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Contextual bottom-up and implicit top-down modulation of anarchic hand syndrome: A single-case report and a review of the literature

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ABSTRACT

Anarchic hand syndrome (AHS) is a rare neurological condition characterized by seemingly purposeful, goal-directed hand movements which the person afflicted by the syndrome is not, however, in control of. By extensively examining a patient with AHS we provide novel neuropsychological and lesion mapping data that shed new light on the possibility of modulating specific symptoms associated with AHS, in particular unilateral apraxia and magnetic apraxia. Moreover, we compared lesion mapping data with an in depth analysis of previous studies in order to explore the neural network responsible for the complex symptomatology associated with this syndrome. We found that non-primarily motor variables (e.g. the nature of the object to be grasped and integration of visuo-spatial feedback in action) play an important role in determining AHS symptomatology. Moreover, we found that lesions involving various different parts of the motor control network (the corpus callosum, the anterior cingulate cortex and the supplementary motor area, the parietal areas and thalamus) are closely linked to partially differing AHS symptoms. The comparison of our data with those reported in previous studies indicate that AHS is a multifaceted and complex syndrome in which the influence of non-primarily motor, emotional and higher-order components may be largely underestimated.

1. Introduction

Anarchic hand syndrome (AHS) is characterized by complex movements of an upper limb, which, although totally involuntary, appear goal-directed and well executed (Della Sala, 2009). Patients do not deny ownership of their anarchic hand (AH) but express the conviction that it has a will of its own or is driven by an external agent (Della Sala, 2009).

A variety of additional disorders may co-occur, namely unilateral limb apraxia, tactile anomia, deficit in interhemispheric sensory transmission, grasping, groping and compulsive manipulation of tools (Scepkowski and Cronin-Golomb, 2003). AHS appears thus to be a multifaceted syndrome, or rather a group of partially separate syndromes, each characterized by specific clusters of signs and putative neuroanatomical correlates.

The existence of callosal and frontal subtypes has been suggested (Feinberg et al., 1992). In the former, intermanual conflict and non-dominant involuntary movements are the main symptoms. These are interpreted as the failure to inhibit the non-dominant hemisphere during tasks requiring dominant-hemisphere motor control or verbal mediation (Feinberg et al., 1992). In the frontal subtype, lesions of the Supplementary Motor Area (SMA), sometimes associated with callosal damage, are crucial. The symptoms are the compulsive manipulation of tools by the dominant hand in addition to grasping, groping and uncontrolled reactivity to visual or tactile stimulation (Feinberg et al., 1992). While purely callosal lesions induce only transitory AHS (Della Sala, 2009), chronic forms usually occur following fronto-callosal damage.

The *dual premotor system theory* (Goldberg and Bloom, 1990) suggests the existence of two mechanisms for action control. The medial premotor system (involving the SMA and the cingulate gyrus) is responsible for internally driven activity (actions planned as the result of an individual's intention). On the contrary, the lateral premotor cortex (PMC) mainly deals with responsive, environmentally driven activities. The coordination of manual activities ultimately depends on a balance between these two systems. SMA lesions result in the disinhibition of lateral premotor system with AHS and automatic responses to objects (e.g.

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grasping) (Goldberg and Bloom, 1990). Due to the role of the SMA in action selection, AHS has also been considered as a deficit in the selection of intentional actions (Frith and Wolpert, 2000).

Although less frequent, AHS after posterior cortical regions or subcortical lesions has been described (Marey-Lopez et al., 2002). However, the variety of AHS symptoms makes it difficult to classify the clinical subtypes (Della Sala, 2009). Moreover, due also to the rarity of the syndrome, clinical case reports are hardly ever corroborated by evidence regarding the potential effects of experimental manipulation (Romano et al., 2014; Jenkinson et al., 2015).

Since the patient reported in this study was young and available for testing, we were able to integrate clinical and experimental approaches. After an in depth neuropsychological assessment, we compared our individual case with the results which emerged from a comprehensive revision of scientific literature on the topic (in Supplementary materials – SM).

We then explored the possibility of modulating two symptoms: unilateral apraxia (UA) and magnetic apraxia (MA). UA is the impaired ability (not due to motor deficits) to enact a motor command with the non-dominant hand. This is usually described as associated with callosal lesions and is thought to be a consequence of the right hemisphere impossibility to retrieve the correct movement concepts which are stored in the left hemisphere (Petreska et al., 2007; Goldenberg, 2013). In the first experiment, we explored the potential role of cognitive disorders in UA.

The compulsive tactile exploration and object grasping that often occurs after frontal lobe damage is called MA (Denny-Brown, 1958). As the salient visual characteristics of the objects (affordances) are fundamental in determining MA (McBride et al., 2013), we explored whether objects of a dangerous nature in the vicinity of the hand would modulate the symptom expression. In addition, by manipulating the perspective from which the AH was observed, we investigated the hypothesis that higher-order functions linked to body and space representations influence MA.

