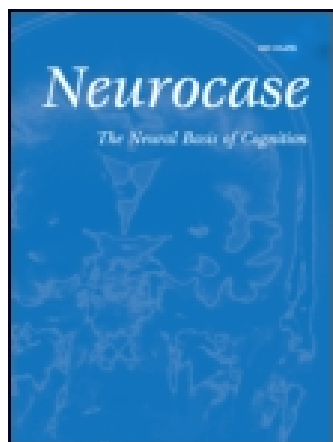


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Unawareness of deficits in ischemic injury: Role of the cingulate cortex

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Unawareness of deficits in ischemic injury: Role of the cingulate cortex

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Reduced awareness of illness is a well-known phenomenon that has been studied in patients with vascular disease, but the precise nature of their executive dysfunction is an intriguing question that still has to be resolved. It would be particularly interesting to study patients with reduced awareness of disease possibly related to vascular lesions of the prefrontal cortex. Due to the clinical importance of the case, here we present a patient with a selective right anterior cingulate ischemic injury and impaired awareness of deficits. We suggest that the cingulo-frontal area dysfunction may represent one of the corresponding neurobiological substrates of his persistent unawareness, which has not yet been evaluated in the literature on patients with acquired brain injury (ABI).

Keywords: Anterior cingulate cortex; Unawareness of deficits; Executive function assessment; Behavioral assessment of the dysexecutive syndrome; Case study.

The patient RL had previously read the information sheet about his rights and signed the informed consent for the use of his personal data for scientific purposes and research. The neuropsychological battery was previously approved for use on patients with mild cognitive impairment by the ethic committee of the Department of Psychology.

THE CONCEPT OF “IMPAIRED AWARENESS”

The construct of awareness is a complex entity at an operational semantic level (Bach & Davis, 2006). The awareness of illness is the more general theoretical term used to describe the ability to perceive, recognize, and evaluate a specific deficit in sensory, perceptual, motor, affective, or cognitive functioning and also to consider the impact of these disturbances on basic and instrumental daily-life

activities (see Amanzio et al., 2013). Following acquired brain injury (ABI), deficit awareness is a complex construct encompassing the ability to recognize deficits, understand the related functional implications, and set realistic goals accordingly (Crosson et al., 1989; Fleming, Strong, & Ashton, 1996). Unawareness leads to some negative effects such as increased stress and burden for families and health personnel, reduced patient–caregiver interactions, and poor adherence to treatment (O’Keefe et al., 2007).

The neurocognitive approach highlights how impaired awareness is linked to brain pathology, particularly concerning focal lesions, motivational and emotional factors, and concomitant cognitive disturbances (McGlynn & Schacter, 1989). In particular, research has been carried out on patients with reduced awareness and brain injury and has shown the importance of the role of the frontal

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lobes (Agnew & Morris, 1998; Bach & Davis, 2006; McGlynn & Schacter, 1989; Ownsworth, Clare, & Morris, 2006; Ownsworth et al., 2007). Impaired awareness is frequently reported following right-hemisphere damage (Devinsky, 2008), superior temporal, inferior parietal, and thalamic ischemic lesions (Starkstein, Fodoroff, Price, Leiguarda, & Robinson, 1992) and may also be seen in neurodegenerative disorders, such as frontotemporal dementia (FTD), Alzheimer's and Parkinson's diseases (Amanzio et al., 2010, 2011, 2013; O'Keefe et al., 2007); these distinct pathologies exhibit overlapping symptoms in the context of overlapping circuit specific dysfunction.

A PROPOSAL FOR A HIERARCHICAL THEORETICAL FRAMEWORK TO UNDERSTAND THE ARISING OF UNAWARENESS

Considering the neurocognitive approach and patients with a reduced awareness affected by ABI, the model proposed by Stuss, Picton, and Alexander (2001) and Stuss and Anderson (2004) represents an interesting theoretical framework. The authors hypothesize four distinct hierarchical levels, where the processing in turn operating in a modular manner at any level of the hierarchy, so that damage in one functional domain may result in a definably different awareness disorder. Indeed, one of the most intriguing features of deficits involving awareness is the presence of striking dissociations between different aspects of the functional domains. Such an example is the reduced self-awareness for behavioral deficits in comparison to physical deficits in brain injury patients (Prigatano & Altman, 1990). The hierarchy represented in the model by Stuss and collaborators is organized in such a way that higher levels use the modeling abilities of lower levels; also a bottom-up flow of sensory information and arousal signals activate generator neurons at high levels.

At the *lowest level*, the brainstem reticular system mediates the arousal aspects of consciousness. The *second level* of awareness involves the sensory and motor regions of the neocortex, which in turn, sustains the analysis of incoming sensory information and the construction of complex motor activity. As neurological impairments at this level are domain-specific, impaired awareness reveals itself as a disturbance of knowledge (Berti et al., 2005; Bisiach & Geminiani, 1991; Pia, Neppi-Modona, Ricci, & Berti, 2004). Domain-specific unawareness

identified as anosognosia¹ has been studied in stroke hemiplegic patients due to posterior lesions, who overestimated their abilities or denied that they were unable to move a paretic limb. This represents the second neuropsychological syndrome of stroke involving the right hemisphere and has been verified in 17–28% of all patients with vascular lesions (Sinanović, 2010). At the *highest level* of conscious processing, the frontal lobes are considered particularly important for self-awareness. There is a growing evidence of considerable functional and anatomical specificity within the frontal regions and a general agreement on the presence of two major functional divisions, the dorsolateral prefrontal cortex (DLPF-C) and medial prefrontal cortex (MPF-C) regions representing, respectively, the *third* and *fourth levels* (Stuss & Anderson, 2004; Stuss et al., 2001). The DLPF-C is more implicated in those aspects including the sequence of behavior and formation of mental sets, while drive, motivation, and will are associated with the MPF-C. Executive models of self-awareness have been developed focusing on the disruption of hypothetical higher order executive processes of self-monitoring and control (Schacter, 1990; Stuss & Levine, 2002). Following ABI, “self-awareness” refers to a broad range of metacognitive skills, from the ability to recognize deficits and understand the cognitive and functional implications deriving from them to setting realistic goals and anticipating possible future difficulties related to the illness (Ownsworth et al., 2007, 2008).

