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Anarchy in the brain: Behavioural and neuroanatomical core of the anarchic hand syndrome

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ABSTRACT

An individual's inability to control the movements of their own hand is known as the Anarchic Hand Syndrome. The hand may perform apparently purposeful actions but acts as if it has a will of its own. Although the syndrome was first described over a century ago, the nature of the condition remains, for the most part, obscure, in particular in terms of the definition of the main symptoms and the underlying neural networks.

The present study compares the results from in-depth assessments, made at repeated intervals (2, 4 and 7 months from the lesion onset) of the anarchic hand symptoms in three patients suffering from various different forms of brain damage. An investigation of direct grey matter damage and structural connectivity allowed us to compare the grey matter lesions and white matter disconnections in the three patients.

A "core" characteristic relating to anarchic hand symptoms was identified, involving, in particular, both apparently purposeful movements (i.e., magnetic apraxia, grasping, bimanual incoordination, disorders in manual dexterity and action sequencing) and non-purposeful movements (i.e., levitation, synkinesis and mirror movements). Furthermore, ideomotor apraxia may also be associated with this syndrome. No overlapping areas of grey matter lesions were found in the three patients. In contrast, a pattern of common white matter disconnections was found, which involves inter-hemispheric disconnections (via corpus callosum), the long intra-hemispheric tracts (via SLF, IFOF and Arcuate) and the descendent tracts (corticospinal tract). These results are discussed in terms of awareness of motor intention.

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1. Introduction

The anarchic hand syndrome (AHS) represents a fascinating neurological phenomenon that is characterised by involuntary, apparently purposeful movements of a hand. These movements are non-volitional and the patient does not have any inhibitory control (Della Sala, Marchetti, & Spinnler, 1991). Despite the initial documentation on the syndrome dating back to Goldstein's report in 1908, it has largely remained an enigma over the years. Goldstein's account offered a comprehensive portrayal of the primary symptoms of AHS, including the inability to suppress undesired actions of the hand, the perception of the hand as having its own will, and the anthropomorphism of the disobedient limb. However, a certain degree of confusion on the characteristics of AHS has lasted up to our days. The ambiguities regard, in particular, the differences between the "anarchic" and "alien" hand phenomena (Marchetti & Della Sala, 1998) and the underlying idea that AHS might stem from a deficit in body representation rather than constituting a distinct syndrome. In their seminal study, Marchetti and Della Sala (1998) clarified the difference, delineating the "alien" hand syndrome (now known as asomatognosia, Jenkinson, Moro, & Fotopoulou, 2018) as a manifestation of a body ownership disturbance which is characterised by the feeling of the hand being foreign, unknown and not part of the individual's body (or sometimes even missing, Moro et al., 2024). In contrast, AHS pertains to alterations in the sense of agency (Jenkinson, Edelstyn, Preston, & Ellis, 2015), as a result of which the patients recognise the hand as their own but claim they cannot control its movements.

The challenges in defining AHS extend beyond the complexity of its symptoms. The multifaceted nature of the syndrome is characterised by the fact that it may be the result of a wide variety of lesions involving different brain structures (for an in-depth review of the literature, see Supplementary Materials – B in Moro et al., 2015). Lesions involving the medial frontal areas and the corpus callosum (CC) are linked to the anterior expressions of the syndrome (e.g., Banks et al., 1989; Chan & Ross, 1997) and in some cases, the lesions extend to the corona radiata and basal ganglia (BG; e.g., Brainin, Seiser, & Matz, 2008; Bakheit, Brennan, Gan, Green, & Roberts, 2013). The posterior form of the syndrome is identified with posterior lesions that involve the CC and temporal-parietal-occipital cortices (Groom, Ng, Kevorkian, & Levy, 1999; Mark, 2007). Although the co-occurrence of AHS and CC disconnections is frequent, cases of AHS have been reported after parietal lesions, without any damage to the CC (e.g., Lavados et al., 2002; Panda, 2010) or in thalamic lesions (Nowak, Bösl, Lüdemann-Podubecka, Gdynia, & Ponfick, 2014; Park, Kim, Kim, Jeong, & Jung, 2012).

The first hypotheses on the nature of the AHS focused on unmasking frontal activities relating to the generation of anarchic hand symptoms (in particular, apparently purposeful movements) as a consequence of interhemispheric disconnections or the disconnection between intrahemispheric medial and lateral frontal systems (Feinberg, Schindler, Flanagan, & Haber, 1992; Goldberg & Bloom, 1990). Specifically, the coordination of bimanual actions depends on two mechanisms: i) the stream of communication between the two hemispheres for internally driven actions and ii) the connections between the supplementary motor area (SMA) and lateral premotor cortex (PMC), which are engaged in the inhibition–release equilibrium that occurs during movements relating to externally cued actions. Lesions to the SMA and its inhibitory leverage on the PMC disrupt this balance, leading to the predominance of lateral network activity and the emergence of automatic, uncontrolled responses to environmental stimuli. Furthermore, lesions to the SMA can lead to a deficit in the selection of intentional actions (Frith & Wolpert, 2000).

More recently, a tripartite model of motor awareness that includes awareness of motor intention, motor monitoring and general motor abilities identifies AHS as a disorder in the aware motor intention (Pacella & Moro, 2022). Motor intention is defined by "positive, pro-active volition" which induces the initiation of an intentional action, and "negative volition", namely the capacity to inhibit actions that are not appropriate (Haggard, 2019; Seghezzi & Haggard, 2022). During both processes, individuals are aware that they are the agent of the action intention. A lack of this awareness characterises AHS patients during anarchic hand activity. In AHS, the core issue is that the affected hand initiates actions without the conscious intention of the patient, and the patients are typically aware that these actions are not under their voluntary control. However, at the moment of the generation of intention to move, patients are not aware that they are themselves the source of the movement. This deficit in the awareness of motor intention underscores the disruption of the normal process where the brain generates a conscious intention before executing a motor action. In fact, AHS patients deny that they are the agent of their upper limb movements, which they report are being performed by the hand of its own will and which they are unable to inhibit. Nevertheless, monitoring of the action in progress is preserved and patients maintain a certain degree of control over the affected limb's voluntary (i.e., not anarchic) movements. This theoretical framework of AHS aligns not only with frontal and callosal manifestations but also with the posterior variants of the syndrome. The parietal lobe is known to play a crucial role in integrating sensorimotor functions relating to the body, movement, and self-awareness (Sirigu et al., 2004), and it has been identified as being crucial to motor awareness and the sense of agency (Desmurget & Sirigu, 2009).

Since the clinical and anatomical presentations are extremely variable, the potential existence of a core profile relating to AHS has yet to be explored. This would imply a set of symptoms common to these various different manifestations and that may be explainable as being the result of shared lesion and disconnection correlates.

