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Running head: a double dissociation between tool-gesture production and knowledge

Title:

Knowing how to do it or doing it? A double dissociation between tool-gesture production and tool-gesture knowledge.

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Abstract

Deciding how to manipulate an object to fulfill a goal requires accessing different types of object-related information. How these different types of information are integrated and represented in the brain is still an open question. Here, we focus on examining two types of object-related information – tool-gesture knowledge (i.e., how to manipulate an object), and tool-gesture production (i.e., the actual manipulation of an object). We show a double dissociation between tool-gesture knowledge and tool-gesture production: Patient FP presents problems in pantomiming tool use in the context of a spared ability to perform judgments about an object's manipulation, whereas Patient LS can pantomime tool use, but is impaired at performing manipulation judgments. Moreover, we compared the location of the lesions in FP and LS with those sustained by two classic ideomotor apraxic patients (IMA), using a cortical thickness approach. Patient FP presented lesions in common with our classic IMA that included the left inferior parietal lobule (IPL), and specifically the supramarginal gyrus, the left parietal operculum, the left premotor cortex and the left inferior frontal gyrus, whereas Patient LS and our classic IMA patients presented common lesions in regions of the superior parietal lobule (SPL), motor areas (as primary somatosensory cortex, premotor cortex and primary motor cortex), and frontal areas. Our results show that tool-gesture production and tool-gesture knowledge can be behaviorally and neurally doubly dissociated and put strong constraints on extant theories of action and object recognition and use.

Introduction

Grasping a pen and stroking it against a sheet of paper, picking up a mug of tea, or typing on your computer keyboard are all but a small subset of actions that are an essential part of our everyday life. This ability to dexterously manipulate tools (i.e., man-made small manipulable objects with a particular function) is dependent on the integration of different types of information: we may need to 1) recognize the target object that we want to use, as well as the function it performs so as to understand whether it fulfills our intended action; 2) extract volumetric properties of the to-be-used tool, such as its center of mass or size, in order to shape our effectors accordingly; 3) understand the tool’s spatial location in relation to the effectors; and 4) retrieve use and grasp programs that are typical of the target object. How all this information is integrated and represented is still an open question.

One way to address this question has been to understand how different types of information pertinent to acting on objects are related to one another cognitively and neuronally. For instance, much has been debated about whether recognizing an action (or an object) and performing that action (or manipulating that object) are related but independent types of information, or whether action-related (or object-related) information is reducible to the sensory motor aspects of tool-gesture production (or object manipulation; e.g., Gallese & Lakoff, 2005; Mahon & Caramazza, 2005; Rizzolatti, Fogassi, & Gallese, 2001). Importantly, data on ideomotor apraxia (IMA; i.e., a deficit typically characterized by difficulties in pantomiming the use of tools prompted by verbal command. This main deficit may also be associated with impairments in making judgements about tool manipulation, and actual tool use deficits; e.g., Buxbaum and Saffran, 2002) has challenged the latter idea, as these patients are able to recognize and name objects, despite the fact that they are unable to manipulate those same objects (Almeida et al., 2018; Buxbaum, Giovannetti, & Libon, 2000; Buxbaum, Veramontil, & Schwartz, 2000; Cubelli, Marchetti, Boscolo, & Della Sala, 2000; Garcea, Dombovy, & Mahon, 2013; Mahon & Caramazza, 2005; Mahon et al., 2007; Negri et al., 2007; Ochipa, Rothi, & Heilman, 1994; Papeo, Negri, Zadini, & Rumiati, 2010; Rapcsak, Ochipa, Anderson, & Poizner, 1995). Moreover, this radical embodied view of object and action processing has further been challenged by reports that show that our understanding of action verbs is independent from our ability to perform those same (object-related) actions (e.g., Bedny & Caramazza, 2011; Kemmerer, 2015; Papeo et al., 2010), and that the lack of prior experience with action, or the inability to motorically enact these actions, does not impede (or even worsens) object/action recognition (Vannuscorps, Andres, & Pillon, 2014; Vannuscorps & Caramazza, 2016).

Interestingly, IMA may allow us to focus on how other types of action-related information relate to one another. Here, we will examine the overlap between and/or the independence of the knowledge of how to manipulate an object (henceforth tool-gesture knowledge), and the actual manipulation of an object (henceforth tool-gesture production).

Typically, IMA patients present deficits in both tool-gesture knowledge tasks – e.g., performing manipulation judgments such as whether a piano and a typewriter share motor programs when used – and tool-gesture production tasks – e.g., mimicking the use of a hammer, without the hammer in hand (Almeida et al., 2018; Bartolo, Daumüller, Sala, & Goldenberg, 2007; Buxbaum, Giovannetti, et al., 2000; Buxbaum & Saffran, 2002; Garcea et al., 2013; Papeo & Rumiati, 2013; henceforth, we consider as defining criteria for IMA the presence of both deficits, an inability to perform and understand transitive actions). This certainly bodes well with radical embodied views of tool-gesture production and tool-gesture knowledge (Gallese & Lakoff, 2005; Rizzolatti, Fogassi, & Gallese, 2001; Rizzolatti & Sinigaglia, 2010). Under such views, tool-gesture knowledge is mounted on tool-gesture production – i.e., reenacting the motor programs associated with an object is what allows for accessing tool-gesture semantics. Other views on action and object processing may suggest a looser relationship between these two types of knowledge. In perhaps less radical views of the role of sensory motor processes in object knowledge (Barsalou, 2008; Kiefer & Pulvermüller, 2012; Meteyard, Cuadrado, Bahrami, & Vigliocco, 2012), these two types of tool-gesture related processes are more or less dependent on one another.

Another possible view on these two types of knowledge comes from Binkofski, Buxbaum and collaborators (Binkofski & Buxbaum, 2013; see also Rizzolatti & Matelli, 2003). These authors proposed that the dorsal visual stream (Goodale & Milner, 1992) is divided into two independent action streams that are important for successful manipulation of objects, and that focus on different computational goals: the ventro-dorsal stream and the dorso-dorsal stream. On the one hand, the ventro-dorsal stream, a visual stream that goes through the left IPL, integrates visual and action information important for object manipulation, and stores “gesture engrams” (i.e., the features of a specific gesture; Buxbaum, 2001). For instance, the “core” features that compose the action “hammering” include “elbow joint angle”, “shoulder joint angle”, and “grip aperture”, among others (Buxbaum, 2001). On the other hand, the dorso-dorsal stream, a majorly bilateral stream that goes through SPL, processes volumetric information to inform reach and grasp movements, and translates motor representations into a motor execution program (Binkofski & Buxbaum, 2013). These authors then suggest some independence between the two types of knowledge. A related view regarding the relative independence between tool-gesture knowledge and tool-gesture production suggests that our relationship with tools may be perceived as a problem-solving issue, where we use mechanical knowledge (e.g., in order to cut we need two objects: one abrasive and hard, and another soft) to interact with manipulable objects. The ventro-dorsal stream computes mechanical knowledge, while the dorso-dorsal stream is responsible for perceiving object affordances, as well as creating a motor simulation to make judgments about the best way to manipulate an object (Osiurak & Badets, 2016; Osiurak, Lesourd, Navarro, & Reynaud, 2020). Yet, other views suggest that these two types of information may be independent but integrated in some sort of action-specific working memory system (Cubelli et al., 2000).

Understanding whether tool-gesture knowledge and tool-gesture production are independent from one another is of major interest in the field for at least two reasons. Firstly, it may bring another key challenge to (radical) embodied theories by demonstrating that not only is the ability to recognize a tool or an action independent of the ability to enact (object-related) actions, but that knowledge about how to act upon an object is, in the same vein, independent of enacting those same actions. Secondly, the typical association between deficits with tool gesture (knowledge or production) in many IMA patients (Buxbaum & Saffran, 2002) led to the assumption that these two tasks are dependent on the same mechanisms. Thus, rarely patients and healthy participants are assessed with both tasks: IMA patients perform tool-gesture production tasks (Goldenberg, Hermsdörfer, Glindemann, Rorden, & Karnath, 2007; Hoeren et al., 2014; Jax, Rosa-Leyra, & Buxbaum, 2014; Randerath, Goldenberg, Spijkers, Li, & Hermsdörfer, 2011; Watson & Buxbaum, 2015), whereas neurotypical participants perform tool-gesture knowledge tasks along with fMRI and neurostimulation techniques (Boronat et al., 2005; Canessa et al., 2008; Garcea & Mahon, 2012; Ishibashi, Mima, Fukuyama, & Pobric, 2018; Ishibashi, Ralph, Saito, & Pobric, 2011; Myung, Blumstein, & Sedivy, 2006; Ruotolo, Kalénine, & Bartolo, 2019). Thus, showing that these two tasks are not dependent on a singular component will impact the interpretation of many studies. Here, we describe two patients with a tool use impairment and with a yet unreported double dissociation between tool-gesture knowledge and tool-gesture production. Patient FP presents problems in pantomiming the use of tools in the context of a spared ability to perform manipulation judgments about an object's manner of use. Conversely, Patient LS is able to pantomime tool use, but is impaired at performing manipulation judgments. We will start with a behavioral description of the performance of our patients, followed by describing the locus of brain damage using a cortical thickness approach. Based on our findings, we propose different interpretations and implications of this study.