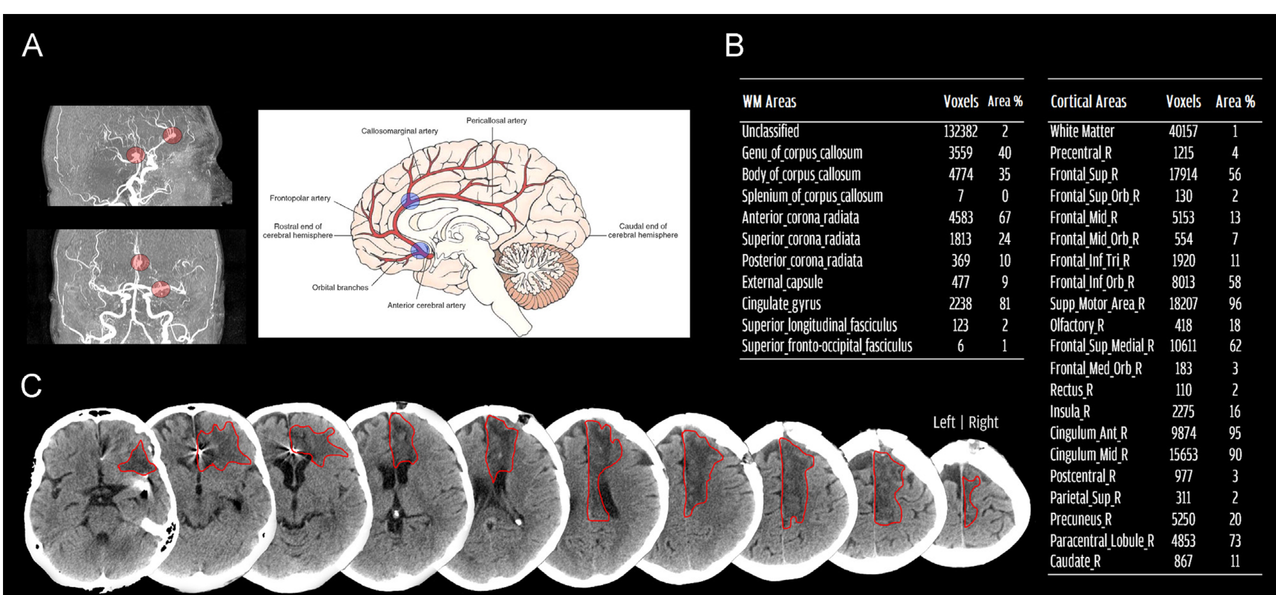
2. Case report

Two aneurisms (in the right middle cerebral artery at the main distal division and in the right pericallosal artery, at the origin of the callosomarginal artery) were diagnosed in VR, a 47-year-old, right-handed Brazilian woman (17 years of education) who had been living in Italy for 15 years (Fig. 1 A). To prevent dangerous bleeding, the patient underwent neuro-surgery.

When she regained consciousness after pharmacological sedation, VR was mutacic and presented with eye motor impersistence, left leg plegia and minimal signs of left arm paresis (MRC (Medical Research Council, 1986), upper limb: 4/5; lower limb: 0/5) without sensory deficits. A CT scan showed the presence of haemorrhagic damage in the frontal cortex, right anterior and middle cingulate gyri and the right paracentral lobule. White matter damage involved the Corpus Callosum (genu and anterior part), the anterior corona radiata and the cingulum (Fig. 1B and C).

Two months after surgery, general cognitive functions, language and verbal memory were recovered, while deficits in calculation, visuo-spatial and frontal executive functions were observed (Table 1). Lower limb paralysis, urinary and fecal incontinence persisted.

VR complained her difficulties with her left hand (LH) which behaved in an uncontrolled manner. For example, when she was having lunch, her LH took hold of the food while her right hand (RH) was using a fork normally; during a medical examination, it went into the pocket of the doctor's white coat; during conversations, her left index finger went into her nostril. To deal with these embarrassing situations, VR used her RH to hold down the other hand (restraining action) (Feinberg et al., 1992). Grasp reflex and impulsive and involuntary groping towards objects were present. To release an object, she used her RH to seize it from her LH, saying “This left hand is stealing and this one is giving back”. She handled everything (“I cannot have anything in front of me because 'she' takes everything”). Diagonistic dyspraxia (i.e., LH acting at cross-purposes to the RH (Tanaka et al.,



WM Areas	Voxels	Area %
Unclassified	132382	2
Genu_of_corpus_callosum	3559	40
Body_of_corpus_callosum	4774	35
Splenium_of_corpus_callosum	7	0
Anterior_corona_radiata	4583	67
Superior_corona_radiata	1813	24
Posterior_corona_radiata	369	10
External_capsule	477	9
Cingulate_gyrus	2238	81
Superior_longitudinal_fasciculus	123	2
Superior_fronto-occipital_fasciculus	6	1