UNAWARENESS AND IMPAIRED EXECUTIVE FUNCTIONS: THE CONSCIOUS AWARENESS MODEL (CAM)

The relationship between reduced awareness and impaired executive functions may represent a fruitful approach for patients with different neurodegenerative diseases and with ABI. In particular and considering ABI patients, aspects of executive functioning related to the level of awareness included reasoning (Malec, Machulda, & Moessner, 1997; Ownsworth, McFarland, & Young, 2002), idea generation or fluency (Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Ownsworth & Fleming,

¹The term “anosognosia” is used to describe a failure in recognizing the presence of neuropsychological impairment at the modular functions level (perception, action language: anosognosia for emiplegia, for unilateral neglect, for fluent aphasia).

2005), mental flexibility (Burgess et al., 1998; Trudel, Tryon, & Purdum, 1998), self-regulation and error behavior (Bogod, Mateer, & MacDonald, 2003; Burgess et al., 1998; Ownsworth & Fleming, 2005), individuals' ability to self-monitor their performance with the impact of error (online awareness) and their ability to update self-knowledge related to impairments (Ownsworth et al., 2008; Vuilleumier, 2004). Thus, measures for self-regulating errors provide a method that can be useful to examine the contribution of neuropsychological factors in awareness deficits particularly taking into consideration the MPF-C (Ownsworth et al., 2007). At this level, the conscious awareness model (CAM) (Agnew & Morris, 1998; Litvan et al., 1996, 1997, 2003; Ryan, Tree, Morris, & Gontkovsky, 2006) developed to explain awareness deficits in Alzheimer's disease, may be applied in both neurodegenerative disorders (O'Keefe et al., 2007) and brain injury patients (Ownsworth et al., 2002; Prigatano, 1999; Sherer et al., 1998). This model includes a comparator system within the central executive to monitor mismatches between a personal database and the perception of failure on cognitive tasks or behavioral activity. When a mismatch is detected, a signal is sent to the metacognitive awareness system (the fourth level Stuss model), which leads to a conscious experience of failure. If the executive system is not functioning properly, the comparator mechanism may not pick up mismatches, and therefore failures in cognitive performance may not achieve metacognitive output or conscious awareness. We have recently observed in mild Alzheimer's disease (AD) patients that, if the comparator mechanism for monitoring attentive performance was compromised, patients lost the ability to recognize their disturbances and errors (Amanzio et al., 2011, 2013). Indeed, it is now clear how reduced awareness is related to deficits in metacognition, i.e., the ability to shift and inhibit a response, self-monitoring and set-shifting (Amanzio et al., 2011, 2013). It is interesting to note in the case study, that AD patients with reduced awareness of disease showed higher dysfunction of the MPF-C² with a role played by the dorsal division of

anterior cingulate cortex (ACC) in response selection and performance monitoring during an fMRI-response-inhibition-task (Amanzio et al., 2011). These results suggested that lesions in the cingulate area could be associated with reduced awareness. Consistent with these findings, Johnson et al. (2002) used functional imaging and concluded that the MPF-C and cingulate cortex were important structures in order to access a sense of self, and were consistent with previous brain lesion studies on patients diagnosed with impaired self-awareness. Reduced cingulate activity following infarcts or surgery can contribute to behavioral disorders including diminished self-awareness. However, spontaneous lesions of the ACC, such as tumors and strokes, typically involve adjacent areas preventing the study of well-circumscribed ACC lesions (stroke and epilepsy rarely provide examples of isolated cingulate dysfunction) (Devinsky, Morrell, & Vogt, 1995). ACC appears to be involved not only in lesional unawareness disorders but its dysfunction has also been characterized in "functional" awareness disorders including conversion disorder (Perez, Barsky, Daffner, & Silbersweig, 2012; Saj et al., 2009). Perez et al. (2012) suggest that there is a functional-unawareness neurobiological framework which includes the posterior ACC, the posterior parietal cortex, and the DLPF-C that facilitate interaction between awareness and intentional, cognitive control circuits.

As the ACC dysfunction represents one of the corresponding neurobiological substrates of the reduction in self-awareness (Amanzio et al., 2011, 2013), we consider that the presentation of this particular case study is of particular relevance for the literature. Indeed, no previous studies have investigated a reduction in awareness of cognitive and behavioral deficits following selective ischemic injury of the ACC.

CASE REPORT

A 76-year-old, right-handed person (RL) complained that he did not feel well. He had a persistent headache and weakness. He was examined by doctors at the emergency unit of the Martini Hospital in Turin. His medical history revealed normal developmental milestones. He had been a smoker in his youth and reported a family history of ischemic disorders. In particular, his mother had died of cerebral ischemia and his father had died of acute myocardial infarction.

²As Amodio and Frith (2006) have suggested, medial frontal cortex (MFC) is referred to a network of brain regions including anterior cingulate cortex (ACC), the temporoparietal junction, the superior temporal sulcus and the temporal poles.

The remote pathologic anamnesis revealed two otorhinolaryngological interventions for sinusitis and a benign prostatic hypertrophy treated with tamsulosin.

RL had been to school for 8 years, had worked as an electrician, was married, and had two sons. He lived with his wife in their apartment. He was retired but he still worked occasionally.

The first examination was carried out in the hospital emergency department. RL appeared alert, with preserved topographic and time orientations. He spoke correctly, although there were a few interruptions when the medical records were examined. The neurological exam revealed no nystagmus or other cranial nerve deficits. RL maintained Mingazzini I and II for more than 60 s. The segmental cerebellar tests were all correct. RL ambulated independently and showed symmetrical tendon reflexes. The surface sensitivity was preserved.

