Investigation into the cognitive underpinnings of apraxia: insights from motor working memory and pantomiming object use

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List of abbreviations

ACL-K	Aphasia Check List – short version
AG	Angular gyrus
AIC	Akaike Information Criterion
ANOVA	Analysis of variance
AO	Actions with objects subtask
BF	Bayes Factor
BG	Basal ganglia
BIC	Bayesian Information Criterion
BS	Block span
CT	Computed tomography
DLPFC	Dorso-lateral pre-frontal cortex
DS	Digit span
EHI	Edinburg Handedness Questionnaire
FDR	False discovery rate
FEW	Family-wise error
GLME	Generalized linear mixed effects
GoP	Virtual grasping of object pictures
GP	Globus pallidus
HADS	Hospital anxiety and depression scale
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
IPS	Intraparietal sulcus
IQR	Interquartile range
JHU	Johns Hopkins University
KAS	Kölner (Cologne) Apraxia screening
LH	Left hemisphere stroke patients
LH-	Left hemisphere stroke patients without apraxia
LH+	Left hemisphere stroke patients with apraxia
LH+GoP	Left hemisphere stroke patients with apraxia in the virtual grasping group

LH+IPB	Left hemisphere stroke patients with apraxia exhibiting irregular pantomime behaviors (combined LH+GoP and LH+ToP)
LH+RPB	Left hemisphere stroke patients with apraxia exhibiting regular pantomime behaviors
LH+ToP	Left hemisphere stroke patients with apraxia in the tracing group
LME	Linear mixed effects
MCA	Middle cerebral artery
MFG	Meaningful gestures subtask
MLG	Meaningless gestures subtask
MNI	Montreal Neurological Institute
MRC	Medical Research Council scale
MRI	Magnetic resonance imaging
mRS	Modified Ranking scale
MTG	Middle temporal gyrus
mWM	Motor working memory composite score
NIHSS	National Institute of Health Stroke Scale
NPM	Non-parametric mapping
PCA	Principal component analysis
RH	Right hemisphere
SD	Standard deviation
SLF	Superior longitudinal fasciculus
SMG	Supramarginal gyrus
SPL	Superior parietal lobule
STG	Superior temporal gyrus
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
ToP	Tracing of object pictures
TPS	Time post-stroke
VLSM	Voxel-based lesion-symptom mapping
WM	Working memory
WMS-R	Wechsler Memory Scale - Revised

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1. Introduction

Imagine an artist unable to translate creative visions into coherent brushstrokes upon a canvas. Picture the hand of a chef fumbling, unable to execute the delicate techniques honed through years of culinary practice. Now, expand this lens of observation to the seemingly mundane and effortless tasks that pertain our daily routines – the sweeping of a toothbrush, the familiar grip of a coffee mug or the regular manipulation of a pen while writing. Yet, the delicate harmony between intended action and executed motor behavior that underlies our motor control can be disrupted in patients with the disorder of limb apraxia.

1.1. History, definition, and clinical manifestations of apraxia

Apraxia, a term etymologically derived from the Greek roots 'a- 'denoting 'without' and 'praxis' meaning 'action', literally translates to 'without action'. The first documented appearance of this word can be traced back to the work of Steinthal (1871), who used the term apraxia to articulate the disconnection between movement and its intended purpose while describing an aphasic patient with difficulties in performing intentional acts with objects, such as holding a pen upside down. However, it was not until the early 20th century that scholarly investigations into apraxia began to gain momentum, predominantly driven by the seminal work of the psychiatrist Hugo Liepmann – a student of Carl Wernicke – on the taxonomies of apraxia (Goldenberg, 2003). Notably, Liepmann, (1907) distinguished between three canonical taxonomies of apraxia – *ideational, ideo-kinetic* (or *ideomotor*), and *limb-kinetic* apraxia – to illustrate different manifestations of disturbances in the 'government of the limbs by the mind' (as cited by Goldenberg, 2014). Some of these clinical subtypes of apraxia remained in use in contemporary definitions of apraxia to denote disturbances related to the planning of intended actions (*ideational apraxia,* Poeck, 1983), or to disruptions in the precise execution of motor plans (*ideomotor apraxia*, De Renzi, 1980). However, the prevalent inconsistencies in the use of these terminologies among researchers have blurred the boundaries between the different taxonomies of apraxia, and as a result, the use of these subtypes has been strongly debated in recent decades (Goldenberg, 2014; Buxbaum and Randerath, 2018).

Beyond Liepmann's classical taxonomy of apraxia, current definitions of apraxia reveal a certain degree of consensus, but still remain partially varied (for a review of different definitions see Baumard and Le Gall, 2021). Nevertheless, apraxia can be defined as an acquired cognitive-motor disorder leading to deficits in the execution of voluntary and goal-directed actions. Importantly, these impairments cannot be attributed solely to lower-level sensori-motor disturbances (e.g., ataxia, paresis), language comprehension deficits (e.g., aphasia), and/or general cognitive impairments (e.g., dementia, Goldenberg, 2013; Cubelli, 2017).

The core manifestations of apraxia within the clinical setting frequently include deficits in (i) the imitation of meaningful and/or meaningless gestures, such as hand positions, finger configurations and bucco-facial expressions, (ii) the production of communicative movements, such as emblems – symbolic gestures with established cultural relevance (e.g., 'thumbs-up' gesture) – as well as pantomimes of object use, which involve demonstrating the appropriate use of familiar objects without physical handling or manipulating, and (iii) the actual use of tools/objects (Osiurak and Rossetti, 2017). As apraxia is a heterogenous syndrome, patients commonly exhibit clinical dissociations in these praxis deficits, wherein, patients may display impairments in one or two specific categories. For example, dissociations are frequently observed based on the symbolic nature of the gestures: some patients are specifically impaired in imitating meaningless gestures, while their imitation of meaningful gestures is preserved (Bartolo *et al.*, 2001; Achilles *et al.*, 2019). It is worth noting that certain descriptive definitions of apraxia classify patients with apraxia into different subtypes based on the distinct clinical motor deficits they display in specific body parts (e.g., limb- or bucco-facial apraxia) or within a particular action domain (e.g., imitation or pantomime apraxia, Cubelli, 2017; Tessari *et al.*, 2021).

1.2. Functional relevance and impact of apraxia

Apraxia affects a substantial portion of patients with lesions to the fronto-parietal praxis network within the left hemisphere (LH), with prevalence rates ranging from 28% to 57% (Donkervoort *et al.*, 2000; Zwinkels *et al.*, 2004). Notably, in approximately 40% to 88% of patients with apraxia (Kertesz *et al.*, 1984; Donkervoort *et al.*, 2006), the symptoms can persist for over three months after stroke, highlighting the long-term impact of this motor-disorder. Apraxia is also observed in patients with lesions to the right hemisphere (Stamenova *et al.*, 2010; Ubben *et al.*, 2020) and in neurodegenerative diseases, including Parkinson's disease (Matt *et al.*, 2019), Alzheimer's disease (Derouesné *et al.*, 2000), semantic dementia (Cotelli *et al.*, 2014) and cortico-basal degeneration (Stamenova *et al.*, 2011).

Furthermore, apraxia following LH stroke is considered a potent predictor of reduced subjective well-being (Wyller *et al.*, 1997) as well as increased dependence on caregivers (Bjorneby and Reinvang, 1985; Sundet et al., 1988). The latter mainly arises from the evident challenges apraxic patients face in performing activities of daily living, such as eating (Foundas *et al.*, 1995), bathing (Hanna-Pladdy et al., 2003) or teeth-brushing (Goldenberg and Hagmann, 1998). The negative functional impact of apraxia on patients' lives extends beyond their daily routine activities, affecting their neurorehabilitation outcomes after stroke. Importantly, patients with apraxia are less likely to return to work compared to non-apraxic stroke patients (Saeki *et al.*, 1995). Additionally, their engagement in social interactions is more prone to compromise due to their reduced use of communicative gestures (Borod *et al.*, 1989).

1.3. Cognitive processes underlying apraxic deficits

Apraxia constitutes a complex and multifaceted disorder that manifests itself through different forms of observed behavioral motor deficits. However, although apraxia 'manifests in the domain of action, it has its roots in deficits which are not specific to action' (Liepmann, 1929, as cited by Goldenberg, 2003). The multiple manifestations of apraxia can be attributed to a spectrum of cognitive impairments, which can be categorized as either 'praxis-specific', intricately linked to motor planning (e.g., body schema), or 'non-specific', encompassing more generalized disruptions in cognitive functioning (e.g., executive functioning, Goldenberg, 2014; Baumard and Le Gall, 2021). This array of cognitive processes can be independently disrupted to a varying degree by lesions affecting distinct regions within the left lateralized fronto-parietal praxis network (Randerath, 2020).

Some of the major cognitive functions contributing to apraxic deficits include structural processing (Goldenberg and Hagmann, 1998; Osiurak *et al.*, 2010), visuospatial processing (Goldenberg and Karnath, 2006; Jax *et al.*, 2006), executive functions (Barbieri and De Renzi, 1988; Canzano *et al.*, 2016), memory (Buxbaum and Saffran, 2002; Bartolo *et al.*, 2003), language and semantic processing (Mengotti *et al.*, 2013; Achilles *et al.*, 2016), and body schema or body image (Goldenberg, 1995; Buxbaum, 2001; Dafsari *et al.*, 2019). For a comprehensive overview of each of these cognitive functions, along with examples of their common clinical manifestations in patients with apraxia who have deficits in a corresponding cognitive function, the reader is referred to *Table 1*.

Table 1. Cognitive processes contributing to apraxia and examples of their common manifestations in patients with apraxia.

Cognitive function	General definition	Common manifestation of deficit in patients with apraxia
Body schema	Internal representation of the body and its various body parts.	Deficits in perceiving the position of different body parts, leading to inaccurate hand positioning relative to the face/body during imitation, such as pointing to the ear when intending to point to the nose.
Structural processing	The perception and analysis of object properties, such as shape, size and orientation.	Difficulties in manipulating objects correctly based on their structural attributes, such as holding the wrong end of a pen while attempting to write.
Visuospatial processing	Understanding spatial relationships between different body parts, and between the body and objects.	Deficits in coordinating movements in relation to external objects and/or different body parts, leading to actions that are out of sync and poorly coordinated, such as misaligned grasping of objects.
Executive functions	Higher-order cognitive processes that are involved in planning and executing goal-directed actions.	Deficits in adjusting an ongoing action plan in response to changes, and in selecting the most appropriate action among a range of alternatives.
Memory	Processes involved in retaining and recalling motor-related information, including working memory and manipulation knowledge.	Deficits in remembering the sequence of actions required to perform a complex action plan, resulting in awkward or fragmented movements, such as forgetting to add tea leaves when preparing a cup of tea.
Language and semantic processing	Retrieval and comprehension of action-related and object-related knowledge and concepts.	Deficits in conceptualizing the proper use of objects based on contextual relevance, leading to misuse of objects, such as using a spoon to write.

