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Rehabilitation and Modulation aimed at ameliorating awareness in Anosognosia for Hemiplegia

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SUMMARY

Background: Anosognosia for hemiplegia is a multifaceted syndrome that has a detrimental impact on the patient. Various theories based on behavioural and neuroanatomical data have been proposed to explain the mechanisms underlying the symptoms. These approaches have resulted in the development of a number of different procedures aimed at reducing symptoms or enhancing residual awareness. The article reviews rehabilitation attempts and their effects on individual cases and groups of patients.

Material/ Methods: A selection of material was made using indexed articles published between 1987 and 2019. The inclusion criteria were: i) the presence of a neuropsychological assessment and ii) the presence of one or more methods specifically used to reduce AHP symptoms, or to enhance residual forms of awareness.

Results: The review indicates that intervention procedures have moved from bottom-up to more cognitive and metacognitive approaches. In fact, initially anosognosia for hemiplegia was considered to be a co-occurrent symptom of other neuropsychological conditions (e.g. spatial neglect) and interventions were borrowed from the rehabilitation techniques that had had success in relieving these other disorders. When anosognosia was identified as an independent syndrome and residual forms of awareness were demonstrated, procedures attempting to modulate awareness started to focus on specific components of the disease, such as visual perspective, motor monitoring and the updating of beliefs.

Conclusions: Although further research is needed in this field, the most recent approaches seem to give more stable, lasting results than earlier methods. A timeline for interventions relating to anosognosia is suggested, and ethical issues are also discussed.

Keywords: anosognosia for hemiplegia; implicit awareness; emergent awareness; anosognosia theories; rehabilitation methods; rehabilitation ethical issues

INTRODUCTION

Anosognosia is defined as the lack of or reduction in awareness in a patient of his or her own disorder [1,2]. In the context of this paper, the disorder in question is the paralysis of one side of the body (hemiplegia). Data on the prevalence of anosognosia for hemiplegia (AHP) in right brain damaged (RBD) patients are not consistent, ranging from 15% [3] to 54.1% [4]. A first reason for such a wide variability depends on the method used to assess patients. Della Sala and colleagues[5] found that the frequency of AHP in a group of left-brain damaged patients can range from 10% when assessed by means of a structured interview [6] to 40% when the patients are asked to evaluate their ability to perform specific bimanual tasks (e.g. VATAm [5]).This should not be surprising as there are different measures for the various different aspects of awareness. For example, some studies have reported that patients who verbally admit their motor deficits may then attempt bimanual tasks as if they can in fact use both hands [7,8,9] or even attempt potentially dangerous tasks [10,11].

In contrast, Marcel and colleagues [7] reported on patients who verbally denied their impairments but then adopted strategies to compensate for their hemiplegia in everyday tasks. Within this scenario, every attempt to establish the frequency of AHP following a brain lesion needs to take into account the multifactorial aspects of this syndrome. The lesion onset/assessment interval is also crucial to establish the prevalence of AHP, since it tends to attenuate or resolve itself within a few weeks of the brain damage [12,13]. In a longitudinal study, Vocat and colleagues [14] assessed evidence of AHP in 58 right-brain damaged patients over 6 months. Three days after the lesion, 32% of the patients showed anosognosia for their hemiplegia. This percentage decreased to 18% in the second assessment, 7 days after the brain lesion, and it dropped to 5% in the 6-month follow-up. This variability in awareness is further complicated by the fact that motor impairment tends to improve, and patients are increasingly exposed to information related to their impairment.

Therefore, it remains unclear whether there has been a clear improvement in the patient's awareness or there are other factors which may mitigate the most evident manifestations of an underlying lack of awareness [8,13]. Moreover, despite the fact that spontaneous recovery is relatively frequent, patients who are diagnosed with AHP tend to have a negative prognosis involving longer hospital stays and a reduced likelihood of living independently after being discharged [15,16], indicating a growing need to find ways to enhance awareness. Within this complex scenario, theoretical interpretations of AHP are crucial to guide potential interventions and it is therefore important to briefly consider some of the theories on AHP that have had a major impact on rehabilitation methods.

Due to the frequent co-occurrence of disorders, AHP was initially considered as a symptom associated with spatial neglect [17] or the consequence of other cognitive deficits such as amnesia [18], or executive dysfunctions [19,20]. The first neuroanatomical data seemed to support these hypotheses. Extensive cortical and subcortical fronto-parietal damage, encompassing areas underlying other cognitive functions, was considered to be the most frequent anatomical-correlate [4]. However, dissociations between AHP and these other disorders have been described and as a result AHP then started to be considered as an independent syndrome [21].

A theory was proposed suggesting that AHP may arise from the patient's inability to form motor intentions [22]. Nonetheless, in a study where muscular activity was recorded during patients' attempts to move paralysed upper limbs [23], it was demonstrated that motor intention is spared in AHP patients. The hypothesis was thus formed that AHP disorders involve the system relating to motor monitoring rather than motor intention. This idea was supported by evidence of a role played by the premotor cortex in the syndrome [24] and by further behavioural results [25,26,27,28]. However, this does not explain all of the symptoms of AHP, such as the inability to update delusional beliefs based on social feedback or to recognise difficulties experienced in day to day activities. In addition, neuroanatomical studies show that cortical areas other than the premotor cortex play a role, in particular the right insula [29]. For this reason, and due to the fact that the insular cortex plays a crucial role in all subjective feelings and bodily self-awareness, AHP has mainly come to be considered as a specific bodily-self disorder [30].

A contribution on the part of emotional processes has also been considered to be significant since the middle of the last century [31]. Weinstein and Kahn [31,32] suggested that the lack of awareness is a subconscious repression which is used as a defence mechanism by the patient in order to deal with the realisation of their new condition involving disability which can cause shock or depression. Alternatively, this lack of emotional reaction has been considered as a direct consequence of damage to the right (frontal) hemisphere, regarded by some authors as being specialised in the processing of negative withdrawal-related emotions [33,34] or for emotion regulation [35,36,37].

At the end of the last century, it became clear that none of these theories alone could explain the multifaceted, complex nature of AHP. A more complex model was proposed by Vuilleumier (the ABC model [38]) in which the author suggested that awareness relies on a set of neuropsychological functions mediating three different processes:

- Appreciation;
- Belief;
- Check.

Appreciation may be impaired a a result of sensory deafferentation and/or neglect which would in effect prevent the patient from appreciating his/her deficits. However, AHP only emerges when additional deficits in cognitive or affective functions occur in association with the individual's incapacity to Check and verify the distorted experiential evidence and delusional interpretations. These processes are necessary in order for patients' beliefs concerning their paralysis to bealtered [38]. The role played by AHP patients'resistance to updating their beliefs concerning their own body and motor abilities has been discussed in the most recent models concerning AHP [39,40,41]. This failure to update self-referred beliefs may be caused by a functional disconnection between the regions processing top-down beliefs about the self and those processing bottom-up errors regarding the current state of the body [34,42].