In this study, three approaches were integrated to achieve a comprehensive characterisation of AHS. First, an in-depth analysis of the patients' symptoms was carried out, taking into account not only the "positive" symptoms described by the patient and observed by the examiners but also the "negative" ones, namely those symptoms that would be expected to be present based on the previous literature but do not appear in the cases under examination (Moro et al., 2024). This comparison with the existing literature on the subject represents the second line of investigation and is even more useful in the case of rare syndromes (Beccherle et al., 2023), such as AHS, for which large group studies are impossible. A third approach involved a thorough neuroanatomical investigation of the lesions involved in AHS, which was conducted with the aim of comparing three patients with different manifestations of the syndrome. Studying the white matter disconnections made it possible to overcome the limitations relating to lesion mapping studies. By means of this, we were able to go beyond the role of discrete, direct cortical lesions in the patients' symptoms and identify the contribution of structures that were apparently spared but were somehow involved in the deficit via white matter disconnections (Thiebaut de Schotten, Dell'Acqua, Ratiu, Leslie, Howells, Cabanis, Iba-Zizen, Plaisant, Simmons, Dronkers, et al., 2015; Pacella et al., 2020).

Although only three case studies are reported in the current study (two of which were previously discussed in Moro et al., 2015; Pacella et al., 2021), we anticipate that the neuropsychological approach involving an in-depth analysis of symptoms, the comparison with previous literature and the neuroanatomical investigation will permit us to advance some hypotheses on a potential symptomatological and neuroanatomical AHS "core". Based on the reports accompanying the neuroimages available, it was found that the three patients represent anterior-callosal, posterior-callosal and parietal lesions, respectively. However, an MRI/DTI investigation for two of the three patients and the analysis of the probability of disconnections in all three of the patients made it possible to identify some previously hidden aspects in common in their lesion patterns and enabled a comparison of these with similarities and differences in the three patients' symptoms.

2. Methods

We report all data exclusions (if any), all data inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. *Case reports*

AA is a 78-year-old right-handed man with 8 years of education. He suffered a right hemisphere ischemic stroke as a consequence of surgery for ascendant aorta replacement and myocardial revascularisation. The symptoms indicating left hemiplegia that occurred after surgery completely recovered after the first two months, and the subsequent assessment also excluded sensory deficits (Table 1). Cognitive functions were partially compromised in terms of attention, verbal fluency and spatial representation. AA presented with bilateral ideational and ideomotor apraxia and disorders in interhemispheric tactile transmission. He reported difficulties in bimanual coordination and claimed that his left hand did not do what he wanted. It moved independently, touched people and objects or grasped them without letting go, and did not cooperate with the other hand. He also reported that his left hand tended to imitate the movements executed by his right hand. All of these symptoms were observed and systematically recorded by the physiotherapist and psychologist. These persisted over time (Table 2) despite the recovery of general cognitive functions. Bilateral apraxia and spatial disorders persisted in the 7-month and 1-year follow-up checks.

BG is a 71-year-old, right-handed woman with 13 years of education. She had emergency cardiac surgery for an aneurysm in the ascending aorta artery (for a detailed description, see Pacella et al., 2021). Two months later, the initial motor weakness in her left arm had recovered while the somatosensory deficits persisted. She showed cognitive deficits in memory and spatial representation that, however, recovered in two months. Only executive function deficits persisted in the assessment at 4 months from the lesion onset, along with unilateral left-hand ideomotor apraxia and bimanual incoordination. She complained that her left hand disturbed the right one, sometimes blocking it. She also described her hand as behaving in an uncontrolled manner, as if it had its own will. It went to touch people around her and disturb them; furthermore, it sometimes wandered in the air as if it was looking for something.

VR is a 47-year-old, right-handed woman with 17 years of education. She suffered a haemorrhagic stroke during neurosurgery to resolve two aneurysms in the right middle cerebral artery and right pericallosal artery. A detailed description of VR's clinical symptoms has been previously reported (Moro et al., 2015). Two months after surgery, she presented with paralysis in the left lower limb, accompanied by urinary incontinence, while the motricity of the upper limb was spared. There were no sensory deficits. Cognitive functions were partially compromised in terms of spatial memory and calculation. Unilateral left ideomotor apraxia was present. There were no deficits in interhemispheric tactile transmission. VR complained that her left hand behaved in an uncontrolled manner (e.g., during a medical examination, it went into the pocket of the doctor's white coat and during conversations her left index finger went into her nostril). She also reported impulsive and involuntary groping towards objects with grasping, and difficulties in letting objects go (in fact, she used her right hand to prise them from her left hand). She also complained of synkinetic right-hand movements. This was confirmed by a clinical observation that documented the presence of synkineses, with movements which were precise and coordinated in amplitude and timing, mirroring the left-hand trajectory (Table 2).

The study was approved by the local research committee and conducted in accordance with the Helsinki Declaration. All participants gave informed consent prior to taking part in the study.

Table 1 – Results from the clinical and neuropsychological assessments. AA, BG and VR's performances in sensory-motor and neuropsychological tasks administered 2 and 4 months after the lesion onsets are reported. The scores are corrected for age, gender and education. In bold, the pathological scores. + = presence of deficit: - = absence of deficit; n.a = not administered tasks. L = left; R = right.

	AA		GB		VR
	2M	4M	2M	4M	2M
SENSORY-MOTOR SYSTEM, LEFT HAND					
MRC Scale (Florence et al., 1992)	4	5-	5-	5-	4
R-Nottingham Sensory Assessment (Lincoln, Jackson, & Adams, 1998)					
Light touch	2	2	**0**	**0**	2
Temperature	2	2	**1**	**1**	2
Pinprick	2	2	**0**	**1**	2
Pressure	2	2	**0**	**1**	2
Tactile localisation	2	2	**0**	**1**	2
Kinesthesia	3	3	**0**	**1**	3
Interhemispheric tactile localisation	+	+	+	+	–
GENERAL FUNCTIONS					
Mini-Mental State examination (Folstein, Folstein, & McHugh, 1975)	**23.2**	30	24.86	28.86	29
SPATIAL FUNCTIONS (BIT Wilson, Cockburn, & Halligan, 1987)					
Line Bisection	**0**	**1**	**5**	9	9
Albert	**16**	36	**28**	36	36
Copy of geometrical shapes	**1**	4	**0**	4	4
Comb test (McIntosh et al., 2000)	**–.12**	**–.36**	0	0	0
Razor test	**–.12**	**–.03**	0	0	0
VERBAL MEMORY	–	–	–	–	–
VISUO-SPATIAL MEMORY	n.a	n.a	+	–	+
CALCULATION	–	–	–	–	+
FRONTAL FUNCTIONS					
FAB (Appollonio et al., 2005)	14.7	17.9	**10.7**	**11.9**	13.1
Motor sequences	**2**	3	**1**	**1**	**1**
Conflicting instructions	**2**	3	**1**	**0**	3
Go no Go	**2**	**2**	**2**	3	3
Grasping	3	3	3	3	3
APRAXIA					
Ideomotor Apraxia (Spinnler & Tognoni, 1987)	**L = 37 R = 39**	**L = 39 R = 41**	n.a	**L = 39** R = 61	**L = 39** R = 69
Ideational Apraxia (De Renzi & Lucchelli, 1988)	**14**	**17**	18	18	20
Bucco-facial apraxia (Spinnler & Tognoni, 1987)	20	n.a	20	n.a	20

2.2. *The assessment of anarchic hand symptoms*

Based on two recent reviews of the literature (Moro et al., 2015, updated in Pacella et al., 2021), five categories of symptoms were taken into consideration in the assessment of AH, with patients' symptoms being recorded at 2- and 4-month intervals from lesion onset. For AA, an assessment at 7 months was also performed (Table 2).