Given the finite number of cognitive processes governing the complexity of human behavior in relation to the vast array of observable phenomena, the coupling of clinical symptoms to specific cognitive functions is far from being systematic (Levi-Strauss, 1958). Consequently, disruptions to a singular cognitive function may contribute to a diverse spectrum of apraxic deficits, while a single outwardly observed manifestation of apraxia could be evoked by intricate impairments across multiple cognitive domains (Baumard and Le Gall, 2021). For instance, impairments in body image or body schema (Schwoebel and Coslett, 2005) frequently emerge as major contributors to the various manifestations of apraxia (Goldenberg, 1995). These encompass primarily deficits in imitation (Goldenberg and Karnath, 2006) and, secondarily, deficits in pantomiming object use (Buxbaum, 2001), further extending to actual object use (Canzano *et al.*, 2016). Particularly noteworthy is the role of impaired body representations in elucidating the presence of effector-specific forms of apraxia (Cubelli, 2017), as well as distinct activation patterns of sensorimotor representations for actions oriented ‘toward the body’ versus ‘away from the body’ (Ruotolo *et al.*, 2022). Concurrently, the prevalent deficits in pantomiming object use observed in patients with apraxia are associated with a myriad of cognitive impairments extending beyond body schema deficits. These include deficits in visuospatial processing as well as memory impairments encompassing working memory (Bartolo *et al.*, 2003), semantic memory (Goldenberg *et al.*, 2003) and manipulation knowledge (or visuo-kinesthetic engrams, Rothi *et al.*, 1991; Buxbaum, 2001).

Since the cognitive processes underlying apraxic deficits are broad and multifaceted, the scope of this dissertation precludes an exhaustive examination of all contributing cognitive functions. Instead, this introductory chapter will focus on three critical dimensions that are important for the understanding of apraxia and that are of direct relevance to the current work. Therefore, subsequent sections will meticulously delve into the intersection of apraxic deficits with the following cognitive impairments: (i) aphasia, (ii) memory impairments and (iii) neglect.

1.4. Interplay between apraxia and aphasia

Among individuals with apraxia following lesions to the left hemisphere (LH), the most frequently co-occurring cognitive deficit is aphasia. Aphasia is characterized by phonological, syntactic and/or semantic processing deficits, which culminate in disruptions of language comprehension and/or production abilities (Tippett *et al.*, 2014). In fact, early researchers conceptualized apraxia as '*an obvious amplification of aphasia*' in patients with aphasia (Steinthal, 1871; as cited by Goldenberg and Randerath, 2015). Thus, these researchers suggested that apraxia and aphasia represented varying degrees of symptoms within the spectrum of a common neuropsychological disorder. However, the independence of apraxia from aphasia has been strongly substantiated through documented cases demonstrating a double dissociation between the two neurological conditions (Baumard and Le Gall, 2021), as well as through differential variations in their severity (Lehmkuhl *et al.*, 1983). In particular, while some cases of LH stroke patients exhibit apraxia without concurrent language deficits (Selnes *et al.*, 1991), others exhibit aphasia but retain proper praxis functions (Kertesz *et al.*, 1984). It is important to note, however, that this dissociation is not symmetrical in occurrence, as reported instances of apraxia without concomitant aphasia are rarer in comparison to cases of aphasia without apraxia (Papagno *et al.*, 1993; Weiss *et al.*, 2016).

1.4.1. Associations and dissociations at the clinical level

The co-morbidity of aphasia and apraxia is to a large extent moderated by stroke-induced disturbances in semantic processing mechanisms, which reciprocally support both praxis and language systems (Roby-Brami *et al.*, 2012). Within the praxis domain, these mechanisms notably encompass the recognition of actions, identification of objects, recognition of action-object relationships, and the integration of these elements into cohesive action plans (Rounis and Binkofski, 2023). Evidence from large cohort studies ascertains that the performance of LH stroke patients with apraxia in meaningful actions, which require substantial semantic knowledge, is positively correlated with the severity of their aphasic deficits (Mengotti *et al.*, 2013). In contrast, equivalent correlations are absent for the production of meaningless gestures, which are devoid of semantic content (Achilles *et al.*, 2016; Weiss *et al.*, 2016). Accordingly, deficiencies in producing (novel) meaningless gestures could serve as a robust marker for discerning apraxic deficits from those related to concomitant aphasia following LH stroke (Schmidt and Weiss, 2021).

However, the differentiation between apraxia and aphasia is rendered more difficult on tests of pantomiming object use (i.e., meaningful action; Goldenberg and Randerath, 2015). In case of pantomimes, access to semantic knowledge concerning the shape and function of objects constitutes a crucial prerequisite for accurately demonstrating their use (Randerath *et al.*, 2011*a*). Consequently, instances of defective pantomiming the use of objects independent of concurrent aphasia in patients with apraxia are rare and are usually restricted to cases with atypical lateralization of brain function (Alexander and Annett, 1996).

1.4.2. Associations and dissociations at the neuroanatomical level

At the neuroanatomical level, the high comorbidity of apraxia and aphasia subsequent to lesions in the left hemisphere (LH) has been primarily attributed to the anatomical proximity as well as partial overlap of brain regions implicated in praxis and language functions (Papagno *et al.*, 1993; Roby-Brami *et al.*, 2012). In particular, patients diagnosed with both apraxia and aphasia prominently show common lesions in the inferior frontal gyrus (IFG) and inferior parietal lobule (IPL) of the LH (Mengotti *et al.*, 2013; Goldenberg and Randerath, 2015). Notably, Broca's area, a region within the left IFG, plays a dual role by supporting praxis (e.g., action recognition and encoding) and language functions (e.g., verbal fluency; Binkofski and Buccino, 2004; Nishitani *et al.*, 2005). A specific sub-region of Broca's area, designated as Brodmann's area 44, has been posited to function as a supra-modal hub for semantic processing. Damage to this region was associated with co-manifestation of apraxic and aphasic deficits, especially apraxic impairments pertaining to the production of meaningful gestures and pantomimes (Weiss *et al.*, 2016).

Notably, also distinct neuroanatomical pathways were shown to underlie apraxia and aphasia. Specifically, LH stroke patients with apraxia often suffer from additional lesions within the premotor cortex, a crucial region for motor planning. Conversely, patients with aphasia predominantly suffer from additional lesions within the insula and the superior temporal gyrus (STG) of the LH, which are important regions for language processing and comprehension (Goldenberg *et al.*, 2007; Fridriksson *et al.*, 2015; Weiss *et al.*, 2016).

1.4.3. Cognitive praxis model: The dual-route model of gesture production

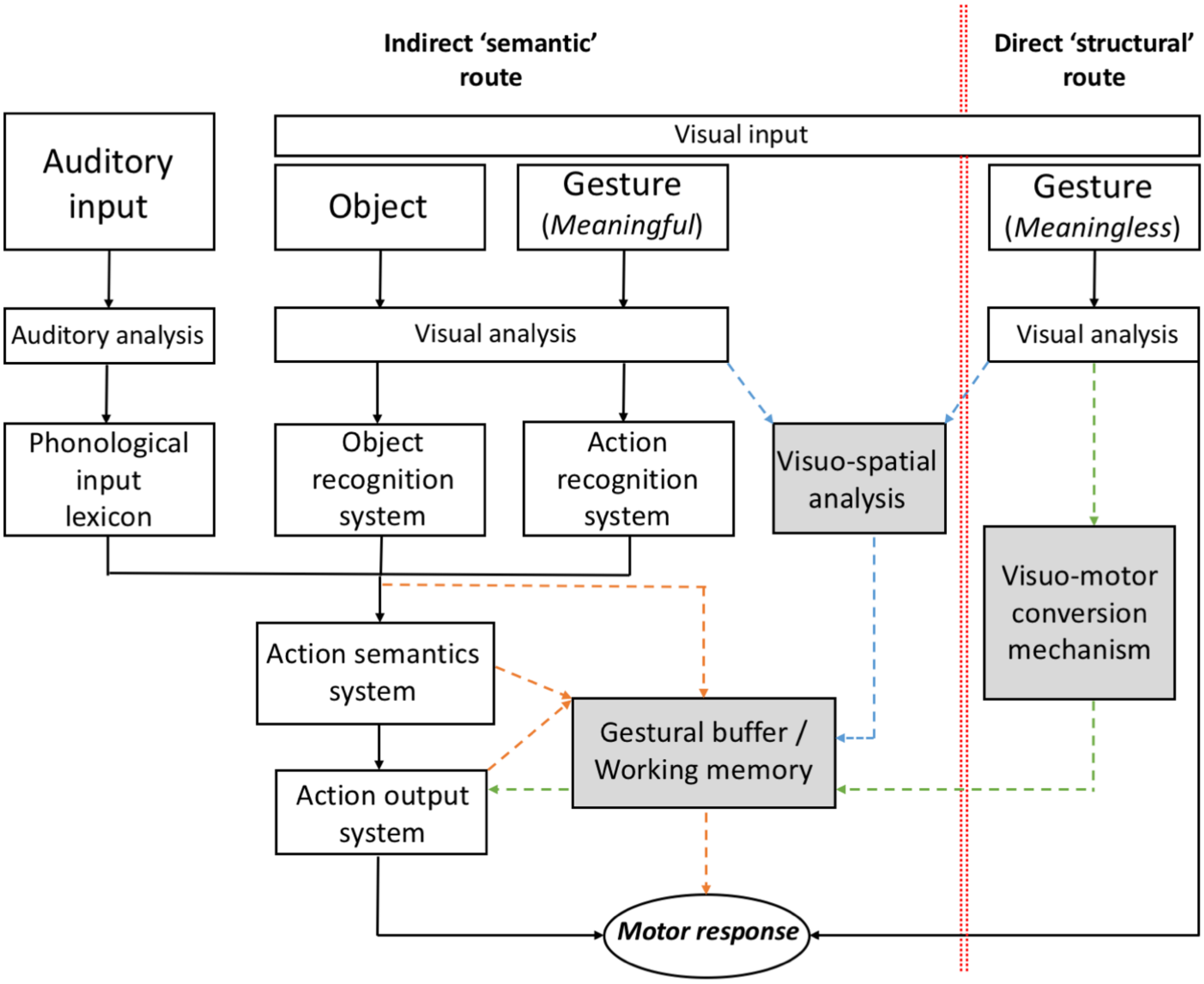
Informed by the language system models, Rothi *et al.* (1991) introduced the dual-route model of gesture production to elucidate the different profiles of praxis deficits observed in apraxia. At its core, this model posits that sensory information received from various modalities is processed through distinct input lexicons before being transferred to an action output lexicon, which subsequently integrates kinesthetic information related to the physical attributes of the intended action. Within this framework, sensory inputs, including auditory, visual information about objects and visual information about gestures are processed through a phonologic input lexicon, an object recognition system and an action recognition system (or action input lexicon), respectively (see *Figure 1* for a simplified schematic representation of the cognitive praxis model). The transfer of information from these input systems to the output system is mediated via an action semantics system, which constitutes a repository of acquired action-related knowledge that is partially independent from other forms of semantic knowledge (Roby-Brami *et al.*, 2012). This route, centered on the action semantics system, is termed the indirect 'semantic' route and is primarily responsible for generating meaningful actions – both transitive (actions involving objects) and intransitive (actions not involving objects). Concomitantly, the model delineates a direct 'structural' route that bypasses the action semantics system, establishing a direct connection between sensory inputs and the output lexicon. This route is primarily responsible for producing novel or meaningless gestures driven solely by the conversion of visual cues into motor responses.