Experiment 1

In this experiment we assessed Patients FP and LS in terms of their praxis performance and compared them with an age-matched control group. Both Patients were assessed on tool-gesture production and tool-gesture knowledge – our main tasks in the study. Moreover, both Patients went through an action naming task, and Patient FP and the controls also performed a series of auxiliary tasks on object naming and semantic knowledge. Although these were not part of the formal screening batteries, they were included as tests that allowed us to screen specifically how other object-related processing was performed by these patients. No part of the study procedure was pre-registered prior to the research being conducted. The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the corresponding author through email. Full access to the data will be granted on request without conditions. Legal copyright restrictions prevent public archiving of the various assessment tests and instruments used in this study, which can be obtained from the copyright holders in the cited references. We report how we determined our sample size in the control group, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

Methods

Participants

Patient FP

Patient FP is a right-handed man with 15 years of education. He was referred to the Neurology Department of *Centro Hospitalar e Universitário de Coimbra (CHUC)* in 2017, when he was 59 years-old, complaining of progressive difficulties in spoken language, writing, and reading. Curiously neither him nor is wife reported difficulties in his interaction with objects or when performing complex actions. Despite the language impairment, he still lived an independent life and tried to maintain his job as a business man in accounting, managing a small company of five employees. The diagnosis of FP, based on an extensive investigation for degenerative dementia which included MRI, CSF biomarkers and genetic testing, was Primary Progressive Aphasia (PPA) probably in the spectrum of Fronto-Temporal Dementia.

We started by two brief screening tests to assess cognitive decline: Mini-Mental State Examination (MMSE: Folstein, Folstein, & McHugh, 1975; Portuguse version: Guerreiro et al., 1994) and Montreal Cognitive Assessment (MoCA: Nasreddine et al., 2005; Portuguese Version: Simões et al., 2008). In the MMSE, Patient FP scored 28 (out of 30), which, for his education level and age, is 2 standard deviations (SD) below the normative values for the Portuguese population (mean (M) = 29.54; standard deviation (SD) = 0.71; Freitas, Simões, Alves, & Santana, 2015). In MoCA, Patient FP scored 20 (out of 30), his result is 3SDs below the normative values for his age and education (M = 27.51; SD = 2.13). In this specific test, he was impaired at calculus and picture naming (overall loss of 6 points; Freitas, Simões, & Santana, 2014). The total score of these two brief cognitive screening tests show that Patient FP presents a cognitive decline, but at the time of the assessment, he had specific difficulties that comprise calculus and naming tasks (these difficulties led him to lose 6 points in MoCA). Patient FP also performed poorly in the Trail Making Test – B (TMT-B; subtest of MoCA that assesses executive functioning and mental flexibility), but Patient FP explained his performance due to difficulties in ordering letters in alphabetical order.

Patient FP was further assessed with a neuropsychological comprehensive battery adapted to the Portuguese population - *Lisbon Battery for Dementia Assessment* (BLAD; Guerreiro, 1998). His performance was at ceiling in logical reasoning (Raven Progressive Matrices), abstract knowledge (understanding of proverbs) and visuospatial abilities (drawing a clock, a cube, a flower and a house). He also did not show difficulties in picture-name matching. However, he presented impairments in semantic knowledge (semantic fluency for the animal category), and in episodic memory tests (the Wechsler Memory Scale) where he showed severe impairments in associative knowledge and a moderate loss of information in delayed recall. In language testing, Patient FP presented semantic and phonemic paraphasic errors in spontaneous speech, with preserved sentence repetition. Patient FP presented flawless grammatical comprehension tested by basic and complex orders of the Token Test. In writing, he presented dysgraphia, swapping letters inside words and made mistakes especially in irregular words. He also had surface dyslexia in reading. Moreover, he had problems with mental calculus. He did not have problems in color identification and naming, nor in discrimination between the left and right sides of the body. Patient FP gave us full written informed consent in accordance with the Ethics Committee of the Faculty of Psychology and Educational Sciences of University of Coimbra.

Patient LS

Patient LS is a right-handed woman, with 18 years of education. She was admitted in the Neurology Department of *Hospital de Santa Maria* in Lisbon in 2013, when she was 59 years-old, with a naso-ethmoidal tumor. She had a reversible cerebral vasoconstriction syndrome (RCVS), possibly from the use of vasoconstrictive drugs during and after surgery. This resulted in callosal and left fronto-parietal ischaemic lesions as assess by structural magnetic resonance imaging (MRI).

Patient LS presented anomic aphasia (with word finding difficulties especially for objects). She also presented a memory impairment in delayed recall (she recalled 1 out of 3 words). She showed agraphia in the context of normal calculus and reading abilities. She also revealed symptoms of right graphesthesia, bilateral visuomotor ataxia, and oculomotor apraxia.

She gave us informed consent for evaluation and case reporting according to the Ethics committee of the Faculty of Medicine of the University of Lisbon. Patient LS was assessed during her admission after her surgery. She did participate in the main experiments (tool-gesture production and tool-gesture knowledge tasks), and she went through part of the action naming test. She did not perform the auxiliary tasks due to medical issues unrelated to her neurological condition.

Controls

Ten right-handed volunteers, 9 women and 1 man, selected as a convenience sample, served as controls after providing written informed consent in accordance with the ethics committee of the Faculty of Psychology and Educational Sciences of University of Coimbra. These participants were matched on age (mean (M) = 63.5; SD = 6.72) and level of education (M = 14.4; SD = 1.27) to our two patients. Our controls did not have an history of neuropsychiatric illness or cognitive decline (as assessed by MoCA; M = 27.1; SD = 1.7). Each control completed the battery of tests described in the procedures in a 1h session. All participants gave written informed consent in accordance with the ethics committee of the Faculty of Psychology and Educational Sciences of University of Coimbra.

Procedure

All participants underwent on our main behavioral experiments: the tool-gesture production tasks, and tool-gesture knowledge tasks. Furthermore, all participants went through an action naming task (Patient LS performed a shorter version of the action naming test). Moreover, to better understand the performance of Patient FP, he and the controls also performed a series of auxiliary tasks on object naming and semantic knowledge.

Main behavioral experiments

Tool-Gesture Production

In order to assess tool-gesture production, our participants were asked to 1) pantomime the use of tools from verbal command (e.g., “show me how to use a hammer”; this was done without any object present); 2) and demonstrate tool use (with the object in hand) from verbal command and with the object placed in front of the patient on the table (e.g., when given a hammer, participants would have to perform the action with the object in hand). The tool-gesture production experiment was done in separate runs within a session (pantomime was always presented first). All participants used their dominant right-hand. We followed Garcea and collaborators (2013), and used their stimuli for each tool-gesture production condition. Garcea and collaborators (2013) list of objects included everyday tools (i.e., small manipulable objects that are familiar to most if not all individuals). For Patient FP, we used 17 objects in both tasks (a screwdriver, a clothespin, scissors, pliers, a corkscrew, a bottle opener, a hairbrush, a hammer, a pen, a wrench, a bottle, a mug, a paint brush, tweezers, a spray bottle, a stapler, and a hole-puncher). For Patient LS, in the demonstration of tool use condition, we used the exact same 17 items with the exception of a pen (i.e., a total of 16 items). In the pantomime condition, we use these same 16 items plus 3 extras (a paint roller, a spoon and a dust cloth). Performance was recorded and scored with 1, 0.5 or 0 by a trained experienced rater based on the following system: 1 point was given when the gesture was completely correct; 0.5 points were given when it had minimal errors – i.e., when the gesture was recognizable and correct but the movement amplitude was not right or there were minimal errors in the fingers configuration; and 0 points were given when the gesture was unrecognizable, omitted, presented in an incorrect sequence of actions or when the participants used a body part as an object. When participants failed at their first attempt, they were given a second chance to correct the gesture and they received 0.5 points. There were no time constraints performing the tasks.

We classified errors of our control participants and patients based on whether the fitted on one of four categories: 1) Spatial errors (e.g., wrong movement amplitude, wrong posture of finger/hand or arm during the tool use, and use body-part-as-tool (BPAT)); 2) Temporal errors (e.g., incorrect sequencing of actions, delete or add a new movement); 3) Content errors (e.g., preservations, a pantomime not associated with the target), and 4) Other errors (e.g., no response to a tool). For each trial, we used the recorded videos to score their performance according to FABERS protocol (Power, Code, Croot, Sheard, & Rothi, 2010; for detailed error descriptions check Appendix F from Power and colleagues, 2010).

