

ERROR-BASED TRAINING AND EMERGENT AWARENESS IN ANOSOGNOSIA FOR HEMIPLEGIA

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Running title: Analysis of errors in Rehabilitation of anosognosia.

Abstract (max 150 words)

Residual forms of awareness have recently been demonstrated in subjects affected by anosognosia for hemiplegia, but their potential effects in recovery of awareness remain to date unexplored. *Emergent awareness* refers to a specific facet of motor unawareness in which anosognosic subjects recognize their motor deficits only when they have been requested to perform an action and they realize their errors.

We recruited four participants with anosognosia for hemiplegia in the chronic phase after a stroke. They took part in an 'error-full' or 'analysis of error-based' rehabilitative training program. They were asked to attempt to execute specific actions, analyze their own strategies and errors and discuss the reasons for their failures. Pre- and Post-training and follow-up assessments showed that motor unawareness improved in all four patients.

These results indicate that unsuccessful action attempts with concomitant error analysis may facilitate the recovery of emergent awareness and, sometimes, of more general aspects of awareness.

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Key words: anosognosia for hemiplegia; rehabilitation; action planning; emergent awareness; judgments of action test.

Introduction

The most recent research on Anosognosia for Hemiplegia (AHP) shows that this *denial of motor paralysis contralateral to a brain lesion* (Babinski, 1914) is a multi-componential syndrome, including variable patterns of deficits and manifestations (Cocchini et al., 2010). Although AHP represents a neurological syndrome that has been well described in neuropsychological literature, there is still a debate about whether the various different expressions of unawareness are manifestations of independent abnormalities, a single primary deficit or a combination of deficits (Fotopoulou, 2013).

Clinical and experimental approaches, integrated with an increasing quantity of results from neuroimaging techniques (Fotopoulou et al., 2010; Vocat et al., 2010; Moro et al., 2011), have demonstrated the limits of theories explaining AHP as the result of single deficits (Babinski, 1914; Bisiach, 1986; Mc Glinn & Schacter, 1989; Starkstein et al., 1992; Feinberg, 1997; Frith et al., 2000; Heilman & Harciarek, 2010).

Thus, multifactorial hypotheses have been suggested (Vuilleumier, 2004; Davies et al., 2005; Mograbi & Morris, 2013). These emphasize the role of combinations of various deficits in causing different clinical expressions of the syndrome. Marcel and colleagues suggest that AHP may be the result of a patient's overestimation of self-performance associated with a lack in mental flexibility (Marcel et al., 2004). The Two Factor theory (Davies and al., 2005) proposes

that the syndrome might emerge due to the synergic effect of a neuropsychological deficit and a more general cognitive impairment.

A more complex idea is proposed in the ABC Model (Vuilleumier, 2004) where awareness relies on a set of neuropsychological functions mediating Appreciation, Belief and Check processes. Appreciation may be impaired as a result of sensory deafferentation or neglect, but AHP would emerge only when additional deficits in cognitive or affective functions occur, together with the subject's incapacity to check and verify the distorted experiential evidence and delusional interpretations. Indeed, these processes would be necessary in order for the subjects beliefs concerning their paralysis to be altered (Vocat et al., 2010).

The role of resistance in patients to updating their beliefs concerning their own body and motor abilities has been emphasized in the most recent models concerning AHP (Fotopoulou, 2013; Vocat et al., 2013) and anosognosia for cognitive deficits in mental deterioration (Mograbi & Morris, 2013).

More recently the existence of residual forms of awareness in subjects affected by AHP has been investigated. After the first seminal reports (Ramachandran, 1995), a double dissociation between explicit and implicit awareness for motor deficits was experimentally investigated by comparing verbal reports and requests to actually perform actions (Cocchini et al., 2010; Moro et al., 2011). When this dissociation is present and implicit (but not explicit) awareness is spared, AHP patients verbally deny their paralysis but act as if they know they cannot move their paralyzed body parts, e.g. planning and executing bimanual actions substituting the paralyzed arm with another part of the body. Viceversa, in the case of explicit (but not implicit) awareness, patients declare that they are not able to move their body parts but try to perform actions as if these parts moved normally (e.g. standing up or clapping their hands). Residual

forms of implicit awareness have been also demonstrated by means of recording reaction times and errors in response to verbal or visual stimuli associated with hemiplegia-related deficits (Nardone et al., 2007; Fotopoulou et al., 2010).

Another dissociation in AHP that has been demonstrated concerns self- and other- referred perspectives. It has been shown that the lack of awareness can specifically relate to a patient's own deficits (1st person deficit) or also concern other people's impairments (1st and 3rd person deficit). While in the first case patients deny their own paralysis but recognize deficits in other patients, in the second they fail to recognize motor impairment both in themselves and in other subjects (Marcel et al., 2004; Moro et al., 2011).