Cortical Areas	Voxels	Area %
White Matter	40157	1
Precentral_R	1215	4
Frontal_Sup_R	17914	56
Frontal_Sup_Orb_R	130	2
Frontal_Mid_R	5153	13
Frontal_Mid_Orb_R	554	7
Frontal_Inf_Tri_R	1920	11
Frontal_Inf_Orb_R	8013	58
Supp_Motor_Area_R	18207	96
Olfactory_R	418	18
Frontal_Sup_Medial_R	10611	62
Frontal_Med_Orb_R	183	3
Rectus_R	110	2
Insula_R	2275	16
Cingulum_Ant_R	9874	95
Cingulum_Mid_R	15653	90
Postcentral_R	977	3
Parietal_Sup_R	311	2
Precuneus_R	5250	20
Paracentral_Lobule_R	4853	73
Caudate_R	867	11

Fig. 1. Pre and post-surgery neuro-imaging data. A. Red circles indicate the two aneurisms as they appeared in the pre-surgery MRI (sagittal and coronal plans); blue circles indicate the location of the aneurisms in a sagittal schematic drawing; B. Quantitative estimates of the damaged brain regions are reported. In the table, for each brain region the sum of grey and white matter lesioned voxels (first column) and the percentage of lesioned voxels (second column) are shown. The lesion analysis was performed by means of MRI-Cron software (http://www.cabiatl.com/mricro/mricron/index.html), superimposing the patient's MRI brain scans on the ICBM152 MRI scan template, previously rotated to match the scan orientation. The definition and labels relating to the anatomical maps are based on the “automated anatomical labelling” template (AAL) (http://www.cyceron.fr/index.php/en/plateforme-en/freeware); C. The patient's lesion is drawn in the axial slices of the post-surgery CT scan recorded at the assessment time. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Neuropsychological assessment. In bold the scores below the cut-off. Raven 38 (Raven, 1956); MMSE – Mini Mental State Examination (Folstein et al., 1975); AAT – Aachener Aphasia Test (Luzzatti et al., 1996); BIT – Behavioural Inattention Test (Wilson et al., 1987); *(Spinnler and Tognoni, 1987); Figure Rey (Rey, 1976); ToL – Tower of London (Allamanno et al., 1987); DT – Dual Task (Della Sala et al., 2010); TEA – Elevator Attention Test (Bate et al., 2001); BADS – Behavioural Assessment of the Dysexecutive Syndrome (Wilson et al., 1996); TMT – Trail Making Test (Giovagnoli et al., 1996); FAB – Frontal Assessment Battery (Appollonio et al., 2005). On the right column the cut-off or Equivalent Score (ES) or percentile value (centile) are reported.

General function		Cut-off/ES/Centile
Raven 48	24.7	ES=2
MMSE	29	24
Language (AAT)		
Token test (total score)	70	63
Oralcomprehension (total score)	63	62
Denomination (total score)	80	62
Writtenlanguage (total score)	74	62
Repetition (total score)	76	62
Spatial functions (BIT)		
Bisection line	9	7
Costructive apraxia* (14)	**9.5**	10
Albert (36)	36	34
Clock Drawing	+	
Figure Rey - Copy	**26**	10° cent
Memory		
Story recall*	14.3	10.5
Spatial supraspan*	**13.11**	10.25
Figure Rey - Recall	**10.5**	10° cent
Calculation (Miceli and Capasso, 1991)		
Addition (20)	**15**	/
Subtraction (18)	**7**	/
Multiplication (34)	**2**	/
Division (29)	**2**	/
Frontal functions		
ToL	16.75	15
DT: digitspan single	**83.33**	84.1
DT:digitspandual	90.38	83
DT: square single	**29**	45.9
DT: squaredual	**22**	48.1
TEA	**7.73**	4.7
BADS (profile score)	14	13
TMT A	**83**	68.03
TMT B	**180**	171.76
FAB	**13.1**	14.3

1996)) was referred once, four months after lesion, while she was hitching up her trousers, with the RH pulling them up and the left AH pulling them down. She manifested personification ("she does not feel afraid"). During complex LH movements (i.e. cutting with a knife), mirror RH movements appeared. These synkinetic movements were precise and apparently coordinated in terms of amplitude and timing, mirroring the LH trajectory. This did not occur with bimanual actions. When VR was asked to place her LH palm down on the table and an object was placed nearby, MA became evident, resulting in an exaggeration of positive exploratory behaviours and a compulsive need to touch objects (Table 2) (Denny-Brown, 1958). She never displayed disownership or reported any feelings of "main étrangère", suggesting that she was affected by anarchic and not alien hand syndrome (Jenkinson et al., 2015) (see the video in Supplemental materials – SM). Other symptoms due to callosal damage are reported in Table 2.

VR's symptoms were monitored with a frequency of 2–3 times a week for the first three months after the lesion onset and at least once a week in the subsequent three months. Unfortunately, these did not change over time.

All procedures were approved by the local ethics committee (CEP, Verona) and informed written consent was obtained prior to the experiment.

Table 2
VR's AHS symptoms and Assessment of callosal disconnection. (n) = number of items; 1=Peru et al., 2003; 2=Moro et al. (2008); 3=Spinnler and Tognoni (1987); 4=De Renzi et al. (1980); 5=Reynolds and Bigler (2003). The Anarchic Hand Symptoms (upper part) have been identified following the definitions reported in the Part A of the SM (Terminology). For Agnosia, clinical non-validated tasks have been used. For Apraxia the procedure and normative values (cut-off) suggested by the cited studies have been followed. The cut-off value for Sequence imitation task is not available.