The first computed tomography (CT), performed on the first day during his stay in hospital, showed normal brain parenchyma and it was negative (see Figure S1, Supplemental Online Material).

The following day, RL who still had a headache and felt unwell—although lesser than earlier on—appeared partially cooperative, not well-oriented in time and space and irritated when further diagnostic investigations were suggested. The magnetic resonance imaging performed on the second day during his stay in hospital showed an ischemic injury resulting from aneurysm involving ACC and extending up to touch the corpus callosum (see Figure 1).

Intracranial magnetic resonance angiogram revealed a left vertebral hypoplasia and widespread irregularities of the carotid siphons wall and the basilar artery. Cutoff at the distal portion of the horizontal section of the right anterior cerebral artery was also diagnosed (see Figure S2, Supplemental Online Material).

After spending a fortnight in hospital in the neurology unit, RL was discharged and given a therapy consisting of simvastatin, gastro-protectants, prostaglandin, cyclooxygenase synthesis inhibitors, and folic acid. Neurology-recommended ambulation focused outpatient's physical therapy.

During the post-acute phase (T0), 15 days after the injury, RL was subjected to a neurological and neuropsychological evaluation. The neurologist reported a negative sensory inspection and symmetric muscle tendon reflexes. Sleep and appetite were considered normal. RL also appeared to be oriented in time and space. At the clinical interview, RL showed reduced awareness of the problems

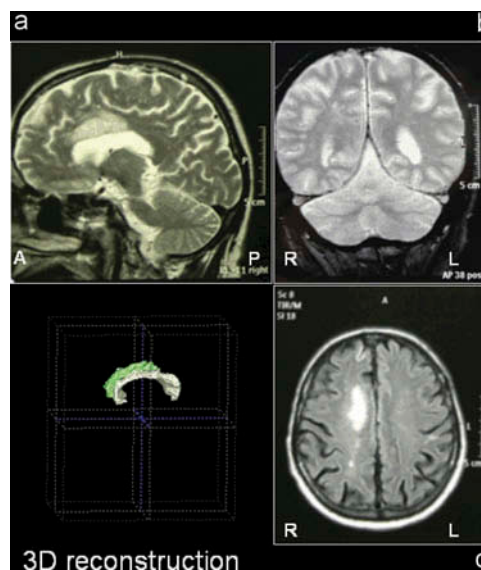


Figure 1. Ischemic lesion of the ACC shown as hyperintensity in the Time Inversion Recovery MRI sequence. The medical report refers a selective ischemic lesion involving the ACC and extending up to touch the corpus callosum. A 3D model on a stereotaxis plane shows the lesion as reconstructed in MRIcron (the lesion was drawn in green color for the online version of the manuscript). MRIcron is a GUI-based visualization and analysis tool for magnetic resonance imaging that can be used to create 2D or 3D renderings of statistical overlay maps on brain anatomy images. Moreover, it aids drawing anatomical regions-of-interest as well as lesion mapping. In the figure, a = sagittal plane, b = coronal plane, c = axial plane, A = anterior, P = posterior, R = right, L = left. [To view this figure in color, please see the online version of this journal].

encountered during daily-life activities, which his wife confirmed. During the neuropsychological evaluation, a clear-cut reduction in awareness at both the cognitive and the behavioral levels was observed.

At a follow-up examination 15 months later, during the stabilization phase (T1), RL appeared to have improved in terms of global cognitive function, with selective executive function deficits and behavioral mood changes still present. As he was unaware of the deficits, he did not understand why he had to undergo a further follow-up assessment and complete the overall neuropsychological battery.

METHODS

Assessment of impaired awareness for cognitive and behavioral deficit

During the neurological examination at T0, a partial and fluctuating awareness of disease required a

thorough neuropsychological investigation. A recognized methodology was applied and it was advisable to diagnose and quantify the severity of the deficit (Anderson & Tranel, 1989). An effective awareness deficit needs to be investigated quantitatively using an integrative approach that can be useful to understand its nature and its cognitive and neuropsychiatric correlates (O'Keefe et al., 2007). For this reason, prior to subjecting RL to the whole neuropsychological battery, the *Awareness Questionnaire for Dementia* (AQ-D; Migliorelli et al., 1995) was used to quantify deficit unawareness (Starkstein et al., 1996). The questionnaire requires a reliable primary caregiver to collaborate and consists of 30 questions divided up into two sections: a cognitive and a behavioral part. The cognitive part assesses cognitive functions and performance in basic and instrumental activities of daily-life activities. The behavioral part assesses changes in interests and mood. Both the patient (Form A) and the caregiver (Form B) were asked the identical questions, but the latter was blinded to the patient's responses. Each question had a score ranging from 0 (never) to 3 (always). The total AQ-D score was calculated as the difference between Form B and A. Patients with a score of ≥ 32 were classified as being unaware, whereas patients with a score of ≤ 14 were classified as being aware of their deficits. Patients who scored between 15 and 31 were classified as borderline (Migliorelli et al., 1995). As to the cognitive and behavioral part respectively, higher scores in the difference between form B and A indicated worse awareness deficits. In addition, we also considered specific items of the AQ-D scale to gather information about reduced awareness within basic and instrumental daily-life activities (ADL and iADL, correspondingly), as well as in depression and disinhibition domains (Amanzio et al., 2013; Starkstein, Jorge, Mizrahi, & Robinson, 2006). As the AQ-D is based on a subtractive index of perception by caregivers and patients, it is essential to exclude any bias in caregivers' judgement (Conde-Sala et al., 2013; Migliorelli et al., 1995): RL's wife had normal neurological and psychiatric evaluations and a negative history of neurological disorders.

