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100 years after Liepmann—Lesion correlates of diminished selection and application of familiar versus novel tools



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ABSTRACT

100 years ago, Liepmann highlighted the role of left ventro-dorsal lesions for impairments in conceptual (rather ventral) and motor (more dorsal) related aspects of apraxia. Many studies thereafter attributed to an extended left fronto-temporo-parietal network. Yet, to date there are only few studies that looked at apraxic performance in the selection and application of familiar versus novel tools.

In the current study we applied modern voxel-based lesion-symptom mapping (VLSM) to analyze neural correlates of impaired selection and application of familiar versus novel tools. 58 left (LBD) and 51 right brain damaged (RBD) stroke patients participated in the Novel Tools Test (NTT) and the Familiar Tools Test (FTT) of the Diagnostic Instrument for Limb Apraxia (DILA-S). We further assessed performance in control tasks, namely semantic knowledge (BOSU), visuo-spatial working memory (Corsi Block Tapping) and meaningless imitation of gestures (IML).

Impaired tool use was most pronounced after LBD. Our VLSM results in the LBD group suggested that selection- versus application-related aspects of praxis and semantics of familiar versus novel tool use can be behaviorally and neuro-anatomically differentiated. For impairments in familiar tool tasks, the major focus of lesion maps was rather ventral while deficiencies in novel tool tasks went along with rather dorsal lesions. Affected selection processes were linked to rather anterior lesions, while impacted application processes went along with rather posterior lesion maps. In our study, particular tool selection processes were rather specific for familiar versus novel tools. Foci for lesion overlaps of experimental and control tasks were noticed ventrally for semantic knowledge and FTT, in

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fronto-parietal regions for working memory and NTT, and ventro-dorsally for imitation of meaningless gestures and the application of NTT and FTT.

We visualized our current interpretation within a neuroanatomical model for apraxia of tool use.

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1. Introduction

At the beginning of the 20th century, Wernicke's student Karl Hugo Liepmann dedicated much of his time and research efforts in detailed descriptions of single cases and group studies to disentangle the complex construct of limb apraxia (e.g., Liepmann, 1920). These have shaped the understanding of limb apraxia until today (Goldenberg, 2003; Kramer, 1925; Randerath, 2022). In patients with limb apraxia, difficulties can be observed during imitating meaningless gestures or meaningful emblems, in pantomiming tool use or in real single- or multi-step tool use. Patients can be impaired selectively in these tasks, but most frequently several tasks are affected. The syndrome of limb apraxia cannot be explained by primary perceptive or motor impairments, instead it is considered a cognitive impairment (Randerath, 2022). Most frequently it has been reported and investigated in right hand dominant patients with damage to the left brain (Buchmann et al., 2020; Liepmann, 1920). Limb apraxia can affect rehabilitation outcome and independence in daily live activities (Unsal-Delialioglu, Kurt, Kaya, Culha, & Ozel, 2008; Wu, Burgard, & Radel, 2014).

For example, in one of our single case studies we reported about Mr. S (Li, Randerath, Goldenberg, & Hermsdorfer, 2007), a patient with limb apraxia. When asking him about his daily life, the patient described that since his bleeding in the left brain (temporo-parietal), he has troubles when interacting with tools and objects: It takes far more time than usual to prepare himself for the day and for leaving the house. This morning he brushed his teeth with soap. He is unburdened by any motor deficits and can move around just fine. Sometimes he has difficulties finding the right words, but particularly his problems in planning actions make him feel insecure.

The relevance of limb apraxia for neurorehabilitation becomes even more apparent when considering the fact that incidences have been reported in many of the most frequently occurring neurological disorders (Buchmann et al., 2020), e.g., after stroke (e.g., Buxbaum, Kyle, Grossman, & Coslett, 2007; Poeck, 1983; Randerath, Goldenberg, Spijkers, Li, & Hermsdorfer, 2010), dementia (e.g., Della Sala, Lucchelli, & Spinnler, 1987; Hodges, Bozeat, Ralph, Patterson, & Spatt, 2000; Johnen et al., 2016) and traumatic brain injury (Buchmann et al., 2020; Falchook et al., 2015; Schwartz et al., 1998). It also has been described or discussed for patients with Parkinson's disease (Kubel et al., 2017; Vanbellingen, Hofmänner, Kübel, & Bohlhalter, 2018), multiple sclerosis (Harscher, Hirth-Walther, Buchmann, Dettmers, & Randerath, 2017; Kamm et al., 2012; Medenica & Ivanovic, 2019; Staff, Lucchinetti, & Keegan, 2009) or psychiatric disorders like schizophrenia (Dutschke et al., 2018; Stegmayer et al., 2016).

1.1. Assessing deficits in settings of familiar and novel tool use

Classic tests to diagnose limb apraxia include gesturing tasks assessing the ability to imitate or pantomime gestures. These are commonly applied in clinical settings. Underlying mechanisms and neuroanatomical correlates of these classic tasks have been profoundly studied in the past century (Buxbaum & Randerath, 2018). In the current study, we concentrate on a less investigated subcomponent: actual tool use. Actual tool use is commonly assessed by use of familiar or novel tool settings (Buchmann & Randerath, 2017; Goldenberg & Hagmann, 1998; Osiurak, Jarry, Lesourd, Baumard, & Le Gall, 2013). Some assessments like the Diagnostic Instrument for Limb Apraxia (DILA-S, Randerath, Buchmann, Liepert, & Büsching, 2017) differentiate between a novel tools test (NTT) and familiar tools test (FTT) and between the evaluation of tool selection and tool application processes. To assess tool selection, patients are asked to select the one tool (e.g., out of three: ladle, bottle opener or spatula) that is best suitable to apply to the presented setting with a recipient object (e.g., fried egg in a pan). Patients suffering from limb apraxia may select the wrong tool (e.g., pick the bottle opener instead of a spatula for taking the fried egg out of the pan). To evaluate the ability of applying the tool in an appropriate manner, patients are presented with the suitable tool and are asked to use the tool and manipulate the setting in front of them. The application of tools (e.g., hammering a nail into wood) is frequently evaluated either by determining whether the action has been executed correctly at first or second attempt (here we label this: Execution) or by a set of defined criteria characterizing how the last shown action was produced (here we label this: Production): functional grasping (e.g., thumb directed towards the hammerhead), proper grip posture (e.g., lateral or tight cylinder grip), suitable movement and spatial orientation of tools and recipient objects (e.g., driving a nail into wood by up- and downwards pounding) (Buchmann & Randerath, 2017; Randerath, Buchmann, et al., 2017). During tool application, patients may have problems initiating a reasonable action, they may persevere an action they showed before or they may show substitute actions that would be accurate for other tools or recipient objects (e.g., hit with a wrench on a screw-nut), or omit details (e.g., use a hammer to press on a nail instead of hitting it). In the novel tools setting (e.g., DILA-S NTT: three unfamiliar tools are presented, but one is best suitable to lift a recipient object out of a socket) it is frequently observed that the wrong tool is chosen. When presented with the correct novel tool, problems with its application at the recipient object typically

include omissions, or attempts that do not lead to a suitable solution. Efforts to solve the task (e.g., use the tool to lift the recipient wooden cylinder out of the socket) appear rather unskilled even at the second attempt. Often it looks as if the patient has problems processing or manipulating the spatial relationship between the novel tool's functional end (e.g., metal hook) and the recipient end on top of the wooden cylinder (e.g., metal ring). A healthy person would insert the tool's hook into the ring of the wooden cylinder, and then swiftly lift the cylinder out of the socket. In apraxia patients, the examiner may observe spatial errors such that the novel tool's functional end (e.g., metal hook) is repeatedly placed next to or on top of the recipient (e.g., on the metal ring on top of the cylinder), or the patient omits to perform a movement that alters the tool's position into a functional solution (e.g., patient omits to rotate the hook to then insert it into the ring).

1.2. Neuroanatomical correlates for tool selection and application

Liepmann's behavioral work with impaired patients and the post mortem analysis of their brain injuries led him to assume early on that skilled movements involve the participation of the entire brain, but are most strongly dependent on the integrity of the left hemisphere (Liepmann, 1908, 1920). More recent observations support this notion: limb apraxia seems most prominent in patients with dementia and in patients with left hemisphere stroke (Buchmann et al., 2020). Modern lesion-symptom mapping studies were in line with Liepmann's early findings (Buxbaum, Shapiro, & Coslett, 2014; Goldenberg & Randerath, 2015; Weiss et al., 2016). Limb apraxia has been linked to lesions in a left fronto-temporo-parietal network (Buxbaum & Randerath, 2018). While many lesion-symptom mapping studies concentrated on imitation and gesturing deficits, evidence from neuroanatomical correlates based on patients with brain damage and apraxic symptoms in actual tool use is scarce.

Selection and application processes in familiar and novel tool use have been investigated in one study that concentrated on neuroanatomical correlates in left brain damaged patients only (Goldenberg & Spatt, 2009). A decade ago Goldenberg and Spatt (2009) reported results from a lesion-symptom mapping study including thirty-eight patients with left brain damage and aphasia. These patients were examined using tests to assess the retrieval of functional knowledge from semantic memory (functional associations), use of everyday tools and objects (common tools) and mechanical problem solving (novel tools: select the best suitable tool to then lift a specifically formed cylinder out of a socket). The authors highlighted two areas to be significantly associated with impaired behavior in this group of unilateral left brain damaged patients. One rather anterior lesion-site was in inferior frontal, middle frontal and premotor areas affecting all experimental tests. The other rather posterior lesion-site was in ventro-dorsal regions such as the supra-marginal gyrus, through the inferior, to superior parietal lobe affecting the selection and application of both novel and common tools and objects. In addition, the authors assessed

a control task to investigate semantic memory (a functional associations test with objects). Only patients with a selective deficit in semantic memory demonstrated particularly temporal lesions.

Martin et al. (2016) studied a large sample of 136 left brain damaged (LBD) patients performing familiar tool use while assessing an object selection and a tool application component. Patients had to select the suitable recipient object (e.g., nail) for a given tool (e.g., hammer) and then manipulate the recipient object with the given tool. They demonstrated that compared to impairments in tool application, deficiencies in the object selection component were specifically related to damage within ventral regions including the anterior temporal lobe. Vice versa, impaired application of familiar tools was particularly associated with inferior parietal lesions.

Another study that concentrated on the application of familiar tool use investigated both right and left brain damaged patients (Salazar-López, Schwaiger, & Hermsdörfer, 2016). Lesion-symptom mapping results were presented for twelve familiar tool use actions (Salazar-López et al., 2016) in 31 patients with left brain damage and 19 patients with right brain damage (RBD). In this study an error-score was used including typical criteria (grasp, movement, direction and space) to evaluate familiar tool use performance. As a control task the authors tested the prescribed manipulation of a bar, which requested goal-directed pre-planning but supposedly should rely less on semantic knowledge. Both patient groups demonstrated better scores in the predefined bar task as compared to solving the twelve familiar tool use actions. A substantial part of either group demonstrated tool use performance below normative Cut-Off-values (RBD: 42%, LBD: 65% of patients). On a group level, RBD patients demonstrated less variance and performed better than LBD patients. Accordingly, the statistical lesion-symptom mapping analysis for the RBD group did not reveal any significant results for familiar tool use. In the RBD group, worse performance in bar manipulation was significantly associated with temporal lobe lesions. For the LBD group, results for producing familiar tool use actions suggested an essential role of ventral as well as ventro-dorsal stream regions (middle occipital gyrus, temporal lobe, Rolandic operculum, premotor cortex) with the inferior parietal lobe as the prime area. In the LBD group, lesioned brain areas related to reduced performance in using the bar largely overlapped with the network that was revealed to be essential for familiar tool use. The authors concluded from their results that goal directed manipulation of non-tool objects and the application of familiar tools share identical processes and neural representations.