The multi-componential nature of AHP is supported ina recent anatomical study on a large group of RBD patients [43]. The study used advanced structural neuroimaging methods and identified three neural systems that contribute to AHP when disconnected or directly damaged: the pre-motor network (for deficits in monitoring motor signals and learning from action failures), the limbic system (for alterations in emotional and memory processing and self-referential, introspective states [44]) and the ventral attentional system (for deficits in appreciating the salience of stimuli referring to paralysis [45]).

Understanding the nature of this complex network may help us to understand why AHP patients sometimes display partially differing symptoms and respond in different ways to experimental modulations and interventions.

The aim of this study is to review the literature on anosognosia focusing on experimental and clinical procedures implemented over time with the aim of reducing AHP symptoms. Procedures, methods and results will be discussed in the light of explanatory reference theories relating to AHP and, when available, neuroanatomical evidence.

Evidence acquisition

A selection of material was made from the indexed articles in the *Science Direct* and *Pubmed* databases published between 1987 and 2019. 'Anosognosia and rehabilitation' and ‘anosognosia and remission’were used as the key terms. The search identified 952 potentially relevant articles. After the removal of doubles and non-English literature, a selection based on the titles was made. Papers regarding disorders other than stroke or other forms of anosognosia (e.g. anosognosia in dementia and traumatic brain injury; anosognosia for apraxia; anosognosia for memory impairment or behavioural disorders) were excluded. In this way, 48 articles remained (Figure 1 for details).

The following **inclusion criteria** were applied to these articles:

- the presence of a neuropsychological assessment and
- the presence of one or more methods specifically used to reduce AHP symptoms, or to enhance residual forms of awareness in at least one patient.

The **exclusion criteria** were:

- anosognosia for deficits other than hemiplegia;
- anosognosia in degenerative syndromes or in developmental disorders;
- theoretical papers
- descriptions of spontaneous recovery from the symptoms. In this way, a further 30 papers were excluded (Figure 1 for details) and 18 papers remained.

Finally, 6 cross-reference papers were added, thus a total of 24 papers (11 group studies and 13 single case studies) were considered in the final review (Table 1).

Evidence synthesis

The 24 papers included in the final selection presented various rehabilitation/ modulation methods that were considered in detail and classified as:

- neurophysiological stimulation;
- neuromodulation techniques or
- cognitive and emotional interventions (see Table 2).

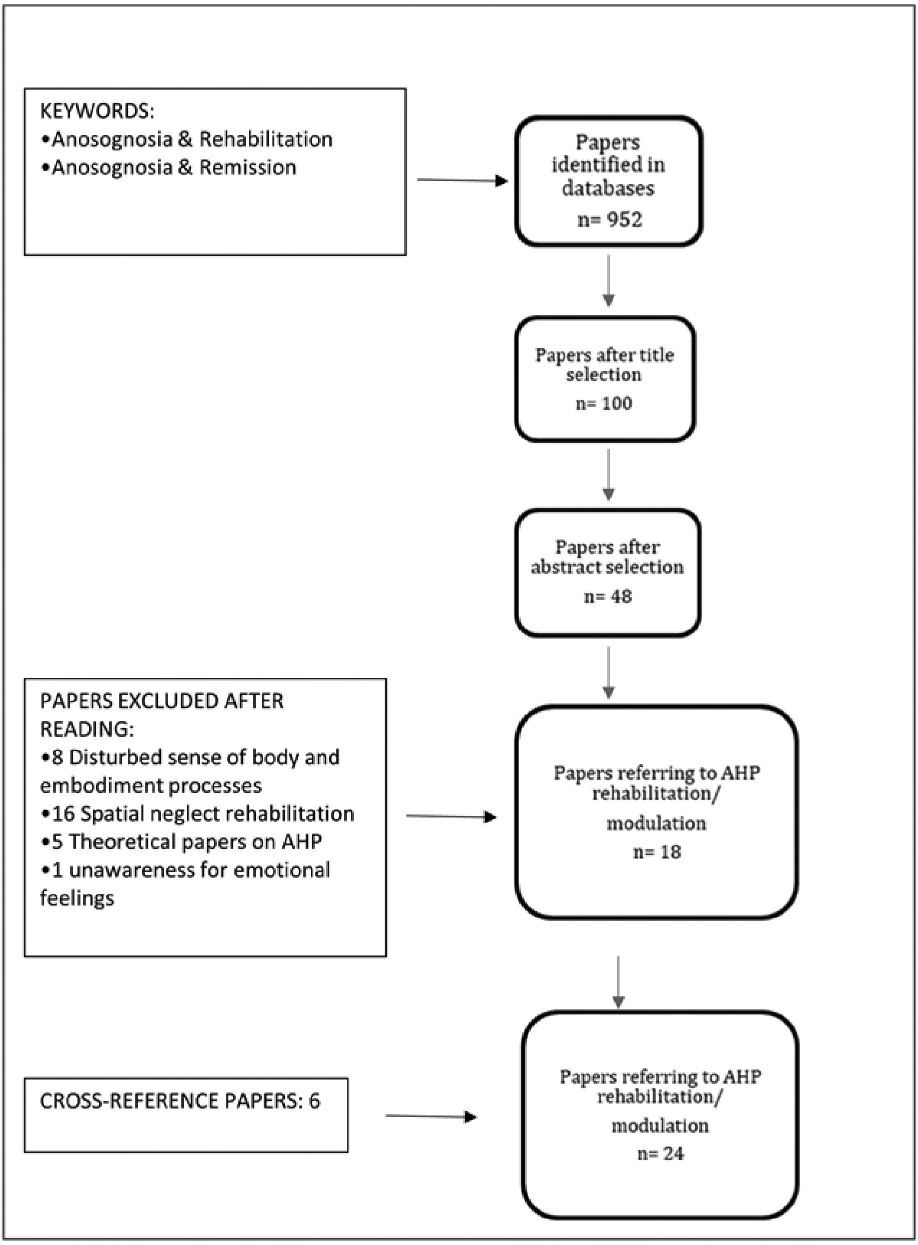

Figure 1. Timeline relating to the selection of papers. AHP = Anosognosia for Hemiplegia.

Table 1. Studies on rehabilitation or the modulation of AHP. Data regarding the patients described in the articles reviewed are reported, along with the interventions and main results. RBD = right brain damaged patients; LBD = left brain damaged patients; AHP = anosognosic patients; HP = hemiplegia; F = female; M = male; SD = standard deviation; VATAm = visual-analogue test for anosognosia for motor impairment; TENS = transcutaneous electrical nerve stimulation; EEG = electroencephalography; DSO = disturbed sensation of limb ownership; ECT = errand choice test