The dual-route model allows to explain the different behavioral dissociations observed in patients with apraxia, particularly those pertaining to the imitation of meaningful and meaningless gestures. For instance, patients exhibiting selective deficits in the imitation of meaningless gestures potentially have impairments in the visuo-motor transformation, which occurs via the direct route, while these patients still maintain access to the indirect route (Goldenberg and Hagmann, 1997; Cubelli *et al.*, 2000). Conversely, patients with impairments in the indirect route may adeptly reproduce meaningful gestures, but have difficulties in describing their meaning (Buxbaum and Randerath, 2018). It is important to note that while the direct route is theoretically posited to also support the production of meaningful gestures, the indirect route cannot sustain the production of meaningless gestures (Tessari and Rumiati, 2004). This accounts for the infrequent observations of apraxic patients with exclusive impairments in producing meaningful gestures (Bartolo *et al.*, 2001, 2003), as well as apraxic patients with more pronounced deficits in imitating meaningful gestures compared to meaningless ones (Tessari *et al.*, 2007). These exceptional cases, however, might result from a deficient reallocation of cognitive resources that are crucial for switching from the (damaged) indirect route to the (putatively functional) direct one (Bartolo *et al.*, 2001; Tessari and Cubelli, 2014).

In addition, the direct and indirect routes are thought to be underpinned by anatomically distinct processing streams (Rumiati *et al.*, 2005). The dorsal 'where/how' stream, stemming from the occipital lobe and extending to the posterior parietal and frontal areas (dorsal premotor cortex), supports the direct route. This stream is presumed to mediate real-time visual coordination of skilled actions. In contrast, a ventral 'what' stream, also originating in the occipital lobe but projecting to the anterior temporal lobe and inferior frontal regions supports the indirect route. This stream is implicated in visual object recognition and the extraction of associated semantic properties (Goodale and Milner, 1992; Milner and Goodale, 2008).

Over the past two decades, Rothi *et al.'s* (1991) original cognitive praxis model has been refined and expanded with additional components and interconnections to account for emergent praxis profiles (the added elements are displayed in gray boxes and dashed lines in *Figure 1*). Notably, Cubelli *et al.* (2000) introduced a gestural buffer that converges the two routes and holds information for motor planning prior to the execution of the motor response. Furthermore, they inserted a conversion mechanism bridging visual analysis and the gestural

Figure 1. Cognitive praxis model.



Schematic representation of the modified cognitive praxis model devised by Rothi *et al.* (1991). *The depicted model integrates recently introduced cognitive mechanisms (represented by grey boxes) and interconnections (represented by dashed lines). Notably, the modified model encompasses the visuo-motor conversion mechanism and gestural buffer introduced by* Cubelli *et al.* (2000)*, the action working memory system introduced by* (Bartolo *et al.*, 2003)*, and the visuospatial analysis component introduced by* Randerath (2009)*. The dashed lines in the colours green, orange and blue represent the interconnections proposed by* Cubelli *et al.* (2000)*,* Bartolo *et al.* (2003) and Randerath (2009)*, respectively.*

buffer on the direct pathway, which supports the transformation of visually analyzed gestures into corresponding motor responses (see green dashed lines in *Figure 1*). Building on this modified model, Bartolo *et al.* (2003) added an integrative working memory (WM) workspace that converges information from all input lexicons as well as the action semantics system, thus facilitating the selection of the appropriate motor response (see orange dashed lines in *Figure 1* and *Section 1.5.2. working memory deficits in apraxia*). Additionally, Randerath (2009) incorporated a visuo-spatial analysis component that enhances visual processing efficiency and reduces the load on WM (see blue dashed lines in *Figure 1* and *Section 1.6.1. visuospatial deficits in apraxia*).

1.5. Interplay between apraxia and memory deficits

1.5.1. Manipulation knowledge hypothesis

Rooted in the cognitive dual-route model of apraxia, the manipulation-based hypothesis or ‘gesture engram theory’ centers on the notion that the production of object-related gesture is accomplished by the retrieval of stored representations of how an object is used or manipulated, termed ‘manipulation knowledge’ (Buxbaum and Kalénine, 2010). This knowledge is also referred to as ‘visuo-kinesthetic engrams’ (Heilman *et al.*, 1982), ‘motor engrams’ (Buxbaum, 2001) or ‘action lexicons’ (Rothi *et al.*, 1991). Manipulation knowledge encompasses implicit sensorimotor memories formed through repeated object use, which contain invariant kinematic and postural features of object-related gestures (Buxbaum, 2001). For example, a stored representation of the grip posture, hand position and the movements of the elbow that match the gesture of hammering (Chaminade *et al.*, 2005). Such stored representations lead to the ‘processing advantage’ of not having to reconstruct gestures *de novo* during each object use (Rothi *et al.*, 1991; Buxbaum, 2017). According to this framework, apraxia might reflect impairments in generating, accessing and using these object-related gesture representations. Supporting this theory, impairments in manipulation knowledge have been shown to underlie apraxic deficits, especially in tests emphasizing the retrieval of stored gestural representations, such as multiple choice questions on object manipulation knowledge (Buxbaum *et al.*, 2003), motor imagery of object use (Buxbaum *et al.*, 2005), and pantomiming object use (Rothi *et al.*, 1991; Buxbaum, 2001; Niessen *et al.*, 2014).

At the neuroanatomical level, manipulation knowledge is posited to be predominantly sub-served by a/the left-lateralized ventro-dorsal stream that generates the to-be-executed motor plan (Binkofski and Fink, 2005), and which might map onto the indirect (semantic) route (Buxbaum and Kalénine, 2010). In particular, manipulation knowledge is presumed to primarily reside in the left IPL (Rothi *et al.*, 1991; Buxbaum, 2001; Binkofski and Buxbaum, 2013; Niessen *et al.*, 2014; Van Elk, 2014). Furthermore, evidence from TMS studies highlights the crucial involvement of the SMG in tasks drawing upon manipulation knowledge, thus, suggesting the SMG to be a central locus for this cognitive function (Pelgrims *et al.*, 2011; Andres *et al.*, 2013). Notably, the manipulation knowledge theory proposes that the stored gesture representations are not rigid, permitting online adjustments based on environmental constraints such as the object's position or size. These sensorimotor corrections are argued to be supported by a/the bilateral dorso-dorsal stream that might correspond to the direct (non-semantic) route (Buxbaum and Kalénine, 2010). Thus, based on the manipulation theory, object-related gestures are complementarily supported by a learning-based ventro-dorsal system, referred to as the 'use system', and an online dorso-dorsal system, referred to as the 'grasp system' (Rizzolatti and Matelli, 2003; Binkofski and Buxbaum, 2013). In addition, the degree of reliance on one system over the other might be affected by contextual task-demands and/or the functional integrity of each system (Buxbaum, 2017). Importantly, an intact 'grasp system' is posited to mitigate deficits in the 'use system' by leveraging sensory and proprioceptive feedback provided by physically manipulating objects. This becomes evident in the better performance of apraxic patients when using real objects compared to pantomiming their use (Rothi *et al.*, 1997, Randerath *et al.*, 2011*b*), and in the improvement of their pantomime performance when provided additional tactile feedback (e.g., pantomiming while holding a wooden piece; Goldenberg *et al.*, 2004; Hermsdörfer *et al.*, 2013).

1.5.2. Working memory deficits in apraxia

Working memory (WM) can be conceptualized as a cognitive system responsible for the temporary storage and manipulation of information retrieved from long-term stored representations (Baddeley, 1986). The potential contribution of WM deficits to apraxia was first introduced by Bartolo *et al.* (2003) to account for a dissociation observed in the single case study of patient V.L. with LH damage, who exhibited selective deficits in pantomiming object use that were associated with verbal WM functions. However, the patient did not manifest any concomitant neuropsychological disorders and showed no impairments in other executive functions nor in apraxia tests of imitation and actual object use. The authors postulated that the observed selective impairment in pantomiming object use might arise from a deficit in a distinct cognitive mechanism necessary for producing this specific gesture, which is considered unique due to being both meaningful and novel. Specifically, pantomimes of object use are seldom executed in daily activities, and consequently, have no perfectly matching motor programs stored in long-term memory for immediate retrieval.

In light of this, Bartolo *et al.* (2003) proposed the existence of a WM workspace (as illustrated in *Figure* 1) that integrates incoming perceptual input and learned knowledge pertaining to the object's function (derived from the action semantics system) with stored motor programs on how to use the object (retrieved from the action output system). This convergence of information within the WM system is indispensable in enabling the production of the intricate and novel pantomiming object use gestures. Consequently, Bartolo *et al.'s*

(2003) proposition of a supplementary WM system enriches the dual-route model (Gonzalez Rothi *et al.*, 1991) by highlighting that deficits in pantomiming object use can originate not only from a global malfunction of the indirect (semantic) route but might also result from a specific impairment within the WM system. Namely, patients with an intact semantic route but a damaged WM workspace, such as patient V.L., remain theoretically capable of imitating meaningful gestures and demonstrating proper object use, however, they exhibit pronounced difficulties in pantomiming object use (Motomura and Yamadori, 1994; Fukutake, 2003).