Thus, for neuroanatomical correlates essential for tool use there has been some evidence suggesting the importance of a preserved left lateralized network including the premotor cortex, inferior frontal, inferior parietal, superior and medial temporal lobe and the occipito-temporo-parietal junction (Goldenberg & Spatt, 2009; Martin et al., 2016; Salazar-López et al., 2016). Thus far, the few studies investigating actual tool use in patients with right brain damage demonstrated that familiar tool use can be affected, however lesion correlates appear to be less specific.

In our previous study (Buchmann & Randerath, 2017) we introduced behavioral results of tool selection and tool-object

application. In our newly developed Familiar Tools Test (FTT) participants successively received five tool use settings. Each setting included a recipient object (e.g., pot with soup and plate) and three tools. Participants first had to choose the best suitable tool out of three (e.g., ladle) to be applied to the recipient object. Subsequently, they were asked to then apply the correct tool (the ladle) to actually perform the action (e.g., scoop soup from the pot into the plate). We also applied an adapted version of the Goldenberg's Novel Tools Assessment (Goldenberg & Hagmann, 1998) (NTT) that has a similar procedure. The FTT and the NTT were applied in 53 stroke patients with either unilateral left brain damage (LBD) or right brain damage (RBD) as well as healthy age and gender matched controls. While LBD patients demonstrated significant worse performance compared to their control group, there were only a few RBD-patients demonstrating difficulties, which on a group level was not sufficient to reach a significant difference compared to their matched control group. However, while patients with left brain damage were impaired most severely on a descriptive level, the LBD and RBD groups did not differ significantly in their performance on any FTT- or NTT-subcomponent, except for the application of familiar tools. Importantly, it was demonstrated in a few single cases that the selection and application of familiar and novel tools can be impaired selectively.

Summarized, the available study results on real tool use thus far suggest lateralization effects and differential processes underlying tool use actions. Tool use deficits appear more strongly pronounced after left brain damage versus right brain damage (Buchmann et al., 2020; Salazar-López et al., 2016). Findings on particular lesion sites associated with novel in contrast to familiar tool use are less clear (Goldenberg & Spatt, 2009), though behavioral dissociations would suggest different correlates. Based on the frequently reported temporal lobe correlates for semantic tasks with common objects (Chao, Haxby, & Martin, 1999; Clarke, 2020; Goldenberg & Spatt, 2009; Kalenine & Buxbaum, 2016; Martin & Chao, 2001), it could be proposed that deficient familiar tool use is more strongly related to ventral lesion sites compared to diminished handling of novel tools. Evidence from imaging studies investigating common versus uncommon tool use with healthy adults supports a division between more pronounced evoked neural patterns in dorsal regions during imagery of uncommon tool use judgments, and in ventral regions while imagining common tool use (Matheson, Buxbaum, & Thompson-Schill, 2017). Further, differences between selection and application processes could be assumed because selective deficits have been reported in single cases (Buchmann & Randerath, 2017). Also, recent reports on lesion correlates of impaired familiar tool use and object selection (Martin et al., 2016) lead to the assumption that affected tool selection processes are specifically associated with rather anterior lesion sites compared to impaired tool application. In the current study we investigated neuroanatomical lesion correlates in LBD and RBD patients for impaired performance in familiar versus novel tool selection versus application. Lesion analysis and additional neuropsychological tests may help to disentangle compounds and contribute to a better understanding of the underlying mechanisms of tool use deficits after brain damage.

1.3. Theories

In accordance with the involvement of a large essential network associated with the complex syndrome of limb apraxia, there exist several theories to explain the underlying mechanisms of tool use deficits. We here describe major accounts differing with respect to their focus. In line with the complexity and heterogeneity of the disorder, all of the proposed components or mechanisms may contribute to the complex function of tool use. This is supported by the fact that each of the accounts finds support by studies investigating different aspects of tool use.

1.3.1. Conceptual knowledge or semantics

Conceptual knowledge or semantics are involved in behavioral planning, perceptual categorization, and inferential reasoning (Tranel, Kemmerer, Adolphs, Damasio, & Damasio, 2003). Several imaging studies have suggested a differentiation between categories of knowledge concerning e.g., structural tool properties (form, material), functional knowledge (context defining what to use the tool for) and manipulative knowledge (how to produce a tool use movement). Functional knowledge refers to those semantic concepts that do not belong to the perceptual or the motor domains (Martin & Chao, 2001). While structural knowledge has been attributed to be primarily processed in the right hemisphere, processing of functional semantics and manipulation knowledge appear rather left lateralized. More precisely, conceptual knowledge about tool properties has been associated with left (functional knowledge) and right (structural knowledge) temporal regions and knowledge about the manipulation or tool application has been associated with left fronto-parietal circuits (Buxbaum & Saffran, 2002; Canessa et al., 2008; Chen, Garcea, Jacobs, & Mahon, 2018; Kellenbach, Hovius, & Patterson, 2005). A study by Martin et al. (2016) investigating familiar tool use in a large sample of patients with left hemisphere damage similarly distinguished a manipulation component (spatio-temporal movement errors) from a conceptual component (incorrect movement content). Conceptual errors resulted from lesions within superior temporal lobe and supramarginal gyrus and spatio-temporal movement errors were mainly caused by more dorsally located lesions, i.e., by inferior parietal damage adjacent to the intraparietal sulcus.

1.3.2. Analysis of mechanical problems and reasoning-based solutions

Analysis of mechanical problems and reasoning-based solutions are needed to use novel tools (Goldenberg & Hagmann, 1998; Goldenberg & Spatt, 2009; Jarry et al., 2013; Lesourd et al., 2016, 2019; Osiurak & Badets, 2016; Osiurak et al., 2009, 2013). Mechanical knowledge which corresponds to knowledge about physical principles is the major element in this theory. Goldenberg argued that the analysis of visuo-spatial relationships of the effector (e.g., hand or tool) and the target (e.g., object or part of the body) and its categorical apprehension of spatial relationships is an essential process for praxis (Goldenberg & Spatt, 2009). For example, to open a lock with a key, a paper-cut copy of a key would not work, the key must consist of rigid material. Further, when inserting the

key, the structure of the key should match the lock's slot and the key's orientation must fit the orientation of the lock's slot. Goldenberg also endorsed the analysis of categorical visuo-spatial relationships to be important for non-tool actions, such as the imitation of meaningless hand postures. The mechanical reasoning-based approach has subsequently been strongly advocated by [Osiurak and Badets \(2016, 2017\)](#). The authors propose that a mental simulation of the tool use action is formed based on the expected effects of the respective tool manipulating the recipient object (e.g., a knife cutting a tomato, see also [Osiurak & Badets, 2016](#)). The authors supporting this approach suggest that mechanical reasoning is also essential for familiar tool use. In support of this idea, thus far, especially left parietal lobe lesions have been reported to specifically affect the selection and application of both novel and common tools and objects, while left frontal regions were associated with deficits in familiar and novel tool use but also with deficits in other tests (semantic control tests) ([Goldenberg & Spatt, 2009](#)). Goldenberg and Spatt proposed that their results fit well with the idea that the contribution of the parietal lobe to tool use concerns rather general principles of mechanical tool-object interactions than action semantics.

1.3.3. Action simulation and working memory

Action simulation and working memory appear to present basic elements for motor cognition ([Hesslow, 2012](#); [Jeannerod, 2006](#); [Pulvermüller, Moseley, Egorova, Shebani, & Boulenger, 2014](#)). The assumption is that the action is mentally simulated before being executed (forward planning) or without being executed (imagery). Ample evidence demonstrates that we plan our actions ahead and thereby take subsequent actions into account ([Johnson, 2000](#); [Randerath, Valyear, Philip, & Frey, 2017](#); [Rosenbaum, Chapman, Weigelt, Weiss, & van der Wel, 2012](#)). A meta-analysis identified a consistent premotor, parietal, and somatosensory network of brain areas that were recruited across imagery, observation and execution of movements ([Hardwick, Caspers, Eickhoff, & Swinnen, 2018](#)). The simulated action model is updated based on the dynamic context allowing for adaptive behavior. In a dynamic environment simulated movement options would need to be evaluated and then selected with respect to their relevance for the given situation. Influential models (e.g., [Cisek & Kalaska, 2010](#)) based on neurophysiological data in non-human primates suggest a large dynamic network with mechanisms specifying actions along a dorsal pathway involving the parietal lobe. Integrative working memory processes supporting the retrieval, maintenance, and linking of relevant information have been suggested to present an essential mechanism for rehearsing or simulating the upcoming action and for dynamically integrating environmental information ([Bartolo, Cubelli, Della Sala, & Drei, 2003](#); [Malouin, Belleville, Richards, Desrosiers, & Doyon, 2004](#); [Pulvermüller et al., 2014](#); [Randerath, 2009](#); [Randerath et al., 2009, 2013](#); [Tessari et al., 2021](#)). Left inferior parietal and frontal regions (apraxia-related lesion sites) have been proposed to represent neuroanatomical hubs essential for working memory ([Gläscher et al., 2009](#); [Jonides et al., 1998](#); [Smith & Jonides, 1998](#)). Further, evidence suggests a hemispheric dissociation between visual/object or verbal (primarily left sided) and visuo-spatial (primarily right sided) working memory

mechanisms ([Barbey, Koenigs, & Grafman, 2013](#); [Smith & Jonides, 1999](#); [Suchan, 2008](#)), which are in line with reports on typical lateralized functional deficits such as more strongly pronounced visuo-spatial hemineglect after right hemisphere damage versus limb apraxia after left hemisphere damage. Left lateralized working memory hubs in inferior frontal and parietal regions have been hypothesized to be critical for tool use deficits in limb apraxia ([Randerath, 2020](#); [Randerath, 2022](#)).

1.3.4. Systems-models

Systems-models that posit a complementary role for on-line and stored information have been used as a template for neuroanatomical models of limb apraxia. A very influential approach suggested two major systems from vision to action, emphasizing the importance of dorsal occipital to parietal (on-line processes) versus ventral occipital to temporal pathways (stored information) for action (e.g., [Milner & Goodale, 2008](#)). A third pathway, the ventro-dorsal route has been found to support a rich interactivity of both stored and on-line information ([Rizzolatti & Matelli, 2003](#)). The interactivity between parietal and temporal regions has been suggested to play a crucial role in the linking of perception and action ([Fogassi & Luppino, 2005](#)). These routes have been later integrated in several accounts and models for limb apraxia ([Binkofski & Buxbaum, 2013](#); [Hoeren et al., 2014](#); [Randerath, 2009](#); [Vry et al., 2015](#)). Ample evidence supports the involvement and division of these systems in tool use ([Bi et al., 2015](#); [Gallivan, McLean, Valyear, & Culham, 2013](#); [Johnson-Frey, 2004](#); [Johnson-Frey, Newman-Norlund, & Grafton, 2005](#); [Lewis, Wing, Pope, Praamstra, & Miall, 2004](#); [Orban & Caruana, 2014](#)): a left-lateralized ventro-dorsal system that is suggested to involve storage and retrieval of memories of tool and action knowledge being integrated into a specific motor plan. A bilateral dorso-dorsal system is proposed to guide movements and translate information on-line from vision to motor execution. In addition, an inferior parietal – inferior frontal pathway has been proposed for action selection. A theoretical contribution that discussed the evidence for these systems-models in greater detail is the “Two Action Systems Plus (2AS+)” framework for tool use by [Buxbaum \(2017\)](#).