The first set of symptoms was grouped as *apparently purposeful or semi-purposeful* AH movements. These include all the symptoms associated with involuntary movements relating to reaching and grasping, such as groping (i.e., repeated movements of reaching toward a stimulus based on the mere proximity of the stimulus), magnetic apraxia (i.e., when tactile stimuli or the presence of objects near the hand trigger the grasping of the object), and grasping and forced grasping reflex (i.e., the inability to release the grip). In this category, other symptoms are included, such as utilisation behaviour (i.e., apparently appropriate use of objects in inappropriate contexts) and the compulsive manipulation of tools.

Non-purposeful AH movements are considered to be those movements that do not suggest an apparent goal, such as exploratory behaviours (i.e., movements of the hand in the surrounding environment), repetitive and stereotypical movements, self-oriented movements involving grasping, compulsive self-manipulations (i.e., self-grabbing), levitation (i.e., uncontrollable upward movements of the arm) and nocturnal movements.

The *uncontrolled bilateral hand movements* category includes all those situations in which one hand interferes with the action of the other hand. This may include: intermanual conflict (i.e., where the AH attempts to contrast the other hand); diagnostic dyspraxia (i.e., cross-purposeful actions of the AH triggered by voluntary actions carried out by the other hand) or abnormal AH responsiveness to the movements of the other hand, for example with mirror movements (i.e., when the AH reproduces the same movements performed by the other hand). Synkinesias is the opposite condition and this may occur when the patient is asked to perform a task with the AH but the other hand simultaneously carries out the same movement.

Typical *disconnection symptoms* are unilateral apraxia, agraphia or tactile agnosia and disorders in interhemispheric sensory transmission.

Other symptoms are grouped in the category of *other AH-related symptoms* and include AH unresponsiveness (i.e., when, in the absence of paralysis, the hand does not respond to the patient's commands), bimanual incoordination and

Table 2 – AA, BG and VR's Anarchic Hand symptoms as assessed in the repeated assessments. In italics are the categories of symptoms usually associated with Anarchic Hand Syndrome, based on Moro et al., 2015. + = presence of the symptom; – = absence of the symptom; imp = impossible to assess.

		AA			BG		VR	
		2M	4M	7M	2M	4M	2M	4M
Purposeful AH movements	Magnetic apraxia	+	+	–	+	–	+	+
	Grasping	+	+	–	+	+	+	+
	Forced Grasping	+	–	–	–	–	+	+
	Groping	+	+	–	–	–	+	+
	Compulsive manipulation	–	–	–	–	–	–	–
	Utilisation behaviour	–	–	–	–	–	–	–
Not purposeful AH movements	Exploratory behaviour	+	+	–	–	–	–	–
	Repetitive movements	+	+	+	–	–	–	–
	Self-grabbing	+	+	+	–	–	–	–
	Levitation	+	+	+	+	+	+	–
	Nocturnal movements	–	–	–	–	–	–	–
Uncontrolled bilateral hand movements	Intermanual conflict	–	–	–	+	+	+	–
	Diagonistic dyspraxia	–	–	–	+	+	+	+
	Responsiveness to actions performed by the intact hand	–	–	–	+	+	–	–
	Mirror movements	+	+	+	+	–	–	–
	Synkinesis	+	+	+	–	–	+	–
Disconnection symptoms	Unilateral apraxia	Bilateral	Bilateral	Bilateral	+	+	+	+
	Agraphia	–	–	–	–	–	–	–
	Tactile Agnosia	–	–	–	–	–	–	–
	Interhemispheric sensory transmission	+	+	+	Imp	Imp	–	–
Other AH related symptoms	Unresponsiveness	–	–	–	+	+	+	+
	Dexterity disorders	+	+	+	+	+	+	+
	Bimanual incoordination	+	+	+	+	+	+	+
	Tapping (rhythm disorders)	–	–	–	+	+	+	+
	Deficit in sequencing	+	+	+	+	+	+	+
	Lower limb hypostenia	–	–	–	–	–	+	+
	Mutism (initial)	–	–	–	–	–	+	+
Hand related feelings	Alien hand	–	–	–	–	–	–	–
	Personification	–	–	–	–	–	+	+
	Restraining action	–	–	–	+	+	+	+
	Autocriticism	–	–	–	–	–	–	+
	Avoidance behaviours	–	–	–	–	–	+	+

dexterity disorders, and deficits in performing movements in sequence and in reproducing or maintaining a rhythm (i.e., tapping). Sometimes hyposthenia in the lower limb (without motor disorders in the upper limb) and akinetic mutism are also reported, in particular in the acute phase.

Finally, in the *hand-related feeling* category, non-motor symptoms described in AH are grouped, such as alien hand (or main étranger, i.e., the feeling that the hand does not belong to the patient), personification (i.e., when the patient addresses to the hand and sometimes speaks to it as if it was another person or a child), restraining actions (i.e., the attempts to block AH movements, putting it under the legs or in a pocket or using the other hand to prevent movements), avoidance behaviour (i.e., when the patient unintentionally withdraws the affected hand from environmental contact or stimuli) or exaggerated frustration toward the AH (i.e., autocriticism).

Information on the presence of these symptoms was collected by means of direct observation on the part of the neuropsychologist and the physiotherapist in the context of rehabilitation training, but also during the execution of daily life activities and when the patient was resting in the hospital ward. In addition, a specific interview was conducted with the patients. This interview confirmed that all three patients were aware of their symptoms. For each assessment, information was collected within a period of a week. In the presence of disagreement about a symptom between the examiners and patients, clarifications were given by the examiners and the symptom was discussed until an agreement was reached. In cases where there were doubts, the examiners devoted another one or two days to further observation.

2.3. *Neuroanatomical investigation*

The patients' lesions were manually drawn on the native 3D-T1MRI scan (BG, AA) and CT scan (VR) in the axial slices and then reconstructed as a 3D region of interest (ROI) with MRIcroN. The lesions were contoured by a first anatomist and then checked by two other blind expert anatomists. The CT scan and corresponding Regions of interest (ROIs) for the lesion were normalised to the MNI152 in MIPAV (version 11.1.0, https://mipav.cit.nih.gov/) by applying affine and elastic deformation from the identification of common anatomical landmarks on the patients' images and the MNI152 template. The same landmarks identified in the patients' native space were applied to the lesion ROI transformation. The MRI scan and ROIs were then spatially normalised onto an MNI template by means of SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/~spm).