The AQ-D was also administered during the stabilization phase together with the *self-regulation skills interview* (SRSI; Ownsworth, McFarland, & Young, 2000), a clinical tool that is used to assess higher levels of self-awareness and self-regulation skills, which implies insight, motivation, and the use of compensation strategies. This is a 6-item

clinician-rated questionnaire focusing on one of the following difficulties typically involved in ABI: memory problems, poor attention and concentration, depressed mood, anger and frustration, and lack of motivation and poor communication skills. Items are scored on a scale of 0 (very high level of skills) to 10 (very low), reflecting level of awareness, self-rating of motivation, strategy knowledge, or use of strategies (Ownsworth et al., 2000). The SRSI is able to predict relative success or disability in social, vocational, or educational roles and in rehabilitation programs (Ownsworth et al., 2000).

Neuropsychiatric and functional assessment

Due to the complexity of the phenomenon, an overall neuropsychiatric assessment was chosen aiming to look into RL's behavioral and psychological functioning and identify areas of strength and weakness during the post-acute phase and in the stabilization period. RL was assessed in three one-hour experimental sessions on three different days of the same week and the caregiver was not present. Behavioral mood changes were assessed by means of specific scales.

- (1) *Apathy Evaluation Scale-Clinician version* [AES-C] (Marin, Biedrzycki, & Firinciogullari, 1991): This is an 18-item clinician-rated questionnaire, ranging from a minimum of 18 points to a maximum of 72 points. Items are scored on a 4-points scale with descriptors for the clinician version. On this scale, a score of less than or equal to 37.5 was suggested to be a cutoff 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 depression. A score of 0–7 is considered to be normal. Scores of 20 or higher indicate moderate, severe, or very severe depression, and are usually required for entry into a clinical trial.
- (3) *Hamilton Anxiety Rating Scale* [HAR-S] (Hamilton, 1959): This is a 14-item questionnaire; each one is defined by a series of symptoms which measure both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where a score greater than or equal to 15 indicates mild

severity, 18–24 mild to moderate severity, and 25–30 moderate to severe.

- (4) *Disinhibition Scale* (Starkstein, Garau, & Cao, 2004): This is a 26-item questionnaire that assesses abnormal motor behavior, stereotyped routines, psychosis, hypomanic behavior, and poor self-care. Each item is scored on a scale of 0 (no abnormal behavior) to 4 (extreme abnormal behavior). On this scale, a total score of 16.9 was suggested to indicate disinhibited behavior. There are not cutoff scores for the individual subscales.
- (5) *Mania Scale* [MAS] (Bech, Rafaelsen, Kramp, & Bolwig, 1978): This is a 11-item clinician-rated scale that covers symptoms such as elevated mood, irritability, sleep, increased activity, talkativeness, flight of ideas, self-esteem, noise level, and sexual interest. Each item is scored on a scale of 0 (not present) to 4 (severe). On this scale, a total score of 15 was suggested to indicate hypomanic behavior.

Handedness was assessed by means of the *Edinburg Handedness Inventory* (Oldfield, 1971) using RL self-reporting hand-use. The level of autonomy held by the subject in basic and instrumental activity scales were assessed, respectively, with the *Autonomy in Daily Living* (ADL: Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) and the *Instrumental Activity of Daily Living* (IADL: Lawton & Brody, 1969).

Neuropsychological assessment

- (1) *Premorbid intellectual efficiency* was measured using the *Brief Intelligence Test* [TIB] (Colombo, Sartori, & Brivio, 2002; Sartori, Colombo, Vallar, Rusconi, & Pinarello, 1995) that is the Italian version of the *National Adult Reading Test* by Nelson (1982). Based on a reading task, it consists of a list of 34 words with irregular accents and 20 control words with high-frequency usage. The total number of errors in pronunciation provides the TIB error score: this is used to estimate IQ scores using the regression of equations that considers sex, age, and schooling (Sartori et al., 1995). Indeed, TIB error score is highly correlated with WAIS full-scale IQ, verbal IQ, and performance IQ in normal Italian adults (Sartori et al., 1995).
- (2) *Global cognitive functions* were assessed by means of the *Addenbrooke's Cognitive Examination-Revised* (ACE-R: Mioshi, Dawson, Mitchell, Arnold, & Hodge, 2006). The ACE-R is a brief cognitive battery that evaluates five cognitive domains: attention/orientation, memory, verbal fluency, language, and visuospatial abilities. Higher scores indicate better cognitive functioning. There are two cutoff total ACE-R scores (88 with a sensitivity of 0.94 and 82 with a sensitivity of 0.84). The administration of this battery also permits the acquisition of the *Mini-Mental State Examination* score (MMSE: Folstein, Folstein, & McHugh, 1975), by adding up the scores in the shaded boxes on the right-hand side of each test.
- (3) The *cognitive domain* was also analyzed by using an extensive battery assessing memory (*Corsi Test*: Spinnler & Tognoni, 1987; *Digit Span*: Spinnler & Tognoni, 1987; *Wechsler Memory Scale*, Subtest 4 and 7: Wechsler, 1945), language (*Token Test*: De Renzi & Vignolo, 1962), and visuoconstructive abilities and praxia (*Coping Design*: Gainotti, Miceli, & Caltagirone, 1977; *Ideomotor Apraxia Test*: Spinnler & Tognoni, 1987). Attention and executive functions were analyzed with: the *Montreal Cognitive Assessment* (MOCA: Schweizer, Al-Khindi, & Macdonald, 2012); the *Attentional Matrices* test (Spinnler & Tognoni, 1987); the *Trial Making part A, B* (TMT: Reitan & Wolfson, 1994); the *Stroop Test—Short version* (Caffarra, Vezzadini, Zonato, & Venneri, 2002), and the *Winsconsin Card Sorting Test* (WCST: Berg, 1948). The *Bells Test* (Gauthier, Dehaut, & Joannette, 1989) was used to exclude unilateral visual-attentional neglect.
- (4) *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, Alderman, Burgess, Emslie, & Evans, 1996). The BADS is composed of 6 subtests: 1. *The Rule Shift Cards (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 Action Program (AP)* examines the ability to solve a closed-ended sequential problem, where the subject is presented with a set of materials. 3. *The Key Search (KS)* subtest examines

the ability to solve an open-ended problem. 4. *The Temporal Judgment (TJ)* subtest measures cognitive estimation. 5. *The Zoo Map (ZM)* subtest assesses planning, sequential behavior, and ability to use feedback in problem-solving. 6. *The Modified Six Elements (MSE)* test assesses ability to divide attention, task scheduling, performance monitoring, and prospective memory. Each subtest is scored on a scale of 0 (severely deficient) to 4 (normal performance). The sum of the 6 subtests' profile scores yielded the total score on the battery (Wilson et al., 1996).