In addition to its crucial role in sub-serving pantomiming object use, WM has been shown to support and modulate actual object use as well as imitation. In the domain of actual object use, the WM system functions as an intermediary buffer that converges manipulation knowledge (i.e., how to use an object) with the intended goal of the to-be-executed action in order to formulate a successful action plan (Randerath *et al.*, 2011*b*). Notably, in situations where multiple potential action plans are viable for a single object, WM resolves the ensuing conflict by determining, and ultimately selecting, the action plan that holds greater relevance to the intended goal (Randerath, 2009). Additionally, the complexity of the intended action can proportionally influence the cognitive load exerted on WM: complex actions entailing a multitude of movements may place a more substantial workload on WM compared to less complicated actions (Randerath *et al.*, 2011*b*). This might provide a potential explanation for the disturbances exhibited by patients with apraxia in executing sequences of meaningless gestures (Weiss *et al.*, 2001) and of object use pantomimes (Weiss *et al.*, 2008). Within the domain of gesture imitation, studies in healthy participants (Rumiati and Tessari, 2002) as well as in patients with lesions to the LH (Toraldo *et al.*, 2001) suggest that WM temporarily retain the observed gesture from its initial perception to its subsequent re-production. Importantly, when imitating meaningful gestures, as opposed to meaningless gestures, the cognitive burden on WM may be alleviated by the accessibility of the gesture’s representation from long-term memory (Toraldo *et al.*, 2001).

Given the proposed role of WM mechanisms in modulating performance across multiple praxis tasks, one might raise the question: could there be a specialized component within WM dedicated for processing motor information such as gestures and object-related actions?

1.5.3. Specialized ‘motor’ component of working memory

Building on Baddley and Hitch's (1974) multicomponent model of working memory (WM) that introduces two modality-specific and independent WM components for processing auditory/semantic content (verbal WM) and visuospatial information (visuospatial WM), recent studies suggest the presence of an additional WM component specialized for processing motor-related information such as static bodily postures or dynamic purposeful actions (for a review see Galvez-Pol *et al.*, 2020). This motor WM subsystem is posited to temporarily encode, retain, and retrieve visually observed (elementary or complex) information related to body movements or actions, and to operate independently of both verbal and visuospatial WM (Bardakan *et al.*, 2022).

Evidence supporting a specialized motor WM subsystem is primarily derived from dual-task experiments. In these studies, during the initial encoding stage, healthy participants were instructed to memorize a series of body-related movements for subsequent replication while performing a secondary task that taps on either verbal, spatial or body-related processing. On the one hand, the implementation of a spatial or verbal secondary task caused minimal to no interference in the retrieval of meaningless body gestures (Smyth *et al.*, 1988; Smyth and

Pendleton, 1990, Woodin and Heil, 1996*a*) or object-related gestures (Rumiati and Tessari, 2002). On the other hand, substantial reductions in the WM capacity for these motor gestures were reported when the concurrent secondary task tapped on sensorimotor processing such as tube pressing (Rumiati and Tessari, 2002), rhythmic finger tapping (Smyth *et al.*, 1988, Woodin and Heil, 1996*a*), or merely observing another individual's body movements (Smyth and Pendleton, 1990). In addition, the 'enactment effect' further emphasizes the notion of a specialized motor WM subsystem, particularly, by showing that actions are better retrieved when actively executed during encoding as opposed to when they are verbally encoded (Russ *et al.*, 2003).

1.6. Interplay between apraxia and neglect

Visual neglect, also referred to as spatial inattention, is characterized by an impairment in the spatial allocation of attention, typically observed after lesions to the right hemisphere (RH; Buxbaum *et al.*, 2004). Intriguingly, visuospatial attention deficits can also occur following damage to the LH (Beis *et al.*, 2004; Becker and Karnath, 2007), especially within the left fronto-temporal areas (Beume *et al.*, 2017), and tend to affect allocentric (object-centered/tool-object relationship) spatial processing more than egocentric (body-centered/hand-object relationship) one (Kleinman *et al.*, 2007). Moreover, deficits in spatial attention following LH lesions are notably less common (observed in approximately 17% of cases), present with milder symptoms and tend to persist for a shorter duration post-stroke compared to those arising from RH lesions (Beume *et al.*, 2017). Notably, studies in RH stroke patients highlighted the potential association of neglect (Goldenberg *et al.*, 2009) as well as impairments in allocentric visuospatial processing (Ubben *et al.*, 2020) with apraxic deficits, particularly those related to imitation. Concurrently, a strong link was reported between apraxia and neglect in patients with a stroke to the LH (Civelek *et al.*, 2015). However, a study in a large cohort of patients with rather chronic LH stroke revealed a clear dissociation between apraxic deficits and spatial attention impairments (Timpert *et al.*, 2015).

1.6.1. Visuospatial deficits in apraxia

Randerath (2009) expanded the praxis model by adding a component responsible for the visuospatial processing of both meaningful and meaningless gestures (see *Figure 1).* This component processes intrinsic spatial relationships between different body parts as well as extrinsic spatial relationships between body parts and external objects, and between objects and recipient targets (Randerath *et al.*, 2011*a*). This visuospatial component plays the pivotal role of reducing the complexity of visual information that must be processed, and thus, akin to the chunking benefits in language learning (Gobet *et al.*, 2001), it serves to alleviate the cognitive load on WM in which the spatial configuration of a gesture must be retained before its execution (Goldenberg and Karnath, 2006; Goldenberg and Spatt, 2009). Notably, a recent study reported that a PCA component representing this visuospatial processing component was associated with lesions to the SMG and the AG of the left hemisphere (Schmidt *et al.*, 2022).

The processing of intrinsic spatial relationships supports the categorization of the different body parts forming a gesture (i.e., body part coding) and the encoding of gestures as spatial relationships among a ‘limited set of discrete body parts’ (Goldenberg, 1996; Goldenberg and Karnath, 2006). It has been posited that apraxic deficits in the imitation of meaningless gestures primarily arise from disrupted sensorimotor processing and integration of these spatial interconnections (e.g., discerning the relative position of the hand to the head or mouth; Randerath *et al.*, 2011*a*). In particular, these visuospatial processing mechanisms sustain the imitation of (meaningless) arm/hand positions (Schwoebel and Coslett, 2005).

Whereas, the imitation of finger configurations, in which there is a higher spatial proximity between the relevant body parts (i.e., fingers), is considered to be supported by representations of structural properties of body parts (Tamè *et al.*, 2017; Schmidt *et al.*, 2022). Thus, the observation of exclusive apraxic deficits in imitating (meaningless) arm/hand positions alongside preserved ability to imitate (meaningless) finger configurations can be attributed to visuospatial deficits in intrinsic coding of spatial relationships between different body parts, while deficits in structural processing can account for the inverse dissociation. These dissociations are also observable at the neuroanatomical level, wherein, deficits in the imitation of hand positions are associated with more parietal lesions (including the IPL) while more frontal lesions (including the IFG) are associated with impairments in the imitation of finger configurations (Goldenberg and Hagmann, 1997; Haaland *et al.*, 2000; Dovern *et al.*, 2011; Kleineberg *et al.*, 2023). It is crucial to note that evidence from patients with a stroke to the RH indicates a notable discrepancy from these observations. Specifically, visuospatial processing deficits (here neglect) were more closely associated with the imitation of finger configurations than with the imitation of hand positions in RH stroke patients (Goldenberg *et al.*, 2009).

Visuospatial processing mechanisms are also essential for extrinsic coding of the relationship between body parts and external objects (e.g., adjusting the hand and fingers' configuration to grasp a hammer), as well as between an object and its target (e.g., estimating the distance to- and location of a nail from a hammer; Goldenberg, 2009, Randerath *et al.*, 2011*a*). These mechanisms might be sub-served by the SMG, which has been associated with the dynamic updating of spatial positions of body parts through online processing of contextually relevant spatial parameters during the execution of object-directed actions (Vingerhoets, 2014; Reynaud *et al.*, 2016). Deficits in these extrinsic visuospatial mechanisms can be manifested during object-related action or pantomime execution in the form of errors in the trajectory of the arm/hand movements, inaccuracies in grasp calibration, misorientation of the object/tool position with respect to the body or the recipient object as well as mislocation errors (Canzano *et al.*, 2016; Scandola *et al.*, 2021).

2. Methodological considerations

2.1. Mixed effects models

The use of mixed-effects models has gained increased popularity in (cognitive) neuroscience research (e.g., Koerner and Zhang, 2017; Overhoff *et al.*, 2021), since this method provides a robust statistical framework that overcomes shortcomings of using traditional multiple regression models as well as standard and repeated ANOVAs. These mixed models - linear mixed effects (LME) models for normally distributed data and generalized linear mixed effects (GLME) models for other distributions - were shown to be robust in the presence of sphericity and homoscedasticity violations, missing data, within-subject variability, as well as covariance between predictor variables (Quené and van den Bergh, 2008; Brown, 2021).

Mixed-effects (or multilevel) models are termed 'mixed' as they incorporate the influence of both fixed and random effects in explaining variability in an outcome measure. Fixed effects, which are also included in conventional regression models, examine population-level trends that are theoretically expected to persist across various measurements, such as the influence of therapy type (categorical predictor) or time-post stroke (continuous predictor) on rehabilitation outcomes. However, these general trends may vary across levels of some grouping factors, such as across individual patients (e.g., some showing rapid improvement than others) or across experimental tasks (e.g., some motor tasks are performed better than others). The inclusion of random effects within a mixed-effects model addresses this problem of interdependence inherent in clustered data by accounting for the individual variability within patients and/or experimental tasks. In particular, random effects constitute clusters of dependent data points that are derived from an identical higher-level group, such as different scores of the same patient. Essentially, random effects permit the model to capture and adjust for individual deviations from the average group trend, termed *random intercepts*, that might otherwise bias the results. In addition, random effects can also include *random slopes*, which account for variabilities in how different factors are affected by a fixed effect. For example, the progression of patients' responses to a therapeutic intervention may vary across time, with some patients showing more rapid improvement than average at the onset of therapy followed by less or no improvement at later stages. For more details on the applications of mixed models see Jiang and Nguyen (2021).

2.2. Lesion-symptom mapping

The lesion method, originating in the mid 19th century, has been pivotal in mapping the brain's cognitive architecture, notably linking certain brain structures to their associated cognitive functions, such as the seminal link between Broca's area and speech production (Broca, 1861). This investigation of the functional brain anatomy is rooted in the foundational premise of localization of function (i.e., distinct cognitive functions are localized within specific brain regions), where damage to a specific brain region would translate into deficits in its associated cognitive tasks (Finger, 2009). While initially investigating evidence from single cases of brain-damaged patients, the lesion method has recently witnessed methodological advancements allowing a shift towards examining the neural correlates of cognitive functions in larger groups of brain-damaged patients (Rorden and Karnath, 2004). Importantly, group-level lesion analyses have optimized the statistical inference of the neural structures underlying specific cognitive deficits by mitigating the limitations caused by individual variability in brain organization and lesion distribution (Robertson *et al.*, 1993).