To identify the grey matter structures encompassed by each lesion, the patients' normalised lesions were then compared with the AAL brain atlas. The multiplication of the three binary lesion ROIs via the fslmaths tool of FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) allowed for the investigation of potentially common lesioned voxels in the three patients.

The Disconnectome tool (part of the BCBToolkit software; Foulon et al., 2018) allowed for the indirect investigation of white matter tract disconnections in the three patients. This tool produced a percentage overlapping map from each lesion ROI that took into account the inter-individual variability of tractography in the healthy subjects dataset (Foulon et al., 2018). In the resulting disconnectome map, the voxels show the probability of disconnection from 0 to 100% (Thiebaut de Schotten et al., 2015). The three disconnectome maps were then thresholded via fslmaths tool (FSL, link) to consider voxels with above 50% probability of disconnection. Indirect disconnection results of patient BG are reported in Pacella et al., 2021. VR's lesion was reported and discussed in Moro et al.'s 2015 paper; here, those data are updated with the analysis of the probability of disconnection and shown in Supplementary Materials S1.

The thresholded maps were binarised and multiplied via fslmaths to obtain an intersection map representing disconnections which were common to the three patients. Finally, the binary intersection map was employed to mask the patients' disconnectome maps, which were then used to extract the mean disconnection values of common voxels via fslstats.

Furthermore, for AA, a neuroanatomical, in vivo investigation of the white matter was conducted following the same procedure as in Pacella et al., 2021, via a standard DTI tractography. A diffusion-weighted imaging (DWI) sequence was carried out, acquiring 48 diffusion-weighted volume directions along with 6 volumes having no diffusion gradient (B0) at a b-value of 2000 sec/mm^2. The imaging parameters were set with a repetition time of 6000 ms and an echo time of 97 ms. Voxel dimensions were maintained at 2 × 2 × 2 mm with a slice thickness of 2 mm. The field of view (FOV) was set to 256 mm with a resolution of 128 × 128.

To mitigate distortions, an additional image with no diffusion gradient was captured but with reversed phase-encode blips. This facilitated the estimation and correction of susceptibility-induced off-resonance fields using the TOPUP tool within FSL. Subsequent correction for motion and geometric distortions was executed using the EDDY tool.

The computation of diffusion tensors and whole-brain deterministic tractography was conducted utilizing StarTrack software. Spherical deconvolutions were performed employing a damped Richardson-Lucy algorithm with a fixed fibre response parameter of 1.5 and a geometric damping parameter of 8. Four hundred algorithm iterations were executed with an absolute threshold of .0025. Whole-brain streamline tractography employed a modified Euler algorithm with an angle threshold of 45° and a step size of .5 mm.

Tract dissections were carried out using Trackvis (see Supplementary Material S2 for a description of the tracts dissection) on tracts previously identified on the patient's disconnectome map, enabling an inter-hemispheric comparison of lesioned tracts and their spared homologues in the contra-lesional hemisphere, with the exception of the corpus callosum (for the same analysis conducted on BG's DWI, see and Pacella et al., 2021).

3. Results

3.1. *Anarchic hand symptoms*

The results from the repeated observations of AH symptoms are shown in Table 2. Here, for each category of errors, the symptoms recorded for the three patients were compared.

Apparently purposeful or semi-purposeful movements. All three patients suffered from this category of symptoms at two months from lesion onset. In particular, magnetic apraxia and grasping were recorded and persisted at the 4-month assessment (but not magnetic apraxia in BG). In AA and VR, these were associated with forced grasping and groping.

Among the *non-purposeful AH movements,* upper limb levitation is the only common symptom between the three patients, and this only recovered over time in the case of VR. AA also showed explorative and repetitive movements and self-grabbing.

Uncontrolled bilateral movements were more present in VR and GB than in AA. Indeed, the first two presented with intermanual conflict and diagnostic dyspraxia. BG also showed exaggerated responsiveness relating to the AH. Mirror movements were present in AA and GB, and synkinesis was present in AA and VR, but only in the case of AA did these persist over time.

Ideomotor apraxia was present in all three patients. However, while VR and BG presented with unilateral left-hand apraxia, AA suffered from bilateral apraxia. In the Imitation test carried out by De Renzi and colleagues (De Renzi, Faglioni, Scarpa, & Crisi, 1986), he not only failed in terms of the final score but also in all of the sub-scores, and a detailed examination of his performance showed that his finger gestures were more impaired than his hand gestures, and motor sequences were more impaired than postures, with a similar involvement of meaningless and meaningful movements. AA (but not VR and BG) suffers from bilateral Ideational apraxia, indicating a form of crossed apraxia (i.e., following right hemisphere lesion). Instead, VR and BG presented with the typical left hand unilateral callosal apraxia. Among the other disconnection symptoms, only disorders in interhemispheric sensory transmission are reported in AA (but it is noteworthy that in BG, this is not testable due to sensory deficits).

Among other *AH-related symptoms,* dexterity disorders, bimanual incoordination and deficits in sequencing were common to all three patients. Unresponsiveness and tapping deficits were present in VR and BG, while only VR presented with lower limb hyposthenia and mutism (which had been resolved by the 4-month assessment).

Finally, *hand-related feelings* were mainly evident in VR who showed symptoms of arm personification, avoidance behaviour and autocriticism, while restraining actions were also performed by BG.

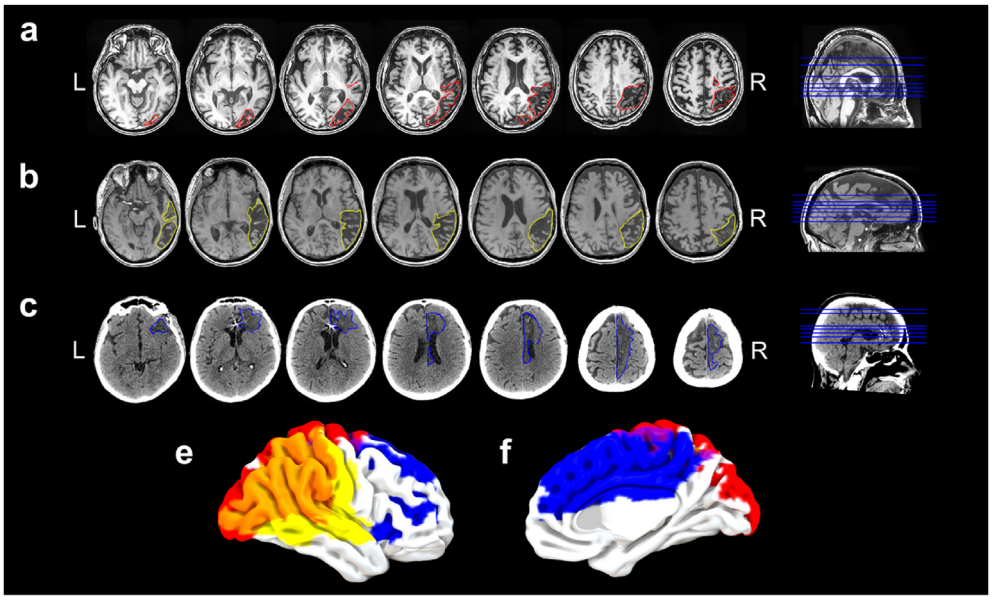

Fig. 1 – Grey matter involvement in the three patients' lesions. AA's (a) and BG's(b) 3D-T1 MRI image and VR's (c) 3D-CT scan image and lesion mapping. Axial and sagittal views are shown with the drawing of the lesion in the right hemisphere. e) Lateral view and f) medial view of areas of lesion overlapping in AA (red), BG (yellow) and VR (blue). Orange-coloured surface reflects the overlap between AA and BG. Purple-coloured surface indicates the overlap between AA and VR. Note that there is no overlapping among the lesions of the three patients. L: left. R: right.

