Gesture errors in left and right hemisphere damaged patients: a behavioural and anatomical study

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ABSTRACT

Objective. Erroneous gesture execution is at the core of motor cognition difficulties in apraxia. While a taxonomy of errors may provide important information about the nature of the disorder, classifications are currently often inconsistent. This study aims to identify the error categories which distinguish apraxic from non-apraxic patients. *Method.* Two groups of mixed (mouth and limb) and bucco-facial apraxic patients were compared to non-apraxic, left and right hemisphere damaged patients in tasks tapping the ability to perform limb and mouth actions. The errors were analysed and classified into 6 categories relating to content, configuration or movement, spatial or temporal parameters and unrecognisable actions. *Results.* Although all the above error typologies may be observed, the most indicative of mixed apraxia is the content-related one relate to content in all the typologies of actions (transitive and intransitive), and configuration errors in transitive ones. Configuration and content errors in mouth actions seem to be typical of bucco-facial apraxia. Spatial errors are similar in both apraxic and right brain damaged, non-apraxic patients. A lesion mapping analysis of left-brain damaged patients demonstrates that all but the spatial error category are associated with the fronto-parietal network. Moreover, content errors are also associated with fronto-insular lesions and movement errors with damage to the paracentral territory (precentral and postcentral gyri). Spatial errors are often associated to ventral frontal lesions. *Conclusions.* Bucco-facial and mixed apraxic patients make different types of errors in different types of actions. Not all errors are equally indicative of apraxia. In addition, the various error categories are associated with at least partially different neural correlates.

Keywords: Apraxia; mixed and bucco-facial apraxia; error classification; apraxic errors; lesion mapping; brain damage

Introduction

Performing actions is characterised by errors which are usually minimal and can easily be corrected. However, in the case of Apraxia (*literally = without action*), patients are incapable of performing actions that they were able to perform before the lesion onset. The symptoms cannot be attributed to elementary sensory-motor deficits or language disorders (Zadikoff and Lang, 2005; Goldenberg, 2013; Bartolo & Ham, 2016). Apraxia usually occurs after left hemisphere lesions (LBD), although cases have also been reported after right hemisphere damage (RBD, Vanbellingen et al., 2010; Stamenova, Roy, Black, 2009; Petreska, Adriani, Blanke, Billard, 2007; Donkerwoort, van den Ende, Stehmann-Saris, Deelman, 2000; Barbieri & De Renzi, 1988) and in degenerative syndromes (Rohrer, Rossor, Warren, 2010; Zadikoff and Lang, 2005). Various forms of apraxia have been described, with symptoms involving the upper limbs, face, eyes, legs or trunk (Petreska et al., 2007) during transitive or intransitive actions (i.e. with or without an object; Rapcsak, Ochipa, Beeson, Rubens, 1993; Dumont, Ska, & Schiavetto 1999; Goldenberg, 2013; Canzano et al., 2016). Apraxia may be associated with disorders in gesture recognition (Buxbaum, Johnson-Frey, Bartlett-Williams, 2005; Pazzaglia, Smania, Corato, Aglioti, 2008) or with a lack of awareness of the symptoms (Canzano, Scandola, Pernigo, Aglioti, Moro, 2014; Kush et al., 2018; Scandola et al., 2020).

Various categories of errors have been described in apraxia (Leiguarda, Clarens, Amengual, Drucaroff, Hallet, 2014). In the case of *Ideational apraxia* (i.e. the inability to conceptually organise intended actions, De Renzi & Lucchelli, 1988), patients seem to have no idea of how to perform certain actions. *Ideo-motor apraxia* affects the planning of actions that have been conceived correctly. In this case, the most typical errors regard the sequence, timing and spatial organisation of movement and postures (Gonzalez-Rothi, Ochipa, Heilman, 1991). A loss of dexterity or deftness characterises *Limb-kinetic apraxia,* with errors involving hesitations and disruptions to the smoothness of movements (Liepmann, 1920, cit. in Goldenberg, 2013). Finally, *Visuo-imitative apraxia* is a specific deficit relating to the imitation of novel, meaningless gestures with other gesture abilities spared (Goldenberg & Hagmann, 1997).

A consistent categorisation of gesture errors is difficult, the problem being to identify those errors which are typical of apraxia and those which are also present in non-apraxic patients. In ideational apraxia, content and sequence errors (with omissions and object misuse) are mainly reported (De Renzi & Lucchelli, 1988; Haaland & Flaherty, 1984), while in ideo-motor apraxia, spatio-temporal and movement errors are described (Gonzalez-Rothi et al., 1991; Poeck, 1982; McDonald, Tate, Rigby, 1994). Errors in movement sequences are reported in both subtypes of apraxia (Bartolo, Della Sala, & Cubelli, 2016; Goldenberg, Daumüller, & Hagmann, 2001; Gonzalez Rothi, Mack, Verfaellie, Brown, & Heilman, 1988; Hanna-Pladdy, 2001; Lehmkuhl, Poeck, & Willmes, 1983; Leiguarda et al., 2014; Ochipa, Gonzalez-Rothi, & Heliman, 1992; Pilgrim & Humphreys, 1991; Raymer, Maher, Foundas, Heilman, & Gonzalez Rothi, 1997; Rumiati, Zanini, Vorano, & Shallice, 2001; Schwartz et al., 1998). Action errors in RBD seem to mainly concern timing, action configuration (Hanna-Pladdy et al., 2001; Mengotti, Ripamonti, Pesavento, Rumiati, 2015), perseveration (Haaland & Flaherty, 1984) and the finger imitation (Achilles et al., 2016) of meaningless actions (Tessari, Canessa, Ukmar, Rumiati, 2006).

The main aim of the present study was to ascertain the error categories which specifically indicate that a patient is apraxic during tasks involving the imitation of gestures. This was done by comparing the errors made by four groups of patients: left hemisphere damaged non-apraxic patients (A); limb and bucco-facially apraxic patients (MA); bucco-facially apraxic patients (BFA) and RBD non-apraxic patients. We checked for other neuropsychological symptoms and the various categories of errors were then analysed.

The second aim was to analyse the neural correlates of these categories. A good deal is already known about the lesions associated with apraxia (see Goldenberg 2013) and several investigations regarding the brain damage associated with failure in specific types of tasks (i.e. imitation, pantomime and the use of tools) have been conducted (Goldenbergh & Karnath, 2006; Goldenberg Hermsdörfer, Glindemann, Rorden, Karnath, 2007; Buxbaum & Kalenine, 2010; Kalenine & Buxbaum, 2016; Buxbaum, Shapiro, Coslett, 2014; Hoeren et al., 2014; Sperber, Wiesen, Goldenberg, Karnath, 2019). Nevertheless, to the best of our knowledge, an analysis of the specific grey and white matter regions which are damaged in patients who make various categories of errors has never been carried out. This may represent a valuable source of information regarding the underlying mechanisms of apraxia and provide novel data that will be useful in terms of improving the diagnosis and treatment of the disorder.