1.3.5. Monitoring processes

Monitoring processes are strongly needed in sequential multi-step tool use settings (e.g., preparing breakfast) with multiple objects to choose from and when executing action steps in a certain order to achieve a goal (having breakfast). Deficiencies have been attributed to executive problems, impaired semantic knowledge and to general limitations in cognitive capacities ([Bailey, Kurby, Giovannetti, & Zacks, 2013](#); [Giovannetti et al., 2002, 2021](#)). Disturbances in naturalistic actions have been demonstrated to be less lateralized than the other described praxis functions: bilateral frontal regions have been suggested to essentially support the selection and sequencing of meaningful multistep actions ([Fortin, Godbout, & Braun, 2003](#); [Hartmann, Goldenberg, Daumüller, & Hermsdorfer, 2005](#); [Lurija, 1992](#); [Schwartz et al., 1998](#)). Bilateral medial frontal regions and the inferior parietal cortex for example have also been associated with the structuring of visuo-spatial material without involvement of actions (e.g.,

ordering bars from shortest to tallest) (Tracy et al., 2011), supporting the idea that these regions serve a more general monitoring function. Influential models (e.g., Cisek & Kalaska, 2010) based on neurophysiological data in non-human primates propose a large dynamic network with mechanisms collecting information for action selection in basal ganglia and prefrontal regions. Frontal regions may therefore play a meaningful role for selection processes during both familiar and novel tool use.

In line with the neuroanatomical model of limb apraxia by Randerath (2020) and a long history of apraxia models (Cubelli, Marchetti, Boscolo, & Della Sala, 2000; Liepmann, 1920; Randerath, 2022; Rothi, Ochipa, & Heilman, 1997) we hypothesize that every single one of the above mentioned approaches account best for at least one of the different aspects of limb apraxia and deficient tool use. The question remains, which weight the approaches have for the respective sub-components: selection versus application and novel versus familiar tool use. By reporting neuroanatomical and behavioral correlates, we hope to contribute to the unravelling process.

1.4. The current study

As a continuation of the efforts to understand essential underlying mechanisms and neuroanatomical correlates of tool-object interactions, the current patient study will address problems in tool selection and tool application in real tool use settings. We assessed impaired behavior with our test battery for limb apraxia (DILA-S, Randerath, Buchmann, et al., 2017) and applied lesion-symptom mapping (voxel-based lesion-symptom mapping; Bates et al., 2003) in 109 unilateral stroke patients (58 LBD and 51 RBD). We have used the DILA-S, since the Familiar and Novel Tools Test (with five tool use settings each) were developed in such a way that the processes for administering and performance evaluation were similar for both subtests. Based on above described data (e.g., Salazar-López et al., 2016), we have to expect meaningful lesion correlates for deficient tool use to be lateralized to the left hemisphere.

For tool selection it is assessed whether the best suitable out of three tools is chosen correctly within two attempts (Selection Score). We hypothesize that tool selection processes particularly for novel tools need simulation processes for mechanical problem solving. Dorsal lesions in parietal regions, which are typically reported to support action simulation and visuo-spatial structuring, are hypothesized to particularly affect novel tool selection. We propose that familiar tool selection in contrast largely depends on learned associations. Ventral lesions in temporal regions, which are typically related to functional associations, are proposed to particularly affect familiar tool selection. Preserved mechanical problem solving may support the impacted process of familiar tool selection, but may not suffice to achieve perfect results. This imperfection may be related to the fact that we can simulate different options for actions. For the selection process it is possible to simulate and specify either a suitable (correct tool selection) or an unsuitable substitutive action (wrong tool selection, e.g., choosing a bottle-opener to dip into the soup pot instead of selecting a ladle for scooping). Lesions

in frontal regions that typically are associated with executive monitoring processes may affect selection processes of both tool types, since in both settings the tool has to be chosen from a relatively cluttered scenery (three tools and a recipient object).

Provided with the correct tool in hand, the tool's application was evaluated via two different approaches: whether or not the action was executed correctly (Execution Score), and the amount of correctly produced action criteria (Production Score). The Execution Score rated the patient's success versus fail within two attempts per tool use setting. For the qualitative Production Score the fulfillment of four criteria was rated: grip-formation, grip-orientation, movement-content and movement-orientation. We expect lesions in left fronto-temporo-parietal regions to be associated with deficits in applying the tools, with an overlapping hotspot in left inferior parietal regions. Again, a relative division of impaired application and associated lesion sites is expected with regards to tool type: familiar tools and rather ventral regions versus novel tools and rather dorsal regions.

1.4.1. Summary of hypotheses

We expect a strong left lateralization of tool use deficits and interpretable lesion correlates. While affected selection processes may be more readily attributed to rather anterior lesion sites, action specification processes may be rather associated with posterior lesion sites in a fronto-temporo-parietal network. Impacted familiar tool use is hypothesized to be centered in lesions along the ventral pathway, while deficiencies in novel tools are proposed to emphasize lesion sites in rather dorsal pathways. An overlapping hotspot is suggested in the connecting of the ventro-dorsal route and particularly the left inferior parietal lobe. Our neuropsychological control variables (a. meaningless action production task, b. working memory task, c. semantic knowledge task) should accordingly show hotspots in associated lesion sites (a. inferior parietal, b. lateral prefrontal and c. temporal).

2. Methods

2.1. Participants

The study design was approved by the ethical committee of the University of Konstanz (#10/2014). All patients took part in the study voluntarily. Informed consent was obtained from patients or their authorized relatives. The study was conducted in accordance with the Declaration of Helsinki. Privacy rights were observed. Please note, that data sets of 32 LBD and 20 RBD patients have been included in the present study, that have been already incorporated in our behavioral study (Buchmann & Randerath, 2017).

Participants were recruited from the neurorehabilitation center “Kliniken Schmieder” in Allensbach, Germany from 2014 to 2020. Furthermore, all patients had to be right-handed, had to have preserved vision, understand simple instructions, have an available brain scan of sufficient quality (CT or MRI) showing their first unilateral brain damage and had to be able to withstand testing sessions of at least 30 min.

We included a total of 109 patients with either unilateral left (LBD, $N = 58$) or right hemisphere stroke (RBD, $N = 51$). Measured by time since stroke onset, patients were classified to the subacute (stroke onset 3 weeks to 6 months ago; 97.2%) or chronic phase of illness (stroke onset more than six months ago; 2.8%). None of the patients suffered from any other neurological or psychiatric disease. All patients were right-handed. Handedness was diagnosed with the lateralization quotient published by [Salmaso and Longoni \(1983\)](#). All included patients had a quotient >60 indicating strong right-handedness. All patients were tested with their neurologically unaffected ipsilesional hand (LBD: left, RBD: right).

Frequently, left hemisphere damage can lead to impaired language production and comprehension difficulties. In order to ensure that patients understand instructions of the implemented tasks, we applied the “Token” subtest of the Aachener Aphasia Test (AAT; [Huber, Poeck, Weniger, & Willmes, 1983](#)) and calculated an error score by summing up the items of the AAT Token Test that were not solved correctly. Only those participants remained included in the study, that understood the instructions of the Token Test. Measuring deficits in language production, the “Naming” subtest of the Aachener Aphasia Test was further applied. Since we refrained from applying the other subtests, a qualification of aphasic profiles is not possible at this point. For aphasia severity see [Table 1](#) (Cut-Offs correspond to the original scores published in the AAT manual). Taking influences of visuo-spatial deficits like neglect into account, we additionally assessed visuo-spatial processing performance by using the Star Cancellation and Line Bisection Tests ([Plummer, Morris, & Dunai, 2003](#); [Wilson, Cockburn, & Halligan, 1987](#)). For patients with neglect symptoms, all material used for limb apraxia assessment was presented in the unaffected hemispace. Beside language and visuo-spatial deficits, motor skills as well as semantic knowledge were

further examined. The contralesional arm and hand function was tested by using eight items of the WMFT (Wolf Motor Function Test; [Wolf et al., 2001](#)). Deficits in semantic knowledge were diagnosed by four object-related picture-based subtests (subtests I, II, III, V) of the BOSU (Bogenhausener Semantikuntersuchung; [Glindemann, Klintwort, Ziegler, & Goldenberg, 2002](#)). A total error score was computed by adding up the errors of the four subtests. Working memory performance was assessed using the Corsi Block Tapping forward span. Patients were asked to mimic the experimenter after she had tapped a sequence of three to nine spatially separated blocks attached to a board ([Schellig, 2011](#)). For further demographic information and data on the conducted neuropsychological tests please see [Table 1](#).

2.2. Assessment of Limb Apraxia – the Diagnostic Instrument for Limb Apraxia

The applied Diagnostic Instrument for Limb Apraxia – Short Version (DILA-S) is described in detail in [Randerath, Buchmann, Liepert, and Büsching \(2017\)](#). The DILA-S has been developed to extensively assess the subtypes or domains of limb apraxia ([Randerath, Buchmann, et al., 2017](#)). Thus, it includes tests assessing the imitation of meaningless (with permission from the author: [Goldenberg \(1996\)](#)) and meaningful gestures, pantomime of tool use (revised from [Goldenberg, Hartmann, and Schlott \(2003\)](#)), use of novel (revised from [Goldenberg and Hagmann \(1998\)](#)) and familiar tools (new) as well as a naturalistic action task (revised from [Schwartz, Segal, Veramonti, Ferraro, and Buxbaum \(2002\)](#)).

To verify comprehension of task instructions, the DILA-S provides up to three practice trials for each apraxia task. The DILA-S is a standardized and reliable test method. Cut-Off values are based on the performance of a healthy right-handed control group ($N = 82$, 5th percentile as reference

Table 1 – Demographic and clinic data.