Anarchich hand symptoms			
Purposeful movements	Magnetic apraxia	+	
	Grasping	+	
	Forced Grasp	+	
	Groping	+	
	Compulsive manipulation	–	
	Utilization Behaviour	–	
Non-purposeful movements	Exploratory behaviour	–	
	Repetitive Movements	–	
	Self grabbing	–	
	Levitation	–	
	Nocturnal movements		
Opposite hand related movements	Intermanual conflict	–	
	Diagonistic Dyspraxia	1	
	Responsiveness	–	
	Mirror movements	–	
	Syncinesie	+	
Other symptoms	Unresponsiveness	+	
	Dexterity	+	
	Bimanual incoordination	+	
	Tapping	+	
	Sequence	+	
	Lower limb Sensory Deficit	+	
	Lower limb Motor Deficit	+	
	Mutism (initial)	+	
Strategies or feelings	Alien hand	–	
	Personification	+	
	Restraining action	+	
	Autocriticism	–	
	Avoidance Behaviours	+	
Agnosia		Left	right
Intramanual tactile localization test (10)[1]		10	10
Interhemispheric tactile localization test[1] (15)		15	15
Haptic recognition test (acc., 12)[1]		12	12
Haptic recognition test (sec)[1]		169"	200"
Finger agnosia			
Indication on denomination (10)[2]		10	10
Denomination her fingers (10)[2]		10	10
Denomination fingers in a picture (10)[2]		10	10
APRAXIA		Left	Right
Ideomotor (72, cut-off 53)[3]		39	69
Ideative - pantomime (90, cut-off 82)[4]		35	90
Ideative - use (90, cut-off 90)[4]		80	90
Bucco-facial (20, cut-off 20)[3]		20	
Sequence imitation (40)[5]		9	29

2.1. Systematic revision of the literature

With the aim of comparing this case report with previous studies, a comprehensive revision of scientific literature on AHS was carried out (see SM for details). A selection of studies of Pubmed indexed articles published between 1981 and March 2015 was performed, using as the key terms"'Anarchic hand', and/or 'alien hand'. The results of the revision are shown in detail in the SM and commented in the Discussion.

This approach enabled us to systematically organize the AHS symptoms terminology and calculate the different frequency of motor and non-motor symptoms in the various different AHP subtypes (resulting from right or left fronto-callosal, callosal, antero-posterior mixed or thalamic lesions).

3. Experiment 1. Unilateral left apraxia: an analysis of gestures

Unilateral Apraxia following callosal lesions is usually explained as a consequence of the right hemisphere impossibility to retrieve the correct movement concepts which are stored in the left hemisphere (Petreska et al., 2007). Nevertheless, it is possible that other underestimated components of action, mainly mediated by the right hemisphere, play a role in the disorder. In this case the deficit might be not restricted only to meaningful actions when executed on verbal command but also to meaningless actions and in general to actions executed on imitation.

To understand the exact nature of UA, we used a task developed by Buxbaum et al. (2000) in which the spatial components of a variety of gestures (i.e. meaningful action on command and imitation, meaningless imitation gestures and use of objects) were analyzed using very well controlled and detailed qualitative criteria. This was integrated with a qualitative analysis of errors typology (De Renzi and Lucchelli, 1988).

3.1. Methods

First, the patient was verbally requested to perform 10 transitive (imagining using specific implements) and five intransitive gestures (Verbal Command condition). Then she was asked to imitate 15 meaningful gestures (Meaningful Imitation condition) and 15 meaningless gestures (i.e. Meaningless Imitation condition) performed by the examiner. Each meaningless movement was obtained by modifying a meaningful gesture. It had similar characteristics to the original action in terms of the plane of movement (vertical/horizontal), moved joint (shoulder/elbow/wrist/fingers), grip (hand open/clenched/partially open) and oscillation (present/absent).Finally, VR was asked to perform 10 transitive gestures using real implements (Use condition).

Two independent experimenters (different from the experimenters who carried out the clinical assessment) observed VR's performance in a video and rated: (i) the four components of the gesture (grasp, trajectory, amplitude and timing; 0=non-recognizable gesture, 4=correct execution) (Buxbaum et al., 2000) and (ii) the qualitative nature of the gesture errors (De Renzi and Lucchelli, 1988) (1/0 score=presence/absence of error). The concordance between the two observers was at .977 (Kendall's W coefficient of concordance, from 0=no concordance to 1=perfect concordance (Kendal, 1948). In case of discordant ratings, examiners re-checked the video until an agreement was achieved.

Non-parametric analyses were performed in order to analyse VR's gestures. In particular, we considered VR's right hand performance as a control measure. Using the Mann–Whitney test we compared the right and the left hand performance with the actions divided in four categories (Meaningful Imitation and Command, Meaningless and Use). Wilcoxon tests were then used to explore whether the left hand performance differed among action subtypes (Meaningful Imitation and Command, Meaningless and Use).