Methods

Preliminary classification of errors

A series of studies was selected using Pubmed indexed articles published between 1986 and 2018 and the key terms 'Assessment of Apraxia', 'errors in gestures', 'errors classifications in apraxia'. Articles written in languages other than English were not included and any articles referring to degenerative syndromes, developmental disorders or specific forms of apraxia (e.g. apraxia of speech, unilateral apraxia, constructional apraxia, apraxic agraphia, dressing apraxia, orienting apraxia and magnetic apraxia) were excluded.

Twenty-two articles (see Supplementary Materials, SM-A) fit all the criteria. These were used to formulate a comprehensive classification (Table 1; for error definitions, see SM-A): i) errors in the content of actions; ii) temporal or iii) spatial errors; iv) errors in hand or mouth configuration; v) errors concerning movement and lastly vi) actions which were to be considered as destructured since they were not recognisable (Gonzalez Rothi et al., 1988; Mozaz et al., 1992).

CONTENT	CONFIGURATION HAND	CONFIGURATION MOUTH	MOVEMENT	TEMPORAL	SPATIAL	UNRECOGNISABLE ACTION
Perseverative intrusion	Hand configuration	Mouth configuration	Movement (hand, mouth, finger)	Acceleration	Amplitude increase	Unrecognisable gesture
Omission	Body Part as object	Mouth/object contact		Slowdowns	Amplitude reduction	
Related content	Finger position	Conduit d'approche of mouth position	Sequencing error: - sequence order - step omission - step addiction - perplexity - occurrence	Rythm alteration	Object misorientation	
Unrelated content	Orientation of the hand			Delay	Misplacing of action with respect to the body	
No content	Orientation of the limb		Clumsiness	Unsustained action	Movement direction	
Object omission	Object/hand contact					
Object substitution						
Verbalization						
Conduit d'approche						
Misuse						

Table 1: Error categories. The classification of errors resulting from the analysis of the literature and subsequently used for video evaluation is reported.

Participants

Sixty brain damaged patients were recruited at the IRCCSs Santa Lucia (Rome) and Sacro Cuore Hospital (Negrar, Verona). They gave their informed consent and the procedure was approved by two local Ethics Committees. The study was carried out in accordance with the guidelines of the Declaration of Helsinki (2014). All of the patients were right-handed (Briggs & Nebes, 1975) and were in sub-acute or chronic post-stroke phases. They did not suffer from deficits in verbal comprehension (Aachener Aphasia Test, Luzzatti, Willmes, de Bleser,1996) or attention (Attentional Matrices, Spinnler & Tognoni, 1987), conditions which might compromise the execution of the experimental task. For patients with symptoms indicating unilateral spatial neglect (Line Bisection –Wilson *et al*.,1987), the stimuli were positioned on the right side of the patient so as to ensure that they were able to see them (Table 2).

Subject	Age (years)	Gender (M/F)	Education (years)	Lesion interval (days)	AAT comp (z point)	RAVEN	Line Bisection	FAB	TULIA TOT (cut-off 194)	Upper Face Apraxia (cut-off 38.43)	Lower Face Apraxia (cut-off 400.04)	Object Use	Group
1	69	F	13	121	1.3	32.5	9	9	235	45.25	435.5	14	A-
2	40	F	18	130	1.56	30	9	8	236	44.5	420.75	14	A-
3	68	M	5	139	0.66	27.5	9	7	236	43.75	412.5	14	A-
4	62	M	13	81	-0.7	29.5	9	9	238	45	434.5	14	A-
5	38	F	13	33	-0.2	27	8	9	235	43	429.25	14	A-
6	49	M	13	38	0.8	32	9	9	240	44.75	422.75	14	A-
7	41	F	17	230	-0.2	31	8	9	231	40.5	428.25	14	A-
8	66	M	13	52	-0.95	28.5	9	7	217	39.25	425.5	14	A-
9	73	F	5	66	-1.45	20	8	2	207	44	425.75	14	A-
10	64	M	8	57	na	35	9	9	235	43.5	434	14	A-
11	52	F	13	70	na	na	na	na	233	44.75	420.25	14	A-
12	65	M	17	268	na	na	na	na	235	45.25	407.25	14	A-
13	72	M	17	27	na	na	na	na	240	45.25	432.25	14	A-
14	78	M	17	150	na	na	na	na	237	44	424.5	14	A-
15	62	F	5	27	na	na	na	na	219	40	425	14	A-
16	71	F	13	67	na	na	na	na	195	45.25	425.5	14	A-
Mean	*60.63*	*50.00*	*12.50*	*97.25*	*0.09*	*29.30*	*8.70*	*7.80*	*229.31*	*43.63*	*425.22*	*14*	
SD	*12.68*		*4.49*	*71.65*	*1.04*	*4.07*	*0.48*	*2.20*	*12.99*	*1.97*	*7.66*	*0*	
17	57	M	13	31	1.17	35	9	9	225	39	**306.5**	14	BFA
18	66	M	13	227	1.17	26.5	8	3	205	**24**	**290.5**	14	BFA