3.2. *Neuroanatomical investigation*

An observation of the patients' lesions revealed three different anatomical profiles (Fig. 1, the proportion of involvement for each area, for each patient is shown in Supplementary Material S3). While an antero-medial lesion characterises VR (Moro et al., 2015), AA suffered from posterior damage involving the supramarginal and angular gyri, the superior parietal cortex and the lateral and medial occipital cortices. This pattern partially involves the same areas as in BG's lesion (Pacella et al., 2021). However, the intersection of the three patients' lesions showed that there are only two voxels in the right precuneus (out of 26.083, AAL template) that overlap. Thus, based on the lesion mapping analysis, it could be seen that the patients had different lesion locations. The lesions overlaps of patient pairs (see Supplementary Table S4) show i) a common involvement of the precuneus and precentral gyrus for BG and VR, ii) shared lesion location on the superior frontal gyrus, SMA, and paracentral lobule for AA and VR, iii) the involvement of the precentral and postcentral gyri, the rolandic operculum, the insula, parietal and occipital cortices, superior and middle temporal and fusiform gyri, and precuneus for AA and BG.

The indirect white matter disconnection observation confirmed the involvement of antero-medial disconnections for VR and the involvement of the body of the corpus callosum (Supplementary Fig. S1), and a similar pattern of AA's disconnections (Fig. 2a) as described for BG (Pacella et al., 2021). The tractography performed on AA's DTI confirmed the involvement of long fronto-parietal, fronto-temporal and fronto-occipital connections, temporal-occipital fibres, cortico-spinal projections, and short fronto-insular connections (Fig. 2b), and the posterior corpus callosum (Fig. 2c). The control tractography, performed on two tracts that were not observable on the indirect white matter investigation, confirmed that AA's medial frontal connections were spared from the lesion (Fig. 2d).

The intersection of the disconnectome maps of the three patients revealed common white matter disconnections (Fig. 3). These included long fronto-parietal tracts, such as the superior frontal-longitudinal tracts (SLF II, and SLF III). SLF II connects the angular gyrus and the middle frontal gyrus, and SLF III connects the supramarginal gyrus to the pars opercularis and triangularis of the inferior frontal gyrus (Thiebaut de Schotten et al., 2011; Rojkova et al., 2016). The intersection also included the inferior fronto-occipital fasciculus (which originates in the occipital lobe and terminates in the inferior frontal lobe, Catani, Howard, Pajevic, & Jones, 2002) and the arcuate fasciculus (that connects the inferior parietal lobe and lateral temporal and the inferior frontal cortices, arching around the Sylvian fissure, Catani & Mesulam, 2008). Furthermore, the projectional cortico-spinal tract is involved. Finally, a common involvement of the posterior part of the corpus callosum was found.

4. Discussion

This study focuses on a comparison of three patients who show similar symptoms of a very rare clinical condition, despite the fact that they suffered apparently different forms of brain damage. Although AHS was initially described at an early stage in the study of neuropsychology (Goldstein, 1908), it remains a mystery and is a source of crucial questions about the underlying mechanisms of motor awareness and goal-oriented actions. What makes us the agent of our actions?

