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Unawareness of bipolar disorder: the role of the cingulate cortex

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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 the role of the anterior cingulate cortex (ACC) 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 task battery and with behavioral assessment of mood changes in terms of apathy and disinhibited behavior. Unaware patients showed frontoparietal hypo-perfusion, with a significant reduction of task-sensitive activity in the bilateral superior and middle frontal gyrus, putamen, insular, and ACCs.

Keywords: remitted bipolar disorder patients; awareness deficit; response inhibition; anterior cingulate cortex; fMRI

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 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 2-year period, impaired awareness of treatment, associated with a high number of hospitalizations, considerably increases the risk of negative clinical outcomes (Yen et al., 2008). Since it has been found that awareness could be impaired in 60% of bipolar disorder patients in remission (Dias, Brissos, & 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 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 behavioral conflict resolution, and working memory (Dias, Brissos, Frey, & Kapczinski, 2008; Trevisi 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, Flekkoy, Ronneberg, & Opjordsmoen, 2006) or bipolar outpatients in remission (Yen et al., 2002). Indeed, the WCST has been criticized in that it involves different components of executive functioning (Dimitrov et al., 1999; Keefe, 1995). 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 anterior cingulate cortex (ACC) (Amanzio et al., 2011; Palermo, Leotta, Bongioanni, & Amanzio, 2013). Interestingly, it has been observed that BD-st patients fail to activate areas

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associated with performance of the Stroop test (for healthy subjects, see Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001) such as the dorsolateral prefrontal cortex (DLP-C) and ACC (Strakowski 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, Brisson, and Carita (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 color test and Stroop color-write test) for which ACC is known to play an important role (Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter, Botvinick, & Cohen, 1999; Casey et al., 1997; Raichle 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 color 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 functional MRI (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.

1. Methods

1.1. *Subjects*

The study group included 10 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 10 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.

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 6 months prior to undergoing the neuropsychological evaluation; history of serious mental disorder in first-degree relatives.

1.2. *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

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 (male/female)	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

Notes: 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.

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 et al., 1999; Ventura 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 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, Biedrzycki, & Firinciogullari, 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 behavior.
(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 the severity of manic symptoms. Scores are based on patient-reported symptoms over the previous 48 h 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 $\leq$ 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 et al., 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: (1) 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; (2) 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 3 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).

1.3. *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 1 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 *brief intelligence test* (TIB) (Colombo, Sartori, & Brivio, 2002; Sartori, Colombo, Vallar, Rusconi, & Pinarello, 1995), 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, Dehaut, & Joannette, 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: Amanzio et al., 2013; Wilson, Alderman, Burguess, Emslie, & Evans, 1996). 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 element (MSE) test.[2] *Perspective-taking abilities* were tested using *theory of mind visual stories*

(ToM1 and ToM2; Amanzio, Geminiani, Leotta, & Cappa, 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 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; Koren et al., 2004). 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).

1.4. *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.

1.5. *fMRI acquisition and data analysis*

The fMRI assessment was performed at the CCS fMRI, 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 × 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 × 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 × 1 mm and slice thickness was 1 mm (1 × 1 × 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) 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 behavior (Braver et al., 2001; Picard & Strick, 1996). We operationally defined the locations of the volume of interest as $y = 6 \pm 9$ mm [mean ± standard deviation (SD)] and $z = 40 \pm 9$ mm. Within this volume of interest, a fixed general linear model with separate subject predictors (aware versus unaware subjects) was computed (Amanzio et al., 2011).

Finally, the lateralization was investigated using an 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, fMRI analyses were conducted on three aware and two unaware patients (see Table 1, Section 1.2).

2. Results

2.1. *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

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)	

Notes: 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.

Table 3. Go/no-go response inhibition test.

	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

Note: Results expressed for aware and unaware patients.

& 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 4 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).

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).

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.

2.2. *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 (ROI) analysis performed on the cingulate area ($y = 6 \pm 9$ mm and $z = 40 \pm 9$ mm) using the fixed general linear model revealed a significant difference between groups (aware versus unaware patients), $p < 0.001522$, $t = 3.178$.