- (5) *Perspective-taking abilities* were tested using *Theory of Mind visual stories (ToM1 and ToM2)*: Amanzio, Geminiani, Leotta, & Cappa, 2008): the subject has to solve problems involving: first-order attributions of false belief (of the type "A thinks X") and second-order attributions of false belief (of the type "A thinks B thinks X"). Each story is followed by a ToM test question and two control questions (memory and comprehension). A total of eight stories were presented to RL: four for the first-order false belief test and four for the second-order false belief test. A score of 1 was given for correct answers, a score of 0.5 was given for a second attempt at the correct answer, and a score of 0 was given for the wrong answer (Amanzio et al., 2008, 2011).

Response inhibition task assessment

RL was asked to perform a response inhibition paradigm (go-/no-go task, adapted from Braver, Barch, Gray, Molfese, & Snyder, 2001). He 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. RL had to respond by pressing a button with his right index finger. Only letters from the Italian alphabet were used in order to avoid confounding factors (Amanzio et al., 2011). Before and after the test, the patient was asked to provide an estimate on the number of errors made in the experimental session.

POST-ACUTE PHASE RESULTS (T0)

At T0, the neuropsychiatric evaluation detected mood changes at a disinhibition level (characterized

by apathy and abnormal motor behavior) and the onset of a moderate apathetic syndrome in the absence of major depression, somatoform anxious symptomatology or hypomania. Given the current clinical picture, the neurologist did not consider it appropriate to prescribe an antidepressant or an anxiolytic therapy. It is important to note that the AQ-D showed a clear-cut reduction in global awareness, in iADL and depression domains of awareness, respectively (Table 1).

The neuropsychological assessment revealed that the premorbid intellectual level fell within the statistical norm (TIB). RL had difficulty on the MMSE and ACE-R. The higher frontal type cortical functions appeared in short supply when measured on the MOCA screening test. RL exhibited a low level of impairment in the visuospatial domain (constructional apraxia in two- and three-dimensional coping design). The BADS revealed impaired executive functions. In particular, RL showed executive function deficits related to flexible thinking, cognitive shifting, and inhibition of dominant responses assessed with TMT-B, WCST, and Stroop test, respectively.

RL also achieved low scores on selective attention and processing speed tests. Visual perception, as measured using a cancellation test (Bells Test), mentalizing ability (ToM1, ToM2), logical memory and verbal paired-associate learning (Wechsler Memory's Subtests 4 and 7), short-term memory for numbers (Digit Span), spatial memory (Corsi Test), and constructional praxis with elements of programming (Coping Design) were all normal. Finally, there was not a tendency towards perseverative thinking (% WCST perseverative errors) (Table 2).

As to the performance obtained on the response inhibition test, RL committed almost twice as many errors compared to healthy controls. Nevertheless, as a result of a training session, he was to neither envisage the number of errors that he might have committed nor, subsequently, demonstrate the ability to monitor his own performance after the administration of the test (Table 3).

15-MONTH FOLLOW-UP AND STABILIZATION PHASE RESULTS (T1)

RL refused any follow-up visits at 6 and 12 months, saying he was in perfect health, attesting in such a way problems with monitoring his cognitive and behavioral deficits. He was contacted by phone but he said that he did not understand why he

TABLE 1
Awareness of deficits, neuropsychiatric and functional assessment

	<i>T0 (post-acute phase)</i>			<i>T1 (stabilization phase)</i>			<i>Cut-off</i>
	<i>Caregiver</i>	<i>RL</i>	<i>Total score</i>	<i>Caregiver</i>	<i>RL</i>	<i>Total score</i>	
Awareness assessment							
AQ-D overall [90]	47	14	33	48	11	37	≤14
AQ-D cognitive part [66]	37	9	28	39	8	31	
AQ-D behavioral part [24]	10	5	5	9	3	6	
AQ-D ADL	2	0	2	2	0	2	≤4
AQ-D iADL	25	9	16	28	8	20	≤4
AQ-D depression	12	5	7	9	3	6	≤4
AQ-D disinhibition	1	0	1	0	0	0	≤4
SRSI [60]						30	
Neuropsychiatric assessment							
AES-C [72]			30			25	≥37.5
HDR-S [67]			5			6	≤7
HAR-S [56]			4			6	≤17
Disinhibition scale [96]			23			19	≤16.9
Apathy			8			9	
Abnormal motor behavior			5			3	
Stereotypy			1			1	
Hypomania			3			2	
Psychosis			0			1	
Poor self-care			2			3	
MAS [44]			5			4	≤15
Functional assessment							
ADL [8]			4			5	6
IADL [6]			6			5	5

Maximum scores of the tests are shown in square parentheses. Regarding the HDR-S, HAR-S, MAS, Disinhibition and SRSI scales higher scores indicate more severe symptoms. In the case of AES-C, lower scores indicate more severe symptoms. Regarding the functional evaluation, higher scores indicate better performance. 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 means absence of a normative cut-off for that assessment tool.

had to undergo another clinical evaluation, as he did not have any neurological deficits or cognitive impairment, despite the persisting difficulties his wife reported. However, after numerous requests, RL agreed to undergo a new neuropsychological assessment 15 months after the initial evaluation (during stabilization phase).