Tool-Gesture Knowledge and Tool-Functional Knowledge

In order to assess tool-gesture knowledge, all participants took part in a Function and Manipulation Triplets Test (word version) developed by Buxbaum and collaborators (Buxbaum et al., 2000; provided in Appendix 2 of their article). In these tests, participants are asked to select the odd one out of a triad of objects. In one of the tests (the manipulation test), three objects are presented – two of them share the manner with which they are manipulated, and so the odd one out can only be selected based on information about how to manipulate an object (e.g., in the triplet typewriter, piano and stove, the first two objects are “tapped” with the fingertips). In the other test (the function test), two of the three objects share function, and so the odd one out can only be determined based on information on an object’s function (e.g., in the triplet record player, radio and telephone, the first two objects are used for listening to music). These are widely used tests in many experiments with healthy participants or IMA patients for assessing manipulation and functional knowledge, and as a behavioral marker of IMA

(Boronat et al., 2005; Buxbaum & Saffran, 2002; Buxbaum, Veramontil, et al., 2000; Canessa et al., 2008; Collette et al., 2016; De Bellis et al., 2016; Garcea et al., 2013; Garcea & Mahon, 2012; Ishibashi et al., 2018, 2011; Kable, Kan, Wilson, Thompson-Schill, & Chatterjee, 2005; Kellenbach, Brett, & Patterson, 2003; Myung et al., 2006, 2010; Riccardi, Yourganov, Rorden, Fridriksson, & Desai, 2020; Ruotolo et al., 2019). We used the original tests of Buxbaum and collaborators (2000, 2002) in order to assure that function and manipulation conditions were equally difficult, and in both, visual similarity between the triplets could not be used to infer the correct response. We run the manipulation and function tests independently. Patient FP and the controls judged 14 triplets from the manipulation condition and 16 from the function condition. Patient LS judged 13 and 12 triplets, respectively – i.e., Patient LS went through all the triplets from the manipulation condition that Patient FP and the controls went through except one, and all of the function triplets except 3.

Other action and object-related tasks

Action Naming

In order to assess the ability to name actions, we used an action naming battery (the Object and Action Naming Battery; Druks & Masterson, 2000). Patient FP and controls were instructed to name one-hundred pictures of actions with a single verb (whenever possible). A shorter version with seventeen pictures of the original test was applied to Patient LS.

Auxiliary tests: Object Naming, and Semantic Knowledge

We asked Patient FP and controls to name a widely used set of black and white line drawings of animals, fruits, vegetables, tools, furniture, musical instruments, and kitchen items (Snodgrass & Vanderwart, 1980; e.g., Marques, Raposo & Almeida, 2013). We also assessed these participants on their semantic memory by using 55 questions of the Pyramids and Palm Trees test (Howard & Patterson, 1992 - picture version). Finally, to assess conceptual understanding of manipulable objects, participants went through a task (“the central attribute test”) where they were presented with a sentence that they had to judge as correct or incorrect. The test was visually presented to Patient FP (and the controls) and the experimenter helped him when he showed difficulties in reading the sentences. In these sentences, one object and a particular feature/attribute were presented and the participants had to verify if they went together (e.g., “Are pliers normally used in the kitchen?”, or “Is a screwdriver used together with a screw?”; i.e., property verification task).

Analysis

We computed three modified t-tests to assess the performance of our patients in comparison with our control group, or with one another, using the software provided by Crawford and colleagues (e.g., the Revised Standardized Difference Tests; e.g., Crawford & Garthwaite, 2002; Crawford, Garthwaite, & Porter, 2010; Crawford, Garthwaite, & Wood, 2010). The first modified t-test compares the test score of each patient with a control group. The software takes as input the mean and standard deviation of the scores of the healthy controls, the sample size of the control group, and the score of the patient (Crawford & Garthwaite, 2002). This test was used in our main behavioral experiments (tool-gesture production and tool-gesture knowledge) and in the auxiliary tests performed by Patient FP. We also used two additional t-modified tests, to better understand the differences between the performances of Patient FP and Patient LS in the tool-gesture production and tool-gesture knowledge tasks. In the second test, the goal is testing if a single case meets the criteria for a dissociation – strong or classical - between the two tasks. Here, the software takes as input for each task the mean and standard deviation of the scores of the healthy control, the sample size of the control group, the correlation between the scores of the controls on the two tasks, and finally, scores of the patient for both tasks (Crawford et al., 2010). Finally, in the third test we used a classical statistical test to compare the performance of our two patients’ scores with the healthy controls, allowing us to check if our patients differ from one another in a specific task. The software requires the standard deviation and sample size of the scores of the controls, and the scores of the two patients in a specific task (Crawford et al., 2010). The percentage of correct responses for each task is presented in brackets. No part of the study analyses was pre-registered prior to the research being conducted

Results

Figure 1. Example of the errors committed by Patient FP during the pantomiming task. In this figure we show how Patient FP pantomimed the use of a corkscrew. Patient FP used his index finger and he rotated the entire hand in circle in parallel with the table, then he closed his fist and raised his arm. However, these gestures were followed by a correct description of how to use a corkscrew – one has to twist the tip of the corkscrew and then "squeeze" the handles to pull out the cork.

Tool-Gesture Production

Patient FP was unable to pantomime the typical manipulation associated with the objects that were presented, and his performance was statistically different from control group (26%; $t(9) = 9.5$, $p < 0.001$). All of his errors were classified with 0 or 1, except when Patient FP pantomimed the use of a pen, which was scored with 0.5 – he performed the correct movement, but he added an extra gesture: he rubbed the index and thumb fingers (this addition was classified as a temporal error). He also committed 11 spatial errors, some of them due to using an incorrect object grasp (e.g., when pantomiming the use of a hammer, he balanced his arm with the whole-hand open; when pantomiming the use of a stapler, he used an index and thumb to squeeze), and he also made errors where he used a body part as tool (e.g., when he pantomimed the bottle opener and the screwdriver). He said that he did not know what a wrench was, so this was classified as an "other" error (see Fig 2). Patient LS, however, was able to pantomime object use, and her performance did not differ from control group (84%; $t(9) = -0.69$, $p = 0.51$). Specifically, Patient LS failed to pantomime a wrench because she pantomimed a screwdriver instead, and presented spatial errors in pantomiming the hair brush and the staples. Importantly, these two patients differ from one another on this task ($t(9) = 6.53$, $p < 0.001$). Our results are not altered if we restrict our analysis to the items that Patients LS and FP have in common (i.e., 16 tools): Patient FP continued to score below the controls (28%, *t(*9)= -8.590, p < 0.0001), whereas the performance of Patient LS is not statistical different from the control group (81%, *t*(9)= -0.944, p= 0.37). When we compare the performance of both patients with one another, their performances are statistically different *(t*(9) = -5.67, p < 0.0005).

Interestingly, despite being unable to pantomime, Patient FP was able to describe the movements necessary for using the target tool. For instance, when asked to pantomime the use of scissors, Patient FP mentioned that "scissors have two holes, we put the fingers inside them and do an open-close movement". Although he was able to describe how to pantomime, he was not able to perform the right movement to pantomime the use of scissors. He pantomimed the use of scissors by opening and closing the thumb and index fingers as a tweezer (see the Figure 1 for another example of his performance).

Moreover, Patient FP showed impaired performance when he had the object in his hand (although slightly improved; 76%; *t*(9) = 4.88, *p* < 0.001). Patient LS performed at ceiling when she had to demonstrate tool use (see Table 1 for more information).

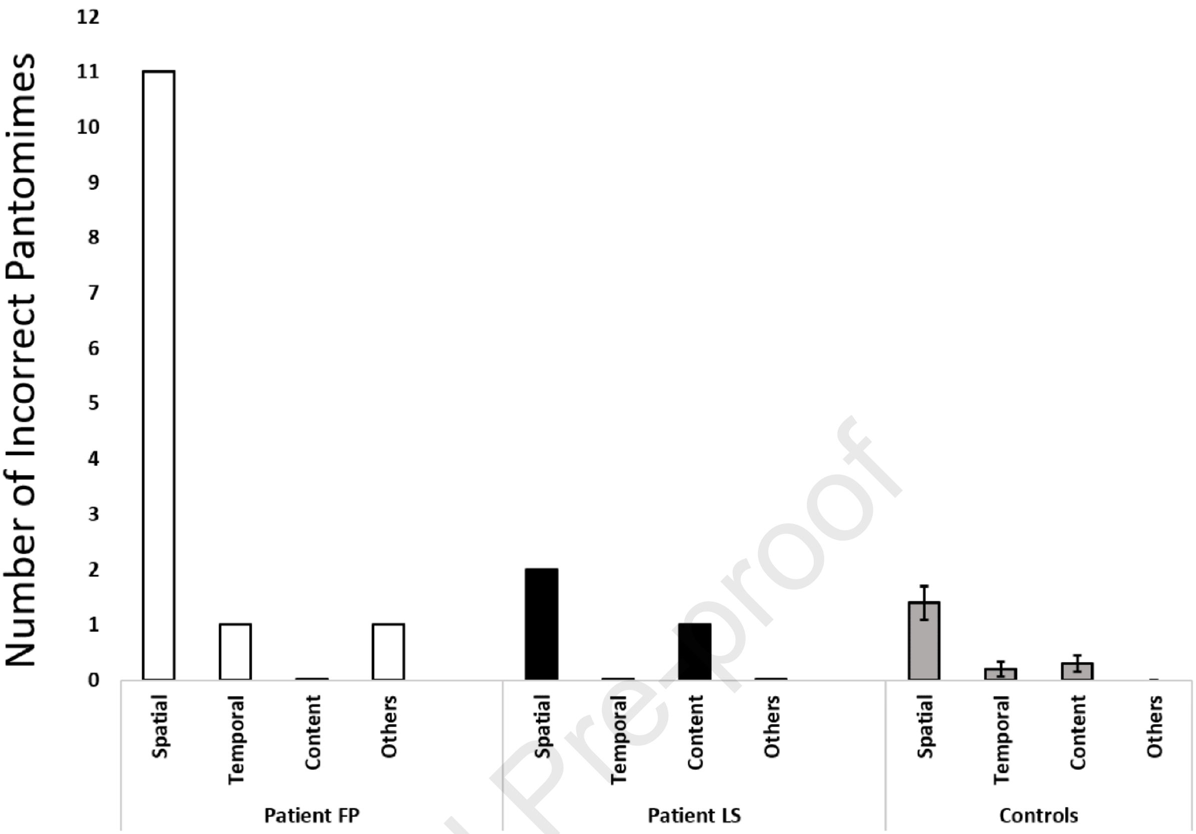

Figure 2: Behavioral errors of Patient FP, Patient LS and the controls in the pantomime task. Patient PF presented 13 errors out of 17 pantomimes, Patient LS presented 3 errors out of 19 pantomimes, and Controls presented an average of 1.9 errors out of 17 pantomimes (SD=1.1).