Finally, in order to analyse the various frequencies of the different typologies of error, a log-linear model was used. This allowed us to analyse binomial data with the same flexibility as an ANOVA analysis. As post-hoc analyses we used Bonferroni corrected, χ^2 tests."

3.2. Results

VR's LH (but not her RH) failed in all the conditions (Mann–Whitney, $W=16$, $p<.0001$), although her performance appeared to be significantly facilitated in the Use condition in comparison to the other conditions (Wilcoxon tests: Meaningful/Command: $V=35$, $p=.0156$; Meaningful/Imitation: $V=32.5$, $p=.0491$; Meaningless/Imitation: $V=34$, $p=.0298$).

The most frequent errors were in hand position, sequence and conduits d'approche (Table 3) (De Renzi and Lucchelli, 1988). A log-linear model was fitted onto data using the Error Type (perplexity, sequence, omissions, conduits d'approche, perseverations, position, awkwardness and substitutions) and the Conditions (Meaningful/ command, Meaningful/imitation, Meaningless/imitation, Use) as main factors. Only the Error Type was significant ($\chi^2_{(7,21)}=37.224$, $p<.0001$). We analyzed the frequencies for each Error Type (Chi-squared tests Bonferroni corrected). Errors in Position ($N=24$) were more frequent than Perplexity ($N=5$, $\chi^2_1=12.448$, $p<.05$), Substitution ($N=6$, $\chi^2_1=10.800$, $p<.05$), Perseveration ($N=4$, $\chi^2_1=14.286$, $p<.01$) and Omissions ($N=1$, $\chi^2_1=21.16$, $p<.001$), while they did not differ from errors in Sequence and Conduits d'approche, which in turn were not significantly more frequent than the other types of error (Table 3).

The presence of all the possible errors in the task rules out the possibility that lack of motor dexterity or poor action control explain the UA as also suggested by the patient's comments to her attempts of execution. Indeed the patient sometimes expressed verbally her total inability to plan and organize the action ("I do not know how I can do this…").

Our results suggest that LH apraxia following corpus callosum lesions is not limited to verbal commands but also occurs in imitation and use of objects, although objects facilitatethe correct action sequence. In addition, there are more errors in Meaningful actions on command than in Imitation conditions supporting the hypothesis of a defective inter-hemispheric transmission of concepts from the left hemisphere. Spatial functions influence performance, at least in left HA, probably due to the right hemisphere lesions.

Table 3
Analyses of Gesture components. In the upper part, the scores for gesture production are reported for each task condition. (n)= number of trials; LH= left hand; RH= Right hand. In the lower part of the table qualitative analyses of the LH errors are reported, divided for condition and typology of error. Pos: Position; Seq: Sequence; Perp: Perplexity; Cond: Conduits d'Approche; Subs: Substitutions; Pers: Perseverations; Omis: Omissions; Unr: Unrecognisable Gesture or Awkwardness (Buxbaum et al., 2000).

Conditions	Grasp		Trajectory		Amplitude		Timing		Tot score	
	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH
Meaningful (command) (60)	**27**	57	**32**	54	**33**	60	**41**	59	**133**	230
Meaningful (imitation) (60)	**35**	60	**38**	60	**40**	60	**54**	60	**167**	240
Meaningless (imitation) (60)	**35**	59	**25**	60	**28**	59	**44**	60	**132**	238
Use (40)	**29**	39	**28**	38	**27**	38	**33**	40	**117**	155
Total score	**126**	215	**123**	212	**128**	217	**172**	219		
Kinds of errors (LH)	**Pos**	**Seq**	**Perp**	**Cond**	**Subs**	**Pers**	**Omis**	**Unr**	**Tot score**	
Meaningful (command)	8	2	2	5	3	3	0	2	**25**	
Meaningful (imitation)	6	5	0	1	2	1	1	1	**17**	
Meaningless (imitation)	5	3	1	5	0	0	0	5	**19**	
Use	5	0	2	2	1	0	0	0	**10**	
Total score	**24**	**10**	**5**	**13**	**6**	**4**	**1**	**8**		

4. Experiment 2. Magnetic apraxia: nature of objects and visuo-spatial perspective

To investigate potential top-down or bottom-up modulations of MA, we used a three step task and manipulated the object nature and the perspective from which the patient observed her hand.

4.1. Methods

First step: VR was asked to keep her hands still, palm down on the table, while the examiner randomly moved 10 objects towards her LH. Half of these were neutral (i.e. a glass, a pincushion without pins, an unlit candle, closed scissors and a file for shaving wood) and half were potentially dangerous (i.e. a broken glass, a knife, a lit candle, a saw and a pincushion with pins).Each object was presented a variable number of times (from 10 to 20) for a total of 69 trials for neutral objects and 64 trials for dangerous objects. The number of grasping, movements of attraction (i.e. LH approaching the object and touching it but not picking it up) and inhibited responses (her hand remained still for at least 5 s) were recorded (see Fig. 2A).