Finally, a specific residual form of awareness in AHP has been identified as 'emergent awareness' (Moro et al., 2011; Moro, 2013). This refers to the instance in which patients deny their motor deficits but become aware of them when asked to actually perform an action using the affected body part. The notion of emergent awareness is related to a model of awareness based on a three level hierarchy (Crosson et al., 1989) which classifies unawareness as follows:

- i) intellectual awareness, i.e. the generic ability to recognize a deficit (e.g. "I suffered a stroke");
- ii) emergent awareness, in which a patient becomes declaratively aware of his/her deficits only when asked to perform an action with the affected body part (i.e. by 'confrontation'; e.g. "I thought I was able to do this action, but now I'm realizing it is impossible for me") and
- iii) anticipatory awareness, i.e. the ability to anticipate the effects of his/her deficit, admitting to his/her inability to perform an action before it becomes evident in a real situation (e.g. "I cannot jump because of my paralysis").

The theory posits a hierarchical relation between the three levels so that anticipatory awareness is thought of as the highest level and thus the first one to be affected in AHP, followed by emergent and then by intellectual awareness. However,

this hierarchical relation has not been empirically tested and it is possible that different patients may show different degrees of deficit in these three forms of awareness (Marcel et al., 2004; Moro et al., 2011). In fact, a recent study empirically demonstrated that when patients were asked to perform movements with their affected body parts, emergent awareness manifested in a group of patients who were more generally unaware of their deficits (Moro et al., 2011). This finding suggests that intellectual and perhaps even anticipatory awareness may increase by means of failed attempts at performing an action.

Using this finding as a starting point, the aim of this study is to investigate the potential role of action attempts and corresponding error analysis in the rehabilitation of AHP patients. While some attempts at rehabilitation have been documented in case studies or series (Fotopoulou et al., 2009; Cocchini et al., 2013; Besharati et al., in press), there is no generally accepted evidence-based treatment and there have been no group studies or randomized controlled trials. Thus, a case series of new techniques that may improve awareness in AHP still have a value in the literature and may act as feasibility studies for the future implementation of some of these techniques. This study aims to evaluate the feasibility of applying a specific intervention centred on the execution of actions normally carried out 'in a day-to-day context', and to allow for necessary calibrations before future, larger studies can be successfully designed.

Four chronic AHP patients followed an individualized program aimed at awareness recovery. They were first asked to judge their own ability to perform specific actions (anticipatory awareness) and subsequently to attempt that action. During and after their attempts, they were invited to discuss their performance (emergent awareness) in an exploratory fashion with support from the clinician. The provision of concurrent emotional support was considered

essential in order to assist patients to deal with the potential emotional impact of the realization of their failures and related disabilities. Repeated baseline measures guaranteed the stability of the patients' lack of awareness before the intervention and permitted us to exclude the possibility of spontaneous recovery. A set of pre- and post- intervention assessments (in addition to follow-up examinations) were used to evaluate the effects of the intervention on various facets of motor awareness.

Methods

Participants

Four patients with damage to the right hemisphere and left sided hemiplegia, recruited consecutively over an 18 month period from the Department of Rehabilitation at the Sacro Cuore Hospital (Negrar - Verona, Italy), gave written, informed consent to their participation in the study. The patients were included in the study on the basis of the following criteria: (1) clinical diagnosis of anosognosia for hemiplegia (AHP - Bisiach et al., 1986); (2) total or nearly total contralesional motor deficit (Medical Research Council scale score of 0 or 1; Florence et al., 1992); (3) right vascular hemispheric lesion, as detected by CT investigations and confirmed by neurological and neuropsychological assessments and (4) no known psychiatric or neurological history.

The participants clinical and demographical data are reported in Table 1. They spent varying periods of time (range: 30-85 days) in a Neurological Department before their admission in the Rehabilitation Unit, depending on their general post-stroke clinical condition.

They were recruited for the intervention here described in the chronic phase following onset (stroke-to-assessment interval: 72-144 days) and started the training one or two days after an in depth, specific assessment of AHP (Figure 2B). At that time, neurological examination

revealed that three of them (patients 2-3-4) presented with a visual field deficit, and one (patient 2) also suffered from a serious proprioceptive deficit. He could not identify the position of his left limbs and any movements passively administered to his left arm (Vocat et al., 2010). As shown in Figure 1, the lesions (CT scan) of the four patients were all different. Patients 1 and 3 presented with subcortical ventral lesions, apparently limited to the basal ganglia in the case of patient 3. Patients 2 and 4 showed wide hemispheric damage involving the right fronto-temporal-parietal networks. The lesion analyses indicated that the gray matter structures involved are the insula, the basal ganglia, the temporal superior cortex and the Heschl gyrus. In the white matter, the regions damaged in all the patients are the internal capsule, the sagittal stratum, the external capsule, the superior longitudinal fasciculus and the uncinata fasciculus.

Please Figure 1 and Table 1 near here

While in the Rehabilitation Unit, all of the participants participated in a daily program involving motor training, neuropsychological rehabilitation for neglect and art therapy. Patients 2, 3 and 4 did not do any specialized rehabilitation training for anosognosia during this time.