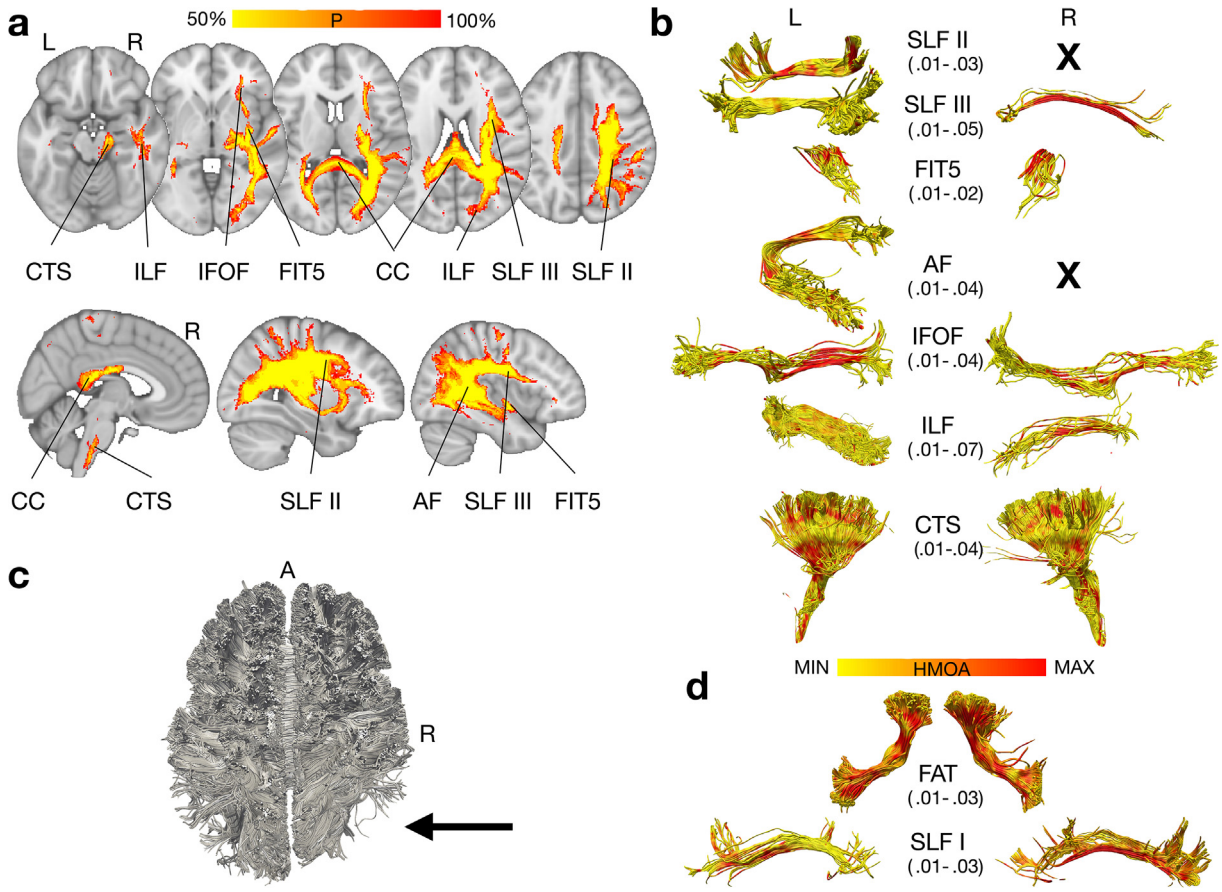

Fig. 2 – AA's white matter disconnections. a) The indirect white matter investigation revealed the involvement of cortico-spinal tract (CTS), the splenium and posterior body of the corpus callosum (CC), occipito-temporal (inferior longitudinal fasciculus, ILF) and occipito-frontal (inferior fronto-occipital fasciculus, IFOF) connections, posterior insular fibres (fronto-insular tract 5, FIT5), and fronto-temporal (arcuate fasciculus, AF) and inferior and middle fronto-parietal (third and second branches of the superior longitudinal fasciculus, SLF III and II) connections. The colour bar represents the probability of disconnection. b) The reconstruction of association and projection tracts based on the patient's diffusion tensor imaging. 'X' represents the tracts for which tracing was hindered by the lesion. Tracts reconstruction is described in the Supplementary Material S2. The colour bar represents the Hindrance Modulated Orientation Anisotropy (HMOA) value, whose minimum (yellow) and maximum (red) threshold was tailored on each tract pair. The minimum and maximum values are indicated in parenthesis for each tract pair. (c) Axial display n of AA's corpus callosum (CC) reconstruction. The arrow indicates the cortical fibres corresponding to the posterior interhemispheric connections of the CC, whose reconstruction has been hindered by the lesion. d) Two pairs of tracts (frontal aslant tract, FAT, and the first branch of the superior longitudinal fasciculus, SLF I) that were not included in the AA's indirect disconnections results were reconstructed as controls. As for (b), maximum and minimum HMOA values are indicated in parenthesis for each tract. A: anterior. L: left. R: right.

Where does the experience of controlling one's own motor acts come from (Haggard, 2017).

In the past twenty-five years, neuroscientists have made efforts to respond to these questions and understand the motor, affective and social processes which produce a sense of agency (for a review, see Haggard, 2017; Villa, Ponsi, Scattolin, Panasiti, & Aglioti, 2022). However, experimental approaches with healthy subjects encounter the difficulty of distinguishing processes that are actually entangled, such as body versus motor awareness, and in the latter, motor intention versus motor monitoring (Pacella & Moro, 2022). A study of AHS offers the opportunity to disambiguate these aspects, as patients report difficulties in motor intention (i.e., a hand that moves involuntarily) but do not suffer from body representation disorders or deficits in action monitoring.

Unfortunately, group studies of AHS are extremely difficult to carry out due to the nature of the syndrome itself. It is relatively rare as it manifests only when contra-lesional motor deficits are absent and, for this reason, most stroke patients with lesions in the cortico-spinal tract are excluded. To the best of our knowledge, only five previous studies have reported three or more AHS patients (Chan & Ross, 1997, n.3; Lavados et al., 2002, n. 4; Brainin et al., 2008; Panda, 2010; Bakheit et al., 2013), and a direct comparison of neuroanatomical correlates has never been performed. Based on previous reviews of the literature (Moro et al., 2015; Pacella et al.,

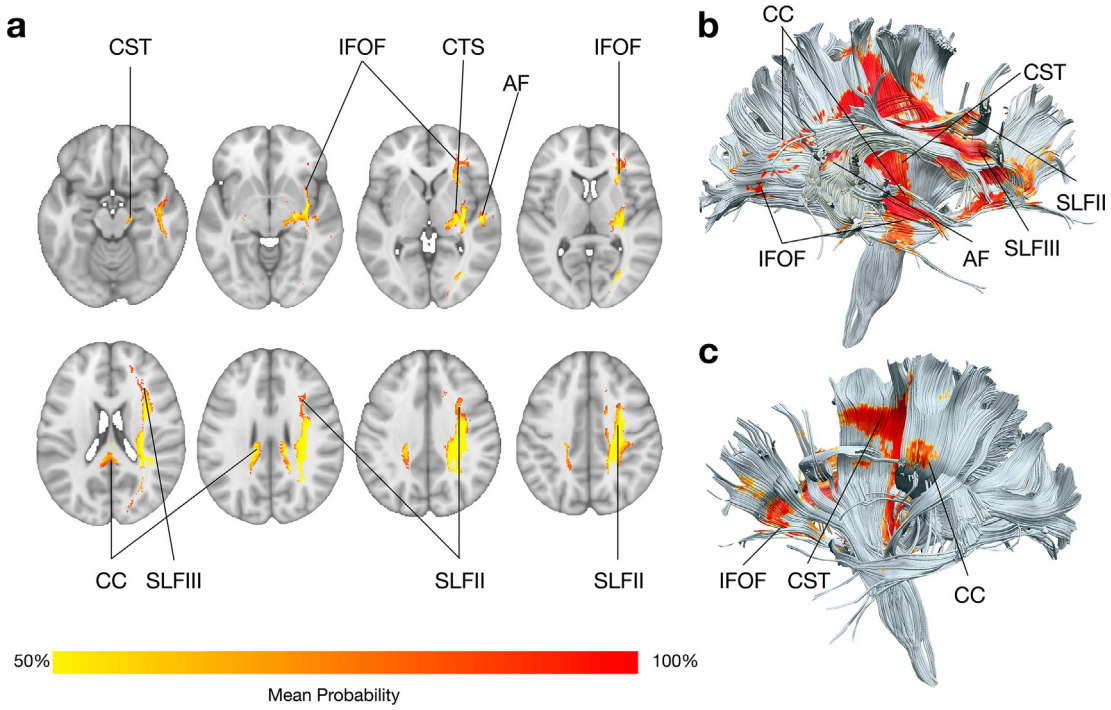

Figure 3 – Mean probability of common white matter tract disconnections. a) Axial view of the common fronto-parietal, fronto-temporal, fronto-occipital, projectional and posterior commisural disconnections. b) Lateral view of the reconstruction of disconnected tracts (right hemisphere). c) Medial view of the disconnected tracts (right hemisphere). The colour bar represents the mean probability of disconnection. AF: arcuate fasciculus; CC: corpus callosum; CST: cortico-spinal tract; IFOF: inferior fronto-occipital fasciculus; SLF II, III: second and third branches of the superior frontal longitudinal fasciculus.

2021), a comparison was made of three patients suffering from the anterior and posterior variants of the syndrome, which allowed us to identify certain core characteristics relating to AHS. Furthermore, an investigation of the white matter disconnections that were common to the three patients provided data on a common neural network which is involved in motor intention and goal-directed actions.