	LBD $N = 58$	RBD $N = 51$
Gender: male/female	34/24	24/27
Age: mean (range)	59.71 (30–79)	59.33 (25–78)
Days since lesion onset: mean (range)	82.93 (18–857)	61.63 (19–212)
unilateral infarction/hemorrhagic stroke	34/24	29/22
Barthel Index: mean (range)	55.91 (10–100) ^a	52.93 (15–100) ^a
Aphasia: N with no/mild/moderate/severe		
AAT Token (comprehension)	22/13/9/14	47/4/0/0
AAT Naming (production)	22/9/10/17	41/9/1/0
Semantic processing (BOSU): number of errors mean (SD); normal/impaired		
sort for major features	1.19 (2.25) 47/11	.31 (.76) 48/3
sort for minor features I	1.34 (1.93) 38/20	.92 (1.16) 39/12
sort for minor features II (increased difficulty)	2.43 (2.15) 32/26	1.86 (1.73) 38/13
sort for color	1.09 (1.87) 32/26	.53 (.90) 32/19
Neglect, total score mean (SD); yes/no		
Line Bisection	8.23 (1.8) 7/45 ^a	7.59 (2.39) 11/40
Star Cancellation	52.36 (3.53) 7/48 ^a	47.47 (9.64) 21/30
Working memory, mean (range)		
Corsi Block Tapping Test	4.22 (2–6)	3.94 (2–6) ^a
Motor function, mean (range)		
Wolf Motor Function Test	2.38 (0–5) ^a	2.03 (0–5)

AAT = Aachen Aphasia Test; BOSU = Bogenhausener Semantik-Untersuchung; LBD = left hemisphere stroke; RBD = right hemisphere stroke.

^a Incomplete dataset/a few missing values.

point) and the distinction between mild, moderate and severe apraxia was drawn for each subset in reference to the performance of 20 LBD and 5 RBD patients who were diagnosed apraxic. Please see the original publication of [Buchmann and Randerath \(2017\)](#) for more detailed information, Cut-Off values and evaluation sheets including images of the used objects per setting as well as the below described evaluation criteria ([Randerath, Buchmann, et al., 2017](#)) (Testing material is freely available online on <https://www.moco.uni-konstanz.de/publikationen/assessments/>).

2.2.1. Imitation of hand gestures

In this task, patients were requested to imitate meaningless (IML) or meaningful (IMF) hand gestures shown by the experimenter. Each imitation test comprises one practice trial and 10 test items. Evaluation was done based on a three-tier evaluation system. Patients achieved up to 2 points per item depending on whether they showed the correct gesture at the first (2 points) or second (1 point) attempt. If both attempts were incorrect, then 0 points were given. A maximum of 20 points for each imitation category could be achieved (per imitation category: 10 items x 2 points).

2.2.2. Pantomime of tool use

Further, patients were instructed to pantomime the use of an object (PTU) by both verbal and visual cues (e.g., verbal: “Show me how to hit a nail with a hammer”, visual: picture of a hammer). The test comprised up to three practice trials and 8 test items. Two evaluation scales, the Production and the Execution Scale, were used. The Production Scale included the qualitative rating of different pantomime characteristics such as the content and orientation of movement as well as the formation of grip (max. 24 points). Further, the Execution Scale evaluated the number of needed attempts with the three-tier evaluation system already mentioned above (0–2 points). On the Execution Scale, a maximum of 16 points could be achieved (8 items x 2 points).

2.2.3. Use of novel and familiar tools

In addition to traditional limb apraxia tasks, two real tool use tasks were applied. An item consisted of three tools and one recipient cylinder (NTT) or one recipient familiar object (FTT) to be manipulated, respectively. In the NTT, three tools and one wooden cylinder in a socket were presented in front of the patients. Afterwards, patients were asked to select the one tool that is best suitable to safely lift a cylinder out of a socket. In the FTT, patients were required to choose the correct familiar tool to handle the recipient object and to demonstrate the correct application. To avoid an influence of visuo-spatial neglect on the tool use assessment, the item-set of the FTT or NTT was shifted towards the unaffected hemisphere. Furthermore, patients exhibiting the symptom of visuo-spatial hemifield deficits were instructed at the beginning of each trial to pay attention to the three tools.

Each test consists of five test items and up to three practice items. For both tests, three evaluation scales were used: one scale to evaluate accuracy of tool selection and two scales to assess the suitability of tool application. For tool selection, it was evaluated how many attempts a patient needed to choose the applicable tool. The selection of the correct tool was

awarded with 0 to 2 points per item (first selection correct = 2 points; second selection correct = 1 point; both attempts incorrect = 0 points; max. 10 points). A tool was determined as being selected as soon as the patients aimed to apply the selected tool at the recipient. For the application of the tools, two scales were used. First, the number of needed attempts was evaluated based on a three-tier evaluation system (Execution Scale, max. 10 points). Thus, execution was evaluated with either 2 points (first use correct), 1 point (second use correct) or 0 points, when the patients needed more than two attempts to correctly apply the tool. Second, we evaluated the appropriate usage of the tool by assessing the following action characteristics: grip-formation, grip-orientation (thumb-direction on tool-handle), movement-content and movement-orientation. Referring to these characteristics, a 4-point Production Score was built (max. 20 points = 5 items x 4 appropriate action characteristics).

2.2.4. Naturalistic action test

Patients were asked to prepare a breakfast consisting of a toasted slice of bread with butter and jam as well as a cup of tea with sugar (NAT; adapted from [Schwartz et al., 2002](#)). For evaluation, the Naturalistic Action Test Score (NAT score, max. 6 points) was derived by combining the Accomplishment Score (amount of completed steps) and the Error Score (amount of errors made while completing the task). Patients received support by the person who administered the test, when they tried to initiate an action but were not able to solve one step of the task for apraxia-unrelated reasons. As an example, if a neglect patient did not perceive the needed objects in one visuo-spatial hemifield, the experimenter asked the patients verbally and by gestures to explore the affected hemifield. For one patient, the NAT has not been conducted.

2.3. General analyses

All behavioral analyses were conducted using IBM SPSS Statistics 27. Behavioral data were analyzed non-parametrically, since tests of normality (Shapiro–Wilk Test and screening of normal probability plots) indicated that the data was not normally distributed in both, LBD and RBD patients ($p \leq .037$).

For the analysis of patients' performance in the apraxia tests, the total scores per task and scale were used. To compare scales with different maximum scores, percentage scores were computed. Statistical significance was determined by reporting p -values two-tailed ($p < .05$) and, whenever computing power was sufficient, exact instead of asymptotic (p_{asympt}) p -values were reported.

Based on our stated hypotheses, we ran a Mann-Whitney-U test to evaluate whether there were differences between LBD and RBD patients' performance in all implemented apraxia tests and the belonging subscales (i.e., Selection, Execution and the 3- or 4-point Production Score). To correct for family-wise error rate, we additionally reported adjusted p -values using the stepwise Holm Bonferroni procedure (p_{adj}) with $k = 11$ comparisons.

To further investigate the complex construct of apraxia and to exploratorily establish which linear components exist within the data, a Principal Component Analysis (PCA) was conducted on 18 variables (all apraxia subtests and additional

neuropsychological tests) with orthogonal rotation (varimax). The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis with $KMO = .836$, which is “meritorious” according to Kaiser and Rice (1974). In addition, 16 of 18 KMO values were above the acceptable limit of .5 (range: .404–.850). Bartlett's test of sphericity ($\chi^2(153) = 1239.05, p < .001$) indicated that correlations between items were sufficiently large for PCA conduction. However, it is to be noted that in fact, normally distributed data are reconditioned for this test.

2.4. Lesion analysis

2.4.1. Lesion data analysis

Voxel-based lesion-symptom mapping (VLSM) was applied to determine neural correlates of the investigated performances in tasks requiring meaningless and meaningful gesture imitation, pantomime of tool use and real familiar and novel tool use. Lesions were therefore semi-automatically delineated from MRI- or CT-Scans. If multiple images with same quality were available, the first recorded scan was used for the analyses.

2.4.2. Lesion delineation

Lesion maps were semi-automatically demarcated by using Clusterize Toolbox for SPM 8 (Clas, Groeschel, & Wilke, 2012; modified version that supports dealing with CT images: de Haan, Clas, Juenger, Wilke, & Karnath, 2015) and normalized with Clinical Toolbox for SPM 8 (downloaded from <https://www.nitrc.org>). The spatial position of the resulting normalized Volume of Interest (VOI) was subsequently checked for each individual by comparison with the respective structural scan. In case of inconsistencies, lesion maps were manually adjusted and corrected by using MRIcron Software (Rorden & Brett, 2000). The examiner was naïve to the clinical profiles of the patients at the time of lesion mapping.

2.4.3. Statistical analysis

In order to identify lesioned voxels that are associated with behavioral deficits, voxel-based lesion-symptom mapping (VLSM) was performed separately for each of the behavioral variables (i.e., total scores of the DILA-S subtests and related subscales) by using non-parametric mapping software (NPM, available with MRIcron software). Statistical non-parametric analyses were computed by using the Brunner-Munzel test for continuous behavior, whereby voxels that were damaged in less than 10 percent of the analyzed patient group (LBD: $n = 6$, RBD: $n = 5$) were ignored. Statistically significant voxels were visualized on the ch2-template in MRIcron. Lesion maps were corrected for multiple comparisons using false discovery rate (FDR) thresholding (5%). Thus, the lower bound intensity value has been set to the critical z-value. For all depicted lesion graphs, the upper bound was fixed to 3.719. Voxels of RBD patients' performance did not survive FDR correction. This could be explained by for example the overall good performance of RBD patients and a low level of variance in their apraxia data, and potentially more distributed lesion sites causing abnormalities in the application of novel tools in individual patients with RBD. Therefore, we focus on lesion results for LBD patients. Lesion locus was determined by both the Automated Anatomical Labelling (AAL) template provided

by MRIcron and by atlases (Kretschmann & Weinrich, 2007; Petrides, 2012). A subtraction analysis with overlays of impaired minus non-impaired patients as defined by the DILA-S manual has been added as additional information in the supplementary material.

3. Results

In accordance with our hypotheses, LBD patients in the current sample demonstrated worse task performance in most subscales of the DILA-S as compared to RBD patients. Except for IML as well as the NTT subscales, statistical comparisons revealed significant differences in the apraxia subscales between the two patient groups (see Fig. 1 and Table 2).

Since real tool use performance can also be selectively affected, we analyzed patients' real tool use performance in the selection and execution subscales more detailed. For determining deficits, we focused on apraxia Cut-Offs per subscale. In both real tool use tests, deficits in selection and execution emerged most often combined. However, there are also some individuals in the present stroke sample that showed selective impairments by showing selection or execution deficits in only one of the two tool tasks. Thus, some individuals selected the correct familiar tool, but showed deficits in selecting the appropriate novel tool (LBD: $n = 8$, RBD: $n = 6$). Others demonstrated deficits exclusively in familiar tool selection, while their performance during novel tool selection was correct (LBD: $n = 5$, RBD: $n = 1$). Regarding tool execution, most individuals demonstrated sole deficits in the FTT (LBD: $n = 20$, RBD: $n = 7$). However, only few individuals showed selective deficits in novel tool execution, while having no difficulties in familiar tool execution (LBD: $n = 1$, RBD: $n = 4$).

The qualitative analysis by use of the Production Score indicated, that LBD and RBD patients primarily made errors in movement-content and orientation in both tool use tasks, FTT (LBD: 53.6% movement-content, 33.3% orientation of movement, 8.7% grip-formation, 4.3% orientation of thumb, total: 69 errors; RBD: 66.7% movement-content, 33.3% orientation of movement, 0% grip-formation, 0% orientation of thumb total: 3 errors) and NTT (LBD: 73.8% movement-content, 26.2% orientation of movement, 0% grip-formation, 0% orientation of thumb, total: 61 errors; RBD: 74.5% movement-content, 23.4% orientation of movement, 0% grip-formation, 2.1% orientation of thumb, total: 47 errors). This underlines that patients mainly experienced difficulties with the tool-object interaction rather than with grasping and holding the tool.