Nevertheless, during motor rehabilitation, they were stimulated in order to improve their awareness, although this was in an aspecific way. There were also many discussions between the patient and their families, doctors, psychologists and other healthcare professionals about the patient's stroke and the subsequent impairments. As indicated by the baseline results in the Bisiach Scale (Figure 2B and Table 3), these interventions did not induce any changes in awareness. Only patient 1 had previously taken part in a specialized one-off video-based awareness training session (Besharati et al., in press) resulting in a partial recovery of his AHP

(Interview for AHP: from 23 to 8; Vata-m: from 22 to 12 for bimanual actions and from 10 to 7 for bipedal actions – higher scores indicating more severe AHP; Della Sala et al., 2009). The error-based training described here started 26 days after the one-off video-based training session.

While the error-based training took place, all patients continued with their standard rehabilitation for motor function.

The procedures were approved by the local ethics committee (CEP of Verona, prot. N. 39216) and the study was carried out in accordance with the guidelines of the Declaration of Helsinki.

Neuropsychological assessment

The general program and the consecutive phases of the assessments and intervention are shown in Figure 2A.

Please Figure 2 near here

General Assessments. Prior to training, all of the patients underwent a neuropsychological assessment for mental deterioration (MMSE - Folstein, 1975), extrapersonal (BIT – Wilson et al., 1987) and personal neglect (Comb and Razor test - McIntosh, 2000), visual extinction (Peru et al., 2006), verbal memory (Story Recall - Spinnler & Tognoni, 1987), executive functions (FAB – Apollonio et al., 2005) and depression (BDI – Beck et al., 1961). The individual results are shown in Table 2.

Please Table 2 near here

Awareness assessment. In order to estimate the stability of the symptoms of anosognosia, prior to the intervention AHP was periodically evaluated in all patients by means of a clinical test (Bisiach Scale, Bisiach et al., 1986). This baseline (Figure 2A and B, Table 3) allowed us to consider the possibility of spontaneous recovery as minimal. Then, immediately prior to and after training (and also at a three-week or more follow-up session), the following two measures were used to assess intellectual awareness: a formal awareness interview (tapping on general awareness of the disease, awareness of the sensory-motor abilities of upper and lower limbs and abilities in everyday activities, Moro et al., 2011) and the VATA-m test (Visual-Analogue Test for Anosognosia for motor impairment; Della Sala et al., 2009)(see Table 3).

These two instruments, added to the Bisiach's Scale, served as 'external' measures of awareness and changes induced by the error-based intervention. To monitor the training, as an 'internal' measure of anticipatory awareness, the Judgment of Action test was administered (see below *Monitoring of the training*).

Training procedure

The training procedure was taken from a previous study carried out by our group which aimed to identify residual forms of awareness in anosognosic patients (Moro et al., 2011). As in that study, patients were asked to declare if they could perform a specific action with their left or right hand, e.g. putting on their spectacles, or with both hands, e.g. cutting a steak (anticipatory awareness). After the verbal response (Yes/No), they were asked to execute the action (right hand actions were used as control trials). No specific instructions regarding possible strategies were given and patients could organize the execution of the action as they

preferred (even making use of other body parts, e.g. legs, chin). All the patients' comments, expressions of perplexity or questions were recorded. During and after their attempts, they were encouraged to reflect upon the reasons for their failure and to discuss them with the neuropsychologist (e.g. "It is impossible to put on my spectacles because I cannot grasp them with my left hand"; "I have opened this bottle but in fact I used my legs to hold it and my right hand to open it. It is impossible with my left hand"). Errors made during training were not scored by the examiner, who monitored the procedure by means of the original version of the Judgments of Action Test (JAT; Moro et al., 2011 - see below).

With all the patients, in the first part of the training program, only left unimanual actions (U) were employed. When patients showed an improvement in their awareness of their left paralysis, bimanual (BM) actions were introduced (for a list of actions see Appendix 2). Thus, the general procedure was always the same (Figure 2A) but the specific training schedule varied among subjects depending on their individual responses (for more details see section *Individual patient timeline*). A maximum of 5 actions were attempted in each session and, after training, a period of time was dedicated to general comments.

Building and Maintaining a Therapeutic Alliance. Training started only after at least one of the two examiners (VM and CB) had established a good relationship with the patient and a context had been established in which they could express their frustrations and be aware of the examiners' intention to help them. Several times during the training sessions, the examiner asked the patients about their feelings and their will to go on with the task. The sessions were never too long (15-20 minutes) and always started with informal, general conversations about the patient's interests and well-being. When the patients showed signs of emotional difficulties or stress, the training was discontinued and emotional support and empathy was provided. The

number of these interruptions (maximum 2 in a session for S2) varied among sessions depending on the general clinical conditions, and the emotional state of the patients, also due to factors external to the program (e.g. frustration during motor rehabilitation, conflicts with hospital staff or relatives).

Monitoring of the training. During training, anticipatory awareness was measured and recorded by means of the first part of the Judgments of Action Test (JAT – Moro et al., 2011), in which subjects are asked to judge their ability to do actions without attempting to actually perform them. Actions which were different with respect to those used during training were included and the aim was to detect the potential of generalization of awareness effects to actions which they had not specifically been trained for.