19	65	F	17	55	1.17	28.5	9	9	222	44	**342.25**	14	BFA
20	59	F	13	127	0.53	31	9	6	207	39.5	**395.25**	14	BFA
21	58	M	17	102	1.3	31.5	9	8	206	45	**385.25**	14	BFA
22	38	F	17	494	0.92	26.5	9	8	209	44.5	**299.5**	14	BFA
23	47	F	17	34	0.66	33.8	9	9	206	**28.5**	**244.5**	14	BFA
25	63	M	5	33	na	na	na	na	236	**33**	434	14	BFA
26	72	M	13	500	na	na	na	na	273	45.5	**398.5**	14	BFA
27	72	F	5	32	na	na	na	na	234	45.25	**392.25**	14	BFA
Mean	*59.70*	*50.00*	*13.00*	*163.50*	*0.99*	*30.40*	*8.86*	*7.43*	*222.30*	*38.83*	*348.85*	*14*	
SD	*10.67*		*4.62*	*186.20*	*0.29*	*3.37*	*0.38*	*2.23*	*21.46*	*7.77*	*61.14*	*0*	
28	86	F	13	119	-0.2	29	9	7	200	**37.75**	**364.25**	**12**	MA
29	66	M	13	227	1.56	26.5	8	6	227	39.75	**381.25**	**12**	MA
30	73	M	8	27	na	na	na	na	208	43.75	**279**	**12**	MA
31	75	M	5	35	-0.6	27	9	8	**180**	45	**353**	14	MA
32	40	M	8	23	-1.39	25	8	9	**98**	43	**321**	**4**	MA
33	52	F	5	165	na	27.2	9	na	**160**	**31**	**328.5**	14	MA
34	63	M	17	155	1.17	**18**	9	7	**132**	45	**334.25**	14	MA
35	63	F	8	268	0.79	22	9	3	**76**	**24**	**206.5**	**8**	MA
36	52	F	13	502	0.53	30.5	9	8	**122**	**27.25**	**340.75**	**13**	MA
37	69	F	8	219	0.92	**16.5**	9	6	**113**	**9.75**	**160**	**12**	MA
38	78	F	13	120	0.15	**16.5**	7	3	**93**	**37**	**354**	14	MA
39	43	F	16	70	0.66	23.5	9	1	**125**	43	**95.25**	**6**	MA
40	62	F	8	105	0.15	**16.6**	9	6	**173**	**32**	**289.5**	**7**	MA
41	66	M	5	197	-0.48	30	9	5	**102**	**34**	**345.5**	14	MA
42	32	M	13	519	1.051	31.5	9	9	**154**	40.25	**361.75**	**12**	MA
43	77	F	5	22	na	29.2	9	na	**193**	39	**374**	**10**	MA
44	73	F	13	206	na	na	na	na	**190**	**33.75**	412	14	MA
Mean	*62.94*	*58.82*	*10.06*	*175.24*	*0.33*	*24.60*	*8.73*	*6.00*	*149.76*	*35.60*	*311.79*	*11.29*	
SD	*14.75*		*4.02*	*148.03*	*0.83*	*5.45*	*0.59*	*2.45*	*45.84*	*9.09*	*84.00*	*3.18*	
45	69	M	5	197	-1.65	**11.5**	**2**	0	230	45.25	433.5	14	RBD
46	47	M	8	80	-0.07	26.8	**2**	4	239	44.75	427.75	14	RBD
48	75	M	8	54	0.71	21	**1**	1	232	45.5	440.25	14	RBD
50	70	M	17	47	0.97	25	7	6	240	45.25	428.5	14	RBD
51	34	M	8	282	-0.07	**12.5**	**4**	3	239	44.25	414.25	14	RBD
53	66	M	5	125	0.71	25	**6**	3	233	45.25	427.5	14	RBD
54	55	F	13	186	-0.86	23.8	**0**	3	231	45	433.25	14	RBD
56	73	M	13	44	na	na	na	na	235	41.25	429.5	14	RBD
57	49	M	13	44	na	31.3	8	9	240	45	410		RBD
Mean	*59.78*	*11.11*	*10.00*	*117.67*	*-0.04*	*22.11*	*3.75*	*3.63*	*235.44*	*44.61*	*427.17*	*14*	
SD	*14.15*		*4.15*	*86.13*	*0.95*	*6.89*	*2.96*	*2.83*	*4.10*	*1.31*	*9.47*	*0*	

Table 2: Demographic and neuropsychological data for each patient. AAT = Aachener Aphasie Test (Luzzatti et al., 1996); Raven test (Raven, Court, Raven, 1988); Line Bisection; FAB = Frontal Assessment Battery (Appollonio et al., 2005); TULIA TOT = total score of the

Test for Upper Limb Ideomotor Apraxia (Vanbellingen et al., 2010); Lower and Upper Face Apraxia (Bizzozero et al., 2000); Object Use is the De Renzi and Lucchelli's Ideational Apraxia test (1988). Bayesian statistical tests on the demographic data were computed in order to verify that the groups were homogenously distributed. All of the statistical tests for differences in age show that the null hypothesis can be accepted (all two-samples comparisons: $BF_{10} < 1/3$ and ESS > 100). For lesion/assessment interval all comparisons are towards the acceptance of the null hypothesis ($BF_{10} < 1/3$ and ESS > 100), but the comparison between MA and A- is not conclusive ($BF_{10} = 0.44$, ESS = 3188.56). There are no differences in the years of education between the groups A- and BFA ($BF_{10} = 0.2$, ESS = 2519.95) and between MA and RBD ($BF_{10} = 0.22$). All the remaining comparisons are not conclusive (all $BF_{10} < 0.8$, ESS > 100). There is a difference in gender between MA and RBD ($BF_{10} = 3.09$), while between A- and BFA ($BF_{10} = 0.28$, ESS = 314.89) and A- and MA ($BF_{10} = 0.29$, ESS = 207.47) there are no differences, and in all other cases there were $BF_{10} < 1.75$ and ESS > 100.

Assessment of apraxia

Limb apraxia was evaluated by means of the Upper Limb Ideomotor Apraxia test (TULIA – Vanbellingen *et al.*, 2010) consisting of 48 items which involve imitating and pantomiming both meaningful and meaningless gestures. A 6-point scoring method (0 = totally incorrect action, 5 = perfect performance) means that performances can be evaluated in terms of scores ranging from 0 to 240 (pathological scores ≤ 194). To assess ideational apraxia, we used De Renzi and Lucchelli's Ideational Apraxia test (1988) in which patients are requested to perform 7 complex actions that require the use of objects. Scores range from 2 (perfect performance) to 0 (totally incorrect performance). A total score <14 indicates apraxia. Finally, the presence of bucco-facial apraxia was ascertained by means of the Upper and Lower Face Apraxia test (Bizzozero *et al.*,2000). In this test, 29 actions are used to assess lower gestures and 9 actions related to upper face gestures, according to the territory of the cranial nerves involved. Each action is scored 1 (correct) or 0 if there are errors in execution. These scores are then weighted considering relative difficulty (cut-off: lower face = 400.04, upper face =38.43).

Depending on their symptoms and lesion side, the participants were then divided into four groups: i) bucco-facial and limb apraxia (MA, n.17) ; ii) bucco-facial apraxia (BFA, n.11) ; iii) LBD non-apraxic patients (A- n.16) and iv) RBD non-apraxic patients (RBD n.13). Four RBD patients were found to be apraxic during the tests and were thus excluded. Furthermore, one LBD patient who suffered from isolated Limb apraxia was excluded as he could not be inserted into any of the groups. One BFA patient was excluded because the brain images were not available. In this way, the final groups were as follows: A- = n.16, MA= n.17, BFA= n.10, RBD = n. 9 patients, for a total of 52 patients. The groups were comparable in terms of age, education and lesion onset-assessment intervals, but not for gender distribution (see Table 2 and SM-B).

Experimental design

The experiment involved 28 videos which had previously been used in studies carried out by Canzano *et al*. (2014) and Scandola *et al*. (2020). They had been recorded using a Sony Handycam HDR-CX115E and showed a female actor performing bucco-facial or limb actions. The videos were used as a model for patients to execute an imitation task. All the actions were meaningful, with 14 of them transitive (10 unimanual limb and 4 bucco-facial actions), and 14 intransitive (10 unimanual limb and 4 bucco-facial actions). The actions were presented as in a mirror reflection with respect to the (always ipsilesional) hand to be used by patients. This avoided difficulties for right hemisphere damaged patients suffering from neglect who used their right hand after observing the model executing the action with her left hand (i.e. on the right-hand side of the screen).

The subjects were seated at approximately 60 cm from a 17-inch monitor (resolution: 1024 × 768 pixels). They were asked to imitate, as accurately as possible, the action they had seen in the video. Their performance was video-recorded, and then analysed by two independent examiners who are experts in apraxia. They assessed the performance of each participant according to the previously defined classification of errors (Table 1). When more than one type of gesture alteration (e.g. misuse of an object and perseveration) occurred, an error was assigned to each category. However, when the action was totally unrecognisable, the “Unrecognisable/Destructured” category was attributed. If there was a discrepancy (concordance at 96.49%), the video was discussed with another examiner until a decision was reached (Fig. 1).