Since novel tool use performance in LBD and RBD patients was similar, we added correlational analyses with neglect tests in order to determine influencing factors such as visuo-spatial skills. Correlations were calculated by using Kendall's Tau. Adjusted p -values using the stepwise Holm Bonferroni procedure (p_{adj}) with $k = 6$ comparisons were additionally reported. Correlational analysis with neglect tests in RBD patients showed, that neither performance in the star cancellation task nor in the line bisection task was correlated with NTT Selection ($r \leq .127, p \geq .135, p_{adj} \geq .27$). However, NTT Execution and NTT Production Scores were significantly

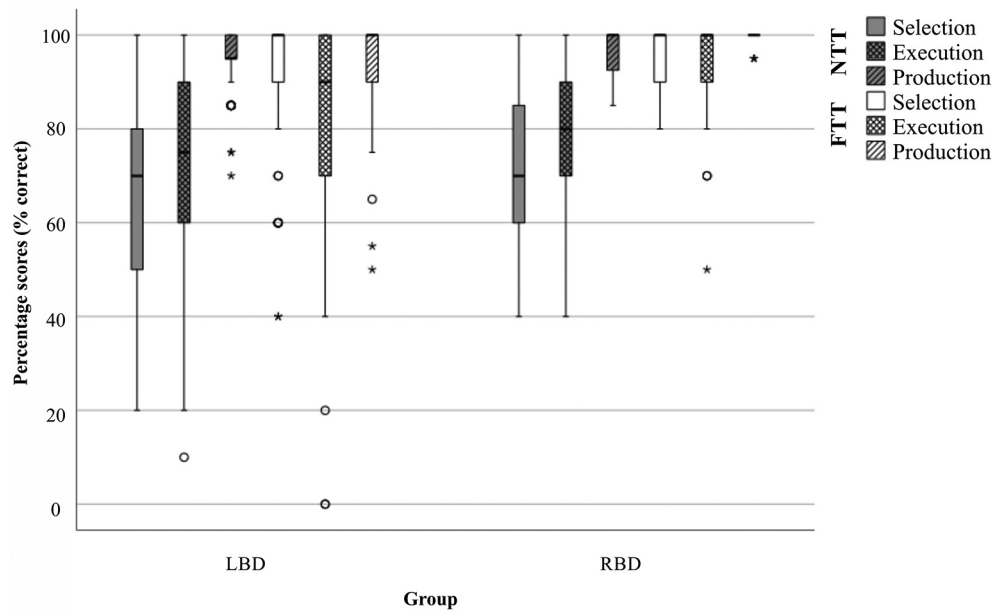


Fig. 1 – Box plots of real tool use subscales for LBD and RBD patients. Boxplots depicted here are based on percentage scores per subscale. Dots: Outlier: scores smaller than the lower quartile minus $1.5 \times$ inter quartile range (IQR). Stars: Extreme cases: scores smaller than the lower quartile minus $3 \times$ IQR.

correlated with at least one neglect test (line bisection: $r \geq .336$, $p \leq .004$, $p_{adj} \leq .02$; star cancellation: $r \geq .324$, $p \leq .065$, $p_{adj} \leq .195$). As might be expected, there were no significant correlations between visuo-spatial skills and NTT performance in LBD patients ($r \leq .189$, $p \geq .085$).

3.1. Principal component analysis

In order to determine how particular variables might contribute to certain components, a PCA was conducted on 18 variables. An initial analysis was run to obtain eigenvalues for

Table 2 – Descriptive data for both patient groups and between-subject group comparison results (Mann-Whitney-U test). Descriptive data described here is based on percentage scores.

Test	LBD	RBD	Group comparison		
	Mean (SD)	Mean (SD)	U	p	p_{adj}
	no/mild/moderate/severe	no/mild/moderate/severe			
IMF	79.31 (17.8) 36/7/4/11	87.16 (13.0) 40/3/4/4	1015.0	.004	.025
IML	72.33 (23.1) 33/8/5/12	80.20 (17.8) 40/3/4/4	1188.0	.075	.301
PTU Execution	56.36 (30.7) 24/9/7/18	83.70 (12.9) 42/7/2/0	647.0	<.001	<.001
PTU Production	76.01 (27.1) 28/7/11/12	95.92 (4.8) 46/5/0/0	609.5	<.001	<.001
NTT Selection	66.72 (19.0) 43/7/4/4	72.94 (15.1) 45/5/1/0	1227.5	.122	.365
NTT Execution	73.62 (20.1) 49/4/1/4	77.06 (15.4) 47/1/3/0	1370.0	.505	1
NTT Production	94.74 (7.2) 51/0/4/3	95.39 (5.7) 48/3/0/0	1443.5	.819	.819
FTT Selection	89.48 (15.5) 46/4/5/3	96.67 (5.9) 50/1/0/0	1108.5	.009	.047
FTT Execution	79.31 (25.1) 30/12/7/9	94.31 (10.2) 44/4/2/1	893.0	<.001	.001
FTT Production	94.05 (11.2) 36/7/8/7	99.71 (1.2) 48/3/0/0	982.5	<.001	<.001
NAT Score	57.02 (37.9) 32/2/9/14	83.66 (22.7) 45/1/4/1	878.5	<.001	.001

each component in the data. Four components had eigenvalues over Kaiser's criterion of 1. These four components in combination explained 67.72% of the variance. Although the scree plot showed an inflexion that would justify retaining only two components, we decided to choose the 4-factor solution stated by Kaiser's criterion. In particular, this is due to the additional consideration of the components' content and the thereby improved theoretical interpretability of resulting components. Table 3 shows the factor loadings after rotation. According to variables clustering on the same components, it may be hypothesized that component 1 represents semantic aspects, component 2 the simulation of action and related working memory capacity, component 3 could potentially represent impaired motor function or general motor inaccuracies and component 4 deficits in visuo-spatial attention (i.e., neglect).

3.2. Lesion analyses results

LBD patients showed highest lesion density in the territory of the left middle cerebral artery (Fig. 2) including the insula, basal ganglia as well as pre- and postcentral gyrus.

Because the apparent functional significance of locations associated with larger lesions is generally diminished by

lesion volume corrections (Karnath, Berger, Küker, & Rorden, 2004) we here refrained from applying this adjustment. In LBD patients, larger lesion volumes are significantly negatively correlated with tool use performance (total scores per task and scale) (NTT: Selection: $r = -.247$, $p = .01$. Execution $r = -.247$, $p = .010$. Production: $r = -.321$, $p = .002$; FTT: Selection: $r = -.216$, $p = .033$. Execution $r = -.414$, $p < .001$. Production: $r = -.353$, $p < .001$).

Based on our behavioral results that demonstrated differences between the selection and execution component in real tool use tasks, we here investigated predominant associations between diminished performance in the real tool use tasks and belonging subscales with critical lesion areas by implementing a VLSM analysis based on 58 scans of patients with unilateral left-hemisphere brain damage.

As can be seen in Fig. 3 the current findings suggest that impairments in grasping and applying novel tools (Production Score) are mainly associated with lesions involving the supramarginal gyrus, basal ganglia, insula, inferior frontal as well as parietal regions. Further, impaired selection of novel tools was linked to precentral and fronto-parietal lesions including the inferior frontal lobe, the inferior parietal lobe (particularly the supramarginal gyrus) as well as basal ganglia with adjacent insula. Albeit less striking, middle temporal

Table 3 – Summary of Principal Component Analysis (PCA) results for apraxia subtests and neuropsychological variables (N = 109 patients).

	Rotated Factor Loadings			
	Semantic processing	Action Simulation	Motor function	Visuo-spatial attention
Pantomime Production	.797	.325		
AAT Token (-: error score)	-.790			
FTT Selection	.760			
NAT Score	.759			.301
FTT Execution	.758	.419		
Pantomime Execution	.750			
AAT Naming	.740			
FTT Production	.687	.430		
BOSU (-: error score)	-.644			-.455
NTT Production		.832		
NTT Execution		.807		
NTT Selection	.318	.542		
IMF	.393		.702	
WMFT (mean)			.654	
IML	.507		.607	
Corsi Block Tapping Test		.308	.562	.394
Neglect (Line Bisection)				.814
Neglect (Star Cancellation)			.328	.697
eigenvalues	7.58	2.27	1.26	1.09
% of variance	42.13	12.59	6.97	6.04

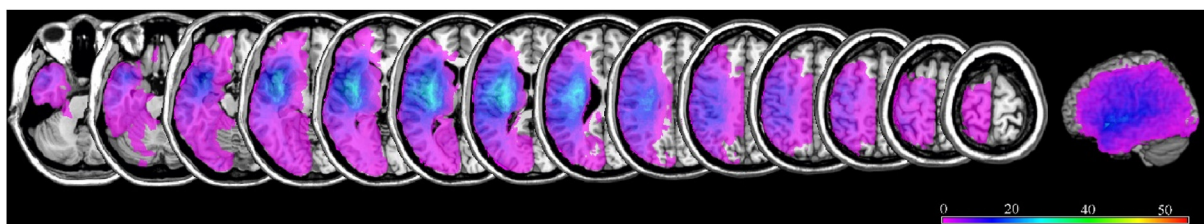


Fig. 2 – Lesion overlay for LBD patients. The color bar indicates degree of overlap of lesions with a total N of 58 patients.