2.2.1. Lesion subtraction analysis

One relatively simple technique is the ‘lesion subtraction analysis’ which compares the overlap in lesions of a group of brain-lesioned patients exhibiting specific cognitive deficits with the lesion overlap of a comparable group exhibiting no equivalent cognitive deficits (Rorden and Karnath, 2004). This method generates a lesion map that identifies the voxels more frequently lesioned in patients with a specific cognitive deficit than those without it, thus, separating regions closely linked to the cognitive deficit from those generally affected by lesions. This technique serves as a descriptive tool, not permitting any systematic statistical inference, and therefore, is typically applied on small sample sizes that do not provide enough statistical power for voxel-based lesion-symptom mapping (VLSM) to be implemented (see *Section 2.2.2. Voxel-based lesion-symptom mapping (VLSM)*; de Haan and Karnath, 2018). Consequently, when applying this analysis it is important to control for the differing comorbidities often present in brain-lesioned patients by ensuring that the contrasted patient groups are matched for additional neurological impairments (Sperber *et al.*, 2020).

2.2.2. Voxel-based lesion-symptom mapping (VLSM)

Another method that is popular in this field is statistical voxel-based lesion-symptom mapping (VLSM) in which statistical tests are performed at the level of individual voxels to discern the association between an observed cognitive deficit (e.g., operationalized as performance on a task targeting this cognitive function) and the lesion status of each voxel (categorically operationalized as lesioned or non-lesioned; Bates *et al.*, 2003; Karnath *et al.*, 2018). The outcome of a VLSM analysis is a statistical map that quantifies the strength of correlation between the severity of a cognitive deficit and the damage to an individual voxel or clusters of adjacent voxels (Bates *et al.*, 2003). Thus, VLSM allows to statistically infer the contribution of specific brain regions to a cognitive function, specifically, whether a brain region does not contribute (no significant association with performance), contributes (association with mild impairment in performance), or is arguably indispensable (association with severe impairment in performance) to the cognitive function of interest (Fellows *et al.*, 2005).

It is important to note that while VLSM provides a fine-grained examination of lesion correlates at an individual voxel level, the validity of its outcomes necessitates addressing the multiple comparisons problem arising from the multitude of statistical tests performed across the voxels (Mirman *et al.*, 2018). Consequently, it is imperative to apply corrections for multiple comparisons to the VLSM results, such as the parametric false discovery rate (FDR; Benjamini and Hochberg, 1995; Genovese *et al.*, 2002) or Bonferroni corrections. In addition, to enhance the validity and ensure adequate statistical power of VLSM's outcomes, it is crucial to specify a minimum threshold for the lesion overlap, such as voxels that are damaged in an insubstantial portion of the patient group – ideally those affected in only 5% or 10% of cases – should be excluded from the analysis (Sperber and Karnath, 2017).

3. Thesis rationale and objectives

The central objective of this PhD thesis is to provide new insights that enhance the current understanding of the intricate cognitive mechanisms that contribute to the disorder of apraxia following stroke to the left hemisphere (LH), as well as to identify their potential neuroanatomical correlates. The PhD thesis specifically focuses on the contribution of cognitive processes associated with the two, recently added components of the cognitive praxis model (Gonzalez Rothi *et al.*, 1991), namely working memory (Bartolo *et al.*, 2003) and visuospatial processing (Randerath, 2009). An additional, yet pivotal, objective of this PhD thesis is assessing and evaluating the effects of aphasia, commonly concomitant with apraxia, on the investigated cognitive processes. Importantly, the ultimate aspired goal of the presented research is to pave the ground for translating the insights acquired in the reported studies into clinical applications and thereby helping to improve diagnostic tools and rehabilitation methods for patients with apraxia.

To achieve these objectives, the thesis will present and analyze findings from two distinct experimental studies involving patients with apraxia following stroke to the LH. Although the two studies were part of separate projects with different patient samples, methodologies and research aims, they employ (partially) complementary approaches in investigating the contribution of different cognitive mechanisms to apraxia and its behavioral manifestations. The integration and holistic discussion of these two studies within this thesis will provide a comprehensive understanding of the cognitive underpinnings of apraxia that surpasses the individual informative value of each study.

Building on the overarching objectives of the PhD thesis, the following synopsis summaries the research aims and relevance of the two studies:

The first study (see *Section 4. Study I*) investigated the differential impairment of a motor subcomponent of working memory (WM) in LH stroke patients with apraxia. The pivotal aims of this study were assessing the specific contribution of the motor WM component to apraxic deficits and showing that the contribution of the impaired motor WM component is independent from aphasia. To achieve these objectives, the study investigated between-test dissociations among healthy participants, LH stroke patients with apraxia and LH stroke patients without apraxia, utilizing three WM tests targeting distinct cognitive domains: a novel motor WM paradigm for motor WM, the digit span (Wechsler, 1987) for verbal WM and the block span (Corsi, 1972; Schellig, 1997) for visuospatial WM. In addition, this study compared the performance on the motor WM paradigm when the LH stroke patients are grouped according to the severity of their aphasia and correlated the motor WM performance with the performance across several apraxia tests.

The second study (see *Section 5. Study II*) investigated the integrity of visuospatial processing mechanisms in LH stroke patients with apraxia exhibiting two distinct strategies during pantomiming the use of objects, namely, virtual grasping and tracing of photographs of objects. Moreover, the study aimed to identify the neuroanatomical underpinnings of the two strategies during pantomime tasks as well as their association with aphasia severity. To achieve these aims, performance on a comprehensive array of apraxia tests as well as VLSM analyses were used to characterize the cognitive processes and explore the potential neuroanatomical substrates of the two strategies applied in pantomime tasks. Moreover, the degree of aphasia severity was correlated with the degree of reliance on each of the two strategies.

Together, the two studies reinforce the overarching objectives of the thesis, providing complementary insights into the multifaceted cognitive mechanisms and neuroanatomical substrates of apraxia following LH stroke.

Please note that the methods and results presented here are related to the following experimental studies.

Study I:

Barddakan M., Schmidt CC., Hesse DM, Fink GR & Weiss PH (2022). Neuropsychological evidence for a motor working memory subsystem related to apraxia. Journal of Cognitive Neuroscience, 34 (11), 2016-2027. doi: 10.1162/jocn_a_01893

Study II:

Barddakan M., Schmidt CC., Kleineberg NN, Richter MK, Bolte K, Schloss N, Fink GR, & Weiss PH (in internal revision). Different strategies affecting pantomime performance in apraxia: virtual grasping and tracing of object-pictures.

4. Study I

The first study systematically investigated the presence of a distinct motor WM subsystem (see Section 1.5.3) by assessing the capacity of LH stroke patients to encode and recall action-related information. The proposal of a specialized motor WM subsystem, distinct from verbal WM and visuospatial WM, would gain substantial support if a selective deficit of motor WM was identified in clinical populations. Patients with a lesion to the motor-dominant LH, particularly those suffering from apraxia, constitute an ideal clinical population for investigating motor WM deficits.

In this study, the performance of LH stroke patients, both with (LH+) and without (LH-) apraxia, was evaluated using standardized tests tapping on verbal and visuospatial WM, alongside a novel task designed to assess motor WM capacity. The newly devised motor WM test did not involve any active motor components given the prevalence of lower-level motor deficits, such as paresis, in the current cohort of LH stroke patients, which would impede a proficient reproduction of movement stimuli. The motor WM test aligns with similar methodologies used in previous studies examining motor WM functions in both healthy individuals (Wood, 2007) and clinical populations (Vannuscorps and Caramazza, 2016), which employed action recognition paradigms. These paradigms are grounded on the well-established connection between action observation and execution, as well as on the theory that the encoding and recall of body-related movements engages the same somatosensory and motor areas involved in action execution (Lu *et al.*, 2016; Galvez-Pol *et al.*, 2018).

Given the prevalent impairments in motor cognition in LH stroke patients with apraxia, the current study examined the following hypotheses:

(i) LH stroke patients with apraxia would exhibit motor WM deficits that exceed (or are disproportionate to) their verbal and visuospatial WM deficits.

(ii) LH stroke patients with apraxia would exhibit more pronounced motor WM deficits compared to LH stroke patients without apraxia.

(iii) The degree of impairments observed in the motor WM test would correlate with the severity of apraxia.

(iv) The performance on the motor WM test would be independent from concomitant aphasic deficits.

Please note that the methods and results presented here are related to the following published experimental study:

Barddakan M., Schmidt CC., Hesse DM, Fink GR & Weiss PH (2022). Neuropsychological evidence for a motor working memory subsystem related to apraxia. Journal of Cognitive Neuroscience, 34 (11), 2016-2027. doi: 10.1162/jocn_a_01893

4.1. Methods I

4.1.1. Participants

This study examined a group of 52 patients who had experienced a first-ever ischemic stroke in the left hemisphere (LH; age in years: μ_{age} = 55.3, *SD* = 11.6) alongside a group of 25 age-matched healthy control participants (μ_{age} = 55.5, *SD* = 8.4), resulting in a total of 77 participants. The group of LH stroke patients was further divided into patients exhibiting apraxia (LH+; N = 28, μ_{age} = 56.5, *SD* = 12.5) and patients without apraxia (LH-; N = 24, μ_{age} = 53.8, *SD* = 10.5). The lesion locations for the LH, LH+ and LH- groups are illustrated in *Figure* 6 *A*, *B* and *C*, respectively. All the participants were right-handed as assessed by the Edinburg Handedness Questionnaire (EHI; Oldfield, 1971). Informed written consent was provided by all participants. The study adhered to the principles of the Declaration of Helsinki and received approval from the local ethics committee.

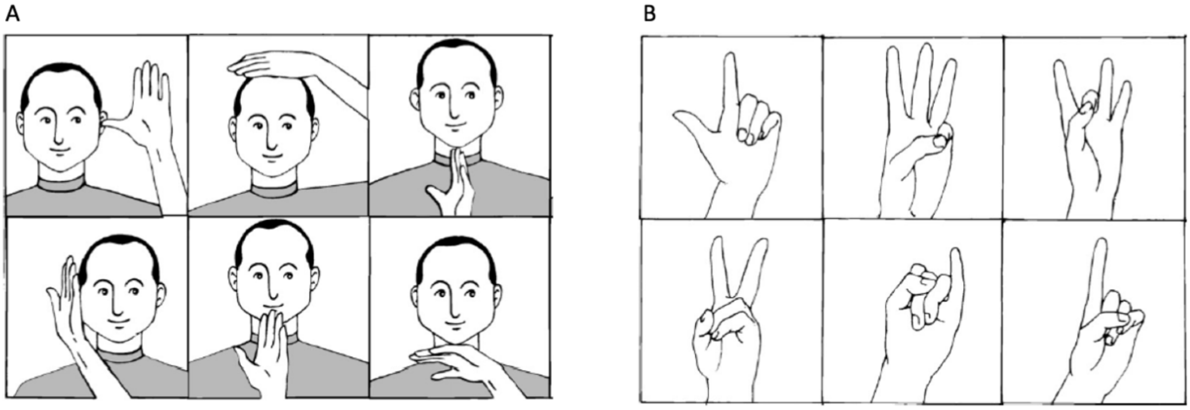
A previous study suggested a large effect size (*d* = 1.42; Cohen, 1988) in performance disparities between patients (here individuals born without upper limbs) and controls in a task related to action working memory (WM; Vannuscorps and Caramazza, 2016). A power analysis conducted using the ‘sjstats’ package (Lüdecke, 2022) in R specified a requirement of a sample size of approximately 56 participants to discern a significant effect (*d* = 0.8, Cohen, 1988) in a linear mixed-effects model that aims for a power of 0.8 and an alpha level of 0.05 (here considering three groups with three measures per group). Therefore, the current cohort of 77 participants is considered sufficient for the study’s primary aim, which is to investigate differences in performance on a motor WM task among LH stroke patients with (LH+) and without (LH-) apraxia as well as control participants that surpasses differences in verbal and visuospatial WM deficiencies.