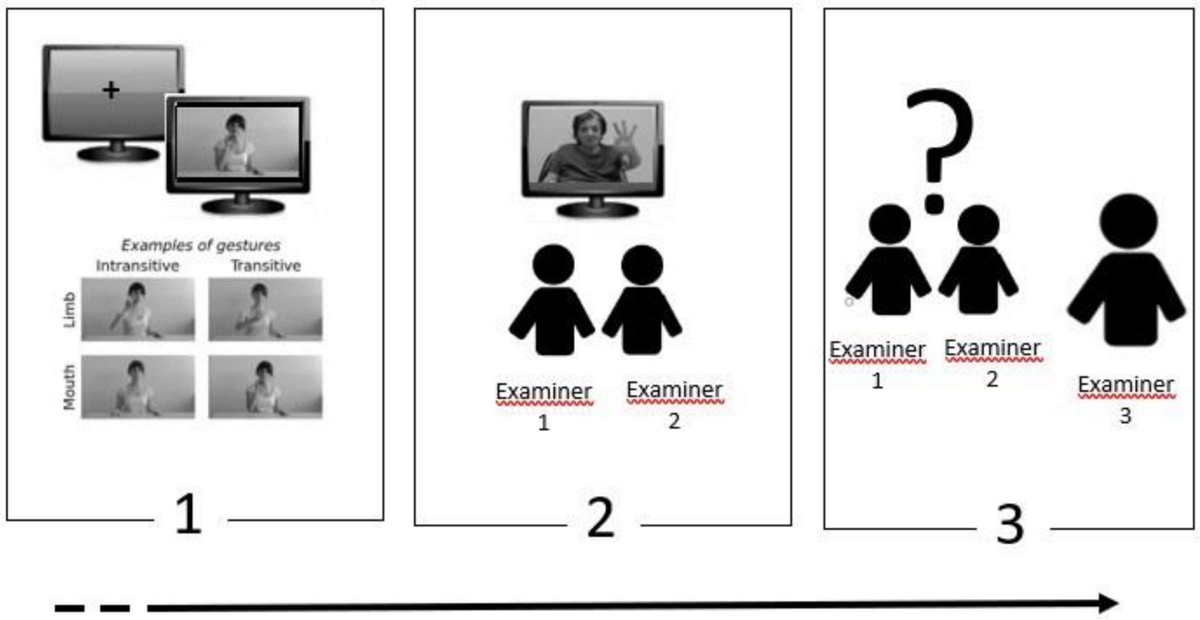


Figure 1: Experimental timeline. In the first phase, the patients were asked to watch and repeat the actions seen on a video screen. In the second phase, two examiners independently observed the actions and classified the errors. In the third phase, if there were incongruencies, a third examiner evaluated the discrepancies.

Statistical analyses

The behavioural data were analysed in 3 steps taking the various different types of actions (i.e. limb, mouth, transitive, intransitive) into consideration. The four groups were compared for: i) the number of errors (checking for demographic and neuropsychological variables) and ii) the error category by means of Receive-Operating Characteristics (ROC, MacMillan & Creelman, 2005). Furthermore, iii) the various different error categories (ROC curves) were compared within each group.

The comparison relating to the number of errors was analysed by means of a Bayesian Multilevel Negative Binomial model (details in SM-C), with, as fixed effects: Group (A-, BFA, MA, RBD), Body Part (Mouth, Limb), Action (T, INT), and the interactions between these. In order to check for demographic and neuropsychological variables, the following factors were used: Gender, Age, Education (years), Lesion Interval (days) and the scores in: Line Bisection, FAB, AAT, Raven matrices (Table 2). To avoid statistical biases, all these demographic and neuropsychological scores were converted in z-scores. The random effects which were grouped by participant were: Body Part, Action and the interaction between them.

These models were computed within the Bayesian framework (Laplace, 1825; Kruschke, 2014), to test both the alternative and null hypotheses for each independent variable. In particular, the null and alternative hypotheses were evaluated by means of Savage-Dickey Bayes Factors (BF_{10}, Dickey & Lientz, 1970; Wagenmakers, Lodewyckx, Kuriyal, & Grasman, 2010). A $BF_{10} > 3$ means that the alternative hypothesis must be accepted (i.e. there is difference in the number of errors), a $BF_{10} <$ 1/3 means that the null hypothesis must be accepted (i.e. there is no difference in the number of errors). Results between 3 and 1/3 are not conclusive. The computation of the BF_{10} for further group-by-group differences (not directly visible in the models) was executed on the resulting marginal posterior distributions.

The second step investigated the error categories which differentiated apraxic from non-apraxic patients. We computed ROC curves since these allow one to determine whether a specific measure (i.e. a category of errors) distinguishes two groups. The Area Under the Curve (AUC) for each typology of error was computed. This is interpreted as "excellent" when AUC = .90-1; "good" if AUC = .80-.90; "fair" if AUC = .70-.80; "poor" if AUC = .60-.70, "fail" when AUC = .50-.60 (Fawcett, 2006).

Finally, in order to understand the errors which were more "useful" in terms of classifying a given group of patients (specifically, MA and BFA versus A- and RBD), we compared the AUC values of each group by means of the De Long test (De Long, De Long Clarke Pearson, 1988).

Statistical analyses were conducted with the R version 4.0.3 (R Core Team, 2020), the rstan package (Carpenter et al., 2017) for Bayesian Statistics, the logspline package (Kooperberg, 2019) to compute Savage-Dickey Bayes Factors and the pROC package (Robin et al., 2011) for ROC analyses. The Bayesian Analyses were computed with 4 chains, 1000 burn-in and 1000 sampling iterations. Bayesian results are shown in terms of the Savage-Dickey Bayes Factor (BF_{10}) and Effective Sample Size, that is an estimation of the number of non-autocorrelated MonteCarlo Markov-Chains iterations (Gelman et al., 2013). All of the Gelman & Rubin's diagnostics (Gelman & Rubin, 1992) were around 1, and always less than 1.1. Estimates from the Bayesian analyses is reported subsequently as the Mode and the 89% Highest Posterior Density Interval.

Lesion mapping

An explorative analysis of the LBD patients' lesions (irrespective of the group) was conducted in order to investigate any potential correlates relating to the various error categories. The scans of 39 patients (15 MRI; 24 CT) were available. Details of the procedure of lesion drawings are in SM-D. A multivariate approach (LESYMAP with sparse canonical correlations; Mirman et al., 2018) was carried out on the scores for each category. We used the number of errors for each individual in each category as continuous predictors (Bates et al., 2003; Rorden, Karnath, Bonilha, 2007). The outcomes of these analyses were superimposed onto T1 templates and then overlapped onto the Automatic Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002) to provide information on the grey matter and onto an atlas of human brain connections (Rojkova et al., 2016) for the white matter.