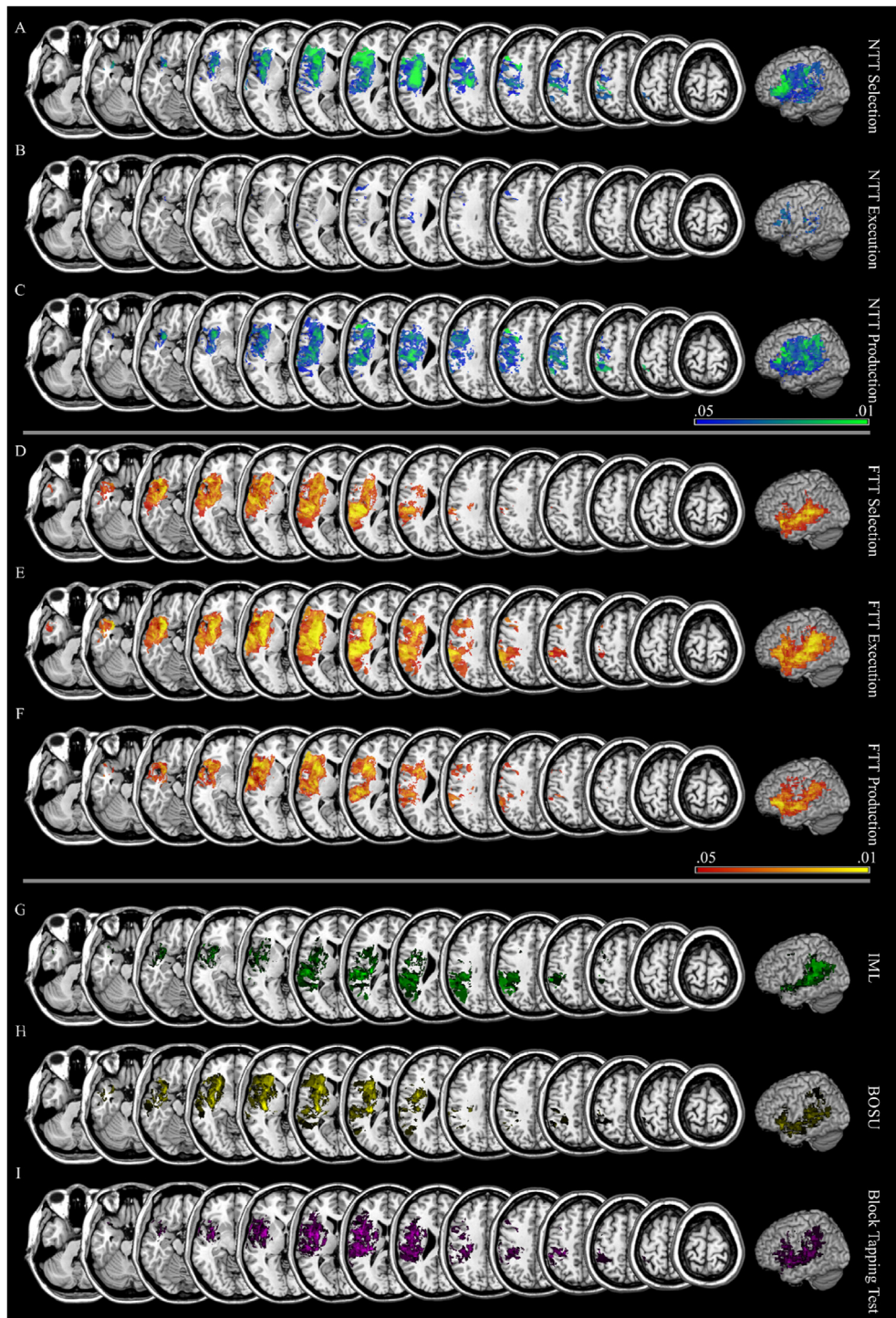


Fig. 3 – VLSM analyses for real tool use subscales (Brunner–Munzel test, FDR corrected with $p < .05$). The first three maps depict lesion locations that are related with an impairment in the Novel Tools Test: Selection (A), Execution (B) and Production (C). Following maps display voxels that are associated with impairments in the Familiar Tools Test: Selection (D), Execution (E) and Production (F). The lower maps depict lesion locations that are related with impairments in the control tests: Imitation of Meaningless Gestures (IML, G), Semantic Knowledge (BOSU; H) and working memory (Block Tapping Test; I). Maps of control variables were not corrected for FDR.

regions showed further associations with impairments in novel tools production as well as selection. Statements concerning the contribution of particular lesion sites to impaired novel tools execution are difficult to make, since lesion maps

are very small due to FDR correction. Fig. 3 further shows that both, impaired familiar tool selection and application are associated with lesions involving an anterior fronto-temporal network extending from inferior frontal to superior and

middle temporal regions. Impairments were further associated with lesions in the basal ganglia, the adjacent insula as well as with lesions in the supramarginal gyrus. Deficits in applying familiar tools (Execution and Production) were additionally linked to lesions in the inferior parietal gyrus.

Lesion overlays for subscales (Fig. 4A–C) further emphasize that impairments in the NTT Selection are associated with rather dorsal fronto-parietal areas, whereas impaired FTT Selection is associated with ventral fronto-temporal regions. A similar picture emerged for diminished Production Scores in both real tool use tasks, whereby overlaps of both tasks were much more pronounced above the sulcus lateralis in lesions inferior frontal, postcentral and supramarginal gyrus.

Furthermore, Fig. 4D depicts associations with additional relevant tasks measuring semantic knowledge (BOSU), working memory (Corsi Block Tapping Tests) and imitation of meaningless gestures. Lesion maps in ventral fronto-temporal regions prove that diminished semantic knowledge (e.g., assessed by the BOSU) went along with impaired familiar tool use, whereas fronto-parietal lesion maps were associated with difficulties in novel tool use and working memory (e.g. measured by the Corsi Block Tapping Test). Furthermore, lesion maps of impaired IML performance demonstrated most overlap with the Production Scores in both real tool use tasks in the left inferior parietal cortex.

4. Discussion

The current study included and focused on a less investigated aspect of the limb apraxia syndrome: the interaction with actual tools to manipulate recipient objects (real tool use). We analyzed lesion correlates in patients with unilateral left or right brain damage after stroke for impairments in the selection and application of familiar as well as novel tools. Our data supports the expected left lateralization of tool use deficits and interpretable lesion correlates. As hypothesized, deficient

behavior was associated with lesions in a left fronto-temporo-parietal network. Along with a large body of literature one obvious overlapping hotspot of the resulting lesion maps showed in the left inferior parietal lobe (Buxbaum & Randerath, 2018). While lower performance in selection processes were more strongly associated with rather anterior lesion sites, impaired action specification processes showed rather posterior lesion maps. Impacted familiar tool use was related to lesion maps covering mostly areas of the ventral pathway, while deficiencies in novel tools showed related lesion maps in rather dorsal pathways. These differential findings between the domains of tool use were most obvious for selection processes. Below we will discuss our results in detail. In accordance with this Cortex special issue, marking 100 years after Liepmann, we also will briefly relate Liepmann's assumptions from a century ago with our current study results. Finally, we will visualize our interpretation within a neuroanatomical working model for apraxia of tool use.

4.1. Behavioral correlates

In our previous behavioral study (Buchmann & Randerath, 2017) we found impaired tool selection and tool application to show predominantly in patients with damage to the left hemisphere: only LBD patients but not RBD patients differed significantly from healthy controls in all tests. Single cases demonstrated that selection and execution processes can be affected separately for both novel and familiar tool use. Our present extended patient sample with 109 patients demonstrated similar behavioral results as before. In most subtests of the DILA-S, patients with left hemisphere stroke performed worse than RBD patients. However, between group-differences in performance levels for the selection and application of novel tools did not reach significance. One reason could be that essential neural correlates for preserved performance in the NTT are more strongly distributed across the hemispheres.

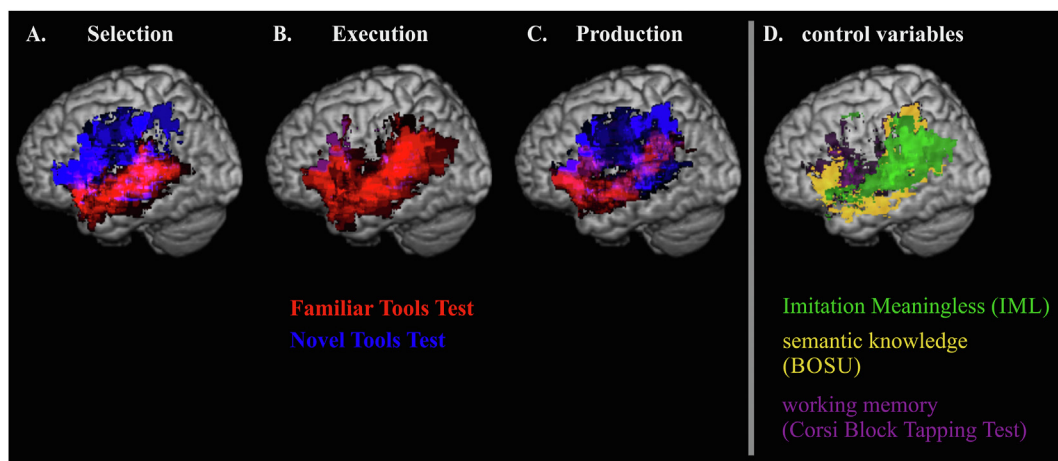


Fig. 4 – Lesion overlays for Selection, Execution and Production components in the real tool use tasks. The FTT is pictured in red, the NTT in blue. The right graph depicts lesions that were associated with control variables representing diminished imitation of meaningless hand-to-body postures (IML, green), semantic knowledge (BOSU, yellow) and working memory (Corsi Block Tapping Test, purple). Maps of control variables were not corrected for FDR.

Our exploratory Principal Component Analysis (PCA) including all participants supports and adds to our interpretations. Two major and two additional components were revealed based on our tool use variables, the control variables (Corsi Block Tapping Test, IML and BOSU) and other neuropsychological assessments (e.g., aphasia, neglect). For interpretation we propose that the first component denotes semantic processing since tests assessing aphasia, familiar tool use, pantomime of tool use and semantic knowledge demonstrated high loadings. NTT Selection and Imitation performance both also loaded on the first component but to a lesser degree, suggesting that these tasks may include aspects of semantic processing. Hypothetically, the share in semantic processing may cover the retrieval from any familiar aspects in these tasks for example the identification of known categorical object- or body-parts or learned mechanical rules. In other words, for the NTT this first component could be interpreted to support relational reasoning by association. The second component may represent action simulation and related working memory processes: mentionable loadings were shown by the subtests of the NTT as well as Production and Execution Scores across all DILA-S tasks plus a control-task assessing working memory (Corsi Block Tapping Test). In the control task patients were seated in front of a board with mounted blocks. The examiner tapped a sequence of blocks and the participants were asked to use their index-finger and reproduce the demonstrated sequence of tapped blocks. The first two PCA components explained most of the variance. Two more components with eigenvalues larger 1 explained less than 7% of variance each. Both demonstrated loadings primarily in control variables. One component (interpreted as motor function) included loadings by the Wolf Motor Function Test and Imitation Scores and may potentially display motor aspects and the influence of clumsiness. Potentially this component may be related to another less investigated component of limb apraxia, Liepmann's category of limbkinetic apraxia (Baumard & Le Gall, 2021). The fourth component (interpreted as visuo-spatial attention) included high loadings primarily by neglect tests and may represent visuo-spatial performance.

4.2. Lateralization

We analyzed lesion correlates of impaired tool use in 58 patients with left hemisphere damage and 51 patients with right hemisphere damage. Our results are part of a long line of evidence going along with Liepmann's emphasis that praxis is solved by large networks in the entire brain. Nevertheless, there are particulars about the left hemisphere and motor-cognitive abilities especially for familiar tool use actions. The current study supported our hypothesis that apraxic deficits can occur in patients with right brain damage, but that the syndrome of apraxia after right hemisphere stroke clearly diverges from apraxia after left hemisphere stroke (Buchmann et al., 2020; Salazar-López et al., 2016). In line with the behavioral results showing less impairment and variability in the RBD group, our VLSM analysis provided no surviving meaningful lesion-symptom maps for the right hemisphere. Similar to results by Salazar-López et al. (2016) who investigated 20 RBD patients, we were not able to present lesion maps surviving

measures of correction despite our relatively large number of RBD patients. This could still be attributed to a lack of power since the impact of right brain damage on praxis performance occurred to a lesser degree in the present sample. Recent findings published by Dressing et al. (2020) who implemented classical apraxia tests in even larger groups of left and right hemisphere stroke patients demonstrated that – similar to our behavioral results – pantomime of tool use deficits were strongly left lateralized. Instead imitation deficits were found in both patient groups after ventro- and dorso-dorsal stream lesions and correlated with hemi-spatial neglect in right brain damaged patients (Dressing et al., 2020). In our current study, we interpret the results only for the LBD group that demonstrated sufficient behavioral variance in the FTT and NTT tasks.