4.1. *A symptomatological core for AHS*

There was a group of symptoms common to all three patients, irrespective of the areas affected by the lesions. Among them, magnetic apraxia and grasping may be considered to be "primary" symptoms of AHS as they are apparently purposeful or semi-purposeful movements and thus clearly manifest the involuntary nature of anarchic hand actions. In magnetic apraxia, the mere visual presence of an object near the hand (or touching the hand) triggers groping movements as well as grasping (Denny-Brown, 1958). The patient is not able to inhibit this behaviour, which is often associated with grasping, as in the case of our patients. It can however sometimes present as an isolated symptom. In previous literature, magnetic apraxia has been reported in the anterior subtypes of AHS following both right or left frontal damage but never in connection with posterior, thalamic or pure callosal lesions (Moro et al., 2015 for review).

Conversely, levitation is usually described following posterior lesions and has not been reported after anterior right hemisphere lesions. We found this symptom involving uncontrollable upward movements of the arm in all three of our patients. In VR and BG, this represented the only sign of unpurposeful hand movements, while in AA, it was associated with exploratory and repetitive movements and self-grabbing. Furthermore, in the patient with an anterior lesion (VR), this symptom was resolved in the first few months and was not recorded at the 4-month assessment.

Other common symptoms, namely, bimanual incoordination, synkinesis or mirror movements, disorders in manual dexterity and action sequencing, are reported in the literature for all of the subtypes of AHS (but not thalamic lesions, see Nowak et al., 2014; Park et al., 2012).

It is noteworthy that ideomotor apraxia was present in our patients, with the difference that in AA's case, bilateral ideomotor and ideational apraxia were diagnosed, while VR and BG suffer from unilateral left-hand apraxia. Thus, while the latter may be configured as callosal apraxia, in the first case, there is probably a form of crossed apraxia following right parietal damage (although the patient was not left-handed). Apraxia is poorly investigated and reported in AHS literature (Alvarez, Weaver, & Alvarez, 2020; Espinosa, Smith, & Berger, 2006; Pappalardo, Ciancio, Reggio, & Patti, 2004; Rohde, Weidauer, Lanfermann, & Zanella, 2002; Ventura, Goldman,

& Hildebrand, 1995; Yamaguchi et al., 2006) and probably deserves more consideration.

Taken as a whole, these data lead us to believe that deficits in motor intention represent the "core" characteristic of AHS, alongside the contemporary presence of "productive" symptoms, that is, involuntary but apparently purposeful movements, and "negative" symptoms (i.e., the incapacity to perform efficacious voluntary actions, in particular bimanual actions, Haggard, 2019). A detailed analysis of our patients' symptoms and a comparison with previous literature on the topic suggest that the classification as anterior and posterior subtypes (Feinberg et al., 1992) does not explain the complexity of the syndrome, which is probably the result of damage to an antero-posterior network involving both lateral and medial structures (see below).

In addition to these "core symptoms", others may or may not be present and this needs to be understood. For example, AA presents with anarchic hand exploratory movements, repetitive movements and self-grabbing, which are not recorded for BG, although the two lesions are very similar. It is noteworthy that BG suffers from somatosensory deficits (absent in AA) which might reduce the general motor activity of the anarchic hand. To support this notion, there is also less unmasking of apparently purposeful, involuntary movements in this patient in comparison to AA and VR (e.g., forced grasping and groping, Table 2).

On the other hand, VR and GB show more symptoms associated with bimanual interactions, intermanual conflict and diagnostic dyspraxia, neither of which are present in AA. This may be due to partially different lesions (see below). Indeed, in previous literature, these symptoms are rarely reported in patients with posterior non-callosal lesions (Spector, Freeman, & Cheshire, 2009). Finally, only VR manifests specific feelings towards her hand (in particular, personification, autocriticism and avoidance).

This wide variety of clinical manifestations relating to AHS in apparently similar patients indicates a need to separate a nucleus for the main AHS symptoms (i.e., magnetic apraxia, apraxia, grasping, bimanual incoordination, mirror movements/synkinesis and levitation) from other associated symptoms that may accompany the disorder but are not essential to the diagnosis. This group of symptoms is consistent with a hypothesis regarding the involvement of a neural network connected to awareness of motor intention.

Anarchic hand syndrome may be considered in some way complementary to motor neglect (MN), the clinical condition where patients underuse the contralesional limbs. Even in the complete absence of sensorimotor deficits, they behave as if their limbs are paralysed (Garbarini, Piedimonte, Dotta, Pia, & Berti, 2013). They ''forget'' to use their contralesional limbs, and when they use them, movements are delayed (hypokinesia), slowed (bradykinesia), and of reduced amplitude (hypometria) (Migliaccio et al., 2014). From a clinical point of view, the motor intention deficit seems to be complementary to that of the anarchic hand because patients are unable to implement an intentional motor program with the contralesional hand and are not aware of their deficit. However, while MN represents a lack of intention to move, with the consequent absence of any planning and execution, in AHS, there are movements which are in some way planned and that appear purposeful, although they are generated out of the patients' awareness. AHS patients are aware of the movements when and after they occur, but they are not able to identify the source of the intention to move. Furthermore, in MN patients there is a deficit in attention towards contralesional body parts. Indeed, patients forget to use their contralesional limbs, but when explicitly asked to move them, they correctly execute movements. Conversely, AHS patients are usually very focused on their anarchic hand (i.e., no attentional disorders towards body parts) but totally unable to control its movements except by forced constraint actions.

This complementarity is reflected in the neural underpinning of the two syndromes. In fact, the involvement of the limbic system and medial structures characterises the lack of motivation in movement initiation for MN patients. Our results indicate that the limbic structures are excluded from the core network contributing to AHS.

4.2. *A neural network for awareness of motor intention*

The neuroanatomical and disconnection analysis conducted as part of this study sheds light on a complex neural network that is shared among the three patients and is potentially useful in terms of identifying the neural core of AHS. The network involves three disconnection patterns, namely the interhemispheric disconnection (via CC), the antero-posterior intra-hemispheric disconnection (via SLF, IFOF and Arcuate) and the involvement of descendent tracts (the CST). Taken as a whole, these findings explain both the productive and negative symptoms of AHS described (Fig. 4).

As expected, the involvement of the corpus callosum was found. This might explain some motor symptoms, such as bimanual incoordination and unilateral apraxia. However, it is noteworthy that these disorders are usually recorded in lesions involving the anterior part and the genu of the CC (Berlucchi, 2012 for review), while in our patients, the common disconnection regards the more posterior part. In VR and BG, the lesions extend in a more anterior direction, which may explain the intermanual conflict and diagonistic dyspraxia as well. In contrast, in AA, whose CC lesion is only posterior, the main symptom of disconnection is the deficit in interhemispheric sensory transmission. The presence of apraxia confirms this difference, which is confined to the left hand in VR and BG but is bilateral in AA. In the latter case, it is thus possible that, rather than a form of callosal apraxia, there is "crossed apraxia" due to the parietal lesion.