Tool-Gesture Knowledge and Tool-Functional Knowledge

When asked to select the odd object based on the manner in which objects are manipulated (i.e., the manipulation judgment condition from Buxbaum and Saffran, 2002), Patient FP responded correctly on 86% of the trials (12 out of 14). His performance was not significantly different from that of the control group (80%; $t(9) = 0.48$, $p = 0.65$). On the contrary, Patient LS was able to answer correctly only on 38% of the trials (5 out of 13), and her performance was statistical different from that of the control group ($t(9) = 3.504$, $p < 0.01$). In fact, our two patients differ from one another on this manipulation (tool-gesture semantics) task ($t(9) = 2.95$, $p = 0.016$). Once again, our results are unaltered if we restrict the analysis to the triplets that both patients judged (i.e., 13 triplets): we found that the performance of Patient FP was not statistical different from our controls (85%; $t(9)= 0.448$, $p= 0.66$), whereas the performance of

Patient LS was statistically below the controls (31%; *t*(9) = -4.031, *p* < 0.005). When we compared the performance of both patients against one another in the manipulation condition, we found that their performances continued to differ (*t*(9) = 3.322, *p* < 0.01).

Test	Patient FP	Patient LS	Controls
Tool-Gesture Production			
Pantomime	26% **	84%	89%
Demonstration of Tool Use (object in hand)	76%**	100%	96%
Tool-Gesture/Functional Knowledge			
Manipulation Judgments	86%	38%*	80%
Function Judgments	81%	100%	87%
Other tests			
Naming Actions	75% **	100%	95%
Naming Objects	60% **	____	94%
Pyramids and Palm Trees	89% *	____	97%

Table 1

Tool Knowledge	93%	____	96%

Behavioral performance of Patient FP and LS, as well as of the controls, in the different conditions of Experiment 1. Here we show percentage correct performance. * p < 0.05; ** p < 0.001 in the comparison between each patient with the controls.

When asked to select the odd object based on function-related information (i.e., the function judgment condition from Buxbaum and Saffran, 2002), Patient FP was able to answer correctly on 81% of the trials (13 out of 16), and Patient LS was able to answer correctly on all the trials (12 out of 12). The performance of both patients was not statistical different from the control group ($t(9) = 0.6$, $p = 0.57$, and $t(9) = 1.39$, $p = 0.2$, respectively; see Table 1 for more information). Importantly, this shows that there were not problems for both individuals to understand the instructions in these tasks, as they perform at the same level as controls in the function knowledge task.

Double dissociation between Tool-Gesture Production and Tool-Gesture Semantics

Importantly, the performance of Patients FP and LS fulfill the criteria for a classical statistically significant dissociation on opposite directions – hence a classical double dissociation (one-tailed t-tests) between pantomime (i.e., tool-gesture production) and manipulation judgments (i.e., tool-gesture semantics) when compared with the differences in these tasks for controls. Patient FP showed a deficit in pantomime but not in manipulation judgments ($t(9) = 6.3$, $p < 0.001$), Patient LS presented the opposite result ($t(9) = 1.86$, $p = 0.048$; see the Fig 3).

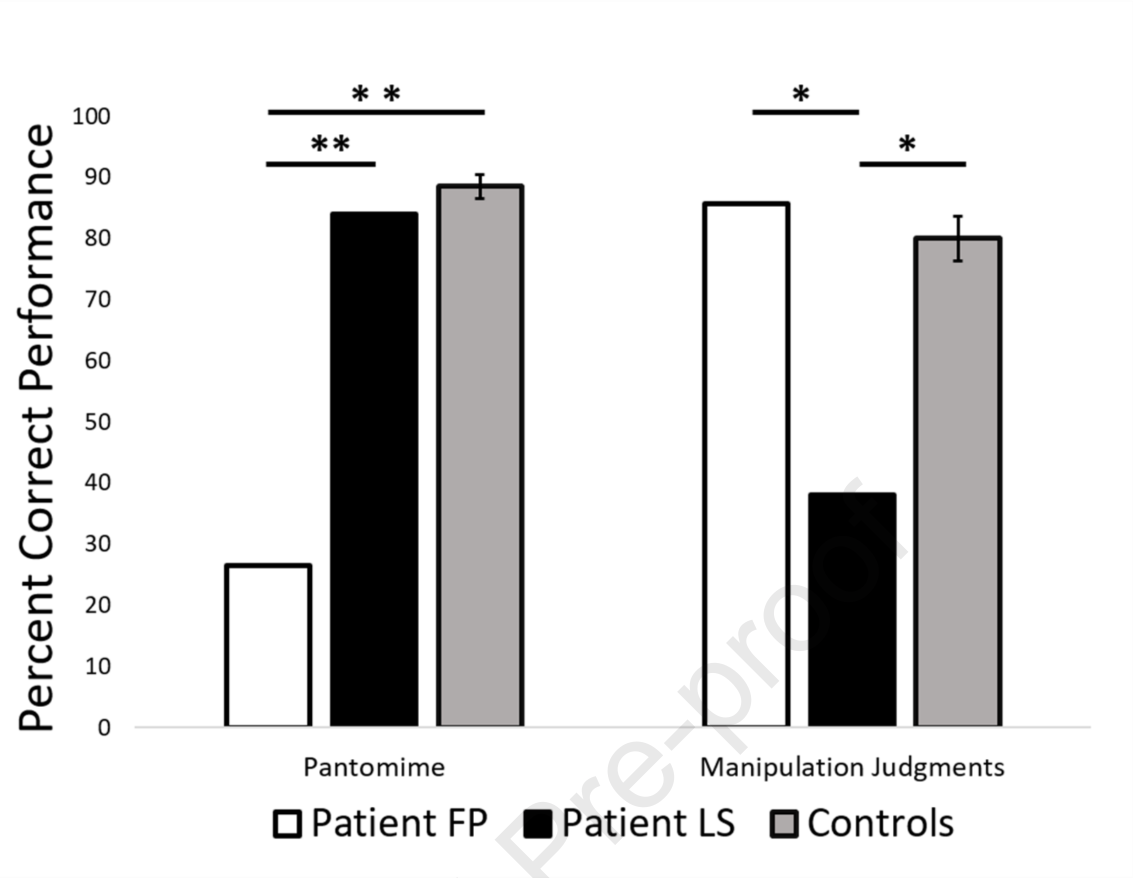

Figure 3. Behavioral performance of Patient FP, Patient LS and the controls in the pantomime task and the manipulation judgments test. The performance of Patient FP in the pantomime task is statistically different from that of Patient LS and of the controls. In contrast, the performance of Patient LS in the manipulation judgments test is statistically different from that of Patient FP and the controls. * p < 0.05; ** p < 0.001. The error bars represent the standard error, and the bars reflect percentage correct performance for each task

Action Naming

Regarding action naming, both patients and controls went through the Druks and Masterson (2000) action naming test. Patient FP was able to name 75 out of a total of 100 action stimuli (75%), whereas Patient LS correctly named all of the 17 action stimuli that she went through. Importantly, the performance of Patient FP was in fact significantly different from that of the controls ($t(9) = 6.55$, $p < 0.001$).

Auxiliary tests: Object Naming, and Semantic Knowledge

Here, we present the scores of the additional tests that Patient FP and the controls went through, besides the main tests.

Regarding object naming, Patient FP was able to name 60% of the Snodgrass and Vanderwart (1980) stimuli (48 out of 80), and his performance was statistically different from the control group ($t(9) = 7.49$, $p < 0.001$). Patient FP's errors were presented across all the categories assessed. Importantly, his performance seems to be more related to a difficulty in naming than to a semantic deficit. For instance, Patient FP had difficulties in naming a picture of a crown or a picture of a baby crawling, but in both he demonstrated no recognition problems: when presented with the picture of a crown he said that it “was worn on kings’ heads”, and when presented with a picture of a baby crawling he said that “it is typical for babies to do this before they start walking”. Nevertheless, these were considered errors and were scored as a 0. Although LS was not assessed with this same task, she also showed anomia for objects with a preserved ability to describe the objects she was unable to name – and she performed within normal range when naming actions.