4.3. Lesion correlates for NTT versus FTT

Left hemisphere lesion overlaps of impaired NTT and FTT Selection were most obvious for inferior frontal areas, whereas the Production Scores in both NTT and FTT demonstrated a clear hotspot of overlap in ventro-dorsal areas, in the inferior frontal and inferior parietal cortex. Otherwise, the selection aspect in familiar versus novel tools delivered largely distinguishable lesion maps in the left hemisphere. Decreased performance in FTT Selection went along with lesions in rather ventral fronto-temporal regions, mainly covering inferior frontal gyrus, superior and middle temporal gyrus, supramarginal gyrus and basal ganglia. In contrast, impaired NTT Selection was associated with rather dorsal fronto-parietal lesion sites, mainly including precentral, inferior frontal and inferior parietal regions with supramarginal gyrus. The differential ventral versus dorsal focus of lesion maps associated with diminished FTT versus NTT can also be observed for Production Scores, but to a lesser degree. Based on our resulting behavioral and lesion correlates, we argue that correlates of conceptual aspects depend on the tool use domain FTT versus NTT. Goldenberg, who investigated familiar versus novel tool use, clearly distinguished between mechanical problem solving and functional knowledge within semantic memory (Goldenberg, 2013, p. 127). Their differentiation may be most pronounced during early processes of tool handling: the selection processes.

4.4. Lesion correlates for action selection versus specification

While deficiencies in selection processes were more strongly associated with rather anterior lesion sites, impaired action specification processes showed rather posterior lesion maps. This is in line with earlier reports on lesion correlates for deficient selection versus application processes during the handling of familiar tools (Martin et al., 2016) and may reflect a different demand on monitoring and action related working memory processes relevant for the retrieval and maintenance of object knowledge and for simulating potential actions (Randerath, 2020; Randerath, 2022). It goes along with recent models differentiating between action specification and action selection (Cisek & Kalaska, 2010).

Liepmann mostly investigated action specification mechanisms and with regards to tool use he mostly focused on

familiar tool use abilities. He attributed conceptual problems to be related to lesions in the parieto-temporo-occipital junction (Liepmann, 1925). However, conceptual aspects likely have to be subcategorized (Buxbaum, Veramonti, & Schwartz, 2000; Goldenberg, 2013), which is why this perhaps has been the least substantiated proposition by Liepmann with regards to limb apraxia and its lesion correlates.

4.5. Suggested mechanisms

We propose that for appropriate tool selection it is important to retrieve concepts from differential semantic systems. When selecting the best suitable familiar tool, semantics of a functional knowledge system are needed. When selecting the best suitable novel tool for a given recipient object, familiarity with physics characteristics or rules is required to allow for relational reasoning about objects and their usage, e.g., by characterizing relationships between structural properties (Goldenberg & Spatt, 2009; Osiurak et al., 2013). We propose that this process also needs to be informed by the perceived object properties (semantics), e.g., material, form or by detected similarities to familiar tools and objects. Simulation processes involving working memory mechanisms may be essential to find solutions for action opportunities. With the choice of a specified action opportunity, the movement output is further specified and adapted on-line. Going along with a large line of literature, the resulting lesion maps of our experimental variables and their overlaps with neuropsychological control variables in LBD patients may feed into the hypothesis of the following underlying mechanisms:

4.5.1. Deficiencies in specifying actions

Overlaps (FTT Production, NTT and IML) in inferior parietal lesion sites could be interpreted to represent impaired action processes with deficiencies in specifying action plans. For movement components Liepmann proposed the left supra-marginal gyrus and adjacent white matter lesions to be the most crucial region for typical apraxia symptoms during gesture production (i.e., problems with imitation, or pantomime of tool use gestures). In line with his early findings, more recent models based on neurophysiological data in non-human primates suggest mechanisms specifying actions along a dorsal pathway involving the parietal lobe (Cisek & Kalaska, 2010). Lesion studies like the one at hand confirm that the left inferior parietal lobe is a critical node in such an action specification network. Our study results, as well as a series of existing limb apraxia studies in the field, highlight the specific impact of lesions in the left inferior parietal lobe in gesture production or real familiar tool use (Buxbaum et al., 2014; Goldenberg & Randerath, 2015; Hoeren et al., 2014; Salazar-López et al., 2016; Weiss et al., 2016). Our behavioral data demonstrates that lower Production Scores are mainly characterized by movement errors which may concern movement-content (e.g., perseverate the last action or substitute the requested action by a different) or movement-orientation (e.g., on a wrong spatial plane or incorrect relation to the target). Frequently, essential aspects of a movement are missing or the participant fails to produce any meaningful tool-object interaction. In line with these results,

an earlier study demonstrated that movement errors in pantomime of familiar tool use have been associated with ventro-dorsal lesions as opposed to rather semantically related communicative aspects of apraxic errors going along with more anterior and ventral lesion sites (Finkel, Hogrefe, Frey, Goldenberg, & Randerath, 2018). Therefore, the overlap in inferior parietal lesion sites across action tasks (FTT Production, NTT and IML) could be interpreted in the sense of a motor-cognitive problem in action specification.

There has been some evidence suggesting that there is a posterior-superior to anterior-inferior gradient in the representation of feedback-to-feedforward motor control, with rather posterior-superior regions contributing more to on-line motor control, while anterior-inferior regions play a greater role in motor-cognitive planning (Binkofski & Buxbaum, 2013; Glover, 2003, 2004; Karnath & Perenin, 2005; Randerath et al., 2010). One fMRI study for example reported inferior parietal regions being significantly involved in feed forward simulation conditions (i.e., imagining using a tool) while updates by visually guided closed-loop feedback control mechanisms (i.e., actual tool application) showed significant activations in superior parietal regions (Macuga & Frey, 2014).

Disrupted action specification could be explained by a system-based failure. Deficient mechanisms that fail to dynamically integrate relevant perceptual and conceptual information may lead to unsuitable action plans. We propose that the left inferior parietal cortex is one major hub for such integrative mechanisms that are typically attributed to working memory functions (Randerath, 2020). Its dorsal and ventral junctions may present entry points driven by attentional processes for processing on-line perceptual or semantic information, respectively. These dynamically and contextually formed action plans may then for example lead to one suitable tool use action plan for a particular context. For slightly similar interpretations see for example Niessen, Fink, and Weiss (2014) or Orban and Caruana (2014).

4.5.2. Action simulation and related working memory mechanisms

Action simulation and related working memory mechanisms have been demonstrated to present basic elements for motor cognition (Hesslow, 2012; Jeannerod, 2006; Pulvermüller et al., 2014). Here we find some overlap in behavioral as well as in neuroanatomical data between working memory and tool handling tasks, especially regarding novel tools. Lesion maps for deficient performance in handling novel tools went along with diminished working memory performance (NTT Selection, NTT Production and Corsi Block Tapping). For NTT Selection we suggest that working memory functions such as manipulating rule-based physics knowledge, monitoring of object-related action steps and action simulation processes (anterior ventro-dorsal stream: fronto-parietal) may be used. Action simulation processes may also be needed for NTT application, introducing trial and error options by use of on-line feedback. In accordance with this idea, NTT Selection and NTT Production share large parts of their lesion maps in fronto-parietal areas.

It has been repeatedly demonstrated that reasoning about mechanical problems such as assessed by novel or unusual tool use tasks can be significantly affected after left brain

damage (Buchmann et al., 2020; Buchmann & Randerath, 2017; Goldenberg & Hagmann, 1998; Goldenberg & Spatt, 2009; Osiurak et al., 2009, 2013). Our findings of overlaps of lesion maps related to reduced NTT performance and the working memory control task in left lateral prefrontal regions could be interpreted as disturbed monitoring of action steps, – perhaps as part of the simulating process that supports mechanical problem solving and related action planning.

Our exploratory principle component analysis that included our real tool use tasks (FTT and NTT Scores), the control variables (Corsi Block Tapping, IML, and BOSU semantic task) as well as other neuropsychological variables may add to this idea. Interestingly, one component (interpreted as action simulation) listed tasks typically affected after left hemisphere damage (tasks producing tool use movements: Pantomime, FTT, NTT as well as one task with tool selection: only NTT) but also the Corsi Block Tapping working memory task. The other component (interpreted as visuo-spatial attention) listed tasks that are typically affected after right hemisphere damage and showed high loads for tasks assessing visuo-spatial hemineglect. This differentiation is in line with a large body of literature suggesting a hemispheric dissociation between visual/object or verbal (primarily left sided) and visuo-spatial (primarily right sided) working memory mechanisms (e.g. Barbey et al., 2013; Smith & Jonides, 1999; Suchan, 2008). Studies investigating neural correlates of working memory repeatedly demonstrated fronto-parietal regions and particularly lateral prefrontal regions to be involved in working memory performance related to monitoring and simulating visually-guided action steps in space (Fortin et al., 2003; Ricciardi et al., 2006; Schwartz et al., 1998; Toepper et al., 2010; Tracy et al., 2011; Wimmer, Nykamp, Constantinidis, & Compte, 2014) as well as in prospective action planning and simulation processes (Fontana et al., 2012; Lorey et al., 2014; Macuga & Frey, 2014; Randerath, Valyear, et al., 2017; Sirigu et al., 1996). In his recent book *Passingham* (2021) summarized that the dorsal prefrontal cortex is thought to be involved in imagining or simulating actions and thereby generating ordered sequences, while the ventral prefrontal cortex is thought to be involved in imagining objects and in associating items for relational reasoning. These findings go along with our line of reasoning for left hemisphere overlaps of lesion maps related to reduced NTT performance and the working memory control task to potentially share disturbed monitoring of object-related action steps as part of the action simulation process. Action simulation and related working memory functions may present a more general mechanism supporting object-related tasks including those involving mechanical problem solving for tool use.

4.5.3. Impairments in semantic knowledge

During FTT, participants handle familiar items for which they have learned how to typically use them. They can draw from memory. Accordingly, lesions associated with lower performance in handling familiar tools go along with ventral lesions associated with diminished semantic knowledge (FTT Selection, FTT Production and BOSU semantic task). Compiling evidence demonstrates that ventral streams (middle and superior temporal) are essentially

involved in the retrieval of functional associations (Buxbaum & Saffran, 2002; Canessa et al., 2008; Chen et al., 2018; Kellenbach et al., 2005). The extensive lesion overlaps on maps of impaired FTT Selection and BOSU object semantics suggest that the tool selection process for familiar tool use action was mostly based on the identification of tools and their typical function. This is in line with other studies addressing tool-object interactions in patients with brain damage (Martin et al., 2016; Salazar-López et al., 2016). Martin et al. (2016) for example demonstrated that lesions associated with deficient selection of recipient familiar objects were specifically within the ventral stream including the anterior temporal lobe. The strong similarity in study outcomes suggests that at least for the present matter it may not be crucial whether the participants need to select the correct tool or the correct target object to allow for appropriate tool-object interaction.