The antero-posterior disconnections account for both the typical "frontal" symptoms, such as purposeful and semi-purposeful movements of the hand (i.e., magnetic apraxia and grasping), and more typical "posterior" symptoms, such as levitation and environmental dependent movements, found to be common to all three patients despite the differing localisation of their lesions. Finally, while the SMA was not directly lesioned in all of our patients, our findings suggest that its normal functioning is disrupted through disconnection via the corticospinal tract (CST). These descendent tract disconnections prevent communication between cortical and subcortical structures, with an imbalance between internal and external driven actions and the appearance of involuntary movements (e.g., mirror movements and synkinesis).

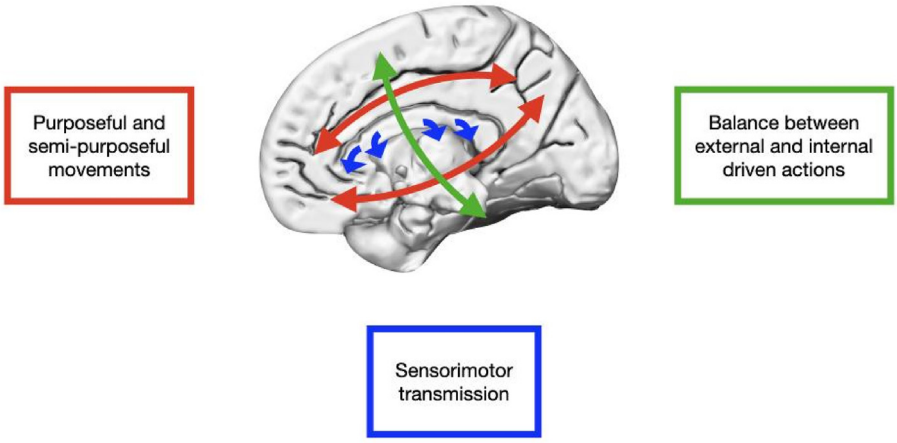

Fig. 4 – The circuitry of motor intention in AHS. The arrows represent brain connections, and AHS core symptoms are indicated in the squares. The red arrows represent intra-hemispheric connections that support the purposefulness and semi-purposefulness of movements (dorsal arrow: superior longitudinal fasciculi, arcuate fasciculus, ventral arrow: inferior fronto-occipital fasciculus). The green arrow indicates the descending pathways that supervise the balance between external and internal driven actions (corticospinal tract). Blue arrows show interhemispheric connections, supporting the transmission of sensorimotor information (corpus callosum).

Finally, only VR displays personification, autocriticism and avoidance behaviours. These symptoms have previously been reported in callosal and cingulate variants of the syndrome, with, however, AHS cases involving feelings of unfamiliarity being reported after posterior lesions (Moro et al., 2015). The cingulate cortex is part of the limbic network and works jointly with primary sensory cortices to form emotional associations (Rolls, 2013). Thus, the extensive involvement of medial and limbic structures in VR via direct lesion and white matter disconnection accounts for the abnormal limb-related feelings displayed by the patient.

Thus, the hypothesis that AHS is a disorder in the awareness of motor intentions is supported by these findings. Intentional actions are the result of multiple decisions that regard not only the decision to carry out an action or not ("whether"), but also the nature of the action ("what"), and the timing of its execution ("when") (Brass & Haggard, 2008; Hoffstaedter, Grefkes, Zilles, Eickhof, 2013; Krieghoff, Brass, Prinz, & Waszak, 2009; Pacella et al., 2022; Zapparoli et al., 2018; Korka, Widmann, Waszak, Darriba, & Schröger, 2022). In AHS, all three of these components are compromised as patients are unable to decide whether or not to perform voluntary actions, and they cannot modify the target of these actions (e.g., when the hand makes inappropriate actions) or decide the moment when the actions are to be performed. Both the "conscious intent" (i.e., the moment when the will to act is generated) and the "consciousness of conscious intent" (i.e., the moment when individuals become aware of this will, Guggisberg, Dalal, Schnider, & Nagarajan, 2011) are impaired.

Levitation, as well as mirror movements and synkinesis, reflect a disruption in the awareness of intended movements, resulting in unconscious hand movements which are independent of the subject's will. Indeed, the involvement of the parietal cortex in motor intention (Desmurget & Sirigu, 2009, 2012) has been previously shown. Notably, rather than an isolated parietal lesion, it is the antero-posterior, fronto-parietal disconnections that explain the symptoms related to environmental dependence and the lack of inhibitory control in our patients.

A lack of motor intention has been seen after damage to striatal pathways (Pacella & Moro, 2022) and uncontrolled behaviours such as mirroring movements have been documented after cortico-spinal tract damage (Solmaz et al., 2018).

With regard to posterior networks, studies on human and animal populations have identified the parietal cortex to be critically involved in an aware intention to move (Andersen & Buneo, 2002; Desmurget et al., 2009) and the occipital cortex is involved in the guidance of goal-directed reaching and grasping movements (Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003). Furthermore, an interruption to the processing of visuo-motor information in the occipital cortex and the processing of information in associative areas (Astafiev, Stanley, Shulman, & Corbetta, 2004; Hilbert et al., 2019) such as the parietal cortex might impair negative volition by triggering explorations in the surrounding area with the impaired contra-lesional hand.

Further studies are needed to support the hypothesis that AHS is a disorder in awareness of motor intention, and further in-depth neuropsychological and neuroanatomical investigations in larger patient cohorts are necessary in order to validate the involvement of a specific network in AHS. The main limitations of the current study are related to the rarity of the syndrome, as the small sample precluded the use of a statistical approach. Nevertheless, the extensive neuropsychological description of the patients makes it possible to provide a comprehensive picture of the symptoms. The lesion analysis approach performed on the three patients did not allow us to control for concomitant symptoms and lesion size. However, the combined lesion and disconnection approach enabled us to create a comprehensive anatomical profile of the patients and the symptoms they had in common.

CRediT authorship contribution statement

Valentina Pacella: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sara Bertagnoli:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Riccardo Danese:** Data curation. **Cristina Bulgarelli:** Data curation. **Valeria Gobbetto:** Data curation. **Giuseppe Kenneth Ricciardi:** Writing – review & editing, Methodology, Data curation. **Valentina Moro:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Data availability

The raw T1 scans of AA and BG, and the normalised lesions, disconnectome maps and AA's diffusion data are freely available at https://github.com/vale-pak/ahs. AA's DWI and VR's CT data anonimisation could jeopardise the quality of the images, imaging data requests should be made to Pr V. Moro upon data sharing agreement.

Legal copyright restrictions prevent public archiving of the neuropsychological assessments which can be obtained from the copyright holders in the cited references.

Analysis code and softwares used in the study are described in the manuscript.

No part of the study procedures and analyses were preregistered prior to the research being conducted.

Declaration of competing interest

The authors declare no competing interests.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2024.10.017.

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