Second step: the same task was performed while VR was looking at her hand in two visual perspectives: directly (first-person perspective, 108 trials) or reflected in a mirror (third-person perspective,102 trials) (Fig. 2B).

Third step: the spatial position of objects was manipulated so

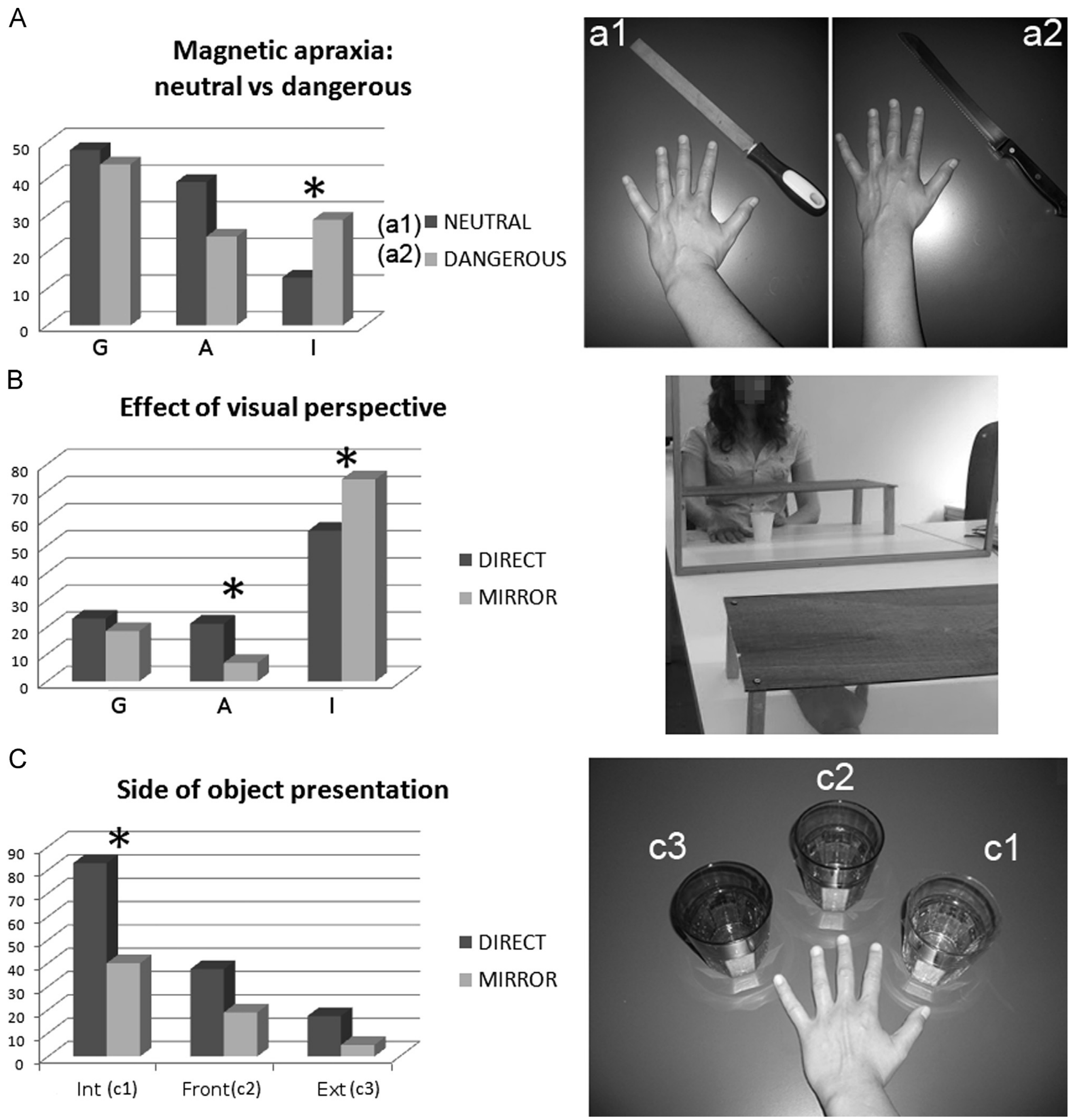


Fig. 2. Magnetic apraxia: top-down and bottom up modulation of automatic responses. A) Number of grasping (G), movements of attraction (A) and inhibited responses (I) are reported for neutral and dangerous objects viewed directly. B) The patient's responses are compared in the direct viewing task and the mirror viewing task. C) The patient's responses to objects presented from different spatial sides are compared. Int=internal (c1); Front= frontal side (c2); Ext=external (c3). *=significant comparison ($p < 0.05$). See the text for a description of the results.

that objects moved towards VR's hand from the internal (Fig. 2c1), the front (Fig. 2c2) or the external side (Fig. 2c3).

Behaviours of grasping, attraction and inhibition of the involuntary responses were analysed using χ^2 tests with Yates correction.

4.2. Results

10 trials performed with VR's RH showed her ability to control this hand. For this, only the data concerning her LH were considered (Fig. 2).

The dangerous nature of objects modified VR's responses, with a significant improvement in her inhibition of movement in the presence of dangerous with respect to neutral objects ($\chi_1{}^2$ corrected Yates: 4.58, $p=.03$).