Regarding semantic knowledge, Patient FP and the controls went through the Pyramids and Palm Trees test and the central attribute test. In the Pyramids and the Palm Trees, Patient FP responded correctly to 84% (49/55) of the questions, and his performance was statistically different from control participants, (89%; $t(9) = 4.3$, $p < 0.01$). In the central attribute test, Patient FP answered correctly to 93% questions (67 out of 72), and his performance did not differ from the control group ($t(9) = 1.99$, $p = 0.078$; See Table 1 for more information). Patients and controls did not have any time restriction.

Discussion

Patient FP revealed a severe deficit for pantomiming in the context of a spared ability to match objects based on manipulation information. In fact, he was able to describe the movements necessary to manipulate objects but was not able to pantomime them (see Fig. 1). Patient LS presented the opposite pattern of performance: she showed problems in using manipulation information to select the odd one out of a triad of objects, but was able to correctly pantomime the use of an object (see Fig. 3). Importantly, and, to the extent tested, both patients showed spared tool recognition abilities (with overall anomia), and most importantly spared understanding of the functions of tools. This dissociation was obtained largely over the same items in Patient LS and FP, discarding potential differences between patients based on item selection.

This double dissociation between tool-gesture production and tool-gesture knowledge has major implications to theories on object and action understanding. Just as action knowledge is independent from aspects pertaining to conceptual knowledge of objects and actions, tool-gesture knowledge and tool-gesture production are also processed independently.

One aspect that may be of interest in this debate is to try and understand how these two patients differ from one another and from classic IMA patients in terms of the locus of the lesions. This is exactly what we tested in Experiment 2.

Experiment 2

Patient FP and Patient LS present a double dissociation in what regards tool-gesture production and tool-gesture knowledge. One interesting avenue here is to compare neural deficits between our patients and a pair of classic IMA patients that were previously reported by our group (Almeida et al., 2018). In particular, these two patients from Almeida and collaborators show both tool-gesture production and tool-gesture knowledge impairments. In this experiment, we contrasted Patients FP and LS against two classic IMA patients in terms of the locus of their lesions. Because Patient FP shows distributed neural deficits due to is neurodegenerative disease, we used cortical thickness to select the major regions of "lesion" by comparing cortical thickness values for our patients (Patients FP and LS) with those of a set of healthy older adults (i.e., we equated lesion site with significant neural atrophy). The cortical thickness approach allowed us to assess the different patterns of brain damage in both patients. We have also manually segmented the lesions of Patient LS to demonstrate that the cortical thickness approach is a reliable method and that cortical thinning corresponds to the lesioned manually segmented areas - the results are very similar to each other, but cortical thickness presented larger frontal damage (see Fig 4 iv and Fig 5 ii to compare the two methods). Then, we compared the areas damaged in our patients with those of the classic IMA patients by overlapping the lesioned areas.

Methods

Participants

Patient FP and LS, two classic IMA patients, and 56 healthy elderly control individuals participated in this experiment.

Healthy Controls

Fifty-six native Portuguese speakers, 33 women, with a mean age of 68.61 (SD = 4.91; and a range between 61-79) and a mean education of 12.21 (SD = 4.84), served as healthy controls for our patients. All the participants were assessed with a brief cognitive screening test – MoCA – and they presented normal cognitive functioning.

Thus, we considered this group as representative of the normal cortical thickness values of elderly healthy individuals. Importantly, all of them gave written informed consent according to the Ethics Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra.

Classic IMA patients

Patient JT and Patient AB were previously reported by Almeida et al., (2018). These patients demonstrated difficulties in both pantomiming objects use from verbal command (52% and 21% of correct pantomime trials respectively), and in selecting an odd object from a triad of object based on information about how to manipulate an object (62% and 69% accuracy in selecting the odd one out based on the manner of manipulation respectively; Buxbaum & Saffran, 2002). Both of these patients were, however, able to select an odd object from a triad of objects based on information about the function of the object (83% and 92% accuracy in selecting the odd one out based on an object's function respectively; Buxbaum & Saffran, 2002). They also presented spared object recognition and naming (94% and 100% accuracy in object naming respectively), and their performance in pantomiming improved when they had the object in hand (94% and 95% correct performance in object use respectively). Below we present a brief description of these patients (a more thorough description can be found in Almeida and collaborators; Almeida et al., 2018).

Patient JT

Patient JT was 33 years old at the time of admission in April 2013, he was right-handed, and had 17 years of education. He had an acute ischemic stroke involving cortico-subcortical lesions in left occipito-parietal areas, the supramarginal gyrus, the intraparietal sulcus, and premotor regions, as revealed by structural MRI. He also had white matter lesions (e.g., centrum semiovale). At the time of admission, patient JT presented with non-fluent aphasia but without difficulties in comprehension, right homonymous hemianopsia, and right hemiparesis from which he recovered almost completely after four days. Other cognitive domains were preserved (e.g., verbal memory and learning, working memory, and executive functions). Patient JT was at ceiling when asked to name objects and actions (Druks & Masterson, 2000).

Patient AB

Patient AB was 52 years old at the time of admission, was a right-handed Portuguese male, and had 9 years of education. He was admitted in June 2013 with a two-week history of language and writing difficulties and right upper limb weakness. Structural MRI showed a subacute lesion in the left parietal lobe and a smaller lesion in the frontal posterior sulcus. At the time of admission, he presented with a mild aphasia with decreased speech output, normal comprehension, and poor repetition of pseudowords (conduction aphasia), a paresis of the right arm, and agraphia. Ten days after his first clinical assessment, his speech was fluent with little deficit. For further information about patients JT and AB see Almeida et al., (2018).

Procedure

In order to determine the differential locus of the neural deficits in our two main patients we first defined the lesion sites in each patient. For both Patients, and because Patient FP presented distributed neuronal loss due to neurodegenerative disease, we obtained cortical thickness maps and then we compared these maps with those of our healthy elderly controls. From these comparisons we extracted a set of regions, where Patient FP and Patient LS presented significantly more cortical thinning than the controls. Parallelly, we also manually segmented the lesions of Patient LS to compare whether the cortical thickness is a reliable method and the thinner areas were the same as the lesioned areas in T2 (see Fig 4 iv and Fig 5 ii to compare between methods). We found that overall the results between cortical thickness and lesion segmentation are very similar, but cortical thickness presented larger frontal damage.

We manually segmented the lesions of the two classic IMA patients based on the report of the neuroradiologist and the T2 image for visual help. Then, we compared the brain areas lesioned in each patient with the typical lesions of classic IMA patients. For Patient LS we compared both the manually segmented lesion, as well as the cortical thickness maps.

MRI data

Patient FP

MRI data was collected on a Siemens Tim Trio 3T MRI scanner with a 12-channel head coil. To acquire the high-resolution structural T1 weighted images, we use a magnetization prepared rapid gradient echo pulse sequence (repetition time [TR] = 1900msec, echo time [TE] = 2.32msec, flip angle = 9°, field of view [FOV] = 256mm, matrix size = 256×256, voxel size = 1×1×1mm, number of slices = 192).

Patient LS

MRI data was obtained on a Philips Medical Systems 1.5T MRI scanner with an 8-channel head coil. To acquire the structural T1 weighted images, we use a magnetization prepared gradient echo pulse sequence (TR = 25msec, TE = 6.9msec, flip angle = 20º, FOV = 200mm, matrix size = 560x560, voxel size = 0.36×0.36×0.5mm, number of slices = 180). Patient LS has a T2 weighted-structural image for coronal (TR = 3672.11msec, TE = 86.04msec, FOV = 220mm, flip angle = 90º, matrix size = 512x512, voxel size = 4x0.43x0.43mm, number of slices = 38) and axial (TR = 738.98msec, TE = 16.12msec, FOV = 230mm, flip angle = 18º, matrix size = 512x512, voxel size = 5x0.45x0.45mm, number of slices = 25) views.

Healthy Controls

MRI data was collected on a Siemens Tim Trio 3T MRI scanner with a 12-channel head coil. To acquire the high-resolution structural T1 weighted images, we use a magnetization prepared rapid gradient echo pulse sequence (repetition time [TR] = 2530msec, echo time [TE] = 3.29msec, flip angle = 7°, field of view [FOV] = 256mm, matrix size = 256×256, voxel size = 1×1×1mm, number of slices = 192).

Classic IMA patients

MRI data was collected on a Philips Medical Systems 3T MRI scanner with an 8-channel head coil. To acquire the structural T1 weighted images, we use a magnetization prepared gradient echo pulse sequence (TR of Patient AB= 9.65msec and TR of Patient JT= 9.68msec and; TE= 4.61msec; flip angle = 9°, FOV = 250 mm, matrix size = 512×512, voxel size = 1×0.49×0.49mm, number of slices of Patient AB= 155 and number of slices of Patient JT= 165). Classic IMA patients have a T2 weighted-structural images for coronal (TR = 3000msec, TE = 80msec, FOV = 220 mm, flip angle = 90º, matrix size = 512x512; Patient JT voxel size = 4.5x0.43x0.43mm and Patient AB voxel size = 4 x0.43x0.43mm, Patient AB number of slices = 31, Patient JT number of slices = 33) and axial (TR = 712.95msec, TE = 16.12msec, FOV = 230 mm; flip angle = 18º; matrix size = 512x512; voxel size = 5x0.45x0.45mm; Patient AB number of slices= 24 and Patient JT number of slices=29) views.

