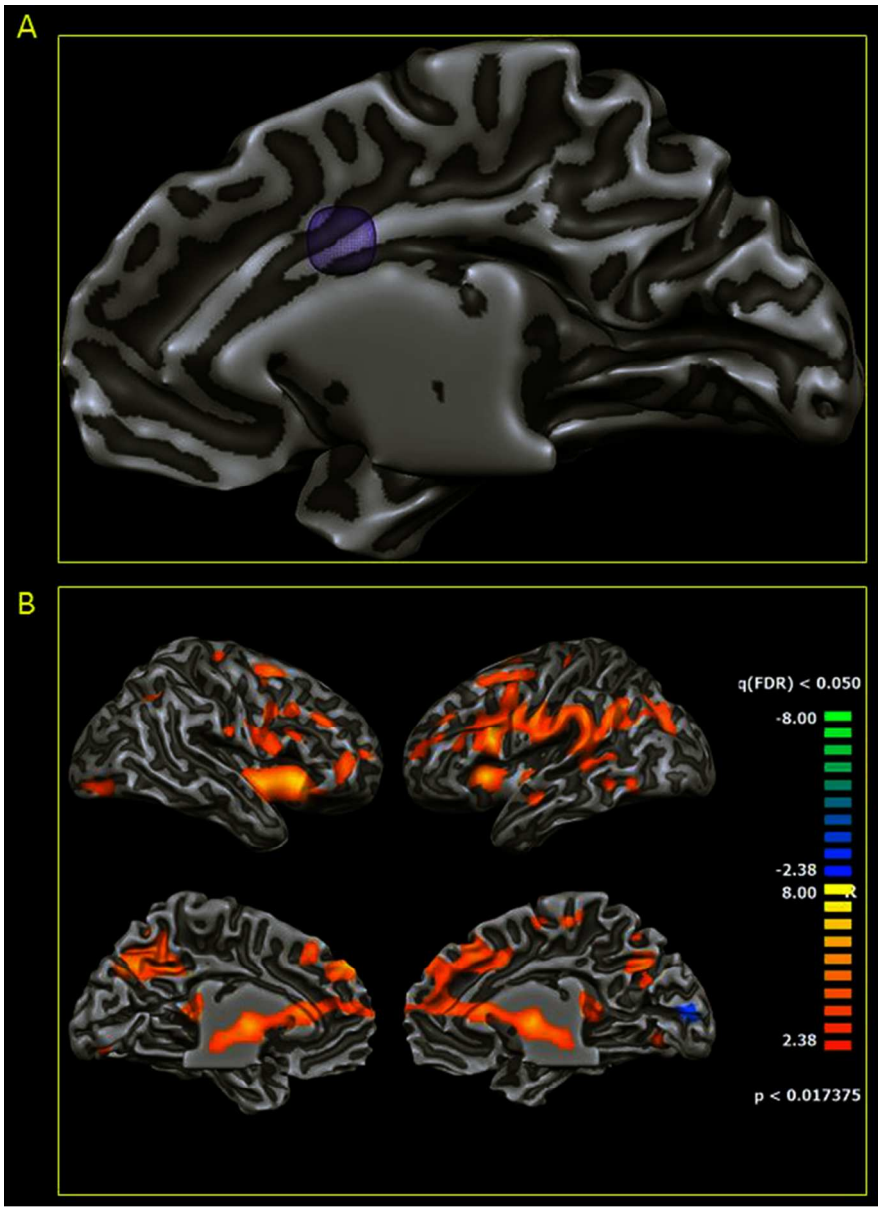
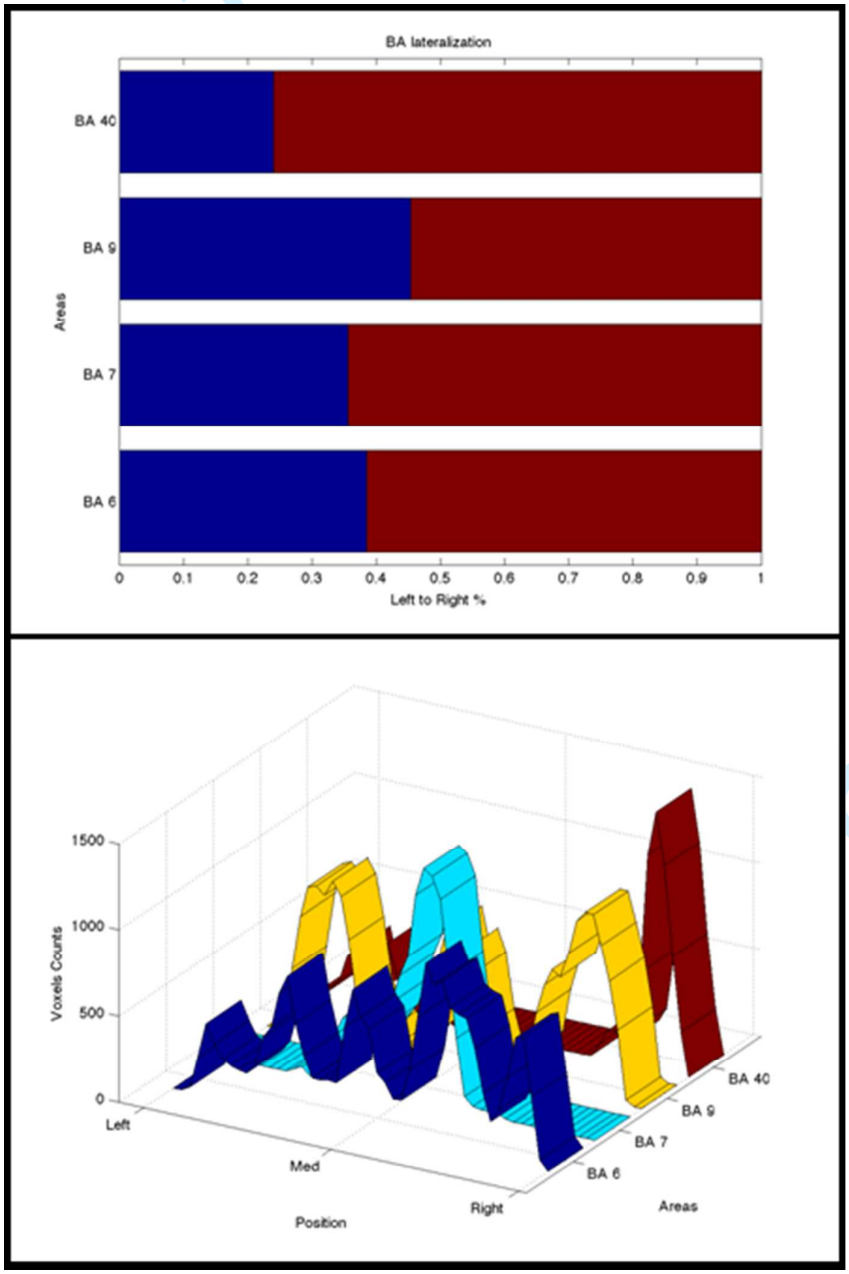


Functional MRI results for the 'no-go' minus 'go' conditions, in the comparison between aware (n = 3) minus unaware (n = 2) patients. Maps were thresholded at q <0.05 cluster-level.
Panel A: The ROI activation cluster is projected on a 3D brain surface with Brain Voyager QX 2.1.
Panel B: The associated activated network derived by the whole brain analysis.

161x221mm (96 x 96 DPI)

Supplemental Online Material

Histograms show the percentage of lateralization of the BOLD signal in the two hemispheres, for each of the two groups. We looked at lateralization under the hypothesis that since the right hemisphere is more involved in awareness, aware patients should show greater right activation. Indeed, the aware group showed more right-lateralized activity compared to the unaware group in BA 6, 7, 9, and 40.