Authors	Participants	Disorders	Sample (gender, age; onset)	Intervention	Main Findings
Cappa, Sterzi, Vallar, Bisiach 1987	2 case studies (RBD)	Severe neglect	4 AHP, (2F, 69-71; 2M, 48-57)	Vestibular Stimulation (20cc ice water – warm water in one patient – for 1 minute)	Temporary remission of personal and extrapersonal neglect, AHP: 2 = unaffected; 1= temporary remission; 1 = long term remission.
Rode, Charles, Perenin, Veghetto, Trillet, Airmard 1992	Single case study (RBD)	chronic neglect, somatoparaphrenia, logorrhea	1 AHP (F, 69; 6 months post-onset)	Vestibular Stimulation (60cc cold water), 2 stimulations 48 hours apart	Temporary remission of all ailments.
Ramachandran, 1994	2 case studies (RBD, reported also in Ramachandran, 1995)	hemiplegia	1(F, 79; 4 weeks post-onset) 1 (F, 76; 2 weeks post-onset)	Mirror box, Bimanual v. unimanual actions, Reaching a tray with glasses on it, Vestibular stimulation (10 cc ice-cold water)	1 patient shows implicit awareness (choosing unimanual action and reaching the tray in the middle). The same patient shows temporary remission with vestibular stimulation 30 minutes after but not 8 hours after treatment
Ramachandran, 1995	4 case studies (reported also in Ramachandran 1994 and 1996)	AHP, hemiplegia, neglect	4(F, 65-78; acute phase)	Bimanual v. unimanual actions, Mirror box	The 3 patients who perform this task choose bimanual actions (i.e. no evidence of implicit awareness). No improvement in AHP in a patient tested with mirror box
Ramachandran, 1996	5 case studies (2 reported also in Ramachandran, 1995)	hemiplegia, spatial neglect	5 AHP (4F, 65-78; 1 M = 56)	Analysis of clinical conversation, Injection of placebo (saline solution) to 'induce' local and temporal paralysis	Remarks during conversation, indicating some degree of awareness (e.g. "perverse sense of humor") After injection of placebo, patients describe their left limb as paralysed (not for right arm)- emotional denial
Berti, Ladavas, Della Corte, 1996	34 RBD (25 HP, 9AHP)	severe hemiplegia, personal and extrapersonal neglect	RBD (49-81, days post-onset = 30-545)	Interview, judgment of capacity to perform upper limb and lower limb actions, judgment before and after attempts to act	During interview, 1 AHP acknowledges motor difficulties for his upper limb and 1 only for the lower limb. 2 AHP show emergent awareness in pre-post action judgments comparison 2 AHP increase awareness after upper limb action attempts (emergent awareness)

Rode, Perenin, Honorè, Boisson, 1998	9 RBD (AHP) 9 LBD	Personal neglect, somatoparaphrenia,	AHP (6F, 52-71; 3M, 63-67) LBD (4F, 40-63; 5M, 48-73)	Vestibular Stimulation (60cc cold water) contralesional ear	8 RBD = temporary amelioration in AHP and personal neglect; 7 RBD increase motor performances; 9 LBD = unaffected
Marcel, Tegnér, Nimmo-Smith, 2004	42 RBD (13 AHP), 22 LBD (2 AHP for leg deficits), 24 healthy controls	Hemiplegia, hemianestesia, extrapersonal and personal neglect	42 RBD (mean age 71.3 - SD=9.0; days post-onset = 55.7 – SD=56) 22 LBD (mean age 71.9 – SD= 8.5; mean of days post-onset = 79.1 – SD=155)	Judgment of capacity to perform actions (tying a knot, clapping hands, shuffling cards) before and after attempts to act	Before action, 24 RBD patients overestimate their abilities in bimanual tasks and 7 in bipedal tasks; 1 LBD overestimates his bimanual abilities Some patients improve awareness after action attempt (8/17 = clapping hands, 7/12 = shuffling cards, 11/21 = tying a knot)
Nardone, Ward, Fotopoulou, Turnbull, 2008	7 RBD (2 HP, 5 AHP) 20 healthy controls	Hemiplegia, spatial neglect	(3F, 4M, mean age 70.7 – SD 11.5)	Attentional-capture paradigm (Dot Probe Task). Responses to a coloured probe ignoring the word that appeared before	AHP show increased latencies to hemiplegia-related words. HP show reduced latencies for emotionally threatening words
Fotopoulou, Rudd, Holmes,Kopelman, 2009	Single case study (AHP)	and spatial neglect	1 (F, 67; days post-onset = 22)	Video rehabilitation	Immediate and lasting AHP recovery
Cocchini, Beschin, Fotopoulou, Della Sala, 2010	30 RBD, 26 controls (19 healthy controls, 7 with orthopedic injury)	Motor deficits, extrapersonal and personal neglect	RBD (11F, 19 M, 29 -87; days post-onset range = 13–149) Controls (14F, 12 M, age range: 32-88)	Execution of bimanual actions (implicit awareness) v. explicit awareness (VATAm)	5 RBD: explicit and implicit AHP; 8 RBD = explicit AHP; 2 RBD = implicit AHP
Fotopoulou, Pernigo, Maeda, Rudd, Kopelman, 2010	14 RBD (7 AHP, 7 HP)	Motor deficits, spatial neglect (1 somatoparaphrenia)	7 RBD (age 56.86 - SD = 18.52; days post onset = 28.29 – SD =8.4) 7 AHP (age 64 - SD = 6.06; days post onset = 18.71 – SD =19.63)	Implicit awareness test consisting of a verbal inhibition task which included emotionally negative non-related deficit context, deficit-related contents or emotional neutral contents	6 AHP are slower than HP in performing the task only for sentences with emotional deficit-related context

Moro, Pernigo, Zapparoli, Cordioli, Aglioti, 2011	24 RBD (12 AHP, 12 HP)	Severe HP, Extrapersonal and personal neglect	AHP (4F, 47- 78, 8M, 40-73; days post-onset = 22-177) RBD (2F, 64-79; 10 M, 51-75, from 27 to 210 days post-onset)	Execution of bimanual actions (implicit awareness) Judgment of proficiency before and after execution (emergent awareness)	5 AHP show implicit awareness; 3 AHP show emergent awareness during actions.
Prigatano, Matthes, Hill, Wolf, Heiserman, 2011	Single case study (RBD)	severe HP, neglect, cortical blindness, somatoparaphrenia	1 AHP (F, 51; from 18 days post-onset to 1-year follow-up)	Assessment of AHP and HP (other than awareness for cortical blindness)	improvement in AHP associated with the ability to move the left index finger for the first time
Beschin, Cocchini, Allen, Della Sala 2012	2RBD, 3LBD (all AHP)	Extrapersonal Neglect	5, (4F, 1 M, 44-75; days post-onset = 50-70)	Prism Adaptation, Optokinetic stimulation, Transcutaneous Electrical Nerve Stimulation	1 RBD improves AHP after each treatment (not neglect); 1 RBD and 1 LBD improve neglect after each treatment (not AHP); 2 LBD show small benefit with prisms and TENS for AHP and with TENS and Optokinetic stimulation for neglect. All ameliorations are temporary.
Ronchi, Rode, Cotton, Farnè, Rossetti & Jacquin-Courtois, 2013	Single case study (LBD)	Extrapersonal and personal neglect, AHP, somatoparaphrenia, aphasia, apraxia, right hemiplegia, hemianestesia and hemianopia	1 ambidextrous LBD (M, 73; days post-onset = 45)	Caloric Vestibular stimulation (60cc cold water, 30 sec.)	Recovery of AHP, extrapersonal and personal neglect, no improvement in motor deficits and aphasia. Awareness persisted 2 days later
Gandola, Sedda, Manera, Pingue, Salvato, Spitoni, Pistarini, Giorgi, Pizzamiglio, Bottini, 2014	Single case study (bilateral lesion)	Extrapersonal neglect, severe AHP, hemiplegia, anosognosia for hemianestesia	M, 63; months post-onset = 7	Transcranial direct current stimulation (F4, following the international 10-20 system for EEG electrode placement, 5x7 cm, area: $35cm^2$, constant current 2mA, 20 min.)	Stimulation to the premotor cortex is effective in on-line (i.e. when movement is requested), awareness only when a visual feedback is given
Besharati, Forkel, Kopelman, Solms, Jenkinson, Fotopoulou, 2014	21 RBD (11 AHP, 10 HP)	hemiplegia, hemianestesia, extrapersonal and personal Neglect, executive functions	21 RBD (13 F, 8 M, 41-90; acute and subacute phase)	Induction of positive and negative emotions	Only negative emotion induction results in a significant improvement of motor awareness in AHP