Results

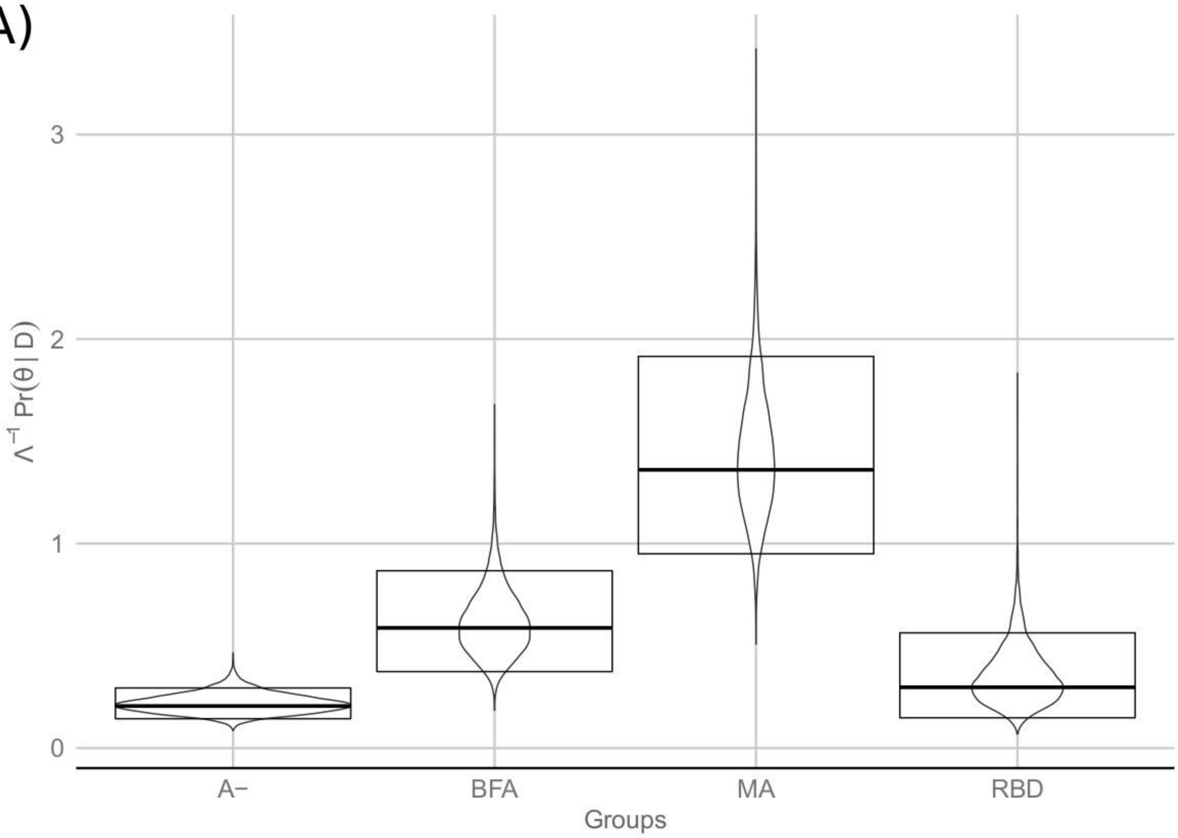
Number of errors - Bayesian Multilevel Negative Binomial model

Results show that the number of errors in Limb and Bucco-facial actions is proportionally equal, as the null hypothesis is true for Body District (BF_{10} = 0.11, ESS = 3354.5). The MA group committed more errors than the other groups (A- BF_{10} = 16569.7, ESS = 3163.8; RBD BF_{10} = 9.5, ESS = 5634; BFA BF_{10} = 4.25, ESS = 5777). A- committed fewer errors than BFA (BF_{10} = 11.9, ESS =3263.2), but the same number of errors as the RBD group (BF_{10} = 0.31, ESS =3031.7). The difference between the BFA and RBD groups was not conclusive (BF_{10} = 0.39, ESS = 5398) (Figure 2).

Other variables, such as Age, Education, Lesion Interval, Line Bisection, Raven Matrix, AAT, the interactions between Body District and Group, and the interaction Body District, typology of Action and Group, showed no impact on the number of errors (all $BF_{10} \leq 0.15$ and ESS > 3858.9, null hypothesis confirmed).Inconclusive results were found for Gender and the interaction between Group and type of Action (all $BF_{10} \leq 0.76$; ESS > 4453). See table SM-C for further details.

Details regarding the frequency and percentage of patients in each group who made the various types of errors are shown in Tables 3 (SM-E for the errors in each action typology).

A)



B)

	Mode	HPDI	
A-	0.219	0.144	0.294
BFA	0.588	0.374	0.867
MA	1.361	0.950	1.915
RBD	0.297	0.148	0.563

Figure 2: The marginal posterior distributions for each group. A: Graphical representation for each group. The rectangle represents the HPDI, the black line represents the mode, and the violin plot indicates the whole marginal posterior distribution. B: Marginal posterior distributions of the estimates for each group.

	MA (n.17)		BFA (n.10)		A- (n.16)		RBD (n.9)	
CONTENT	**n.**	**%**	**n.**	**%**	**n.**	**%**	**n.**	**%**
Perseverative intrusion	3	17.65	0	0	1	6.25	0	0
Omission	5	29.41	1	10.00	0	0	0	0
Related content	1	5.88	0	0	0	0	0	0
Unrelated content	5	29.41	3	30.00	1	6.25	0	0
No content	16[A-]	94.12	7	70.00	6	37.5	6	66.67

Misuse	12	70.59	7	70.00	6	37.5	3	33.33
Object omission	3	17.65	1	10.00	0	0	0	0
Object substitution	0	0	0	0	0	0	0	0
Vocal overflow	3	17.65	0	0	0	0	1	11.11
Conduite d'approche	16[A-]	94.12	7	70.00	4	25	5	55.56
HAND CONFIGURATION								
Hand configuration	10[BFA]	58.82	1	10.00	7	43.75	6[BFA]	66.67
Finger position	11[BFA]	64.71	0	0	5	31.25	4	44.44
Orientation of the hand	8 [BFA]	47.06	0	0	4	25	3	33.33
Orientation of the limb	2	11.76	0	0	0	0	0	0
Object/hand misorientation	11[A-, RBD, BFA]	64.71	0	0	1	6.25	1	11.11
Body Part as object	0	0	0	0	0	0	0	0
MOUTH CONFIGURATION								
Object/mouth position	4	23.53	1	10.00	1	6.25	0	0
Conduite d'approche	8[A-, RBD]	47.06	2	20.00	1	6.25	0	0
Mouth configuration	14	82.35	7	70.00	7	43.75	8	88.89
MOVEMENT								
Whole Movement	7	41.18	2	20.00	3	18.75	1	11.11
Movement of the hand	10[A-]	58.82	2	20.00	1	6.25	1	11.11
Movement of the mouth	9	52.94	5	50.00	7	43.75	5	55.56
Movement of fingers	2	11.76	0	0	0	0	0	0
Sequencing error	0	0.	0	0	0	0	0	0
Sequence order	2	11.76	0	0	0	0	0	0
Step omission	7	41.18	0	0	7[BFA]	43.75	6[BFA]	66.67
Step adding	3	17.65	0	0	0	0	1	11.11
Perplexity	6	35.29	1	10.00	2	12.5	0	0
Occurence/ perseveration	8[BFA]	47.06	0	0	2	12.5	1	11.11
Clumsiness	1	5.88	2	20.00	1	6.25	0	0
SPATIAL								
Amplitude	5	29.41	6 [A-]	60.00	2	12.5	6 [A-]	66.67
Reduction of gesture amplitude	13[BFA, A-]	76.47	1	10.00	3	18.75	3	33.33
Object orientation	8	47.06	3	30.00	2	12.5	1	11.11
Action/body position	14[A-, BFA]	82.35	3	30.00	6	37.5	7	77.78
Movement direction	8[A-]	47.06	2	20.00	1	6.25	2	22.22
TEMPORAL								
Unsustained action	11 [A-, RBD]	64.71	3	30.00	2	12.5	1	11.11
Delay	3	17.65	0	0	0	0	0	0
Rhythm alteration	4	23.53	3	30.00	3	18.75	1	11.11
Slowdowns	2	11.76	1	10.00	0	0	1	11.11
Acceleration	1	5.88	0	0	0	0	1	11.11
DESTRUCTURED, UNRECOGNISIBLE ACTION	13 [A-, RBD]	76.47	4 [A-]	40.00	0	0	0	0