The change in visual perspective also led to an improvement (Inhibition, χ_1^2 corrected Yates: 7.45, $p=.006$) with a significant reduction in attraction responses (χ_1^2 corrected Yates: 7.78, $p=.005$; grasping: χ_1^2 $p>.05$) in the mirror condition. This improvement (see Fig. 2C for the total for grasping and attraction) in mirror condition seemed to be present in all of the three different directions, but it was only significant when the object was presented to internal side (χ_1^2 corrected Yates: 14.79, $p=.001$).

Crucially, VR's involuntary movements appeared in some way to adapt when the objects were dangerous in nature. For example, she never grasped the sharp part of the broken glass or the knife. In a similar vein when the flame of the lit candle was moved towards her AH, it moved away accordingly. Thus, although intentional AH control was impossible, a context-dependent modulation of the motor act was present.

5. Discussion

Our results indicate that AHS is a multifaceted syndrome, where non-motor factors interact with the mechanisms of motor control. External environmental factors, such as the object nature (dangerous or neutral) and the side towards which object is presented, influenced automatic responses. In addition, top-down factors, such as the perspective from which the hand and the objects are observed, seem to be involved in the modulation of symptoms. These results suggest that AHS may be influenced by space, body and action representations.

5.1. Anarchic hand: how many syndromes?

The detailed revision of the literature on the subject provided interesting data regarding the frequency of AHS symptoms and the correlation of these symptoms to cerebral damage (SM).

Environment-dependent behaviours (grasping, groping and MA) represent the main and most frequent expressions of frontal damage. The distinction between these symptoms is not always clear in the literature and MA is probably underestimated. These were found only in the cases of anterior or mixed lesions (with a main role of SMA and Cingulate gyrus, Supplementary D) and never in the posterior or callosal subtypes. Compulsive manipulations of tools (Other, in SM, B and C) is frequent in the anterior and mixed variants as well.

Diagonistic dyspraxia (or diagnostic apraxia, i.e. the condition in which the alien hand acts at cross purposes with the other hand) has always been found to be present after callosal damage, and sometimes also in the other subtypes. In contrast, Agonistic Dyspraxia (when requested to execute an action with one hand, the subject uses the other hand) is rare. Other symptoms frequently associated with callosal lesions are UA, deficits in interhemispheric sensory transmission and bimanual incoordination.

Three symptoms clearly distinguish anterior and posterior AHS. AH unresponsiveness (sometimes associated with akinetic mutism) is reported after medial frontal and cingulate cortex lesions, but never in posterior lesions. In contrast, levitation and exploratory behaviour characterize the posterior subtype.

Levitation is also reported after thalamic lesions. Involuntary self-grabbing is frequent, but when this is associated with self-hitting it seems to be typical of thalamic lesions.

Intentional restraining of actions is not frequently described and probably underestimated. Indeed, rather than symptoms these are considered to be a patients' compensatory strategy to control the hand.

Other frontal symptoms such as urinary and fecal incontinence, lower limb hyposthenia, disexecutive syndrome, synkinesis and motor incoordination are probably underestimated. This represents a limitation in terms of diagnosis and rehabilitation. In fact, although benzodiazepines and botulinum toxin injections were reported to be useful, to date the majority of interventions are behavioural and metacognitive (Sarva et al., 2014, but see Romano et al. (2014)). The Alien Hand is very infrequent in all the AHS subtypes (SM). In fact, patients often express the feeling that their hand has its own mind and willpower (personification), but they do not usually deny ownership of their hand. This confirms that AHS and Alien Hand are two different syndromes, affecting the agency system and the body ownership respectively (Jenkinson et al., 2015).

In keeping with Feinberg's classification (Feiinberg et al., 1992), VR showed symptoms which are usually correlated to the frontal subtype. Nevertheless, she did not show utilization behaviour, i.e. a condition where patients do not complain about their hand movements and tend to explain and justify them. Our patient was worried and annoyed by her hand and her incapacity to stop its movements. In contrast to Feinberg, VR's symptoms concerned the non-dominant hand.

Her unwilled stimuli-driven movements may be explained by the *dual premotor system theory* (Frith and Wolpert, 2000), and considered as frontal release signs, probably due to disconnections between the SMA, (which stores and organizes the motor subroutines related to internal driven movements) and the lateral motor system in the premotor lateral cortex (responsible for movements generated in response to external stimuli). In normal conditions, the anterior part of the SMA inhibits the primary motor cortex, which can initiate a movement only when activity in this area drops (Rizzolatti et al., 1990). When this region is damaged, PMC acts without control and is totally dependent on the environment.

VR's lesion encompasses the SMA almost totally. This may be the cause not only of the LH involuntary movements (driven by object affordance) but also of the errors she made in the selection of intentional actions (e.g. the conduits d'approche) which however remained somewhat possible thanks to the spared activation of the prefrontal lateral cortex (Frith and Wolpert, 2000).