Turnbull, Fotopoulou, Solms, 2014	1 RBD patient	AHP, hemiplegia	1 (F, 'middle age')	Clinical vignette of a psychotherapeutic session	Temporary acknowledgement of motor deficits
Besharati, Kopelman, Avesani, Moro, Fotopoulou, 2015	2 AHP (RBD)	hemiplegia, spatial neglect	2 (1 F, 88; days post-onset =7-58; 1 M, 70, days post-onset = 74 -103)	Video replayed; self-referred v. other-referred videos	Video exposure increases awareness for upper and lower limb motor impairment corresponding to the body part seen in the video. Video of other patients also has a significant effect.
Moro, Scandola, Bulgarelli, Avesani & Fotopoulou 2015	4 RBD/AHP patients, Within participants	Chronic AHP, hemiplegia, hemianestesia, spatial neglect	4 (M, 63-70; days post-onset = 72-144)	Error-based training	Varied but lasting improvements in motor awareness of all 4 pts.
D'Imperio, Bulgarelli, Bertagnoli, Avesani, Moro, 2017	16 RBD (8 AHP, 8 HP) Within participants	DSO, hemiplegia, extrapersonal and personal neglect, Executive functions	8 AHP (3F,53-74; 5M, 47-76, days post-onset = 11-103) 8 RBD (3F, 55-72; 5M 54-75, days post-onset = 52-103)	Judgment of proficiency before, during and after execution of dangerous and neutral actions (emergent awareness)	Temporary emergent awareness Effects of dangerous context
Facchin & Beschin, 2018	Single case study RBD	Moderate neglect, anosognosia for hemianestesia, hemiplegia, hemianestesia, hemianopia	1 (M, 64; days post-onset = 90)	Prism adaptation (11.3°rightward shift), 10 sessions, twice daily for 5 days	Improved neglect but no amelioration of AHP and anosognosia for hemianestesia 2 days and 3 weeks later
Cocchini, Beschin, Della Sala, 2018	43 RBD 30 LBD	Hemiplegia, personal and extrapersonal neglect	RBD (17 F, 26 M, 29-84, days post-onset = 10-199) LBD (16F, 14 M, 40-85, days post-onset = 10-149)	Comparison between scores at the VATAm (explicit awareness) and ECT (implicit awareness)	RBD with AHP: 9 on VATAm, 3 on ECT, 11 on both LBD with AHP: 6 on VATAm, 1 on ECT, 7 on both

Data regarding the patients described in the articles reviewed are reported, along with the interventions and main results. RBD = right brain damaged patients; LBD = left brain damaged patients; AHP = anosognosic patients; HP = hemiplegia; F = female; M = male; SD = standard deviation; VATAm = visual-analogue test for anosognosia for motor impairment; TENS = transcutaneous electrical nerve stimulation; EEG = electroencephalography; DSO = disturbed sensation of limb ownership; ECT = errand choice test

Neurophysiological interventions

This category relates to those methods that trigger a low level, 'bottom-up' process, such as visual attention, multisensory integration or subconscious motor processes.

The first intervention which aimed to assist AHP patients was *Vestibular Stimulation* (VS) [46,47,48,49,50]. This involved irrigating the left ear canal of the pa-

Table 2. The various different approaches to the rehabilitation of Anosognosia for Hemiplegia. The methods are grouped into categories that reflect the underlying techniques that were adopted in terms of the how they approach the syndrome

REHABILITATION/MODULATION METHODS	**INTERVENTIONS**
NEUROPHYSIOLOGICAL INTERVENTIONS	- *Vestibular stimulation* (Cappa et al., 1987; Rode et al., 1992; Ramachandran 1994; Rode et al., 1998; Ronchi et al., 2013 - *Prism adaptation (*Beschin et al., 2012; Facchin & Beschin, 2018) - *Optokinetic stimulation (*Beschin et al., 2012) - Transcutaneous Electrical Nerve Stimulation (Beschin et al., 2012)
NEUROMODULATION	- Transcranial Direct Current Stimulation (Gandola et al., 2014)
STIMULATION OF RESIDUAL FORMS OF AWARENESS	- Implicit awareness (Ramachandran 1994; 1995; Cocchini et al, 2010; Fotopoulou et al., 2010; Moro et al., 2011; Cocchini et al., 2018) - Emergent awareness/action for awareness (pre-post judgment) (Berti et al., 1996; Marcel et al., 2004; Moro et al., 2011; Prigatano et al., 2011; Moro et al., 2015; D'Imperio et al., 2017)
BODILY ILLUSIONS/ CHANGES IN VISUAL PERSPECTIVE	- Mirror box (Ramachandran, 1994; Ramachandran 1995) - Self/other dissociations (Marcel et al., 2004; Moro et al., 2011) - Video recording or mirror (Fotopoulou et al., 2009; Besharati et al., 2015)
EMOTIONAL MODULATION	- Clinical conversations and psychotherapy (Ramachandran & Rogers-Ramachandran, 1996, Turnbull et al., 2014) - Experimental induction of emotional reactions (Fotopoulou et al., 2010; Besharati et al., 2014; D'Imperio et al., 2017)

tient with ice-cold water for a short period of time (see Table 1 for details). This procedure causes a nystagmus to the left side, inducing gaze and head orientation towards the left affected limb. Mixed results were reported for this method, with data indicating temporary benefits [46,47,48,49] and only rarely long-term effects [46,50].