The patient was evaluated in only one session and the caregiver was not present. He was subjected to a comprehensive neuropsychological battery for the assessment of cognitive global impairment (ACE-R: Mioshi et al., 2006); memory (*Corsi Test*: Spinnler & Tognoni, 1987; *Digit Span*: Spinnler & Tognoni, 1987; *Wechsler Memory Scale*, Subtest 4 and 7: Wechsler, 1945); language impairment (*Token Test*: De Renzi & Vignolo, 1962); visuoconstructive abilities and praxia (*Coping Design*: Gainotti et al., 1977; *Ideomotor Apraxia Test*: Spinnler & Tognoni, 1987); and attention and executive function (MOCA: Schweizer et al.,

2012; *Attentional Matrices*: Spinnler & Tognoni, 1987; *complete TMT*: Reitan & Wolfson, 1994; *Stroop Test—Short version*: Caffarra et al., 2002). Dysexecutive syndrome was evaluated by means of the BADS (Wilson et al., 1996).

During the neuropsychological assessment, RL appeared motivated to perform tests quickly and without any interruption. Unfortunately, he did not finish the entire battery as he thought he had fully recovered. At the clinical interview, RL said that his family and friends found him depressed and apathetic, sometimes a little irritable, but that was not true. Considering both the AQ-D and SSRI scores, RL was still unaware of his deficits at both the cognitive and behavioral levels, he was unable to monitor his difficulties in daily-life activities, or envisage what would be the outcome of the situation, or elucidate possible useful interventions to improve his condition. The neuropsychiatric assessment established the persistent apathetic mood orientation

TABLE 2
Neuropsychological assessment

	<i>T0 (post-acute phase)</i>		<i>T1 (stabilization phase)</i>		<i>Cut-off</i>
Cognitive and Intellectual assessment					
MMSE [30]	23.7	ES = 3	25.7		≥24
ACE-R [100]	74		82		≥82
TIB [34]:	19				≤19.8
Estimated IQ total	94.859				≥90
Estimated IQV	94.271				≥90
Estimated IQP	100.182				≥90
Attentional assessment					
Bells test total score [35]	22				≥32
Bells test (right minus left)	0				≤3
Attentional matrices [60]	32	ES = 1	45	ES = 3	≥31
TMT A [500]	119	ES = 0	66	ES = 2	≤94
TMT B [500]	500	ES = 0	226	ES = 1	≤283
TMT B-A	320	ES = 0	99	ES = 2	≤187
Stroop Test—Short version:					
Time interference effect	37.14	ES = 0	41.31	ES = 0	≤36.91
Error interference effect	5.25	ES = 0	7.75	ES = 0	≤4.24
Memory assessment					
Corsi Test [9]	4.25	ES = 2	4.25	ES = 2	≥3.5
Digit Span [9]	4.75	ES = 4	4.75	ES = 4	≥3.75
Wechsler Memory—Subtest 4 [22]	10		12.5		
Wechsler Memory—Subtest 7 [22,5]	15		14.5		
Language assessment					
Token Test [36]	31.25	ES = 2	32.75	ES = 3	≥32.69
Praxia assessment					
Coping design:					
without programming elements [12]	5.8	ES = 0	8.8	ES = 2	≥7.18
with programming elements [70]	65.3	ES = 2	65.3	ES = 2	≥61.85
Ideomotor Apraxia [20]	18.25	ES = 2	18.25	ES = 2	≥16
Executive function assessment					
MOCA [30]	16		21		≥26
BADS [24]	11		11		≥13
RSC	1		1		
KS	0		1		
AP	4		4		
TJ	2		2		
ZM	2		1		
MSE	2		2		
WCST:					
categories completed [6]	0	ES = 0			≥3
% errors	83	ES = 0			≤29.90
% perseverative errors	32	ES = 2			≤42.70
Perspective taking assessment					
ToM-1st type [4]:	4				≥3
comprehension	4				
memory	4				
ToM-2nd type [4]:	4				≥3
comprehension	4				
memory	4				

Maximum scores of the tests are shown in square parentheses. Wherever possible Equivalent Scores (ES) are shown: ES equal to 0 corresponds to a performance of less than 5% of the normal population, thus having pathological meaning. ES equal to 1 indicates a performance to the lower limit of the norm, ES equal to 2 indicates a performance in the standard, ES equal to 3 indicates a performance higher than normal and, finally, ES equal to 4 provide a considerably higher than normal performance.

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 means absence of a normative cut-off for that assessment tool.

TABLE 3
Braver's go/no-go response inhibition test. Comparison with normative data for normal control subjects (Braver et al., 2001)

	<i>RL T0 (post-acute phase)</i>	<i>Normal control subjects</i>
Response inhibition task GO:		
% TARGET	91.66	98.9
RT (ms)	341.72	367
% ERRORS	8.34	1.1
Response inhibition task NO-GO:		
% TARGET	72.5	85.3
% ERRORS	27.5	14.7
Pre-performance judgment	10/40 X	
Post-performance judgment	04/40 X	

T = reaction time. Pre- and post-performance judgments refer to the number of errors RL thought he would do and he did in his opinion.

associated with a certain lack of inhibition. During the assessment, the neurologist found no significant psychiatric symptoms, or hypomania. Although RL seemed to have improved in terms of overall cognitive functioning and showed autonomy in managing the basic and instrumental daily-life activities, he still exhibited deficits in the executive functions assessed through the MOCA, BADS, and Stroop Test.