Patients reported on their own ability to perform a given action using a score from 0 (= totally impossible) to 10 (= ability to execute the action without any difficulty). The task consisted of judging 23 actions (see Appendix 1 for the list of actions), of which 10 were unimanual (5 for each hand -U), 8 bimanual (BM) and 5 bipedal (BP). Target questions concerned the judgments of left unimanual and bimanual actions. Questions regarding the right unimanual actions were presented as a control to check the consistence of the patients' responses (the expected response in this case was stating a total ability to perform the action). Finally, training was never given in terms of awareness of bipedal actions and any improvement in these actions was considered as a secondary effect of unimanual and bimanual training.

Thus, the JAT served as an internal measure of the training and was periodically administered to the patients: in a session before the beginning of the training session (Pre-training in Figure 2); before the introduction of tasks involving bimanual actions (During training in Figure 2) and

at the end of the last training session (Post-Training in Figure 2). Where possible, the test was also conducted in a follow-up assessment session (Follow-up in Figure 2).

In the last session and the follow-up session, this task was combined with the other general, external measures of awareness described earlier (Vata-m, Bisiach Scale and Interview for Anosognosia).

Comparisons were also made with the clinical reports drawn up by the rehabilitation staff concerning motor and functional recovery, cognitive functions and mood.

Individual Patient Timeline. All the patients were supposed to participate in 5 training sessions a week for at least four weeks. Nevertheless the organization of the sessions and the choice of actions to train for were established for each individual case in accordance with the patient's clinical condition and clinical needs (Figure 2). The number of sessions varied from 10 to 17 and their duration from 15 to 20 minutes. All subjects but S3 participated in both unimanual and bimanual actions training.

Statistical analysis

Statistical analyses were conducted separately for each patient on the JAT answers. The analysis of any improvement in awareness referred only to actions which were impossible for the patients (i.e. left unimanual, bimanual and bipedal actions). These data were collectively analyzed by means of a non-parametric test for paired data, the Friedman test, and the Wilcoxon Rank Sum test with the False Discovery Rate (FDR) correction as a post-hoc test (Figure 3). Post-hoc results were also confirmed by parametric tests (t-tests FDR corrected). In addition, in order to verify how awareness changed for each specific type of action, linear regressions on medians were executed (Figure 4). The use of medians (instead of the means)

was due to the small amount of data available for analysis when the various types of action are separated.

To verify any potential effects of training in other measurements of awareness, we analyzed the scores at the Moro and colleagues Interview by means of χ^2 (corrected Yates) analyses. The Vata-m test scores were compared to the scores of deficit severity indicated by Della Sala and colleagues (Della Sala et al., 2009 and reported in Table 3).

Results

The patients' scores in the JAT are shown in Figures 3 and 4.

 Please Figure 3 near here

Globally, the training program had positive effects on all the patients (S1: Friedman $\chi^2(3)=12.34$, $p=.0063$; S2: $\chi^2(3)=23.43$, $p<.0001$; S3: $\chi^2(3)=40.96$, $p<.0001$; S4: $\chi^2(2)=7.6$, $p=.0224$). Indeed, the comparison between the pre-training evaluation (PRE) and the assessment at the end of training (POST) is significant in three subjects (in Figure 3, S1: $W=146.5$, $p=.0029$; S2: $W=130.5$, $p=.0019$; S4: $W=25.5$, $p=.043$, all FDR corrected). In two of them (S2 and S4) the improvement resists over time, as shown by the follow-up assessment (S2: $W=152$, $p=.001$ and S4: $W=41.5$, $p=.0416$, all FDR corrected). In subject 3, there is no significant difference between the pre- and post-training assessments. Nevertheless, his improvement is shown in the comparison between the pre-training and the follow-up assessment ($W=134.50$, $p=.0006$ FDR corrected).

Crucially, Figure 4 indicates that the behaviour of the patients during training is completely heterogeneous. For this reason, individual results will be presented separately.

Please Figure 4 and Table 3 near here

S1. At the baseline assessment, median scores indicate the same degree of deficit in awareness for paralysis related to left unimanual (U), bimanual (BM) and bipedal (BP) actions (median scores (MAD): U 6.00 (.74), BM 6.75 (.74), BP 6.00 (.74); Figure 4, 113 days). When asked to explain the reasons for his scores, this patient complained of pains in his neck, back and left shoulder. No reference was made to hemiplegia., After the first part of the training program (126 days), the JAT indicates that unilateral training was efficacious and the patient's comments confirm this. For example during the attempt to blow his nose, he demonstrated an improvement in emergent awareness saying: "This hand is crazy, it is paralyzed". When he was requested to turn on a light by pressing a button, he said: "I supposed it would be easier; now I'm seeing it is impossible for me"; "The hand does not do what I want it to". Figure 4 shows that his awareness of left upper limb paralysis continues to increase even with bimanual training (median scores (MAD): U= PRE: 6.00 (.74), after unimanual training (U): 4.00 (1.48), POST: 2.00 (0), F: 2.00 (2.97)).