The UA, the bimanual incoordination, the loss of manual dexterity and the rhythm disorders were all probably due to the damage to the corpus callosum. In this regard, Feinberg's model is confirmed by our case and by what we found when revising the literature, i.e. that these symptoms are more frequent with anterior fronto-callosal lesions. In these lesions, UA may involve both the left and right hand (although more frequently for left hand). Conversely, UA involves exclusively the left hand when the lesions are posterior or in the corpus callosum.

Nevertheless, it was possible to exclude the hypothesis of a pure callosal formas our patient did not show diagonistic dyspraxia, the most consistent symptom in this form (Tanaka et al., 1996).

Finally, VR's clinical symptoms involving lower limb paralysis, urinary and fecal incontinence, initial mutism, and deficits in executive functions, visuo-spatial short term memory and calculation all support the involvement of both frontal and callosal structures (Peltier et al., 2010). This was confirmed by the analysis of VR's lesions showing damage to various parts of the complex networks that connect not only lateral and medial frontal cortex, especially SMA, but also these with cingulate cortex, corpus callosum, and parietal regions. This type of lesion is responsible for chronic forms of AHS (Papagno and Marsile, 1995), which was confirmed by the absence of any improvement in our patient six months after the lesion onset.

5.2. Unilateral apraxia

Classical theories explain UA as being due to a disconnection between the right primary motor cortex and the left parietal areas where the motor engrams are sited (Denny-Brown, 1958): in the absence of inter-hemispheric transmission of verbal information, the gesture execution on verbal command is specifically impaired; in contrast, the use of real objects improves performance, also due to the advantage resulting from objects affordance (McBride et al., 2013). VR's performance improved when she used objects in comparison with other conditions. Nevertheless, imitation (with the exclusion of the verbal component) was not sufficient to improve her performance which was maximally impaired in the Meaningless and Meaningful Imitation conditions. Thus, it is possible that in addition to a deficit in inter-hemispheric transmission, the right hemisphere damage contributed to the symptoms. This may also explain VR's spatial errors. Finally, the patient's errors in sequence and"conduits d'approche' suggest that although the representation of the intended goal was spared, VR was not able to execute the AH motor plan in consecutive steps, probably due to lesions involving the anterior part of the corpus callosum, the SMA and the anterior cingulate cortex (Passingham et al., 2010).

5.3. Magnetic apraxia: top-down and bottom-up modulation

In the second experiment, we demonstrated that it is possible to modulate MA.

The effects of stimuli of dangerous nature in terms of evoking adverse bodily and motor responses have been demonstrated previously. Recently, an opposite effect relating to dynamic affordance was found with objects of a neutral or emotional nature (Anelli et al., 2013). While neutral objects are processed faster as they move towards the patient, dangerous objects are processed faster when they are moving away. Thus, the sight of neutral objects induces a dynamic affordance effect while an escape-avoidance effect is provoked by the sight of dangerous objects (Anelli et al., 2013). In concordance with these results, the reduction in the number of attraction movements and grasping induced by dangerous objects may represent an unconscious escape-avoidance response of the motor system.

Nevertheless, we cannot exclude that other cognitive factors, such as the recruitment of limbic (Glodberg and Bloom, 1990) or attentional (Sarva et al., 2014) networks, play a role in this modulation.

Finally, we found modulatory effects of reversed spatial perspective. This is in line with the data from a patient affected by bilateral anarchic hand syndrome due to cortico-basal degeneration (Riddoch et al., 1998, 2000). In a series of reaching tasks, the experimenters manipulated the effects of stimuli familiarity, spatial relations between the hand and the part of the objects used for actions, and the semantic knowledge concerning objects. The results indicate that visual affordances and visual familiarity can directly activate motor actions and that reducing the object affordance can modulate motor responses (Riddoch et al. 1998, 2000).

The mirror forced VR to watch her hand interacting with objects from an unusual third-person perspective and this probably reduced the object's affordance power. These results were supported by a recent single case study involving an AH patient (Romano et al., 2014) in which the mirror box paradigm produced an enhancement of motor control. It is worth mentioning that self-observation in a mirror modifies body representation in deafferentated and hemiplegic people (Ramachandran and Rogers-Ramachandran, 1996; Besharati et al., 2015). In addition, experimental procedures that induce a visuo-tactile conflict (i.e. the rubber hand illusion) can re-awaken AH symptoms (Schaefer et al., 2013) suggesting that modulation of involuntary movements is the result of multilevel processes contemporarily involved in action control and body representation.

6. Conclusion

To sum up, Feinberg, Goldberg and Frith's theories (Feinberg et al., 1992; Goldberg and Bloom, 1990; Frith and Wolpert, 2000) are partially supported by our results. Our report suggests AHS symptoms are the result of an association between top-down and bottom-up factors. The possibility of modulating AH symptoms represents an important issue for the diagnosis and rehabilitation of patients who, although not paralyzed, have lost their autonomy as a consequence of their incapacity to control involuntary AH movements.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2015.10.005.

Video 1. Clinical Observation Of Anarchic Hand And Magnetic Apraxia Symptoms.A video clip is available online.Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.neuropsychologia.2015.10.005.

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