Table 3. For each group, the number and percentage of patients who made different types of errors are shown. For each error category, the number of patients who failed is compared group-by-group by means of χ2 tests. When statistically significant differences

emerged, the label reported in apex of MA or BFA values indicates the groups with a statistically smaller number of patients committing the error.

Specificity of errors – ROC analysis

Table 4 reports the comparisons between the AUC values of the groups relating to the error categories and the action typology.

Configuration errors distinguished MA from A- in all of the action typologies, and in all but Mouth T when compared to RBD. This category was more frequent in BFA only in comparison to RBD and only in Limb INT actions.

Errors of *Content* were more frequently associated with MA as compared to A- and RBD. BFA made more errors in Mouth INT actions than A- and RBD.

In Mouth actions (both T and INT), the *Movement* errors were not able to distinguish between the apraxic and non-apraxic groups. Conversely, in Limb actions (T and INT), this category distinguishes MA from A- and RBD.

The same holds for *Spatial* errors that were not able to distinguish between groups in Mouth actions, while in Limb INT, both of the two apraxic groups and the RBD group made more errors than the A- group. In Limb T, MA made more errors than A- and RBD.

Temporal errors discriminated only MA with respect to A-, and RBD in Limb INT, but there was no distinction between the groups in the other actions.

Finally, regarding *destructured* actions, the only difference between MA with respect to A- and RBD concerned Mouth INT.

Configuration						
Body District	Action	MA v A-	BFA v A-	MA v RBD	BFA v RBD	RBD v A-

Limb	Intransitive	0.82 **	0.528	0.722 *	0.761 *	0.722
Limb	Transitive	0.807 **	0.331	0.765 *	0.411	0.584
Mouth	Intransitive	0.812 **	0.7 *	0.778 *	0.672	0.514
Mouth	Transitive	0.744 *	0.413	0.324	0.522	0.635
			Content			
Body District	Action	MA v A-	BFA v A-	MA v RBD	BFA v RBD	RBD v A-
Limb	Intransitive	0.901***	0.656	0.899 **	0.661	0.49
Limb	Transitive	0.899 **	0.694	0.866 **	0.433	0.625
Mouth	Intransitive	0.877 **	0.822 **	0.843 **	0.804 **	0.635
Mouth	Transitive	0.765 *	0.455	0.765 *	0.455	0.5
			Movement			
Body District	Action	MA v A-	BFA v A-	MA v RBD	BFA v RBD	RBD v A-
Limb	Intransitive	0.726 *	0.672	0.732 *	0.678	0.521
Limb	Transitive	0.831 **	0.662	0.837 **	0.661	0.51
Mouth	Intransitive	0.61	0.581	0.673	0.65	0.424
Mouth	Transitive	0.325	0.328	0.461	0.45	0.635
			Spatial			
Body District	Action	MA v A-	BFA v A-	MA v RBD	BFA v RBD	RBD v A-
Limb	Intransitive	0.801 **	0.778 *	0.471	0.522	0.698
Limb	Transitive	0.925***	0.416	0.778 **	0.583	0.556
Mouth	Intransitive	0.404	0.406	0.461	0.461	0.556
Mouth	Transitive	0.324	0.5	0.395	0.556	0.493
			Temporal			
Body District	Action	MA v A-	BFA v A-	MA v RBD	BFA v RBD	RBD v A-
Limb	Intransitive	0.71 *	0.512	0.716 *	0.506	0.493
Limb	Transitive	0.36	0.484	0.412	0.55	0.573
Mouth	Intransitive	0.441	0.35	0.441	0.35	0.5
Mouth	Transitive	0.5	0.5	0.611	0.611	0.611
			Destructured action			
Body District	Action	MA v A-	BFA v A-	MA v RBD	BFA v RBD	RBD v A-
Limb	Intransitive	0.265	0.4	0.265	0.4	0.5
Limb	Transitive	0.324	0.45	0.324	0.45	0.5
Mouth	Intransitive	0.86 **	0.375	0.882 **	0.35	0.469
Mouth	Transitive	0.471	0.5	0.471	0.5	0.5

*Table 4. The AUC scores of the ROCs divided by category of error, Body District, Type of Action. * = AUC > 0.7; ** = AUC > 0.8; *** = AUC > 0.9.*

Comparison of the error categories between the groups

De Long tests were used to compare MA and BFA with respect to A- in the various action typologies (see SM-F for details).

MA. The results indicated that in Limb INT, *Content* errors distinguished this group from A- more frequently than *Temporal* and *Destructured* errors (D = 2.035, p = 0.046; D = 7.82, p < 0.001, respectively). None of the other comparisons were significant (all D < 1.7 and p > 0.09).

For all of the errors except *Destructured* errors (AUC = 0.265), the AUCs were > 0.7, with the highest AUC for *Content* errors being AUC > 0.9.

In Limb T, the most discriminative errors for MA were *Spatial* (AUC > 0.9) and *Content* (AUC = 0.899). *Configuration* and *Movement* errors were also associated with MA (AUC > 0.8). The comparisons between all of these errors and *Temporal* and *Destructured* (AUC < 0.4) errors were significant, and these latter were not indicative of apraxia in MA (all D > 4.38 and p < 0.001).

In the case of Mouth INT, *Configuration*, *Content* and *Destructured* errors were more indicative of apraxia in MA than in A- as compared to *Spatial* and *Temporal* errors (all D > 4 and p < 0.001). *Content* errors clearly indicated a discrimination between the two groups (AUC = 0.877). In Mouth T, *Configuration* and *Content* errors (AUC = 0.744 and 0.765, respectively) were associated with MA more frequently than all of the other error types (all D > 3 and p < 0.01) which were not indicative of apraxia.