Prism Adaptation (PA) takes advantage of the effect of visuo-motor adaptation (for a review [51,52]). In fact, exposure to prisms produces a lateral shift of the visual field with the result that visual target appears in a displaced position. In this way, when the patient is requested to perform a perceptual-motor movement (i.e. pointing), the movement tends to shift towards the virtual position of the target. A progressive adaptation of movements ensures that errors rapidly decrease until the participantseventually pointscorrectly towards the real target. The prisms are thus removed, and the patient is requested to make further pointing gestures in order to reinforce the sensory motor adaptation achieved. In AHP, PA has been used in a study [53] that compared the effectiveness of three methods (PA, Optokinetic stimulation and Transient Electrical stimulation) in 5 patients in the post-acute phase. For the PA therapy, the participants were exposed to a 10° shift in the visual field toward the contra-lesional side. The procedure required the patients to perform 30 pointing gestures towards visual targets in front of them while wearing the prismatic goggles (for 20 minutes). 3 patients (2 LBD and 1 RBD) improved awareness after PA, but the effects were only temporary and did not last beyond the post-stimulation examination 48 hours later. Some years later, the same research group [53] administered 10 sessions of PA to a patient who was in a chronic phase(Table 1). In the assessments, 2 days after and 3 weeks after the last session, the training seemed to have been efficacious in terms of an amelioration of the neglect symptoms but there was no improvement in AHP and anosognosia for hemianesthesia.

Beschin and colleagues [53] also administered an *Optokinetic Stimulation* (OKS) to their 5 patients. They were asked to look at a computer screen displaying a visual pattern. This was comprised of black and white vertical lines, moving from right to left (for RBD) or left to right (for LBD) in order to obtain a slow phase nystagmus towards the side relating to the paretic limbs. With the optokinetic response still active, the patients were then asked to move their limbs, and tests for AHPwere re-presented. Only one patient improved in terms of awareness, but this improvement did not last more than 48 hours after the intervention. Furthermore, it is noteworthy that this same patient responded to all of the treatments administered.

Finally, again in Beschin et al.'s [53] study, *Transcutaneous Electrical Nerve Stimulation* (TENS) was applied to the 5 patients(details in Table I) on the contra-lesional side of the neck below the occiput, lateral to the spine. Two LBD patients responded to this intervention showing a temporary improvement in both AHP and spatial neglect.

Neuromodulation

Only one study was found that referred to the application of neuromodulation to treat AHP. In this study [55], the effects of *Transcranial Direct Current Stimulation* (tDCS) were investigated in a chronic RBD patient suffering from severe AHP (see Table 1 for details). The patient was asked to judge his ability to perform unimanual finger-thumb opposition movements (e.g.touching the thumb with the ring finger) in three conditions:

- without actually executing the movement;
- after having executed the movement with his eyes closed;
- after having executed the movement with his eyes open.

Before the tDCS intervention, the patient declared that he could perform and had in factperformed the movements requested in all of the trials and in all three conditions. After anodal tDCS over the right premotor cortex (Table 1 for details), (but not after the sham stimulation), the patient showed an increase in aware responses. This only happened in the condition involving movement with the eyes open, while in the other conditions, the number of responses indicating lack of awareness did not change. The improvement, however, did not last beyond the 2-hour post-stimulation assessment.

Stimulation of residual forms of awareness

Research into the mechanisms underlying AHP has identified residual forms of awareness. Although these studies usually do not focus directly on rehabilitation, they are potentially useful for patient management, in particular in terms of re-activation of daily life skills and the prevention of falls.

Implicit awareness has been reported in patients who, although they verbally deny their motor impairment, show a pattern of behaviour indicating that they acknowledge their paralysis on some non-verbal level of awareness [8]. Implicit awareness was initially identified in the seminal studies done by Ramachandran [49,56] who asked his patients to indicate which actions they would prefer to execute, choosing between unimanual and bimanual actions. Some AHP patients demonstrated residual spared implicit awareness by choosing unimanual actions. Similar dissociations have been found when comparisons were made between AHP patients' responses in a clinical interview and their judgments regarding their proficiency at executing bimanual and bipedal actions [6].

In a more recent study [11], 73 patients (30 LBD and 43 RBD) were asked to judge the difficulty of a task (i.e. a test of implicit awareness) and directly estimate their own motor impairment with regard to a second task (i.e. a test of explicit awareness). Up to 27% of the initial sample performed differently with regard to their original estimate in the two tasks, with 21% of them showing a lack of awareness only for the explicit awareness task and 6% only for the implicit awareness task (Table 1). Other studies carried out by Ramachandran [49,56] useda similar method which required patients to reach and grasp a large tray with glasses on it. For a hemiplegic person, the only way to execute this task is by using the ipsilesional healthy hand to reach and grasp the tray in the middle and this was considered an index of implicit awareness. This procedure was experimentally investigated in two subsequent studies [8,9]. Cocchini and colleagues [8] devised a specific task, the Bimanual Task (BMT), to assess implicit awareness for upper limb deficits. The participants were asked to perform 8 simple everyday actions (e.g. holding a two-handled tray; placing toothpaste on a toothbrush). These tasks are usually better performed using both hands but, with specific strategies, they can also be executed with only one hand (e.g. placing the unimpaired hand in the middle of the tray). However, in order to adopt this functional strategy, patients need to have some knowledge of their motor impairment. The patients' responses were evaluated on the basis of the presence of "aware strategies". A similar approach was used by Moro and colleagues [9] who asked patients to reach for and grasp 5 large objects and hold them in a horizontal position (e.g. a wooden rod ora basin). Given the nature of these objects, grasping and holding them required the use of both hands or, in the case of using one hand, grasping the centre of the object. Moreover, the fact that they had been requested to hold them in a horizontal position along their longer axis made it very unlikely that, under normal circumstances, the objects could be grasped by their handles or edges. This task was carried out in three consecutive steps that allowed for a direct comparison (in terms of explicit and implicit awareness) between the responses for each action.

In a preliminary interview, the objects were shown to the patients who were asked to state how many hands they would use to raise and hold them in a horizontal position. If, inspite of the paralysis, the patients declared that they would use two hands (explicit anosognosia); the examiner then demonstrated the action to the patients using both hands and subsequently; they were asked to actually pick up the objects. The distance between the position of the patient's non-plegic-hand and the right-hand edge of the object was measured and recorded.

Shifts in the grasp towards the midpoint of the object were measured (in mm) using the position of the thumb and finger as a measure of implicit awareness. In both studies, some patients showed both implicit and explicit anosognosia; however, dissociations were also found (Table 1 for details).

Nardone and colleagues [57] adopted a different approach to evaluate residual, implicit aspects of awareness. The authors used a Dot Probe task to investigate the hypothesis that attentional responses to visual targets are influenced by the interference of primes (i.e. a word appearing before the target) associated with the patients' motor deficits (e.g. 'walking'). While these primes facilitated the responses of aware hemiplegic patients (i.e. with a reduction in response times), an effect of interference was recorded in AHP patients who showed evidence of increased latencies [57].

Similarly, a verbal inhibition task was administered to patients who were asked to inhibit completing sentences with automatic responses and to provide non-associated endings to the sentences [58]. Three typologies of sentences were presented: neutral sentences (e.g. 'A tow truck is often used to pull broken-down cars off the...'); negative, non-deficit related sentences (e.g.' An ambulance is often used to take people who have been assaulted to the...'); and deficit related sentences (e.g. 'A hoist is often used to lift paralysed patients off the...'). As in the Hayling test (which the methodology was inspired by), the reaction times of responses and errors were noted. Connected completions (i.e. if the response was somehow associated with the initial sentence)were considered as errors (i.e. lack of inhibition). Subsequently, both groups were also asked to explicit ratings of the self-relevance of the same sentences, and this was considered as a measure of explicit awareness. 6 out of the 7 AHP patients in the study were significantly slower than a control group of aware hemiplegic patients in performing the inhibition task with deficit-related sentences than with other emotionally negative themes (relative to non-deficit-related themes). This occurred despite their explicit denial of the self-relevance of the former sentences, indicating a dissociation between implicit and explicit awareness.