Analysis

Cortical Thickness

We used *FreeSurfer* (toolkit version 5; http://surfer.nmr.mgh.harvard.edu) to measure cortical thickness. The general workflow consisted of a normalization procedure, skull stripping, segmentation and estimation of pial surface boundary. Every step was visually inspected and manually adjusted when needed. Gray matter thickness was calculated as the distance between white matter boundary to the pial boundary of each vertex (Fischl & Dale, 2000). We started by extracting whole-brain cortical thickness maps for each patient and for all of the healthy controls independently. Then, we registered the cortical thickness surface of each patient and the average of our controls into the Montreal Neurological Institute (MNI) surface template. In Figure 4, we show the left cortical thickness maps, because apraxia is predominantly associated with the left hemisphere damage.

Apraxia is typically associated with frontoparietal lesions, thus we compared the cortical thickness values of the frontal and parietal lobes of our patients with those of our healthy controls. For statistical analysis, we followed current methods to compare a patient with a group (Jonin et al., 2018; Wallace, Happé, & Giedd, 2009). Patients and healthy controls were compared voxel-by-voxel employing modified t-tests developed by Crawford and Garthwaite (2002), followed by a false discovery rate (FDR) correction at $p < 0.05$. We also removed significant sites that were composed of one single voxel. We ended up with cortical thickness clusters where our patients presented thinner and thicker regions in comparison with our elderly control group (see Fig 5 i and ii).

Lesion segmentation and Overlap

Two classic IMA patients were segmented on the native T1 with the visual help of T2 contrast images and based on the report given by an experienced neuroradiologist. The brain areas atrophied in Patient FP and lesioned in Patient LS were segmented based on the previous results of cortical thickness (for Patient LS we repeated this procedure using the manually segmented lesion maps). We used MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) to draw the lesions of the two classic IMA patients. Then, we used Statistical Parametric Map Software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK), to normalize the lesions into MNI space. We combined the lesions of the two classic IMA patients (Patient JT and Patient AB) into a single image, through MRIcron. Then, we overlapped this combined image with the cortical thickness clusters of Patient FP and Patient LS, separately. In order to understand which lesion sites did our patients have in common with our classic IMA patients, we used the Jülich histological (Amunts & Zilles, 2015) and Harvard-Oxford cortical and subcortical structural atlases (Desikan et al., 2006).

Finally, to show that both lesion-mapping methods used in Patient LS (cortical thickness and manual segmentation) overlap, we manually draw her lesioned areas in order to assure that those areas were similar to the thinner areas given by cortical thickness analysis (compare Figure 4 - iv and Figure 5 - ii).

Results

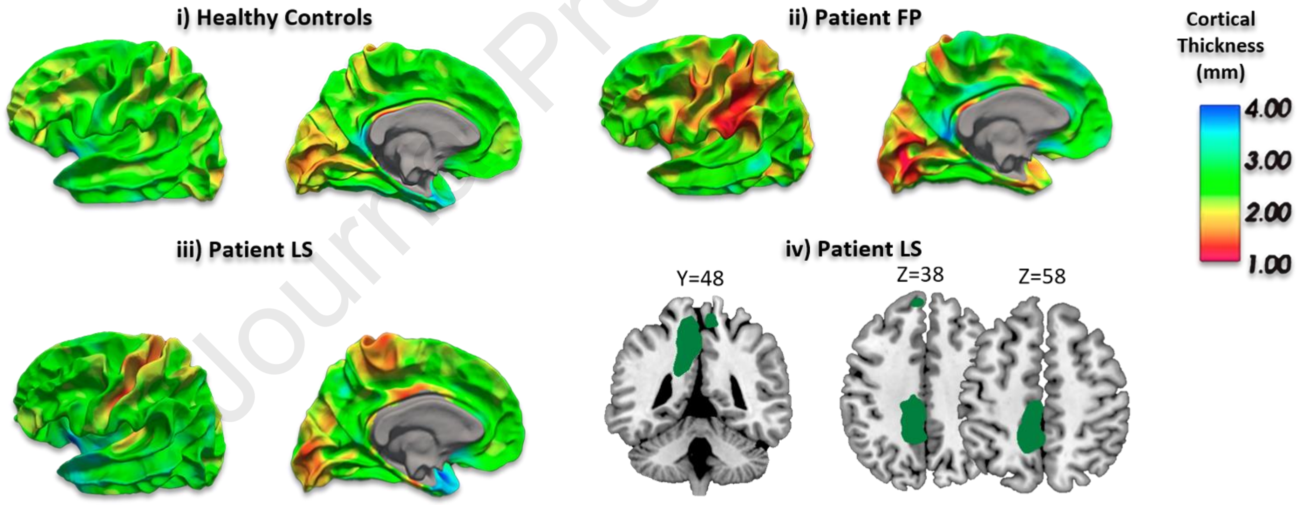

Figure 4: Cortical thickness maps of Patients FP and LS compared with healthy controls, and Patient LS segmented lesion. From i) to iii) we present left hemisphere cortical thickness maps showing the distance between pial surface and white matter in millimeters (mm), in coronal and axial views; in iv) we present the segmented lesion of Patient LS. Image i) shows the mean of cortical thickness for 56 healthy controls, while images ii) and iii) show the cortical thickness for Patient FP and Patient LS, respectively. Green represents the average cortical thickness in a normal brain (2.5 mm); regions that show a reduction in cortical thickness are represented in red, whereas regions that show an increase in cortical thickness are presented in blue. As can be seen, Patient FP and LS presented different brain areas with a significant reduction of cortical thickness. Image iv) shows the manual lesion segmentation of Patient LS.