BFA. In Limb INT, *Spatial* errors were the only ones with an AUC > 0.7 and thus indicative of apraxia. However, this category of errors had an AUC very close to 0.7 (0.698) for RBD as well. In Limb T, no error reached an AUC > 0.7. The greatest AUC was related to *Content* errors (AUC = 0.694).

In Mouth INT, *Content* errors reached an AUC = 0.877, and *Configuration* errors had an AUC = 0.812. These errors much more clearly discriminated between the groups than *Spatial* errors (*Content*: D = 3.454, $p < 0.001$; *Configuration*: D = 2.136, $p = 0.033$), *Temporal* errors (*Content*: D = 4.114, $p < 0.001$; *Configuration*: D = 2.724, $p = 0.006$) and *Destructured* errors (*Content*: D = 3.897, $p < 0.001$; *Configuration*: D = 2.446 , $p = 0.014$). In Mouth T, all of the error types had an AUC ≤ 0.5, and none of the comparisons were statistically significant.

Anatomical results

The results of the investigation are shown in Figure 3 and SM-G. The fronto-parietal network is involved in all of the error categories (except spatial errors), with direct lesions in the supramarginal gyrus and disconnections of the arcuate (anterior and long tract) and superior longitudinal (SLF III, SLF II) fasciculi. Content errors are also associated with insular lesions and fronto-insular disconnections (fronto-insular tract), while lesions in the paracentral (precentral and postcentral areas) territory, with disconnection of a hand-motor tract (inferior motor hand U-tract), are evident exclusively in Movement errors. Spatial errors do not involve the parietal networks but involve the frontal inferior triangularis gyrus and fronto-insular tracts. Finally, when actions are destructured, large fronto-temporo-parieto-insular lesions are present.

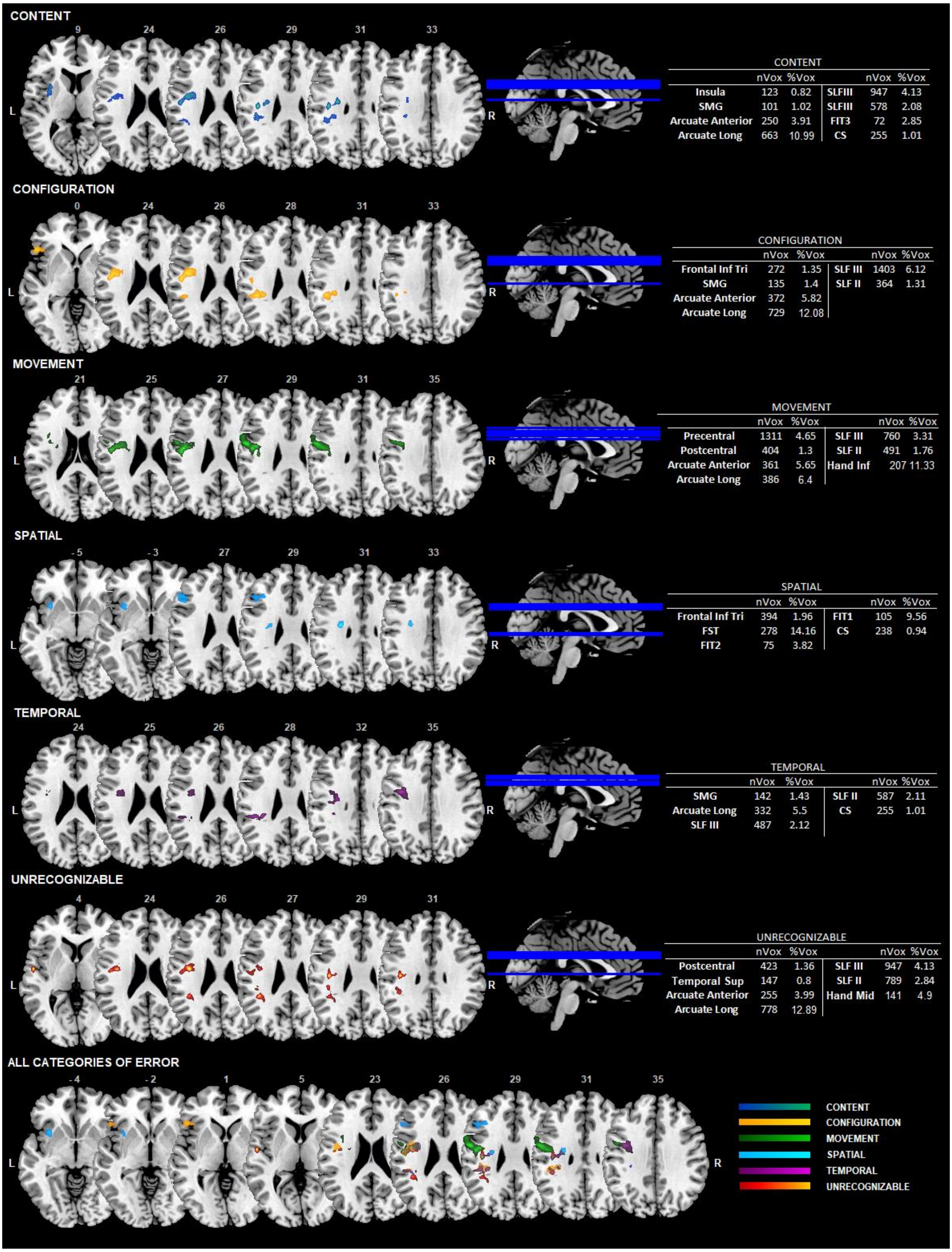


Figure 3: Neural correlates of Apraxic Errors. The lesions associated with the various categories of apraxic errors in the whole group of LBD patients are shown for each category and for all the categories of error, in the axial plan. The numbers above the brain slices

indicate the corresponding MNI axial coordinates. L = left. R = right. In the tables, the number of voxels (nVox) and their percentage respect the structure (%Vox) are reported for each statistically significant lesioned structure. SLF = Superior Longitudinal Fasciculus; Hand Inf. = Hand Inferior tract; FST = Fronto-striatal tract; FIT = Fronto-insular tract; CS = cortico-spinal tract; SMG = Supramarginal Gyrus.

Discussion

The most important result of the present study is the identification of the error types which are more clearly associated with apraxia in gesture imitation tasks. Our in-depth qualitative analysis indicates that all brain damaged patients make errors in gesture execution, both after LBD and RBD. Nevertheless, the differences between the groups we studied were not only quantitative (with MA committing more errors than the other groups) but also qualitative (i.e. with different types of errors). The action typology (i.e. limb or mouth, transitive or intransitive) also had an effect. Furthermore, the neuroanatomical analysis confirmed the specificity of the different error categories. In fact, although a common fronto-parietal "core" network was found for all non-spatial errors, some specificities emerged. Specifically, Content errors were also associated with insular lesions and fronto-insular disconnections, and Movement errors were associated with lesions of the paracentral territory and with disconnections of a hand-motor tract. As expected, Spatial errors are present in RBD patients as well, but in LBD patients these involve an anterior network, including the frontal inferior triangularis gyrus and fronto-insular tracts. Finally, Unrecognisable/Destructured actions, which were never present in the A- and RBD groups, were found in the apraxic patients to be associated with large fronto-temporo-parieto-insular lesions.