Emergent awareness occurs when a patient becomes declaratively aware of his/her deficits only when encouraged to perform, or attempt, an action with the affected body part [59,9]. Before the first experimental investigations into emergent awareness, clinical examinations had assessed this residual form of awareness by asking patients to execute bimanual actions (e.g. washing their face, putting on a pair of gloves) and recording the potential increase in awareness [6]. However, a further specific investigation of the effects of action attempts on awareness was carried out by Marcel and colleagues [7]. The authors asked their patients to estimate their ability to perform unimanual/unipedal and bimanual/bipedal actions (scale 0 = action impossible to 10 = without any problems) and found that 24 out of 42 RBD patients (and only 1 out of 22 LBD patients) overestimated their abilities. In a further three tasks (i.e. tying a knot, clapping hands, shuffling cards), a second evaluation was obtained after RBD patients had attempted the actions. The responses indicated a modulation of awareness in a subgroupof patients (Table 1).

Moro et al. [9] used a similar task. The patients were asked to estimate their proficiency at executing five bimanual actions (e.g. tying a knot, closing a mocha coffee pot) and five unimanual actions (e.g. writing a word, brushing their teeth). They were asked to judge their abilities before, during and after the attempt to actually perform each action. Three judgments were thus obtained for each action: Scores:

- 3 = correct judgment before the request to perform the action;
- 2 = correct judgment only when subjects were about to start the action;
- 1 = subjects became aware of their deficits after failure of the action;
- 0 = the awareness of paralysis did not improve after the failed attempt to execute the action).

Alterations to the patients' judgments provided an index of emergent awareness. The results indicated that 3 out of the 12 AHP patients improved their awareness during\ this procedure. It is noteworthy that these patients were not those who had shown implicit awareness in the same study [9]. This demonstrated a dissociation between implicit and emergent awareness. These data were then confirmed in another study [10] in which16 hemiplegic patients (8 AHPand 8 non-anosognosic) were asked to perform both potentially dangerous and neutral actions and judge their proficiency before, during and after attempting each action. 10 actions involved the full body (e.g. going downstairs; using a wheelchair) and the other10 were only upper-body actions (e.g. cutting their nails with scissors; using a ruler to draw a line). The results confirmed an increase in emergent awareness in the anosognosic patients during the execution of both neutral and dangerous actions (see below for the effects of emotional or dangerous actions). Tasks involving an‘attempt to act’have also been used for rehabilitative purposes in other studies. In an individual case study [60], the patient was periodically examined, starting from the acute phase of her illness until one year after the lesion onset. AHP symptoms reduced with the recovery of her ability to move her left index finger.

A specific rehabilitation program based on emergent awareness and the analysis of errors was administered to 4 AHP patients by Moro et al. [61]. They were asked to execute specific actions, analyse their own strategies and errors and discuss the reasons for their failures. In addition, emotional support was given every time the patients appeared disappointed or frustrated. Pre-training, post-training and follow-up assessments showed that motor awareness improved in all 4 patients with long-term effects for 3 of them. However, the patients' responses to the training were different. For patient 1, the training which focused on unilateral, left hand actions was efficacious, but no effects were found for bimanual and bipedal actions. In patient 2, the effects of the training generalised to all types of actions. Patient 3 showed a significant emotional response: during an attempt to turn on a light, the examiners expressly asked the patient 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 that the situation was cruel, and that he felt as if he was sleeping. He also said:

> *"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 crisis seemed to have the effect of off loading some negative emotions: in an informal conversation he admitted that all his motor deficits and awareness deficits had persisted over time, accompanied by depression. Finally, patient 4's positive response to the programme was immediate. When he failed to execute an action, he did not need to repeat similar actions since his judgment already indicated that he had learnt that these were impossible for him. In the case of bi-manual actions, he activated successful functional strategies that he employed to deal with his disabilities. Thus, the same training programme activated a variety of different reactions in the four patients, providing evidence that AHP may be seen as a multifaceted, complex syndrome.

Cognitive and emotional modulation

During psychotherapeutic sessions, transient awareness and depressive reactions were reported in patients when themes of loss were explored, in particular if this loss was seemingly unrelated to their disabilities [62,35,37]. An approach which aimed to understand what makes paralysis easier to accept was explored by Ramachandran [63]. After a clinical interview with an AHP patient, the patient was informed that they would inject his left arm with an anaesthetic as part of the neurological exam. In reality, the syringe contained a saline solution that did not have any effect on the motricity of the arm. The researcher also said that as an effect of the injection, the arm would be temporary paralysed for some minutes. After the injection, the patient reported that his left arm "seemed to want to do nothing" and was not moving. The same procedure administered to the right arm did not deceive the patient.

The potential effects of inducing emotional reactions was also used as a technique in a number of experimental studies investigating implicit and emergent awareness [57,58,10] and was specifically investigated by Besharati and colleagues [64]. The aim of this latter study was to ascertain whether positive and negative emotions influence motor awareness in AHP. The Hayling test was administered in a two-part experiment. In part 1, the patients were requested to complete a series of sentences with the last word missing from it, as fast as possible (e.g. "The rich child attended a private…." Expected response: school). In part 2, they were asked to complete the sentences with a word that was completely unconnected to the sentence (e.g. "London is a very busy…" potential response:

banana). The emotional modulation was given by means of feedback that was positive or negative. In the two emotional-feedback conditions, feedback was provided in a standardised manner, using predefined sentences in pseudo-randomised order (e.g. “Well done”, “Your answer was very quick”, “That is incorrect”, “You are not doing well in this task”). Measures of awareness were taken before and after the induction of emotional reactions. Only the negative emotion induction condition resulted in a significant improvement of motor awareness in AHP patients as compared to the controls, while no effects were found with positive emotion induction.

Bodily illusions/ Changes in visual perspective

The fact that AHP represents a disorder of the bodily self is widely accepted and various methodshave attemptedto manipulate body representations and induce a recovery of awareness. Ramachandran [55] used his “*Virtual Reality box*” device (previously used with amputees)with a patient suffering from AHP. A mirror was placed vertically on a table in front of the patient, on a sagittal plane with respect to the table and the patient’s chest. The mirror was concealed in a large wooden box and the patient inserted both of her hands into circular apertures cut into the side of the box so that her hands were positioned either side of the mirror. The patient was then asked to look at the reflection of her right, healthy, moving hand (that appeared now in the position of her left hand) and say what she saw. She correctly reported the movements of the hand in the mirror. Then, the procedure was repeated with her left, paralysed hand appearing in the mirror. When the patient looked into the mirror, she saw a hand that looked perfectly stationary. Nevertheless, when questioned, “she maintained that she could clearly see the hand move up and down” ([56], p.33). Thus, the patient’s AHP symptoms had not changed.