DISCUSSION

The case study presented here deals with persistent reduction in the awareness of deficits and refers to a patient with a selective ischemic lesion. Its relevance is represented by the circumscribed insults to ACC, indeed stroke rarely provide examples of isolated cingulate dysfunction. At T0, the neuropsychiatric evaluation detected mood changes at a disinhibition level, the onset of a moderate apathetic syndrome, and the AQ-D showed a clear-cut reduction in global awareness. The neuropsychological assessment revealed difficulty on the MMSE, ACE-R, and a low level of impairment in the visuospatial domain (Coping Design). The higher frontal type cortical functions appeared in short supply when measured on the MOCA. The BADS revealed impaired executive functions. In particular, RL showed executive function deficits related to flexible thinking, cognitive shifting, and inhibition of dominant responses assessed with TMT, WCST, and Stroop test. As to the performance obtained on the response inhibition test, RL committed almost twice as many errors compared to healthy controls.

Fifteen months after the vascular accident, behavioral disorders persisted as well as unawareness of functional impairment and impaired executive functions. RL was unable to detect the presence of the selective cognitive deficits and behavioral changes, even though they were clearly evident for doctors and his family. Persistent unawareness cannot be related to RL's overall cognitive status or memory abilities. Moreover, overall cognitive scales, language comprehension, and copy design improved and it confirmed there was not any residual deficits. Likewise, many brain injury investigations were not able to find a relationship between the level of awareness deficits and generalized cognitive impairment, intellectual functioning, memory, and language (Burgess et al., 1998; Fleming, Strong, & Ashton, 1998; McGlynn & Schacter, 1989; McKinlay & Brooks, 1984; Prigatano, Altman, & O'Brien, 1990). It is important to point out that persistent unawareness and impaired executive functions, as well as a mood change, were observed as residual deficits 15 months after the selective right anterior cingulate ischemic injury. Interestingly, RL showed deficits in specific subcomponents of ACC-related executive functions characterized by response shifting (WCST), inhibition (RSC, Stroop Test, and Braver's go/no-go test), and monitoring (SRSI, inability to recognize errors during the Braver's go/no-go session).

Through the SRSI, we observed deficits in both emergent awareness (online monitoring of errors), which prevented RL from self-monitoring and identifying problems, as they took place, and in anticipatory awareness, that is the ability to accurately predict performance of future tasks showing poor

appreciation of the consequences of his deficits (Toglia & Kirk, 2000). Moreover, it was suggested to measure emergent awareness by monitoring errors on line, as it is linked to ACC and DLPF-C (O’Keeffe, Dockree, & Robertson, 2004). In step with these findings, O’Keeffe et al. (2007) found a relationship between emergent unawareness in FTD patients and dysfunction in the very brain regions, whose activation correlated with error-processing. As FTD patients exhibited a severe “executive unawareness,” as a result of severe levels of frontal executive damage, the authors suggested as a possible interpretation of the phenomenon to use the CAM model by Morris and Hannesdottir (2004). The secondary disruption of a metacognitive awareness could arise of either direct frontal atrophy or due to the breakdown of fronto-subcortical pathways (O’Keeffe et al., 2007). Moreover and consistent with the findings in RL, O’Keeffe suggests that any deficit in response inhibition or cognitive flexibility can affect patients foresight (see RL’s pre-performance judgment in the Braver’s go/no-go test). It is therefore possible that the inability to maintain the cognitive representation of the cognitive performance in the working memory, brought about by executive processes in the frontal lobe (O’Keeffe et al., 2007), and deficit in the integration of negative affect and cognitive control in the anterior mid-cingulate cortex (Shackman et al., 2011) may have a function in the arising of unawareness.

Our recent study on the relationship between impaired executive function and reduction of awareness in Alzheimer-type dementia supports this idea (underlining the presence of the phenomenon in different neurological disorders), especially as regards the RSC of the BADS (Amanzio et al., 2013). We found the ability to inhibit a response, self-monitoring, and set-shifting is an important skill for awareness of deficits (Amanzio et al., 2013). Interestingly, it has been found that the ACC is active during the response inhibition task, where a pre-potent response is overcome, for example, in go/no-go tasks in normal subjects (Braver et al., 2001) and in action monitoring (Amodio & Frith, 2006) and its hypofunctionality was related to a reduction in awareness in AD patients (Amanzio et al., 2011). Moreover, studies conducted in healthy controls and on the neural correlates of self-awareness pointed out the role of the MPF-C and perigenual ACC (Amodio & Frith, 2006; Northoff et al., 2006). It cannot be denied that empirical research has consistently

identified an association between awareness deficits and impaired executive function in ABI (Bogod et al., 2003; Burgess et al., 1998; Ownsworth & Fleming, 2005; Ownsworth et al., 2002). However, a possible explanation that has never been conceptualized up to now in such patients, it might be that it was caused and it is still supported by a structural and functional lesion in the cingulo-frontal area causing a delay in the executive functions of the MPF-C (Amodio & Frith, 2006), disrupting the *internal awareness network* (concerning stimulus-independent thoughts) including midline anterior cingulate/mesiofrontal areas, as well as posterior cingulate/precuneal cortices (Demertzi, Soddu, & Laureys, 2012). As far as subcortical network related to deficit unawareness is concerned, thalamic lesions were found to produce diverse impairments in sensory, perceptual, motor, and cognitive processes (Kumral, Kocaer, Ertübey, & Kumral, 1995), whereas disturbances in mood and self-awareness had previously been observed after right thalamic lesions (Liebson, 2000). Direct damage to the thalamus and/or disruption of connecting pathways in various regions of the cortex (e.g., fronto thalamic pathways) was associated with deficits in awareness and emotional regulation (Bogousslavsky, 1994).