4.1.2. Neuropsychological assessments

The classification of LH stroke patients into patients with (LH+; N = 28) and without (LH-; N = 24) apraxia was based on clinical assessments of gesture imitation and actual object-use (Dovern *et al.*, 2012). In particular, the Goldenberg's imitation tests of hand positions and finger configurations (Goldenberg, 1996) and an adapted version of the De Renzi test for actual object use (De Renzi *et al.*, 1968) were applied. In the imitation tests by Goldenberg, patients are asked to reproduce ten hand positions (see *Figure 2A*) and ten finger configurations (see *Figure 2B*) demonstrated by the examiner. The maximum score in these tests is 20 points, with scores below 17 points (for finger configurations) and scores below 18 points (for hand positions) indicating apraxic imitation deficits (Goldenberg, 1999). In the object-use assessment, patients are required to demonstrate the use of five single tools/objects (hammer, toothbrush, scissors, eraser, and water gun) and two tool-object pairs (key with a padlock, match with a candle). The maximum achievable score in this test is 32 points, with scores below 30 indicating deficits in actual object use (Ant *et al.*, 2019). Stroke patients scoring below the designated cut-off scores in any of the three apraxia tests (hand imitation, finger imitation, and object-use) were classified as having apraxia. Note that patients used their ipsilesional (i.e., left, non-paretic) hand in all apraxia tests.

In addition, the Token test was administered to assess the presence of deficits in language comprehension in the group of LH stroke patients with (LH+) and without (LH-) apraxia (De Renzi and Vignolo, 1962). This test is a valid assessment of aphasia following LH stroke irrespective of the patient's clinical type of aphasia (Orgass and Poeck, 1966). The Token test consists of a set of tokens varying in geometric form (circle or rectangle), dimension (small or big), and color (red, green, yellow, black, or white). The participants are instructed to manipulate a token (or a combination of tokens) following verbal instructions by the examiner. The tasks range from simple commands, such as ‘pick up the red rectangle’ to more complex ones such as ‘put the red circle under the red rectangle’. It is important to note that the Token test primarily assesses deficits in language comprehension, particularly in understanding lexical meaning, that is, identifying which object corresponds to a given word. Accordingly, the Token test is not structured to differentiate between semantic or phonological aphasic impairments. Based on the Token test scores, LH stroke patients can be re-grouped into four groups of differing aphasia severity as follows: no or minimal aphasia (T-scores ranging from 73 to 63), mild aphasia (T-scores ranging from 62 to 54), moderate aphasia (T-scores ranging from 53 to 44), and severe aphasia (T-scores ranging from 43 to 29). For a similar method of patients’ re-classification see Achilles *et al.* (2016).

Figure 2. Example stimuli from Goldenberg's gesture imitation tests



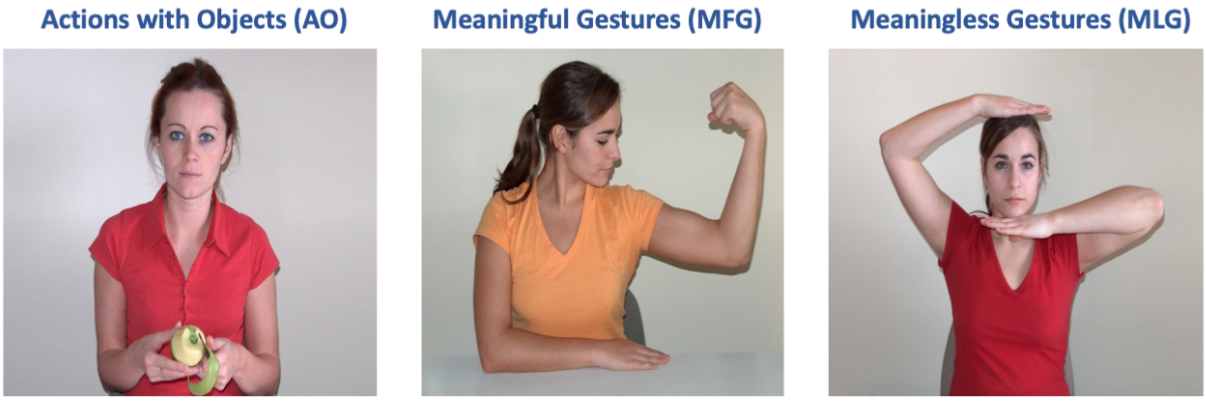
Example stimuli from Goldenberg's tests of imitating ***(A)*** *hand positions and* ***(B)*** *finger configurations. The assessment for hand position imitation included various hand placements relative to the head, with the fingers maintaining an invariant configuration, while the assessment of imitating finger configurations consisted of disparate finger configurations, without regard to the hand’s position relative to the body. Note that the figure depicts a subset of six gestures for each of Goldenberg’s gesture imitation tests, out of the total of ten (for each test) stimuli used in the assessment. The figure is adapted from* Goldenberg *et al.* (2001).

4.1.3. Testing procedure

The assessment of participants included a forward digit span test (DS) and a block tapping test (BS), which serve as standardized instruments for measuring verbal and visuospatial WM, respectively, alongside a newly devised motor WM task. These tests were administered in randomized order for each participant.

For the assessment of verbal WM, the participants were administered the forward digit span test (DS), sourced from the Wechsler Memory Scale – Revised (WMS-R, Wechsler, 1987). The DS test entailed the participant's correct recall of a sequence of digits presented orally by the examiner. For the stroke patients exhibiting deficits in language comprehension (as measured using the Token test), the digits' sequence was displayed visually. Instead of reproducing the sequence verbally, these patients indicated their responses by pointing to digits presented on cards using their ipsilesional hand. The length of the digits' sequence was incrementally increased by one digit, and the digit span (DS) was defined as the longest sequence of digits accurately recalled. For the assessment of visuospatial WM, the participants were tested using the German version of the Corsi block-tapping test (Corsi, 1972) as outlined in the manual (Schellig, 1997), with an alteration for the LH stroke patients who were instructed to use their non-dominant ipsilesional left arm for the task. The task entailed the participant's repetition of a block sequence in the exact serial order as demonstrated by the examiner. For this, participants had to tap consecutively on the respective blocks of a nine-block asymmetric grid. The block sequence's complexity (i.e., length) was incrementally increased by one block, and the block span (BS) was defined as the longest sequence of blocks accurately replicated by the participant.

Figure 3. Example stimuli of the novel motor working memory task


Actions with Objects (AO) **Meaningful Gestures (MFG)** **Meaningless Gestures (MLG)**

The figure illustrates sample images from the motor WM task, which consisted of action-related pictures grouped into three categories: actions with objects (AO; exemplified here by the action of peeling an apple), meaningful gestures (MFG; exemplified here by demonstrating strength through flexing the biceps), meaningless gestures (MLG). It is important to note that consistency was maintained within each category of actions concerning the actress depicting the action as well as her clothing. Specifically, the same actress depicted the actions within the AO subtest, while another actress depicted the actions within the MFG (with an orange T-shirt) and MLG (with a red T-shirt) subtests. In the motor WM task, participants were shown a series of pictures from each subtest and were instructed to recall the sequence of pictures correctly from a set of nine images belonging to the same subtest. With each correct answer, the sequence length of the presented pictures incrementally increased by one additional picture on each successive trial; starting with a pair of two pictures and extending to a sequence of maximum nine pictures. The task concluded if the participant made two consecutive errors in recalling a given sequence of the same subtest.

For the novel motor WM test, static images were shown to the participants, depicting three distinct classes of action-related stimuli performed by two actresses seated at a table, namely: (a) actions with objects (AO), (b) meaningful gestures without objects (MFG), and (c) meaningless gestures without objects (MLG). The three motor WM subtests were administered in a randomized order for each participant. The AO subtest included the following nine items: opening a bottle, dealing out cards, filing a sheet of paper, polishing a shoe, peeling an apple, lighting a candle, hammering a nail into a woodblock, sharpening a pencil and applying toothpaste onto a toothbrush. The MFG subtest consisted of nine items subdivided into three meaningful finger movements (victory sign, OK sign, and luring someone), three meaningful unimanual hand actions (showing physical power by flexing the biceps' muscles, threatening another with one's fist, and boxing), and three meaningful bimanual hand actions (praying, clapping, and lifting the hands up). The MLG subtest was composed of a similar arrangement of nine meaningless gestures implemented from those devised in Goldenberg's (1999) gesture imitation tests. See *Figure 3* for an illustrative stimulus from each subtest category.

Similar to the administration procedures of the DS and BS tests, participants were initially presented with a pair of two pictures from one of the motor WM subtests (AO, MFG or MLG). Each picture was displayed on a computer screen for a duration of three seconds with a brief one-second interval between consecutive pictures. Note that the display time of the action pictures was relatively longer compared to the one used in the DS and BS tests (here a display duration of one second) in order to ensure adequate processing time of the respective picture. This duration is in accordance with previous studies investigating motor WM in which stimuli, both static and dynamic, were displayed for timeframes ranging from three seconds (Vicary *et al.*, 2014; Vannuscorps and Caramazza, 2016) up to four seconds (Lu *et al.*, 2016). After the presentation of a sequence of action pictures, the participants were prompted to recall the presented sequence by selecting action pictures in the correct order from a grid of nine pictures, which consisted of all items corresponding to the respective motor WM subtest. This grid of nine pictures was placed on a table adjacent to the computer, spatially arranged in a 3 x 3 matrix, and revealed immediately following the presentation of the last picture of a sequence. Complementarily to the response method applied in the BS test, participants were required to recall the sequences by pointing to the correct action pictures in their correct order of presentation using their left (ipsilesional) hand. A correct recall (i.e., correct action pictures and order) prompted the presentation of a longer sequence of three pictures, followed by one of four pictures etc. An incorrect (initial) response (i.e., wrong action pictures or incorrect order) led to a second trial with the same sequence length but using different pictures of the same motor WM subtest. A repeated error resulted in the conclusion of the respective motor WM subtest. The motor WM span was defined as the longest sequence of action pictures correctly recalled by the participant for each motor WM subtest.