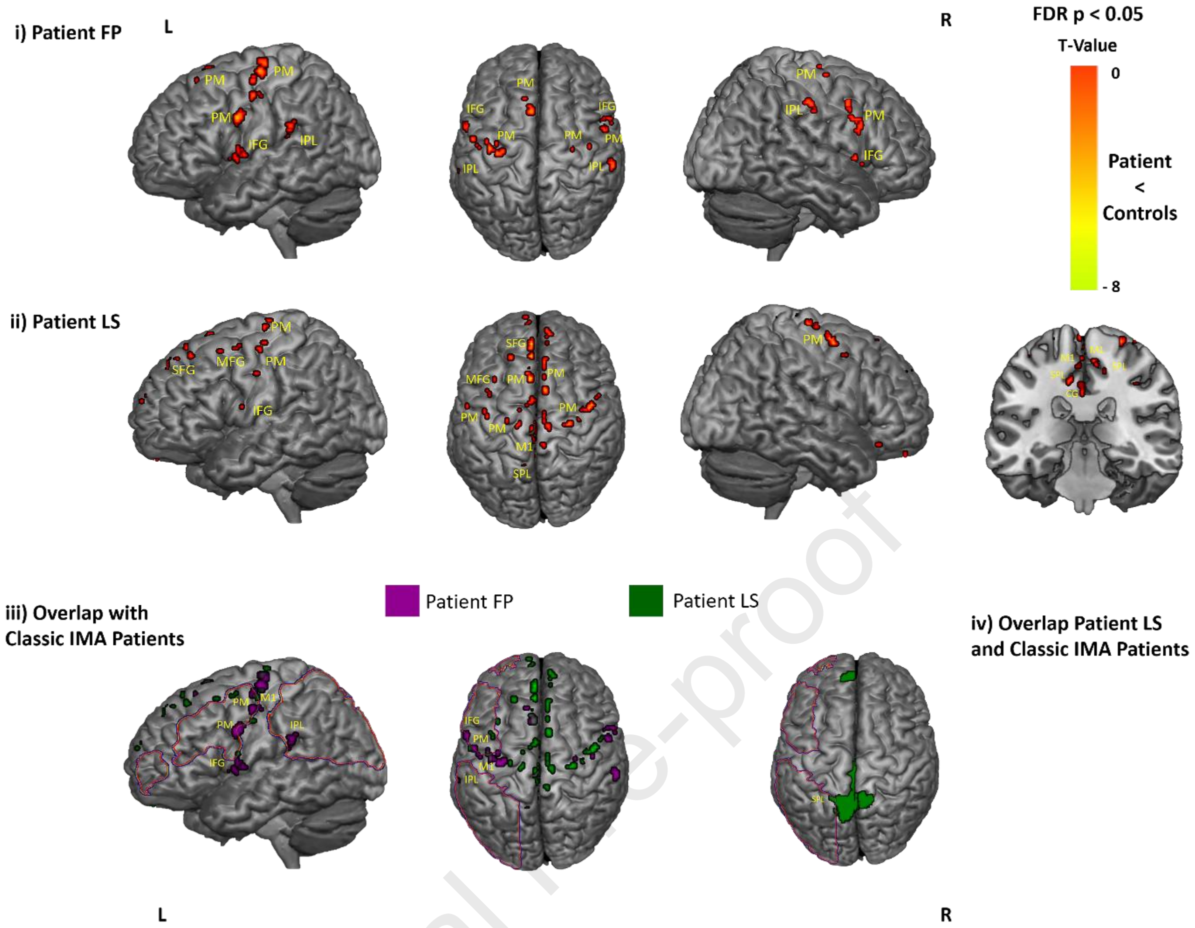

Figure 5: Comparison of cortical thickness maps of Patients FP and LS and the healthy controls (i and ii), and the overlap between the lesioned areas in our patients and those of the Classic IMA patients. The (pink) outlined mask in iii) and iv) shows the regions lesioned in classic IMA patients. The thinner regions are represented in orange/red (negative values) using a modified t-test, after FDR p<0.05 correction. Image i) indicates that the thinner areas in Patient FP are bilateral IPL, and specifically, the supramarginal gyrus, the left parietal operculum, bilateral IFG, bilateral PM, and the left CG. Image ii) shows that the thinner areas in Patient LS are the bilateral PM, bilateral M1, bilateral SPL, left MFG, left IFG, left frontal pole, and bilateral CG, based on the cortical thickness analysis. Image iii) shows the areas in common between Patients FP (purple) and LS (green) with classic IMA patients. Patient FP has in common the left IPL, left PM and left IFG with classic IMA patients. Based on cortical thickness Patient LS has in common the left PM and M1 with Classic IMA patients (iii), and the left SPL, and left S1 based on manual lesion segmentation (iv).

IPL – inferior parietal lobe; SPL - superior parietal lobe; PM- premotor cortex; M1 - primary motor cortex; S1 - primary somatosensory cortex; SFG - superior frontal gyrus; MFG - middle frontal gyrus; IFG – inferior frontal gyrus; CG - cingulate gyrus.

We first defined the locus of the neural deficits in Patient FP and Patient LS by comparing cortical thickness values (see Figure 4) between each patient and our healthy controls. Patient FP and LS showed decreases in cortical thickness in various regions when compared to the healthy controls, and we used these as indexes of their lesion sites (see Figure 4). We compared, voxel-by-voxel, the distance between the orthogonal vector of pial surface and the white matter border, using a modified t-test. Patient FP presented significant reductions of cortical thickness in bilateral Inferior Parietal Lobe (IPL), specifically in the supramarginal gyrus, left parietal operculum, bilateral premotor cortex (PM), bilateral inferior frontal gyrus (IFG), and left cingulate gyrus (CG). On the other hand, Patient LS showed decrements in cortical thickness in more medial regions affecting both hemispheres. She revealed significant reductions in cortical thickness in bilateral medial superior parietal lobe (SPL), within Broadman area 5 and the precuneus, bilateral premotor (PM), bilateral primary motor (M1), and bilateral primary somatosensory cortex (S1), bilateral superior frontal gyrus (SFG), bilateral Supplementary motor area (SMA), left middle frontal gyrus (MFG), left frontal pole, and bilateral cingulate gyrus (CG; Figure 5). As expected, analysis of the manual segmentation of the lesions of Patient LS showed considerable overlap with the cortical thickness analysis – namely, Patient LS revealed bilateral lesions in SPL (larger extension in the left hemisphere), bilateral PM, bilateral M1, and bilateral S1 (particularly focused on the left hemisphere), left SFG, left frontal pole, and left CG. The major difference between LS manual segmentation and cortical thickness analysis is in the frontal areas (IFG, and MFG). Interestingly, the lesions of Patient FP and LS overlap within premotor cortex (in both methods) and IFG (with cortical thickness methods).

We also found regions that presented an increment in cortical thickness when compared to our healthy controls. For Patient FP relative to healthy controls, we found greater cortical thickness in regions of right IPL, right SPL, right SFG, left MFG, bilateral IFG, and right visual cortex (BA17 and BA18). Patient LS presented a significant increase of cortical thickness in left IFG, right frontal pole, bilateral SPL, left IPL, right M1, left hippocampus subiculum, and left paracingulate gyrus (See supplementary Figure S1).

We then investigate which of these lesion sites overlapped with those of our typical IMA patients (the outlined mask presented in Figure 5). On the one hand, both Patient FP and the classic IMA patients presented common lesions in the left IPL, and specifically the supramarginal gyrus, the left parietal operculum, the left PM and the left IFG. On the other hand, Patient LS and the classic IMA patients presented common lesions in regions of the IFG, PM, and M1 (see Figure 5 – image iii) from the inspection of cortical thickness analysis, as well as SPL and S1, from the inspection of the manually segmented lesion (See Figure 5 – image iv).

Discussion

We found different common patterns of lesions between our doubly dissociated patients and our classic IMA patients. Both patients presented an impairment in fronto-parietal networks, however the areas damaged were different. Patient FP revealed atrophy in important areas for IMA such as the left IPL – and specifically the supramarginal, the IFG, and PM (e.g., Amaral, Bergström & Almeida, 2021; Almeida, Martins, Bergström, Amaral, Freixo, et al., 2017; Buchwald, Przybylski, & Kroliczak, 2018; Chao, Haxby, & Martin, 1999; Garcea, Almeida, Sims, Nunno, Meyers, et al., 2019; Goldenberg & Spatt, 2009; Goldenberg et al., 2007; Ishibashi, Pobric, Saito, & Lambon Ralph, 2016; Lee, Mahon & Almeida, 2019; Lewis, 2006; Mahon et al., 2007; Martin, 2007; Peeters, Rizzolatti, & Orban, 2013; Ruttorf, Kristensen, Schad & Almeida, 2019; Walbrin & Almeida, 2021). Conversely, Patient LS revealed bilateral lesions focused on PM, M1, S1, medial SPL, SFG, MFG, IFG, and CG. Interestingly, SPL has also been shown to be involved in IMA (Heilman, Rothi, Mack, Feinberg, & Watson, 1986).

Importantly, our two patients differ in the locus and extent of overlap between their lesions and those of our IMA patients. On the one hand, Patient FP shares lesion sites with our classic IMA patients in left IPL – and specifically in the supramarginal gyrus – in the parietal operculum, IFG, and in PM. On the other hand, Patient LS and the classic IMA patients shared lesion loci in the PM, M1, S1, SPL, and IFG.

General Discussion

In this study, we present two patients with a double dissociation between tool-gesture knowledge (i.e., the knowledge of how to manipulate an object) and tool-gesture production (i.e., the actual motor execution of an object). Patient FP presented with poor performance in an object-specific pantomime task, but normal performance in judging object-specific manipulation similarity, whereas Patient LS revealed the opposite pattern – she was able to pantomime object use in the context of impaired manipulation similarity judgments. This in the context of spared knowledge about the function of tools. Importantly, these patients were tested with virtually the same stimuli over the different tasks.

Moreover, we found different lesion loci and overlap with the lesion profiles of typical apraxia patients for Patient FP and Patient LS. Specifically, Patient FP presented thinner areas in bilateral IPL, IFG, and PM – all of these areas (predominantly on the left) are also affected in the classic IMA patients. Some of these areas – and mainly the left IPL and IFG are viewed as important for action selection and implementation of skilled movements (e.g., Almeida, Fintzi, & Mahon, 2013; Bergström, Wurm, Valério, Lingnau & Almeida, 2021; Buxbaum & Kalénine, 2010; Garcea, Kristensen, Almeida & Mahon, 2016; Goldenberg et al., 2007; Kristensen, Garcea, Mahon & Almeida, 2016; Mahon, Kumar & Almeida, 2013) – thus leading to deficits in pantomiming. Conversely, the pattern of lesions in Patient LS is focused on bilateral SPL, motor areas (bilateral PM, bilateral M1, and S1), and frontal areas (bilateral SFG, left MFG and IFG), leading to deficits in manipulation judgments. Crucially, motor and somatosensory areas (left PM, left M1 and left S1), left IFG, and left SPL are affected in both Patient LS and the classic IMA patients.

Perhaps the computations within the regions that are affected in both Patient LS and the classic IMA patients are somehow dependent on motor imagery. There are innumerous examples of the importance of the computations within M1, PM, and SPL for hand action imagery (Fleming, Stinear, & Byblow, 2010; Hanakawa et al., 2003; Pilgramm et al., 2016; Schulz, Ischebeck, Wriessnegger, Steyrl, & Müller-putz, 2018; Wolbers, Weiller, & Büchel, 2003; Zabicki et al., 2017). Notably, some areas as PM, SMA, M1, superior parietal occipital cortex, and prefrontal cortex have an important goal in movement planning (Gallivan, McLean, Flanagan, & Culham, 2013).

To the best of our knowledge, our study is the first to report a double dissociation between tool-gesture execution and tool-gesture semantics. Nevertheless, two previous cases were reported that show similar deficits in tool-gesture production and tool gesture knowledge. In one of these studies, Rapcsak and collaborators (1995) described an apraxic patient (Patient GW) who had problems in pantomiming transitive gestures but could explain, in detail, the movements necessary to manipulate tools. On the other study, Bartolo and collaborators (2007) reported the case of an apraxic patient (Case 5) with difficulties in judging similarity in the manner with which tools are manipulated, in the context of spared pantomiming. As such, Patient GW presented a pattern of performance that is similar to Patient FP, whereas Case 5 resembles Patients LS. Importantly, these data give credence to the proposal that tool-gesture production and tool-gesture knowledge are independent from one another.