Error categories in apraxia

Our results introduce new elements to the existing knowledge of apraxia. Firstly, the presence of content errors in gesture imitation tasks calls into question the hypothesis that ideo-motor apraxia is exclusively associated with executive deficits (Mozaz et al., 1992). We found that errors involving 'no content' and 'conduite d'approaches' were significantly more frequent in MA than in A-. Thus, ideational features may be disturbed also in ideo-motor apraxia.

The imitation of gestures can be carried out by means of a direct (or non-lexical) route (Gonzalez-Rothi et al., 1991), or a ''visuo-motor conversion mechanism'' (i.e. a system involving a short-term representation of the whole action, see Cubelli, Marchetti, Boscolo, Della Sala, 2000) without involving the semantic route (Gonzalez-Rothi et al., 1991). However, our results suggest that the two routes are not totally independent of each other and that when patients execute meaningful actions, disorders in the semantic route interfere with action processing. Other studies have also found content errors such as unrelated actions (Poek, 1986; Spinazzola, Cubelli, Della Sala, 2003), absence of response (Mc Donald et al., 1994; Hanna-Pladdy et al., 2001), omissions and conduits d'approche (Smania et al., 2000) and unrecognizsable/destructured actions (Smania et al., 2000; Hanna-Pladdy et al., 2001) in patients with ideo-motor apraxia. We also found that, while RBD and A- patients did not commit Unrecognisable/Destructured errors, these were present in BFA and MA groups. In particular, the MA group committed more Destructured actions than both A- and RBD patients, while the BFA group made more errors than the A- group in this category (see below for the comparison of the error categories between groups).

Errors in configuration and movement are considered by some authors as spatial errors (Gonzalez-Rothi et al., 1988; Raymer et al., 1997). However, our behavioural and anatomical results suggest that these error categories are at least partially independent. In our sample, the most frequent Configuration errors in MA were 'finger position', 'object/hand misorientation' and "mouth configuration" (Mozaz et al., 1992; Smania, Girardi, Domenicali, Lora, Aglioti, 2000; Hanna-Pladdy et al., 2001). Spatial errors were also present in MA patients: Amplitude errors were more frequent in MA than than A-, but the most frequent spatial errors were 'reduction of gesture amplitude' and 'action/body position'(Gonzalez-Rothi et al., 1988; Hanna-Pladdy et al., 2001). However, these errors were no different with respect to RBD, who showed more amplitude errors than A- patients. This suggests that other components concur in this category, probably those associated with body representation, the neural correlates of which are distributed in both hemispheres (Berlucchi & Aglioti, 2010; Moro et al., 2008; D'Imperio, Bulgarelli, Bertagnoli, Avesani, Moro, 2017). The possibility that body representations in gesture execution play a role was suggested by Buxbaum and colleagues (Buxbaum, Giovannetti, Libon, 2000; Romano et al., in press) in their revision of Gonzalez-Rothi's model. Furthermore, in a single case report relating to a patient who suffered from callosal disconnection and limb apraxia, misplacing and misorienting objects and errors in body/object relations were found during the finger posture imitation using the left hand (Goldenberg, Laimgruber, Hermsdo, 2001b). These results suggest that an integrated activation of both hemispheres is necessary to guarantee the spatial correctness of actions. Finally, with regard to temporal errors, only "unsubstained actions" (Mc Donald et al., 1994) were more frequent in MA than A- and RBD in the present study (Rothi et al., 1988; Hanna-Pladdy et al., 2001; Spinazzola et al., 2003).

Specificity of errors relating to the various different action typologies

Content and Configuration errors turned out to be the most indicative of the presence of apraxia. With regard to Limb Transitive actions, the errors that discriminated the MA patients from the A- patients were related to Content, Configuration, Movement and Spatial, while there was no difference in the number of errors committed by the BFA group with respect to the non-apraxic groups. In the case of Limb Intransitive actions, all but Destructured action errors discriminated MA from A-. However, the MA patients were no different from the RBD group for Spatial errors. Although the diagnosis relating to BFA does not justify spatial errors, the patients in this group made more errors relating to this category than the A- group and more Configuration errors than the RBD group. The error category which included Unrecognisable/Destructured actions was not indicative of apraxia in the limb gesture imitation task, but this error category did discriminate MA patients from the other groups in Mouth Intransitive actions. Other typologies of error that discriminated MA and BFA patients from the rest in Mouth Intransitive actions were Content and Configuration errors. Very few errors were found in Mouth Transitive actions, for which the only error category that differentiated the MA group from the A- group was Configuration. In the case of Mouth actions, Temporal and Spatial errors were never indicative of the presence of apraxia.

The error categories pertaining to the MA and BFA groups

If we consider the various error categories pertaining to each group, we find that the categories are indicative of apraxia to different degrees. For the MA group, Configuration and Content errors were indicative of apraxia in all of the typologies of actions and represent the only categories specific to apraxia in Mouth Transitive actions. Movement and Spatial errors were only indicative of apraxia in Limb actions. Temporal errors and Destructured actions were always less indicative of apraxia than other categories in Limb actions, except in the case of Mouth Intransitive actions for which Destructured errors were more indicative than Spatial, Temporal and Movement errors.

Given that the BFA patients failed in both Limb and Mouth actions, one might hypothesise that BFA may be a less severe form of apraxia than MA. However, a comparison between the various different error categories did not support this hypothesis since in Limb Transitive actions none of the error categories reached the AUC>7 in the BFA group and in Limb Intransitive actions, the category which was significantly more indicative of apraxia for this group was Spatial errors, which were, as mentioned earlier also present in the RBD patients. Conversely, in Mouth actions, in particular the Intransitive Mouth actions, Content and Configuration errors were more indicative of apraxia than the other errors.

Conclusions

There are some limitations to the present study, the first of them being that the experimental task exclusively investigated ideomotor apraxia. Further studies are necessary to identify specific differences in the typologies of error associated with ideational apraxia. The second limitation is the absence in the sample of patients with limb apraxia only. In our opinion, this might be the result of a different degree of sensitivity of the neuropsychological tests used to assess bucco-facial and limb apraxia, and this may well have induced a bias with regard to the subsequent diagnosis. However, the validity of the classification of the patients in our sample was confirmed by the typologies of the errors made by the BFA and MA patients.

Taken as a whole, our study shows that although in the case of MA and BFA patients various different error categories may be present, not all of these errors are equally indicative of apraxia and therefore cannot all be used to discriminate apraxic from non-apraxic patients. The results also demonstrated that the various error categories are associated with at least partially different neural correlates. Finally, the typologies of action may be associated with the various error categories. To sum up, we consider that these results contribute towards expanding existing knowledge concerning apraxia and provide indications which will be useful in clinical practice.

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Conflict of Interest: None.

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