In contrast, his awareness of deficits in bimanual and bipedal actions did not improve with training (Figure 4). This finding explains the lack of improvement in the follow-up assessment. Indeed, in Figure 3 it seems that all the recovery gained with the training has been lost over time. In reality, the absence of differences in scores between the baseline and the follow-up is

due to bimanual and bipedal actions as the patient's recovery was limited to unimanual actions.

Qualitative analyses of the patient's comments confirmed this result. When bimanual actions were requested, the attempt to activate the left upper limb was always evident and the patient seemed to be surprised about his failure. He often commented: "Yes, I'm managing to do it".

The patient's partial recovery was confirmed by the Vata-m test (Table 3). and S2. For this patient, the effects of training seem generalize to all types of actions. At the pre-training assessment, the scores indicated slightly more awareness for unimanual than bimanual or bipedal actions. Nevertheless, as the first unilateral part of the training program started, the trend towards recovery was evident not only in unimanual but also in bimanual and bipedal actions. Thus, while the scores in all the subsequent assessments appear to be significantly different from the pre-training scores (PRE vs. U: $W= 126, p= .0029$ PRE vs. POST: $W= 130.5, p= .0019$, PRE v. F: $W= 152, p= .001$ – Figure 3), no significant differences are present during the various parts of the training program (U v. POST $W = 44, p = .556$; U v. F: $W = 66, p = .0926$; POST v. F: $W = 51, p = .0864$). This trend might indicate a recovery of anticipatory awareness. His comments are worth noting. For example, when asked to close a coffee pot, before attempting the action he declared: "to do this, I need the other hand. With my right hand alone I cannot...". When faced with new actions to perform he asked: "What do you think if I do not try to do this action?" or "Am I the worst of your patients?".

In addition, when he attempted to perform an action for the first time and discovered that he was not able to, he never needed to make another attempt since he perfectly remembered his previous performance and declared that he could not do it. Thus, each action was tried only once.

The Interview for Anosognosia scores (Pre-training vs. Post-training: $\chi^2_{(1)}=7.94$ $p=.005$; Pre-training vs. Follow-up: $\chi^2_{(1)}= 3.359$, $p = .067$) and the Vata-m confirm this recovery (Table 3).

S3. For this subject, the issue concerning the emotional components of AHP arises in an explicitly marked fashion. Indeed, the trend of his responses is a little particular, as shown by two elements: i) the scores recorded after the first part of the training program (98 days) are worse than the baseline scores and ii) the sudden interruption of training after only 10 days (Figure 3).

In the baseline assessment, the analyses of the patient's responses to JAT questions indicated a certain degree of ambiguity. For example, when asked if he could clap his hands, he replied: "It is not easy. You need to synchronize well!". In response to being asked if he could drive, he said: "It depends: why would I want to drive?" And when asked if he could tie a knot, he replied: "it depends on the kind of the string".

During training he always attempted to perform the actions, repeating: "They are not so hard". When the examiner asked: " Do you think you can do it?" his answer was: "Yes, I think so!" or "Now you will see" and he obstinately continued to try without giving up.

Training sessions were very hard for him from an emotional point of view: he did not want to abandon his attempts and after failing, he asked the examiners if he could try some other actions. At the end of the tenth session and during an attempt to turn on a light, the examiners expressly asked S3 to stop the session as it appeared to be too stressful for him. The patient did not respond but, after a moment of silence, he started to cry and said: "This situation is cruel. It is too easy to speak about awareness for people who are able to walk and to do things". He stated: "I feel as if I was sleeping. Do you have something to wake me up? Do you agree that it

is easier for me to think that my hand is moving and functioning rather than to admit it is not moving?"

This emotional crisis seemed to have a releasing effect: in an informal conversation he admitted all his motor deficits and was emotionally supported. It was considered best to discontinue the training given the patient's increased awareness and his mood. The patient only continued his rehabilitation sessions for neglect and motor recovery.

37 days later, the patient agreed to a follow-up assessment. As shown in Figure 3, his awareness of motor deficits persisted over time. This was confirmed by the results in the Interview for Anosognosia (Pre-training vs. Post-training (and Follow-up): $\chi^2_{(1)} = 11.95$, $p = .0005$). Moreover, in line with the clinical impression and with previous studies (Fotopoulou et al., 2009), the patient's increased awareness of paralysis was associated with a more negative mood.

S4s scores in the interview for anosognosia indicate a moderate degree of deficit in awareness (Table 2): . The patient did not realize that his paralyzes involved normal daily activities indicating a lack of anticipatory awareness (DLA, in Table 2). His response to the training program was immediate (Figure 4) and when he failed to execute an action, he did not need to repeat similar actions because his judgment indicated that he realized they were impossible for him (anticipatory awareness).