Our results thus suggest an alternative understanding of tool-gesture production and knowledge that puts forth a looser relationship between these two action-related types of information. It is certainly plausible that tool-gesture production and tool-gesture knowledge share neural circuitry, but these two networks are not completely (or consistently) overlapping (e.g., Hanakawa et al., 2003). Perhaps one interesting analogy is that of the lexical and non-lexical routes to reading. We may have (at least) two independent routes to get to tool-gesture production: one that goes through tool-gesture knowledge (perhaps action semantics) akin to the lexical route, and one that bypasses action knowledge and follows the biomechanical possibilities of objects, along with rote memory and non-action conceptual knowledge about the target object and motor imagery programs associated.

IPL (shared as a lesion locus between the IMA patients and Patient FP but not LS) may have a central role in this dual route. Goldenberg and colleagues proposed that lesions in the left inferior parietal lobe cause difficulties of apprehending the spatial relationships between multiple objects/multiple parts of the same object, the effectors and the acted upon objects or surfaces (Goldenberg, 2009). In a similar vein, Osiurak and colleagues (e.g., Osiurak & Badets, 2016) suggest that left inferior parietal lobe is paramount in understanding how object-specific mechanical knowledge can be used on the environment to implement our action intentions. Under these frameworks, and in line with the possibility described above, pantomiming could be more impaired by a difficulty to apprehend spatial relations between the different agents of the action (objects, object parts, effectors, etc.), and/or an inability to access a object manipulation program given the mechanical possibilities of the to-be-pantomimed object, the intended action and its surrounding environment. Manipulation judgments may perhaps typically involve apprehending spatial relations and accessing object manipulation based on performing technical reasoning over the target tools and integrating the actor’s intentions, but may also relate to recalling or imagining how to use an object based on priory experiences – that is, these judgments while also potentially dependent on the IPL are not exclusively so, and may be performed without the need to reason about action intention and spatial relations between tool parts, effectors and target objects. Note, in fact, that there is somewhat limited overlap between lesions site for Patient LS and our two IMA cases, potentially suggesting several routes to computing manipulation judgements.

How do these data then relate to reports (e.g., Boronat et al., 2005; Canessa et al., 2008) that suggest that left IPL is central for manipulation judgments? Our data do not contradict those reports – in fact it may add to them in what regards the kinds of knowledge necessary for performing manipulation judgements under different types of stimuli. In Boronat and colleagues, word and picture formats of the manipulation judgement task presented different results in what regards IPL activation. In the word format (what we have used in our study), the authors found greater activation in inferior temporal lobe, frontal areas, and SMA – the latter two in common with the lesions of Patient LS. In the picture format, however, left IPL was highly involved. These differences may be due to the fact that perhaps the sight of an object evokes the kinds of processes that are typical of IPL (e.g., access to a typical motor program; technical reasoning over the mechanical possibilities of an object). Interestingly, Ishibashi and collaborators (2018) found that anodal tDCS to left IPL provoked very weak effects on manipulation judgments. Overall, we are not suggesting that IPL is not central for accessing an object’s manipulation. Nevertheless, making judgements of manipulation similarity may not necessarily depend exclusively on IPL, at least as much as pantomiming an object’s manipulation. In other words, the mechanisms responsible for these two tasks might be similar – and thus explaining many reports of patients that are impaired in both tasks – but are still independent.

This also raises an interesting topic that is central to cognitive neuropsychology: that of the differences between group-based studies and single case studies (e.g., Caramazza & McCloskey, 1988) – or associations and double dissociations – and what kinds of inferences can be made and fed to our processing models. For instance, group studies that used manipulation judgments and pantomiming as a way to test for IMA, have overwhelmingly showed that IMA patients are impaired for both of these tasks (Buxbaum & Saffran, 2002). But clear such symptom associations are not as logically strong as the double dissociation reported here. In fact, there are many cases in the literature that show similar disparities. A great example is the case of the association between object and action recognition and object and action pantomiming – here you may see an association of symptoms in several patients, but single cases can clearly show these two cognitive processes to be dissociable – and this dissociation clearly impacts the kinds of theories that are able to explain object processing (Capitani, Laiacona, Mahon, & Caramazza, 2003; Halsband et al., 2001; Negri et al., 2007). Yet another example relates to understanding action words and simulating those same actions – Papeo and colleagues (Papeo et al., 2010; see also Kemmerer, 2015) show that, at the group level, action (and object) understanding and action (and object) pantomiming are correlated, whereas at the individual level, these processes were dissociable. Thus, while associations of cognitive deficits may be of interest to the field, and may perhaps reflect a typical processing route, this and other paper server as cautionary tales for the importance of double dissociations in carving out dissociable processing routes.

One potentially important aspect in our data, relates to the laterality of the different affected areas, as well as the typical laterality profiles of the (more bilateral) dorso-dorsal stream and the (more left lateralized) ventro-dorsal stream. Interestingly, Patient LS shows bilateral SPL lesions – in line with the bilateral profile of the dorso-dorsal stream. Perhaps this is in line with the potential involvement of the more bilateral dorso-dorsal stream on the manipulation judgments proposed above, in contrast to the more left lateralized involvement of the IPL in object pantomiming.

It is important to note that our study presents some limitations that are related to the nature of neuropsychological research. Specifically, both Patient LS's and FP's general health deteriorated during the period of our experiments, and thus they requested not to continue with testing.

In summary, the results obtained in this study support the existence of a behavioral and neural double dissociation between tool-gesture production and tool-gesture knowledge. This dissociation has major impact on embodied theories – specifically the more radical embodied approaches – as these are hard pressed to explain how tool-gesture knowledge and tool-gesture production can dissociate: i.e., if action understanding requires action simulation (and hence tool-gesture production routines), how can tool-gesture knowledge and tool-gestures production dissociate? We believe that these findings have major impact in our understanding of action and object processing and on the main theories on these topics, as well as on our understanding and assessment of apraxia.

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Competing interests

The authors declare no competing interests.

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Supplementary Material:

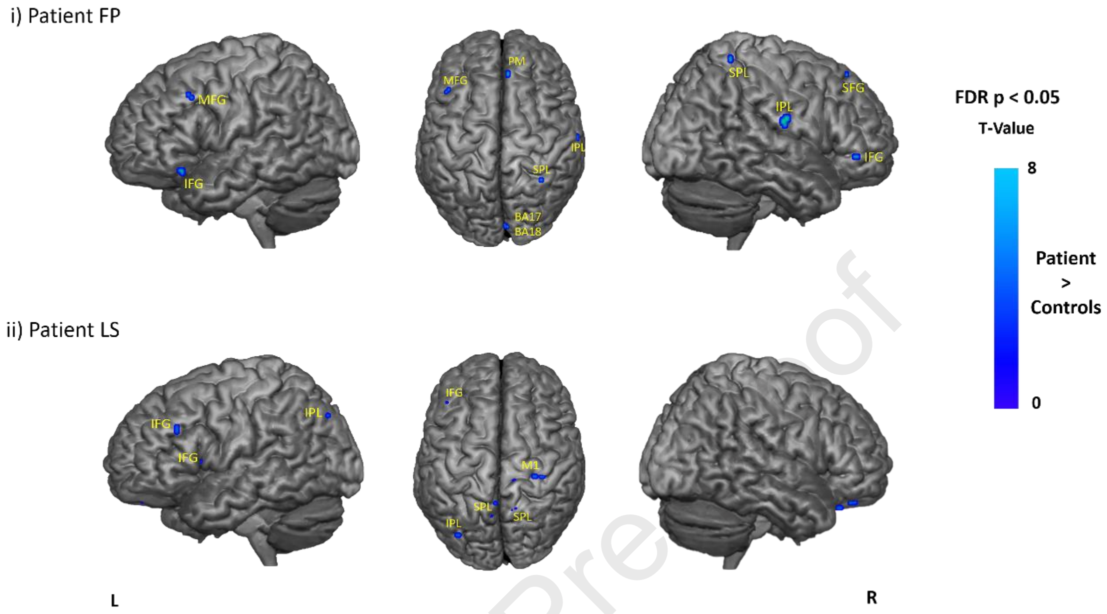

Figure S1: Comparison of thicker areas of Patients FP and LS with the healthy controls. The thicker regions in Patient FP and LS are represented in blue (the positive values) using a modified t-test, after FDR p<0.05 correction. Image i) indicates that the thicker areas in Patient FP are the right IPL, right SPL, the right PM, right SFG, bilateral IFG, left MFG, and right visual cortex (BA17 and BA18). Image ii) shows that the thicker regions in Patient LS are the left IFG, left IPL, left hippocampus, left paracingulate gyrus, bilateral SPL (area 7), right M1, and right frontal pole.

IPL – inferior parietal lobe; SPL - superior parietal lobe; PM- premotor cortex; M1 - primary motor cortex; SFG - superior frontal gyrus; MFG - middle frontal gyrus; IFG – inferior frontal gyrus