Finally, the aware group showed more right-lateralized activity than the unaware group in the inferior, middle and superior frontal gyri; in the superior temporal gyrus, precuneus, supramarginal, and angular gyri; and in the cingulate gyrus (for more analysis, see the Supplementary material).

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
Precuneus	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

Note: 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).

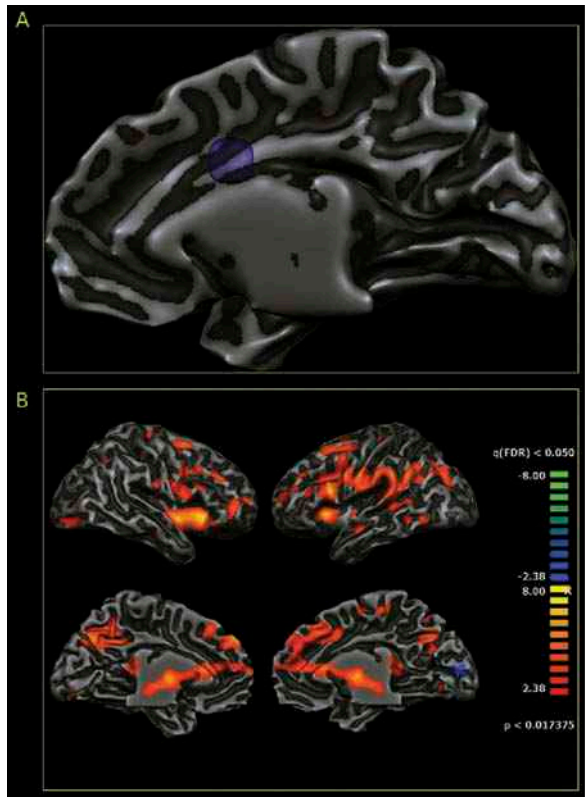

Figure 1. Functional MRI results for the "no-go" minus "go" conditions, in the comparison between aware ($n = 3$) minus unaware ($n = 2$) patients. Maps were thresholded at $q < 0.05$ cluster level. Panel A: The ROI activation cluster is projected on a 3D brain surface with Brain Voyager QX 2.1. Panel B: The associated activated network derived by the whole-brain analysis.

3. 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 (Amanzio et al., 2011; Lezak, Howieson, & Loring, 2004; McGlynn & Schacter, 1989; 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 Samamé, Martino, and Strejilevich (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 above cut-off on the overall neuropsychological battery. Further studies will be necessary in order to confirm this result.

Considering the go/no-go behavioral task, performance by the two groups was consistent with that of Braver et al.'s (2001) control group. 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) was 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 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 et al., 2007). Executive metacognitive functions were previously associated with awareness deficit (Amanzio et al., 2011, 2013; Bewick, Raymond, Malia, & Bennett, 1995; Bogod, Mateer, & MacDonald, 2003; Fernandez-Duque, Baird, & Posner, 2000. Keefe, 1995; O'Keeffe, Dockree, & Robertson, 2004; O'Keeffe et al., 2007; Ownsworth & Fleming, 2005; Ownsworth, McFarland, & Young, 2002; Ownsworth et al., 2007; Palermo et al., 2013; Vuilleumier, 2004).

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 specific task in order to process the information from the other neural substrates with which the ACC communicates (Posner & Reichle, 1994). While the working-memory buffer selection is possible, thanks to the interactions with the 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 & Reichle, 1994). As Devinsky, Morrell, and Vogt (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 the 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 and 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 et al. (2007) supports this hypothesis, the 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 et al., 1995), and parietal region (Leys et al., 1989). Moreover, Vogt (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.

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.

Supplementary material

Supplementary content is available via the 'Supplementary' tab on the article's online page (http://dx.doi.org/10.1080/13554794.2014.917682).

Notes

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.
2. (i) 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. (ii) The AP examines the ability to solve a closed-ended sequential problem, in which the subject is presented with a set of materials. (iii) The KS subtest examines the ability to solve an open-ended problem. (iv) The TJ subtest measures cognitive estimation. (v) The ZM subtest assesses planning, sequential behavior, and ability to use feedback in problem solving. (vi) The MSE test assesses the 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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