Figure 4 shows a better recovery of awareness for unimanual and bipedal actions with respect to bimanual actions. In reality, in this case, the bimanual actions scores indicate the successful functional strategies that the patient employed to deal with his disabilities. For example to detach a piece of adhesive tape, he took hold of his left hand with his right hand and placed his

left index finger in the central hole of the roll of tape. After this (still using his right hand), he placed the roll under his chin to block it, still with his left index finger in the hole. At this point, he used his right hand to tear off a piece of tape. These compensatory strategies represent a confirmation that some awareness has been recovered, as was also confirmed by the Interview for Anosognosia ($\chi^2_{(1)} = 5.03$, $p = .025$) and the Vata-m.

Discussion

Our data seem to indicate that a training program focusing on attempts to perform actions followed by an analysis of any errors made, can contribute to the recovery of awareness of motor deficits in some patients affected by AHP. Indeed, although each of our four patients responded to the program in a different way, all improved their awareness and maintained their recovery over time. This may represent a potentially important result, since evidence of effective treatments for AHP is limited (Kortte & Hillis, 2011; see Prigatano & Morrone-Stupinsky, 2010; Jenkinson et al., 2011).

Transient improvement of awareness has previously been demonstrated as an effect of vestibular stimulation (Cappa et al., 1987; Ramachandran, 1995) or as a result of a combination of various techniques, e.g. optokinetic stimulation, adaptation to the prismatic shift of the visual field to the right and transcutaneous electrical nerve stimulation (Beschin, Cocchini, Allen & Della Sala, 2012). To date, the only clinical approach able to induce a lasting remission of AHP is that which makes use of the patient's self-observation in a third person perspective (Fotopoulou et al., 2009; Besharati et al., 2014). When judgment involving 3rd-person and off-line self-observation are spared, this experimental manipulation can facilitate 1st person awareness (Fotopoulou et al., 2009).

Our results support the suggestion that residual forms of awareness may be very useful for inducing or facilitating the recovery of explicit aspects of awareness. Indeed, our program focuses on a specific residual form of awareness (emergent awareness, Crosson et al., 1989) in order to help patients recognize their motor deficits. In other words, our results indicate that patients may improve their ability to recognize their deficits when faced with their disabilities (emergent awareness) and sometimes they may anticipate the effects of paralysis (anticipatory awareness). Thus, emergent awareness might in these cases represent a resource of progressing from a state of intellectual unawareness to anticipatory awareness. A previous study showed that intending to act and/or actually acting may modify explicit, verbal knowledge of deficits in some AHP patients (Moro et al., 2011). Although the functional mechanisms of this effect are currently unknown, we speculated that an intention to act combined with the patient being informed of his/her failure may bring about an amelioration in the defective system that matches prediction with expected and actual sensory consequences of actions (Blakemore et al., 2002; Fotopoulou et al., 2008). To date, the neural correlates of emergent awareness have not been fully identified. The first evidence (Moro et al., 2011) indicates that emergent awareness may be associated with a large network involving the insula, the Rolandic operculum, the superior temporal gyrus and the white matter in correspondence with the posterior and superior tracts of the corona radiata and the cortico-spinal tract. Among our four patients, the lesions of S1 and S3 do not seem to involve these structures. Conversely, S2 and S4 presented with serious damage both to the Rolandic operculum and the Insula, but the white matter tracts involved in emergent awareness were at least in part spared. Crucially, in none of the patients do the lesions involve the hippocampus, parahippocampal cortex and amygdala. Due to the main role of these structures in the

episodic memory, this certainly represents a pre-requisite necessary in order for the patients to learn from the experience of action attempts and errors.

It is worth to note that although the proposed training focuses on the execution of actions, it involves multiple strategies. In fact, during each attempt to perform actions, the patients were requested to pay attention to their movements, to comment on them and to analyze the possible reasons for their failure. In addition, emotional support was given every time the patients appeared disappointed and frustrated. Indeed, as was clearly demonstrated in the case of patient 3), observing the failure of own attempts to act is potentially a very frustrating experience which may induce reactions of avoidance, isolation and personal detachment if emotional support is not provided. Patient 3's training was interrupted due to a catastrophic emotional reaction following a sort of "explicit discovery" of his paralysis. These reactions may be very important since they may, as in the case of this patient, constitute a crucial step towards a recovery of awareness. Certainly when making decisions about whether it is opportune to rehabilitate AHP patients, a careful cost/benefits equation is needed. When patients do not have any chance of improving their motor and functional abilities, anosognosia may also paradoxically be considered as an emotional strategy for coping. Nevertheless, AHP significantly obstructs rehabilitation efforts and impedes long-term functional outcomes (Pia et al., 2007; Gialanella, Monguzzi, Santoro & Rocchi, 2005; Jehkonen, Laihosalo & Kettunen, 2006) even when the motor deficits present would permit a functional recovery. When the clinical, cognitive and motor conditions of the patient are good enough to permit a certain degree of functional recovery and autonomy, we consider that all potential strategies need to be attempted in order to improve awareness.