4.1.4. Statistical analyses of behavioral data

The performance of each participant on the motor WM task was quantified through a WM composite score (mWM) that constituted the mean of the span scores obtained across the three motor WM subtests. Note that this was achievable given the high inter-correlation observed among these motor WM subtests within the LH stroke patients. In particular, scores on the 'actions with objects' (AO) subtest were positively correlated with scores on the 'meaningless gestures' (MLG) and the 'meaningful gestures' (MFG) subtests in both patients with apraxia (LH+; $r = 0.75$, $p < .001$ and $r = 0.71$, $p < .001$, respectively) and patients without apraxia (LH-; $r = 0.53$, $p < .05$ and $r = 0.53$, $p < .01$, respectively). In addition, the correlation between the MLG and MFG subtests was significantly positive for both LH+ ($r = 0.48$, $p < .05$) and LH- ($r = 0.58$, $p < .05$) groups. While the age-matched controls exhibited marginally significant correlations between the AO and MFG subtests ($r = 0.35$, $p = .05$) and between the MFG and MLG subtests ($r = 0.52$, $p = .05$).

Statistical analysis of the data was conducted using R software (version 4.0.5). Linear mixed-effects models were performed through the lme4 package (version 1.1-27.1; Bates *et al.*, 2015) in order to discern putative performance differences between the age-matched healthy controls and the LH stroke patients, with (LH+) and without (LH-) apraxia, across all administered motor WM subtests. The selection of the optimal linear mixed-effects models was guided by the 'performance' package in R (Lüdecke *et al.*, 2021), which was implemented to compare and evaluate the performance efficiency of various models. Thus, the reported models are those that exhibited the best fit of the data, based on the Bayesian Information Criterion (BIC) as well as the Akaike Information Criterion (AIC), in comparison to other models. The significant effects are reported using F statistics with degrees of freedom determined via Satterthwaite's approximation (Hrong-Tai Fai and Cornelius, 1996). Significant results were further evaluated by post-hoc pairwise comparisons between the factor levels, using paired samples t-tests to the mixed-effects models (implemented via the R package 'emmeans'; (Russell, 2021), adjusted for multiple comparisons using the Bonferroni method with a significance threshold of $p < .05$.

All mixed models included a between-subject factor 'GROUP' with three levels: age-matched controls, apraxic patients (LH+), and non-apraxic patients (LH-), as well as the random factor 'PATIENT' (with random intercepts). The models included either a within-subject factor of 'PRINCIPAL WM' or of 'MOTOR WM' to assess group differences in performance across the principal WM tasks (digit span (DS), block span (BS), and motor WM composite score (mWM)) and the motor WM subtests (actions with objects (AO), meaningful gestures (MFG) and meaningless gestures (MLG)), respectively. In the latter models tackling the motor WM subtests, the BS and DS scores were incorporated as covariates to account for potential influences of visuospatial and verbal WM deficits, respectively. A separate complementary model was conducted on a sample of 35 LH stroke patients, consisting of 18 LH+ and 17 LH- patients, for whom the lesion maps were available (see *Figure 6),* in order to explore the potential effects of age as well as stroke severity (here operationalized by lesion volume in voxels) on WM performance. In particular, the model examined differences in performance between the LH+ patients and LH- patients on the ‘PRINCIPAL WM’ factor (DS, BS, and mWM), while controlling for age and lesion volume (that is, the number of affected voxels).

Given the frequent co-occurrence of language and praxis impairments following LH stroke, the influence of aphasia on WM performance was also assessed. For that purpose, the LH stroke patients were sorted, based on their T-scores on the Token test, into four groups reflecting varying degrees of aphasia severity (for a similar method of patients’ re-classification see Achilles *et al.*, 2016). Complementary to investigating the influence of apraxia on WM performance, two linear mixed-effects models were conducted using the between-subjects ‘APHASIA GROUP’ factor (no/minimal, mild, moderate and severe) to investigate the influence of aphasia on performance in the ‘PRINCIPAL WM’ tasks (BS, DS, mWM) and the ‘MOTOR WM’ subtests (AO, MFG, MLG). The latter model controlled for the potential effects of visuospatial and verbal WM deficits by including the BS and DS as covariates, respectively. It is important to note that in these analyses, the age-matched healthy controls were excluded. However, the patients classified with no/minimal aphasia served as a control group in these analyses, specifically, given their comparable performance to that of healthy controls on the Token test.

A further investigation into the combined influence of apraxia and aphasia on WM performance was conducted using an additional pair of linear mixed-effects models. For these models, standardized z-scores were computed from the raw apraxia test scores of the LH patients in order to normalize the different scoring scales. Afterward, an overall apraxia severity score was computed as the mean of the z-scores across the three apraxia tests (Goldenberg's hand and finger imitation tests, and actual object use), and was included as a covariate in the mixed models investigating differences in performance between LH patients with differing aphasia severity (no/minimal, mild, moderate, and severe) across the main WM tasks (BS, DS, and mWM) and the motor WM subtests (AO, MFG, and MLG). Note that these two models also incorporated the BS and DS scores as covariates.

Finally, six multiple linear regression models were conducted to predict the performance of the LH stroke patients on each of the three apraxia assessments: Goldenberg's test of imitating hand positions, Goldenberg's test of imitating finger configurations, and actual object use. Three models used the principal WM tests (BS, DS, and mWM) as predictors, while another three models used the motor WM subtests (AO, MFG, MLG) as predictors. These regression analyses included a total of 39 LH stroke patients (22 LH+ and 17 LH-) with complete scores available across all the WM tests. Note that there were no significant differences between these sub-samples of patients with and without apraxia regarding age (median age in years and interquartile range, LH+: $M_{\text{age}} = 59$, $IQR = 48 – 64$; LH-: $M_{\text{age}} = 52$, $IQR = 50 – 58$) and time-post stroke in days (LH+: $M_{\text{TPS}} = 487.5$, $IQR = 3 – 2581$; LH-: $M_{\text{TPS}} = 619$, $IQR = 6 – 2563$). As a result of technical and organizational issues, the data included missing values of 12 patients (five LH+ and seven LH-) on the MLG subtest and of one patient on the DS task. Therefore, these 13 patients were excluded from the current regression analyses, which necessitate a complete data set for each patient. With the available data of the 39 LH stroke patients, the implementation of multiple linear regression analyses using three covariates at an alpha of .05 and a power of 80% can detect significant outcomes with a minimum effect size of $f^2 = 0.31$, deemed as a large effect applying Cohen's (1988) standards.

4.1.5. Lesion delineation and voxel-based lesion symptom mapping (VLSM)

Lesion mapping was performed using the clinical MRI (N = 31) or CT (N = 4) scans that were available for the LH stroke patients with apraxia (LH+, 18 of 28; 64.3%) and the LH stroke patients without apraxia (LH-, 17 of 24; 70.8%). Using the free MRIcron software (Rorden and Brett, 2000) all lesions were manually delineated by M.D.H. onto the axial slices of the ch2-template in increments of 5 mm in MNI space by matching or closely matching axial slices of the individual patient's CT or MRI scan. Note that the examiner was blind to the neuropsychological test scores, including the patient's group assignment (i.e., LH+ or LH-) during lesion delineation.

Statistical lesion analysis was performed by means of voxel-based lesion-symptom mapping (VLSM, Bates et al., 2003) using the non-parametric mapping (NPM) software freely distributed with MRIcron (Version 30/04/2016, https://nitrc.org/projects/mricron). In particular, three VLSM analyses were conducted for all LH stroke patients with available lesion maps and complete scores on each of the three motor WM subtasks: actions with objects (AO; N = 35), meaningful gestures (MFG; N = 35), and meaningless gestures (N = 29; 15 LH- and 14 LH+). An additional VLSM was conducted for all LH stroke patients with available lesion maps and motor WM composite score (N = 29; 15 LH- and 14 LH+) to determine the association between lesioned voxels and motor WM functions (as operationalized by the motor WM composite score). Voxel-wise t-test statistics were performed on the scores of the motor WM subtasks and the motor WM composite score, with groups categorized according to the presence or absence of damage in each voxel. Only voxels that were lesioned in at least 5% of the patients (i.e., two patients) were included in the VLSM analysis. The statistical threshold for significant voxels was set to *p* < .05, corrected for multiple comparisons using False

Discovery Rate (FDR) correction (Benjamini and Hochberg, 1995). We report the voxel's maximum Z-value and corresponding MNI coordinates of the significant clusters. The brain regions associated with the significant voxels were identified using the Johns Hopkins University (JHU) atlas (Faria *et al.*, 2012) provided by MRIcron.

4.2. Results I

4.2.1. Clinical and neuropsychological assessments

Age was comparable between the three groups of healthy controls (median age in years and interquartile range: M_{age} = 54, *IQR = 51 – 61)*, LH+ patients (M_{age} = 59, *IQR = 47.5 – 64.5*) and LH- patients (M_{age} = 53, *IQR = 48.5 - 62*). In addition, age was negatively correlated with performance on the block span task, which evaluated visuospatial WM, across all three participant groups: healthy controls (r = -0.43, p = .03), patients in the LH- group (r = -0.65, p < .001) and patients in the LH+ group (r = -0.48, p = .009).

The time interval post-stroke (TPS) was comparable between the LH+ group (median TPS in days and interquartile range: M_{TPS} = 335, *IQR* = 3 – 2581) and the LH- group (M_{TPS} = 415.5, *IQR* = 4 – 2563). In the LH stroke patients (N = 44 out of 52), there was a negative correlation between the TPS and scores on the digit span (DS) task (correlation coefficient: r = -0.35, p = .02), indicating a decline in verbal WM with a longer TPS. According to a recent systematic review, stroke patients exhibit more pronounced deficits in WM functions, both verbal and visuospatial, in the chronic phase as opposed to the subacute phase post-stroke when compared to healthy controls (Lugtmeijer *et al.*, 2021). In line with the categorization by Lugtmeijer *et al.* (2021), the LH stroke patients were divided into 'subacute' (N = 14) and 'chronic' (N = 30) groups based on whether they were assessed within 90 days or after 90 days post-stroke, respectively. A correlation analysis indicated a slight, albeit non-significant, positive correlation in the 'subacute' group between the DS scores and TPS (r = 0.11, p = .07, TPS < 90 days). Conversely, in the 'chronic' group, a negative and non-significant correlation (r = -0.21, p = .26, TPS > 90 days) was observed between the two measures. These findings, although insignificant, imply that the overall significant negative correlation between the DS score and TPS in the entire LH stroke patients might be primarily influenced by the patients in the chronic phase post-stroke. Note that no significant correlations were found between TPS and scores in other WM tests.