However, the notion that self-observation may have a role in improving awareness has been pursued by other authors who have investigated the possibility that self-observation from an external, 3rd person perspective helps AHP patients to recover some awareness. This hypothesis has also been supported by evidence that some AHP patients, although incapable of estimating their own abilities, are however correct in their responses when they are asked to evaluate another person’s motor abilities [63,7,9].

In another study, a patient with severe AHP was presented with a video replay in which she could see herself while she responded to questions from the Berti Interview [6] regardingher motor abilities [65]. While watching the video, the patient spontaneously recognised her condition and, immediately after watching, she admitted her paralysis, saying that she had not been realistic during the previous interview and that she knew now that she could not move her arm. The following day the patient appeared to be still aware of her hemiplegia and remembered the experience with the mirror and her previous anosognosia. Inthe subsequent examinations during four weeks of hospitalisation and in the 6-month follow-up, she still appeared to be fully aware of her deficits. The patient in this study was in the acute phase after the lesion onset and this means that the possibility of a spontaneous recovery could not be excluded. For this reason, the same group devised a second study [66] with a similar procedure involving two patients in subacute and chronic phases. The results confirmed that video-based self-observation has positive effects on awareness that are in some way specific. In fact, the first patient attended multiple, successive sessions of video-based self-observation the target of which was related to awareness of upper limb paralysis and subsequently lower limb paralysis. With consistent stimulation by means of this technique, the patient initially showed an increased awareness specifically of her upper limb paralysis (the body part seen in the video), while her awareness of lower limb deficits ameliorated only after seeing the video which related toleg paralysis.

DISCUSSION

The analysis of literature carried out for this study indicates that systematic rehabilitation of AHP is relatively scanty and recent, although there were some firstattempts to modulate symptomsin the nineteen eighties. Furthermore, this review revealed that the various techniques usedtend to reflect a number of different theoretical approaches. The first interventions that aimed to increase patients' awareness were based on the idea that AHP was a secondary symptom of other diseases (e.g. spatial neglect). A better understanding of the disorder led to a modification of the approach to rehabilitation which became more specificin order to account for the multifactorial nature of this syndrome.We summarized the different methods in three general approaches: i) bottom up approaches; ii) cognitive and metacognitive approaches; self-observation and self-referred beliefs.

Bottom-up approaches

The first interventions involved Vestibular Stimulation (VS) [46,47,48,49]. This was initially used with some success on patients suffering from spatial neglect and, for this reason, its positive effects on AHP were interpreted as the result of an activation of the spatial attentional system [46]. This was based on the idea that spatial neglect and AHP were indeed part of a unitary syndrome [46]. In addition, a degree of recovery ofmotricity was also documented [47,48]. Thus, a hypothesis was advanced that VS activates the undamaged parts of a distributed system underlying multisensory integration and conscious representation of egocentric space [47,48,50]. Only Ramachandran [49] disagreed:he suggested the possibility that, although "highly speculative" in his words, VS might "be a device for reviving repressed memory and for producing insights" (p. 330).

17 patients were treated with VS in the articles reviewed for the purposes of this study (Table 2). In 13 cases, some amelioration of symptoms wasreported, but 12 of these were associated with recovery from neglect and in the case of the last one [49], information concerning neglect was not reported. Unfortunately, a separate evaluation of personal and extra-personal neglect was not carried out in the oldest studies, but when specifically assessed [48,50], personal neglect always improve

alongside the improvement in AHP. Thus, the possibility that VS acts on processes that are not specific to awareness but are instead associated with multisensory integration or body related spatial representation seems to be supported.

Further relevant data comes from observing the duration of the effects. In fact, recovery after VS was only permanent in 2 out of the 17 patients, while in the other 11 cases it was only temporary. There were similar results in experiments using other methods based on sensory-motor adaptation to peripherical stimulations (PA and OKS) or electrical muscular stimulation (TENS). There are fewer patients on whom these methods have been used as compared to VS (PA = 6, OKS = 5, TENS = 5), but the results are subject to the same limitations: only 3 patients improved awareness (3 with PA, including 2 LBD; 1 RBD with OKS and TENS) and then only temporarily. Again, all of them (but 1 RBD in PA program) also made improvements with regard to spatial neglect [53,54].

Taken as a whole, these results might be interpreted as being not very encouraging in that they indicate that methods which focus on bottom-up processes are able, at most,to induce limited, short-term effects in terms of the recovery of awareness.

A similar consideration may be made for neuromodulation induced by means of tDCS that,to the best of our knowledge, has only been applied to one patient [55]. In this case, the improvement was specific to AHP but again, unfortunately, only temporary.

To date, there have been no attempts to combine bottom-up stimulation with specific cognitive rehabilitation. However, this integration might be effective since it contributes towards post-lesional plasticity processes due to an association between the activation of the neural networks directly involved in performing a task (or recruited in order to compensate for the damage to the networks previously assigned to this task) and the less specific, widespread neuromodulation induced by tDCS [67,68].

Cognitive and metacognitive approaches

Another technique that in our opinion deserves to be tested involves a combination of neuromodulation and the assignation of tasks aimed at detecting residual skills, such as those used in cases of implicit and emergent awareness. Dissociations between implicit and emergent awareness have been demonstrated in studies relating to behaviour and neuroanatomy. In fact, while deficits in implicit awareness are associated with the subcortical frontal white matter anterior to and around the basal ganglia [58,9], the sites which are significantly associated witha lack of emergent awareness involve the antero-posterior tracts ofwhite matter which bidirectionallyc onnect the parietal cortex and the precuneus [9].

In about 50% of AHP patients assessed for implicit awareness (20/39, not including [11]; see Table 2), this form of awareness was spared. This may be crucial for patient management, as patients who on some implicit level know that they are paralysed will not try to do anything dangerous (e.g. getting out of a wheelchair) and will ask for help when they find they are not able to do something. This reduces the risk of falls and accidents with potential secondary damage. Nevertheless, the possibility of enhancing this residual capacity by means of specific programmes is yet to be explored.

A first attemptto do something of this nature was carried out in order to enhance emergent awareness by means of error-based and metacognitive training [69]. The mechanisms underlying emergent awareness have not been clear until now, but we hypothesise that the efficacy of this type of training is due to an integration of various different processes, such as cognitive and metacognitive processes (necessary for intention, monitoring and the evaluation of performance) and executive processes (related to action planning and execution). Furthermore, self-referred beliefs and emotional factors are probably also involved, as demonstrated by patient n. 3 in the study done by Moro and colleagues [61]. There is also evidence for this in experiments showing the effects induced when subjects are requested to execute potentially dangerous actions [10]. A common element in patients with emergent awareness is the ability to learn from attempts to act and thus from errors. For this reason, among the theories put forward to explain AHP, the one that best explains emergent awareness and the efficacy of error-based programmes is the theory of beliefs updating [38,40]. When patients are requested to carefully observe their attempts to perform an action, they become able to "Appreciate" their own deficits and "Check" the results of their performance. Furthermore, analysing and discussing the reasons for failure helps them to rethink their previous "Beliefs" concerning their own motor functions [40,41].