Due to its multiple aspects (i.e. attempting actions, verbal analysis of the performance and emotional support), the error-based training may turn out to be an instrument capable of reducing the tendency of AHP patients to overestimate their performance (Marcel et al., 2004). Moreover, it seems to act on all three components of the ABC model (Vuilleumier, 2004); when patients are requested to carefully observe their attempts to perform an action, they seem to become able to 'Appreciate' their own deficits and 'Check' the results of their performance. In addition, the analysis and discussion regarding the reasons for failure may help patients to rethink their previous 'Beliefs' concerning their own motor functions (Fotopoulou, 2012; Vocat et al., 2013).

AHP can be linked to a lack of balance between 'prior beliefs' (predictive internal models of the world formed on the basis of previous learning and genetics; Friston, 2006) and 'prediction errors' (discrepancies between expected and actual inputs based on ascending interoceptive and exteroceptive signals, e.g. Schultz & Dickinson, 2000). We speculate that the intense, difficult experience of failure might lead the patients to feel uncertain about their motor abilities and to doubt their beliefs. Direct and explicit confrontation with their deficit would make them rethink their beliefs so that they become more consistent with their "new" condition (Fotopoulou, 2013; Fotopoulou et al., 2009).

Episodic memory seems to play an important role in the efficacy of training. The role of memory in anosognosia for cognitive deficits has been noted in particular in Alzheimer's Disease (Morris & Mograbi, 2013). In the Cognitive Awareness Model (Agnew and Morris, 1998; Mograbi & Morris, 2013) incoming knowledge concerning the performance of tasks or activities is monitored by comparator mechanisms that contrast this information with that stored in a Personal Database, a specialized storage of long lasting memory representation

concerning the self. When there is a mismatch between the information derived from the immediate experience and the longer-term stored self-knowledge, the output of this comparison leads to an updating of the Personal Database. The resulting information is released via a further mechanism, the Metacognitive Awareness System, that provides consciousness of decision making. All these processes involving comparisons and updating of the Personal Database require multiple preserved memory abilities (Morris & Mograbi, 2013). Although AHP has been linked to lesions in specific cortico-subcortical connections of the awareness network, unlike the more cortical lesions connected to anosognosia in Alzheimer Disease (Mograbi & Morris, 2013), disorientation and memory disorders may also hinder the process of learning from experience in AHP patients.

The patients in this study did not suffer from deficits in verbal memory and they remembered the experiences of the previous sessions correctly. This probably helped in the metacognitive analysis of their own abilities and deficits, and the generalization of learning was confirmed by those who showed anticipatory awareness when they declined to perform an action as they had failed with another similar action the day before (cases 2 and 4)

The improvement in awareness seems to be easier for unimanual than bimanual actions. After specific bimanual training, patient 1 appeared to be aware of his inability to perform unimanual but not bimanual actions. A clinical observation of his performance suggested that he continued to plan bimanual actions as if he could move both hands. In other words, while for unimanual actions the motor plans concerning impossible actions were in some way replaced by new, different plans (which activated the healthy hand or another body part), this did not happen with bimanual actions where the pre-stroke plans of action resisted over time.

The idea that attempts to act may improve awareness would be also supported by the observation that most of AHP patients tend to believe that they can perform actions that they have never tried after the onset of paralysis and actions that they habitually did prior to onset, e.g. driving a car, riding a bicycle. For this reason, we feel that it could be crucial to integrate such error-based action training in more general programs of motor awareness rehabilitation (Gialanella et al., 2005; Hartman-Maeir et al., 2001; Jehkonen et al., 2006).

This study is not without limitations. Firstly, the small number of patients does not permit the generalization of the effects of the training to the multiple possible manifestations of AHP. Indeed, the aim of the study was to evaluate the feasibility of the intervention and to furnish information which may be useful in order to replicate the program with other patients in larger sample. Certainly, it is possible to observe that all our patients seemed to benefit from the training, although in different ways.

Although for ethical and practical reasons a control group was not recruited, there are some reasons that seem to indicate that the improvement might be associated with the training sessions: i) the patients' stroke- training intervals indicate that all the subjects were recruited in a post-acute or chronic stage; ii) the intervals between admission to Rehabilitation Unit and the start of the program allowed us to assess the stability of anosognosic symptoms by means of repeated baseline measures; iii) aspecific interventions, by means of interviews and discussions about clinical conditions, had previously been carried out during the rehabilitation sessions for motor recovery, without inducing any changes in awareness. Finally, S1 had previously participated in another specific training program for AHP which had resulted in a partial recovery of awareness. The gradual resolution of this patient's symptoms supports the idea that AHP is not an all-or- nothing phenomenon and that simply waiting for spontaneous

recovery may not be sufficient. Overall, in clinical practice this case indicates the possibility of combining various different approaches in the different phases of recovery. A closer link up with physiotherapists would also have permitted us to carry out training for pedal and bipedal actions, which would have additional positive effects on motor recovery. Finally, a more specific analysis of abilities in day to day activities would have enabled us to identify more easily any effects of generalization in the recovery of awareness. Despite these limitations, our results suggest that acting on emergent awareness and in general on residual forms of awareness (Fotopoulou et al., 2009; Besharati et al., in press) may represent a valid way to increase verbal and explicit awareness in patients affected by AHP. Further clinical and experimental data will permit a better understanding of the effects of specific training programs in recovery of awareness and of possible integration of different programs in order to respond in the best possible way to patients' rehabilitation needs.