Subsequent familiar tool application may then have drawn upon additional motor-cognitive sources for action specification (posterior ventro-dorsal stream: inferior parietal). Our results again are in line with Martin et al. (2016) who similarly demonstrated that the performance of the typical tool-associated action was linked with ventro-dorsal stream lesions, particularly within the inferior parietal lobe. The additional lesioned sites associated with problems in FTT Production in surrounding central areas reaching into the parietal lobe resemble Liepmann's regions for motor apraxia, which he proposed more than 100 years ago (i.e., limb- and ideokinetic aspects) (Liepmann, 1920).

Further, we propose that the retrieval and maintenance of object characteristics and physic rules could represent a special form of semantics that is essential for novel tool selection and application. Error-monitoring as well as rule retrieval and maintenance (including mathematical rules) have been associated with inferior and prefrontal regions (Bongard & Nieder, 2010; Klein et al., 2007; Levine et al., 2011; Packer & Cunningham, 2009). Functional imaging studies have demonstrated that the lateral and the prefrontal cortex especially in the left hemisphere are activated during rule processing for action and for supporting adaptive behavior (Badre, Kayser, & D'Esposito, 2010; Bunge, Helskog, & Wendelken, 2009; Bunge, Wallis, et al., 2005) as well as during analogical reasoning tasks (Geake & Hansen, 2010) involving retrieval and integration of semantic relationships (Bunge, Wendelken, Badre, & Wagner, 2005; Wright, Matlen, Baym, Ferrer, & Bunge, 2008). Our exploratory PCA results are in favor of the idea that NTT Selection is at least in parts supported by retrieval of associative knowledge, listing NTT Selection (although with smaller load) together with familiar tools selection, application and pantomime as well as our BOSU semantic control task for component 1. The associated lesion map of NTT Selection shows primarily fronto-parietal lesion sites, but taps slightly into adjacent temporal regions. In contrast FTT Selection which loads strongly on the PCA component 1 is more distinctly associated with ventral lesion sites.

Overall, our results support the idea that object-selection versus action-specification related aspects of familiar and novel tool use can be behaviorally and neuro-anatomically differentiated (Fig. 5).

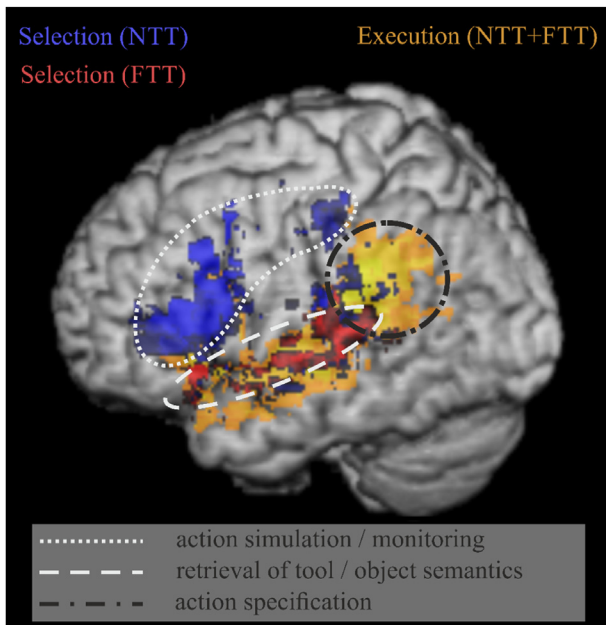


Fig. 5 – Neuroanatomical model for apraxia of real tool use. The working model displays three distinct left lateralized subsystems that are proposed to be essential for appropriate tool use behavior. The fronto-parietal system is proposed to be characterized by its essential role in action simulation including the monitoring and selection of object related action steps in rather anterior parts of the system. This system may also support the maintenance of object related characteristics and physics rules. This fronto-parietal system is particularly involved in selecting and applying novel tools. A ventral system is suggested to be highly relevant for familiar tool and object semantics retrieval. The ventral system appears to be critically involved in the appropriate selection of familiar tools and objects. A ventro-dorsal system with a major spot in inferior parietal regions represents essential parts of an action specification network. It is proposed to be crucial for forming adaptive action plans based on the respective conceptual tool use knowledge and on-line perceptual information. We propose that during tool selection and tool application processes humans dynamically tap into these experienced and specialized systems and continuously integrate bits of motor-cognitive representations into context adapted action plans.

(Colored areas are based on the statistical lesion analyses considering NTT Selection (blue), FTT Selection (red) and FTT and NTT Execution (yellow/orange). The lower bound intensity values were set to critical z-values with $\alpha = .01$).

4.6. Limitations

We have been fortunate to have had the opportunity to study apraxia and its neural correlates of impaired tool use over several years in a neurorehabilitation setting. The results appear logic and can be linked to prior evidence. Still, the current dataset had limited power, and necessary test-choices limit interpretation options.

Further, the lesion analysis for NTT Execution did not demonstrate any circumscribed areas after FDR correction. Here, scores heavily rely on solving the task at first attempt. One explanation may be that many patients but also healthy subjects at their first attempts have troubles applying the novel tool correctly at the recipient cylinder. Thus, difficulties in finding a quick solution may not necessarily be specific to apraxic errors and therefore may not appear lesion site-specific.

As a strong limitation, the interpretation of the exploratory PCA results of course is a subjective decision. Per component, we inferred a shared mechanism across different tasks paying special attention to high loadings. We subsequently tried to contemplate for each involved task (including other neuropsychological variables and control tasks) whether the interpreted mechanisms could be relevant to the respective task. For example, pantomiming tool use (pantomime production, typically applied to assess gesturing) may require a. the retrieval of communicative knowledge as well as b. movement planning while imagining the tool in hand for gesture production (Finkel et al., 2018; Goldenberg, 2017). Accordingly, the pantomime task in our current study showed loadings on semantics (PCA component 1) as well as on action simulation (PCA component 2). Or, for example, in order to tap on each single block in a defined action sequence that needs to be held in memory (Block tapping test, typically applied to assess visuo-spatial working memory), may require a. visuo-spatial attention, b. action simulation and related working memory mechanisms to memorize serial orders as well as c. fine motor skills (Berch, Krikorian, & Huha, 1998; Cavallini, Fastame, Palladino, Rossi, & Vecchi, 2003; Chechlacz, Rotshtein, & Humphreys, 2014). In our study, this goes along with loadings on the according PCA components 2 to 4. Regardless, the current interpretations remain subjective and were proposed based on the results of a clearly limited set of data, requiring further investigation by replication and by implementation of alternative study approaches and tests.

Thus, future studies may consider even larger samples and may include further variables or adapted assessments. For example, kinematic movement analyses may add to a more fine-grained analysis of the movement component and potentially may be more sensitive for picking up on spatial deficits, which could be especially relevant for RBD patients.

4.7. Conclusion

The data is in support of the idea that each of the introductory described accounts may explain different aspects of real tool use best. Therefore, we discussed our results following an integrational perspective. On the one hand mechanical problem-solving may account well for the ability to select novel tools. For this, we proposed, that monitoring of action steps and simulation of the upcoming action contribute essentially to the ability of mechanical problem solving (dorsally, fronto-parietal), but also may include the retrieval of basic physics knowledge or semantics (ventrally, fronto-temporal). Nevertheless, semantics related accounts may explain best the ability to select familiar tools for which tool and object associations are retrieved (ventrally, temporal). We argued including a large body of literature, that action

simulation needs working memory mechanisms that allow for integrating bits of representations into context adapted action plans. We further proposed that planning the action of tool use may be strongly accounted for by prior action simulation. The ability of specifying tool use actions appears to go along with larger and less specific lesion areas as compared to tool selection (but with a major hub ventro-dorsally, parietal). The aforementioned allocation of functions fits well with the dorsal-ventral systems-models account positing a complementary and dynamic role for on-line and stored information. Thus, in parts we can support the hypotheses and contribute to disentangling sub-components and discussing potential underlying mechanisms. However, the current study falls short in providing a concluding answer to the question, which specific weight the different theoretical approaches may have for respective subcomponents of tool use: selection versus application processes and the handling of novel versus familiar tools. The results need to be interpreted with caution while considering the limitations of limited power, necessary test-choices and limited time capacities of studying apraxia in neurorehabilitation settings.

The current manuscript used a neuroanatomical approach in order to contribute to disentangling a fraction of the underlying mechanisms of impaired tool selection and tool application processes. Our findings and interpretations fit well with established and topical neuroanatomical models on motor cognition (Cisek & Kalaska, 2010; Pezzulo & Cisek, 2016). Cisek and Kalaska (2010, p.278) assume “that interaction with the environment involves continuous and simultaneous processes of sensorimotor control and action selection from among the distributed representations of a limited number of response options.” The action specification and selection processes involve perceptive, cognitive and decision-making hubs and loops distributed across the brain. We find this perspective appealing since it allows for the necessary flexibility to interact with a constantly changing world in an adaptive way. We therefore propose that there are no fixed sets of specific tool-object interaction representations in one specific area of the brain that can be completely lost by corresponding brain damage. Instead we follow the hypothesis that during tool selection and tool application processes we dynamically tap into experienced systems with motor-cognitive specialties and continuously integrate bits of representations into context adapted action plans providing specific response options for an affording environment. Damage to certain hubs can yield significant interruptions in these dynamic processes and may contribute to the different facets of the limb apraxia syndrome. Note that already a century ago Liepmann (1920, p.529) illustrated that praxis is dependent on the interplay of many brain territories, and when talking about a so called praxis-region he merely meant that if this region was lesioned it would disrupt the praxis system significantly, representing an essential substructure. Liepmann at the time even described engrams as electrophysiological traces of incoming stimuli (not as invariant cognitive units). We believe that the many controlled studies and elaborately collected data and interpreted evidence in the past century have contributed considerably to a better understanding of the limb apraxia syndrome.

The current study results suggest that tool selection versus tool application related aspects of familiar versus novel tool use can be behaviorally and neuro-anatomically differentiated. We propose that experienced systems with motor-cognitive specialties and integrative mechanisms across fronto-temporo-parietal regions in the left brain contribute essentially to these tasks. On a group level, we found a rather ventral (familiar tools) versus dorsal (novel tools) and anterior (selection) versus posterior (application) focus of lesion maps. In particular, tool selection processes appear to be rather specific for familiar versus novel tools.

Open practices

The study in this article earned an Open Materials badge for transparent practices. Further, the data that support the findings of this study are available on request from the corresponding author, [JR]. The individual's data (and particularly the individuals' brain scans) are not publicly available due to their containing information that could compromise the privacy of research participants.

Additional information

No part of the study was pre-registered prior to the research being conducted. Detailed descriptive data are contained in the manuscript. Further data that support the findings of this study are available on request from the corresponding author [JR]. The individual's data (and particularly the individuals' brain scans) are not publicly available due to their containing information that could compromise the privacy of research participants. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of clinical data, including completion of a formal data sharing agreement and approval of the participating clinic and local ethics committee. In the methods section we report all inclusion/exclusion criteria determining our sample. Inclusion/exclusion criteria were established prior to data analysis. All manipulations, and measures in the study are mentioned in the main text. Digital study materials are available at: <https://www.moco.uni-konstanz.de/publikationen/assessments/>.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual

property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from J_Randerath@hotmail.com.

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Supplementary data

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