Self-observation and self-referred beliefs

Self-observation probably impacts on AHP by means of various processes. The Virtual Reality box (or Mirror box therapy) is extremely efficacious in some clinical conditions, such as phantom limb pain in amputees and motor deficits in post-stroke patients [70]. The method is also effective in cognitive disorders such as body metric disorders [70] and the anarchic hand [72,69]. However, in the only case of an AHP patient reported in literature concerning this device, this manipulation technique did not induce any modulation of the symptoms [56].

Having said that, all 3 of the AHP patients who participated in video sessions in which they watched themselves during a standard examination improved awareness [65,66]. The authors of these studies speculate that the recovery was mediated by the fact that self-observation was executed in a 3rd person perspective, and in "off-line"conditions, namely, at a point in time subsequent to their actual attempt to execute a movement. This combination probably reduces any confounding effect associated with motor planning and helps the patient to update his/her self-referred beliefs and thereby recognise deficits.

Finally, this review of the literature confirmed that emotions do in fact play a important role in AHP. A modulation of symptoms occurs when negative emotions are induced by dangerous situations [10] or negative feedback is given [64]. The use of psychotherapy in cases in which denial is used as a defensive mechanism for coping has also been recommended [62,35,37,73].

CONCLUSIONS

The research reviewed in this article provides a number of relevant indications regarding the rehabilitation of AHP.

First indication which appears that AHP is indeed a specific syndrome, independent from other cognitive disorders such as spatial neglect or somatosensory deficits. However, it is also true that the co-occurrence of these other deficits may impact awareness and thus rehabilitation needs to take into account the patient's whole cognitive profile and also intervene to deal with concomitant symptoms [73,74].

The second indication regards assessment of the condition. A growing body of evidence suggests that AHP following lesions of the left hemisphere may be less sporadic than previously thought [75,76,77,78,11] and AHP in LBD patients may be underestimated due to certain methodological aspects of the assessment procedure [79].

Therefore, due to the multi-faceted nature of AHP, it is clear that comprehensive assessments which also include emotional and motivational components should be made [80]. If this is done, the clinician will be able to identify the modulation and rehabilitation techniques which are the most suitablefor his/her patient, either used alone or in tandem with other procedures. Finally, intervention programmes need to be constantly monitored in order to distinguish between temporary and permanent effects, and follow-up assessments should be carried-out (Figure 2).

While there was no indication of a close relationship between lack of awareness and depression in some studies [18], others have suggested a number of different ways in which these two syndromes may be linked [81]. Therefore, an ethical issue may arise regarding any decisions relating to whether awareness is necessary and useful for the patient or whether the recovery of awareness would only constitute a needless source of suffering. Some anosognosic patients suffer from severe motor deficits and the prognosis concerning their chances of recovery is very negative. In these cases, and when there is no possibility of any degree of recovery of autonomy, it is perhaps advisable to consider whether it is in effect ethical to induce the depressive reactions which may be associated withthe awareness ofdeficits that are permanent. With regard to this dilemma, however, it is also necessary to take into account what the term "recovery" in fact means, as in some situations, even minimal recovery (such as, for example, minimal cooperation in postural transfers) may make a difference in terms of patient management, depending on whether he/she is going home or going into a nursing home. For this reason, any decisions regarding interventions should be taken after an in-depth examination of the patient.

Despite the fact that the literature review was extensive, we only managed to identify a relatively limited number of studies that directly investigated AHP rehabilitation. As such, our final considerations are based on limited evidence. A second limitation, probably linked to the previous consideration, lies in the speculative nature of at least some of the techniques discussed as these derive from experimental studies which were not directly aimed at rehabilitation. In these cases, the efficacy of the techniques is not proven in terms of a structured course of rehabilitation and post-intervention and follow-up assessments. Finally, the data regarding AHP in LBD and the rehabilitation programme for these patients

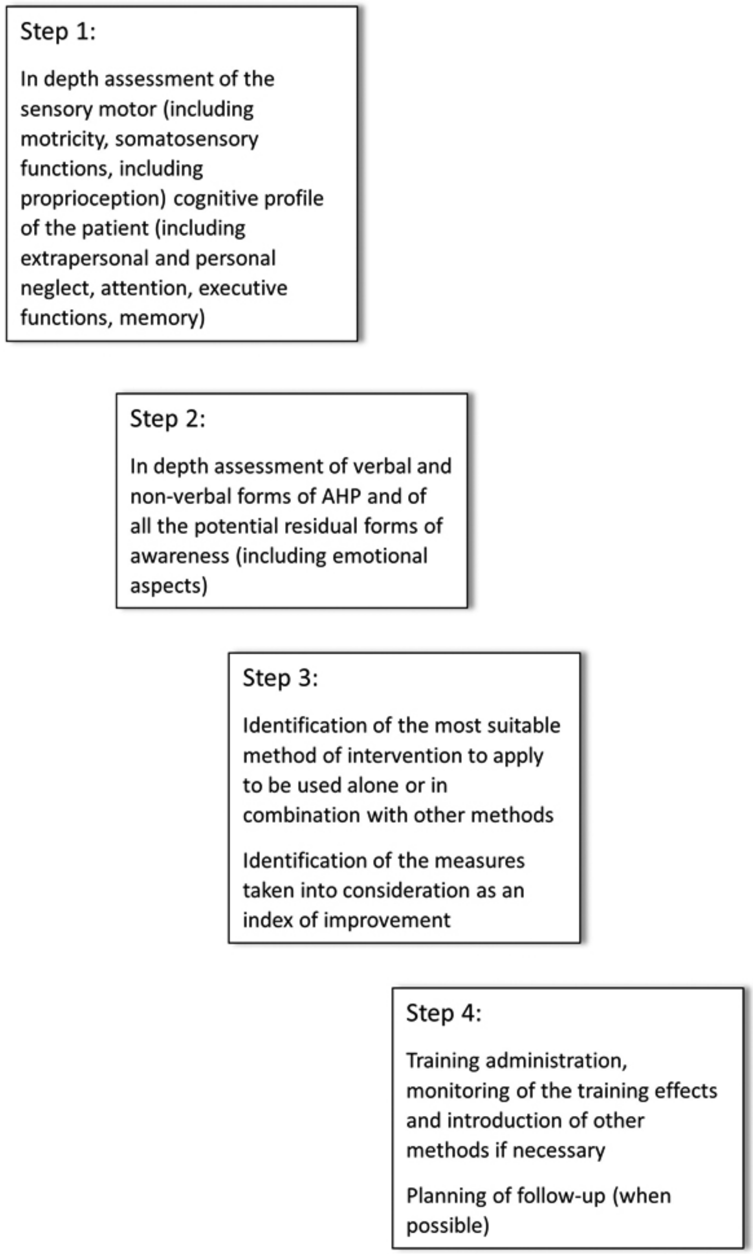

Figure 2.

are limited as at the moment there is still very little research on awareness in LBD. Despite these limitations, we consider that the results of this study will be useful for devising further, controlled studies on AHP rehabilitation and for clinicians working with stroke patients who exhibit a lack of awareness.

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