Awareness deficits may arise due to a disruption at different stages of processing within this integrated network. While the network components have not yet been specifically localized in ABI, the functional nature of ACC is an important topic to understand self-awareness as shown in the present study. Indeed, ACC is considered as an attentional monitoring system that coordinates and integrates the task-oriented sensory, receptive and expressive language, alerting, working memory, response selection, motor planning, and motor response processes within the CNS (Peterson et al., 1999). The attentional monitoring system represented by the ACC (Posner & Raichle, 1994) contributes to ensuring that the elaboration processes in other brain regions have the highest efficiency, in relation to the task demands that take place. The interactions with the DLP-C serve to select the working memory buffer. Interactions with the posterior cortices may serve to amplify the activity of a particular form of perception compared to others. The interactions with the posterior cortices may be direct or mediated by connections with the prefrontal cortex (see Amanzio et al., 2011). ACC encompasses Brodmann areas 25, 24, and 33, also including the caudal part of area 32 (Devinsky et al., 1995). ACC

not only includes modules for emotional, cognitive, motor, and sensory information, but it also integrates inputs from various sources, showing that it has 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). Moreover, the cingulate cortex become active in such a way that it effects activity in other brain regions and modulates visceral, endocrine, motor, and cognitive responses (Bush et al., 2000). In particular, both dorsal ACC and the area of the prefrontal cortex operate together during tasks involving high levels of mental effort (Bush et al., 2000). ACC is also jointly activated with the anterior insular cortex (AIC), suggesting that they serve as complementary limbic sensory and motor regions that respectively engender feeling and motivation (Craig, 2009). As Medford and Critchley (2010) highlighted the AIC-ACC system is crucial for the production of subjective feelings and coordinating appropriate responses; state of feelings emerging from the sensory input of raw data are integrated through representations in conscious awareness. In this way, they appear to be the input (AIC) and output (ACC) components of a system based on self-awareness, as they are also core regions of a “salience network” responsive to a wide range of stimuli (Medford & Critchley, 2010). A fMRI study of self-recognition supports this hypothesis, finding that specific AIC and ACC regions are key areas for integrative self-related processes (Devue et al., 2007). Moreover, AIC is supposed to be a probable anatomical substrate for self-awareness, awareness of others, and the environment on the basis of its afferent representation of body feelings (Craig, 2009). Cingulate tumors and other lesions in humans can cause a variety of affective changes including apathy, disinhibition, and depression (Devinsky et al., 1995). As stated above, changes in mood observed in RL are not surprising. In particular, from a neuropsychiatric standpoint, RL obtained higher scores near the cutoff value on disinhibition, mania, and apathy scales during the first assessment and in the retest. Also, the results suggest that RL has an early mild change in behavior and that this should not be considered as relevant from a psychopathological point of view. Moreover, the results are consistent with Rosen et al. (2005), who demonstrated an association between tissue reduction in the ventral and dorsal portion of the ACC (dACC and vACC/vmSFG) and in the subgenual cingulate gyrus (SGC), in apathy and

in disinhibition, respectively. Importantly, apathy and disinhibition were also identified as prominent features in the first behavioral change stressing reduced behavioral awareness in early AD patients (Amanzio et al., 2011, 2013). This may be considered an important early marker of change that should be assessed in patients with ACC dysfunctions.

The deficits mentioned here are consistent with the self-awareness concept described by Stuss et al. (Stuss & Anderson, 2004; Stuss et al., 2001). MPFC appeared crucial for preserved self-awareness ability and the critical role played by its right frontal part was pointed out (Stuss et al., 2001). The Stuss’ model identify that self-awareness implies self-reflection and metacognitive abilities (Stuss & Anderson, 2004). We have recently demonstrated reduced awareness in AD resulting from a greater impairment of metacognitive abilities related to performing tasks requiring mental set-shifting, monitoring, and inhibition (Amanzio et al., 2011, 2013). Both the aforesaid results and the neurocognitive model defined as the CAM by Agnew and Morris (1998) help us to understand how the executive system contributes to awareness-related abilities (Agnew & Morris, 1998; Amanzio et al., 2011, 2013; Litvan et al., 1996, 1997; Starkstein et al., 1995). In particular, conscious experience of post-injury change requires an interaction between relevant functional domains (e.g., sensory, perceptual, motor, and cognitive functions), comparator mechanisms within the central executive system to detect change, and the conscious or metacognitive awareness system. This feedback system relies upon updates regarding the success and failure experience on performing tasks and therefore contributes to a person’s self-knowledge of personal abilities and impairment (Morris & Hannesdottir, 2004). The present study indicates, whether the comparator mechanism responsible for monitoring attentive performance is compromised at a prefrontal striatal level and if it does not detect mismatches, the patient loses the ability to recognize his disturbances and errors not only in an environmental setting but also during the test session. We observed these phenomena when RL was asked to talk about the unsuccessful experiences in his daily-life activities and we compared his responses with the caregiver’s judgment based on the AQ-D. Moreover, RL was unable to evaluate correctly the number of errors he made in the response inhibition task. As a result referring to RL, a failure in cognitive performance may not

achieve metacognitive output or conscious awareness and therefore lose the ability to recognize his disturbances and errors. These findings previously suggested that deficits of awareness may result from impaired error-processing abilities, implicitly suggesting that an intact process of error-monitoring implies an intact awareness (Hart, Giovannetti, Montgomery, & Schwartz, 1998; O’Keeffe et al., 2004; Zaidel, 1987). We came to this same conclusion in our recent studies (Amanzio et al., 2011, 2013) and this has been confirmed in the present study. We specifically hypothesized that there is a relationship between RL’s lack of awareness, still present in the post-acute phase, and the deficits we observed in specific subcomponents of ACC-related executive functions characterized by response shifting (WCST) and inhibition (RSC, Stroop Test, and Braver’s go/no-go test) and monitoring (SRSI, inability to recognize errors during Braver session).

We think the aforesaid findings are important in order to help clinicians in both the diagnostic phase and the treatment process. Indeed, unawareness assessment can enable better and earlier differential diagnosis. Moreover, clinicians may improve adherence to health treatment in patients, who are more likely to refuse such care using appropriate engagement strategies. This would mean improving the course of recovery and rehabilitation.

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