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Captions to tables and figures:

Table 1. Socio-demographic and clinical data. HD = Handedness (Briggs and Nebes's laterality inventory, 1975); Educ. Yrs = Years of Education; G = gender; VF def = Visual Field Deficit (+) = present; (-) = not present; MRC = Medical Research Council Scale for motor impairment for upper limb (UL) and lower limb (LL); Prcp = proprioception test (Vocat et al., 2010); Hae= haemorrhagic; H= Hydrocephalus; I= Ischaemic; F = Frontal; T = Temporal; P= Parietal; BG = Basal Ganglia. In bold are the pathological scores according to references reported in the text.

Figure 1. Neuroimaging examinations. Select transverse cuts show the patients' lesions (with white boundary lesion demarcation). Right hemisphere is on the right side. We superimposed each patient's lesion on the Automatic Anatomical Label template provided with MRIcro and calculated the number of lesioned voxels in each anatomical region of interest. The tables inserted on the lower left and right sides of the figure show the percentage of lesioned tissue for each damaged area.

Table 2. Patient scores in neuropsychological assessment. MMSE = Mini-Mental State Examination; BIT = Behavioural Inattention Test, behavioural subtests; Canc = line cancellation; C&R = Comb and Razor Test; VE left = Visual extinction to double stimulus; Verb M = Story

Recall; FAB = Frontal Assessment Battery; BDI = Beck Depression Interview; nr = not reported.

In bold are the pathological scores according to references reported in the text.

Figure 2. A. The consecutive phases of the intervention are represented. These were identical for all patients in sequence, but the intervals between lesion onset and the consecutive phases varied depending on each patient's clinical conditions and individual responses to the training.

B. Individual intervals between lesion onset and the consecutive phases of the training. Note that the second part of the training (Bimanual actions) started when the JAT confirmed the examiner's clinical observation indicating the patient's improvement in unimanual actions. The numbers indicate the intervals in days.

Figure 3. Progression of scores for the Judgments of Action Test in the different phases of training. The patients' scores are shown as collected at the pre-training assessment (PRE), after unimanual training (U), at the end of training (POST) and in the follow-up (F) assessment. The bar plot represents the median and the median absolute deviation (MAD – median of the differences from the median) of JAT aggregate scores in Unimanual Left, Bimanual and Bipedal actions for each patient. *: $p \leq .05$; **: $p \leq .01$; ***: $p \leq .001$.

Figure 4. Recovery of awareness trends for each type of action. Linear regression on JAT median values for each patient and each type of action is reported. Unimanual Right scores are showed as a control.

Table 3. Schedule of the sessions of Assessment of AHP. BS = Bisiach's scale. The scale was administered at various intervals between the admission in the Rehabilitation Unit and the Pre-training assessment (Figure 2) and indicated that no changes in awareness occurred in this time (Baseline). AHP = Anosognosia for hemiplegia Interview (Moro et al., 2011); G = General

questions (score 0-2); UL= Upper limb referred questions (score 0-9); LL = Lower limb referred questions (score 0-8); DLA = Daily life activities questions (0-4); VA – bim = VATA-m, bimanual actions (*3.3-8.0 = Mild AHP; ** 8.1-16.0 = Moderate AHP; ***16.1-24.0 = Severe AHP; Della Sala e al., 2009); VATA-m, bip = bipedal actions (*3.5-4.0 = Mild AHP; **4.1-8.0 = Moderate AHP; *** 8.1-12.0 = Severe AHP, Della Sala et al., 2009). In bold are the pathological scores.

Appendix 1. The actions performed in the Judgments of Action Test.

Appendix 2. The actions performed during training.

Appendix 1. The actions performed in the Judgment of Action Test

<i>Unimanual left and right</i>	<i>Bipedal</i>
Drinking	Walking
Combing hair	Jumping
Brushing teeth	Cycling
Writing	Climbing the stairs
Opening a door	Driving
<i>Bimanual</i>	
Tying a knot	
Clapping one's hands	
Dealing cards	
Rowing	
Catching a ball	
Washing hands	
Uncorking a bottle	
Cutting a steak	

Appendix 2. The actions employed during the training

<i>Unimanual left</i>	<i>Bimanual</i>
Brushing clothes	Sharpening a pencil
Using a spoon	Uncapping a bottle
Wiping with a cloth	Inserting a letter in an envelope
Shaving	Lighting a candle
Cutting with scissors	Lacing up shoes
Putting on glasses	Peeling an apple
Scratching forehead	
Touching an object	
Blowing	
Leafing through a newspaper	
Turning on a lamp	
Turning a tap on	
Screwing the top off a bottle	