Regarding the distribution of praxis deficits in the LH+ group (N = 28), almost all of the apraxic patients (27/28, 96.5%) exhibited apraxic deficits in Goldenberg's test of imitating hand postures, while almost half of the apraxic patients (15/28, 53.6%) demonstrated additional impairments in Goldenberg's test of imitating finger configurations. In addition, approximately one-third of the apraxic patients (10/24, 41.6%) showed deficits in the De Renzi test for actual object use. In line with clinical observations, the LH+ group exhibited significant deficits (median T-score and interquartile range: $M_{\text{T-score}}$ = 46, *IQR = 43 – 50*) in language comprehension (as assessed by the Token test) compared to the LH- group ($M_{\text{T-score}}$ = 58.5, *IQR = 50.75 – 73*). Furthermore, among the 42 LH stroke patients (22 LH+ and 20 LH-) for whom an assessment with the Token test was available, the re-classification of patients were as follows: ten showed no or minimal aphasia (1 LH+ and 9 LH-; T-scores ranging from 73 to 63), eight showed mild aphasia (3 LH+ and 5 LH-; T-scores ranging from 62 to 54), 17 showed moderate aphasia (11 LH+ and 6 LH-; T-scores ranging from 53 to 44), and seven showed severe aphasia (7 LH+; T-scores ranging from 43 to 29).

4.2.2. Effects of apraxia on the principal WM tests

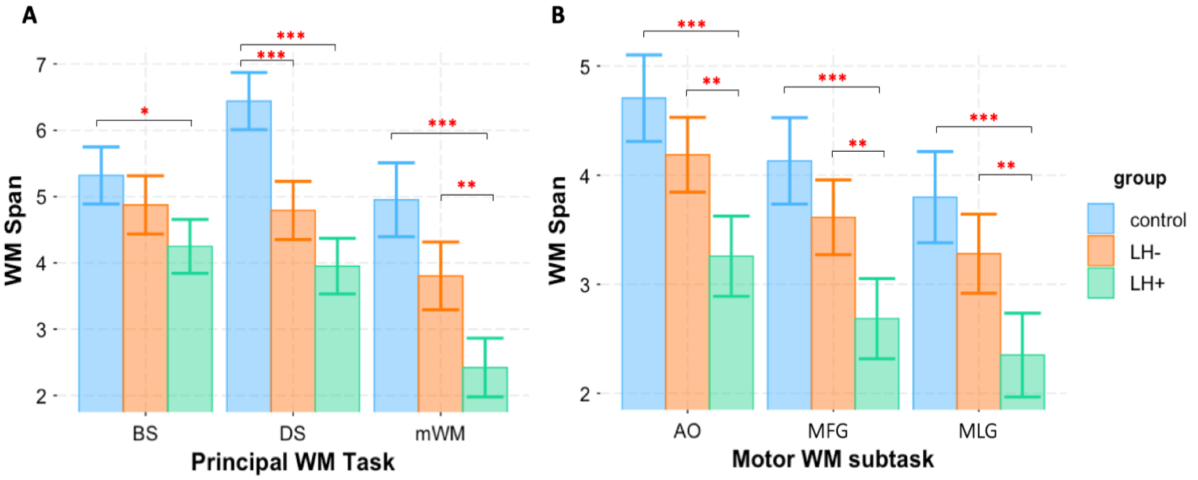
The linear mixed-effects model, which assessed performance differences between the groups of healthy controls, patients with (LH+) and without (LH-) apraxia across the principal WM tasks (digit span (DS), block span (BS), and motor WM composite score (mWM)), indicated a significant GROUP effect [$F_{(2,70.39)}$ = 39.6, p < .001], a significant PRINCIPAL WM effect [$F_{(2,125.98)}$ = 33.05, p < .001], as well as a significant interaction between GROUP and

PRINCIPAL WM [$F_{(4,125.78)} = 5.76$, $p < .001$]. Specifically, the healthy controls outperformed the LH+ patients across all principal WM tests: the DS ($p < .001$), the BS ($p < .05$) and the motor WM ($p < .001$). Moreover, all three groups exhibited lower scores on the motor WM test in comparison to the DS test, that is, the controls ($\mu_{DS} = 6.44$ vs. $\mu_{mWM} = 4.88$, $p < .001$), the LH- patients ($\mu_{DS} = 4.79$ vs. $\mu_{mWM} = 3.75$, $p < .01$), and the LH+ patients ($\mu_{DS} = 3.81$ vs. $\mu_{mWM} = 2.46$, $p < .001$). Notably, pairwise comparisons of between-groups differences revealed that the healthy controls scored better than the LH- patients on the DS test ($p < .001$), while the LH+ patients scored worse on the motor WM test compared to the LH- patients ($p < .01$). Further pairwise comparisons within-groups indicated better scores on the DS compared to the BS test in the healthy controls group ($\mu_{DS} = 6.44$ vs. $\mu_{BS} = 5.32$, $p = .001$). Moreover, only the LH+ patients ($\mu_{mWM} = 2.46$ vs. $\mu_{BS} = 4.25$, $p < .001$) and the LH- patients ($\mu_{mWM} = 3.75$ vs. $\mu_{BS} = 4.86$, $p = .01$) exhibited lower scores on the motor WM test compared to the BS test, a pattern not observed in the healthy controls (see *Figure 4A*).

To corroborate the observation of non-significant differences between the LH+ patients and the LH- patients on both the BS and DS tests, a Bayesian analysis was used, yielding Bayes factors (BF) for each group comparison. Partially aligned with the Frequentist results, the Bayesian analysis revealed anecdotal (i.e., marginal) evidence for no differences in performance between the LH- and the LH+ patients on the BS test ($BF_{10} = 0.86$), as well as anecdotal evidence for a difference in performance between the LH- and the LH+ patients on the DS test ($BF_{10} = 1.94$). Note that for between-groups differences a BF_{10} with a range from 1/3 to 1 indicates anecdotal evidence supporting the null hypothesis, likewise, a BF_{10} with a range from 1 to 3 indicates anecdotal evidence supporting the alternative hypothesis (Raftery, 1995).

In addition, in the specific analysis of the 35 LH stroke patients with available lesion maps, neither age nor lesion size (here used as a measure of stroke severity) showed significant effects. Aligning with the results of the linear mixed-effects model of the entire patient sample, no significant performance differences were observed between the LH+ and LH- patients on both the DS and BS tests. Whereas, a significant decline in performance on the motor WM test was found in the LH+ patients compared to the LH- patients (*p* < .04), suggesting that the observed performance deficits in the LH+ patients on the motor WM test persists even when controlling for age and stroke severity.

Figure 4. Effects of apraxia on working memory performance.



*Panel **A** illustrates the effects of apraxia on the principal WM performance, that is, comparisons between the BS, DS and motor WM (operationalized by the mWM composite score) tests. The LH+ patients performed significantly worse than the age-matched controls across the three main WM tests. However, the LH- patients scored significantly lower only on the DS test compared to the controls. Notably, the LH+ patients exhibited more pronounced impairments on the motor WM test compared to the LH- patients; while the performance of the two groups on the BS and DS tests revealed no significant differences. Panel **B** illustrates the effects of apraxia on the motor WM performance, that is, comparisons across the AO, MFG and MLG subtasks. The LH+ patients performed significantly worse than the LH- patients and controls across all three motor WM subtasks. Whereas, no significant differences in performance were observed between the LH- patients and controls. Note that panel **B** depicts the adjusted mean span values after accounting for the scores on the DS and BS tests. Error bars indicate confidence intervals of 95%, and the asterisks indicate the level of significance of the post-hoc tests (Bonferroni-corrected at * p < .05, ** p < .01, *** p < .001).*

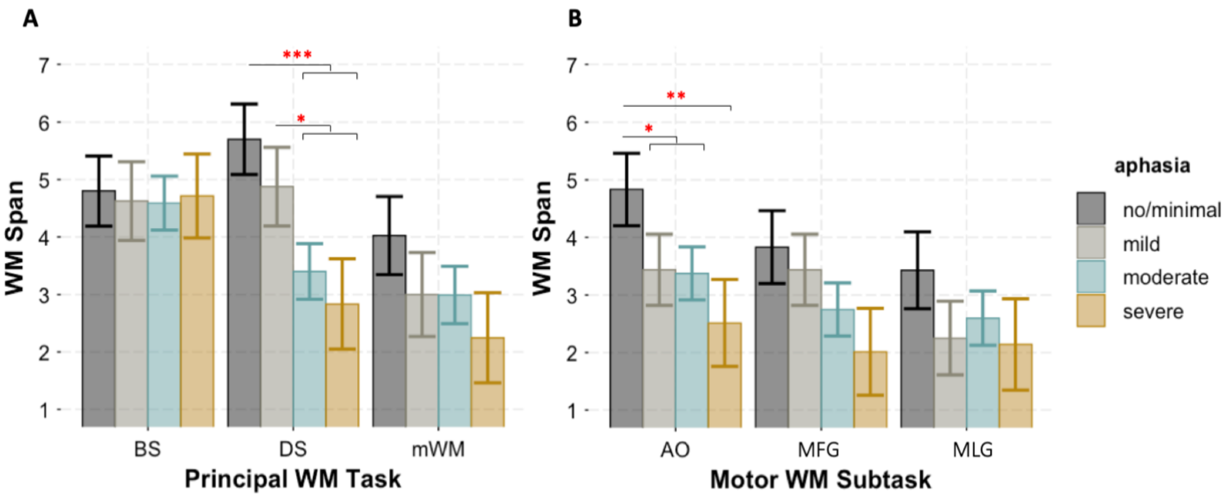
4.2.3. Effects of apraxia on the motor WM subtests

The linear mixed-effects model, which assessed performance differences between the groups of healthy controls, patients with (LH+) and without (LH-) apraxia across the motor WM subtests (actions with objects (AO), meaningful gestures (MFG) and meaningless gestures (MLG)) while adjusting for deficits in verbal WM (DS) and visuospatial WM (BS), indicated a significant GROUP effect [$F_{(2,67.66)} = 13.38$, $p < .001$] and a significant MOTOR WM effect [$F_{(2,127.57)} = 26.67$, $p < .001$], but no interaction was observed between GROUP and MOTOR WM. Subsequent pairwise comparisons examining between-groups differences revealed a lower performance in the LH+ patients across all the motor WM subtests in comparison to the healthy controls ($p < .001$) as well as the LH- patients ($p < .01$). In contrast, no significant differences in performance were noted between the controls and the LH- patients on all motor WM subtests. In addition, pairwise comparisons examining within-groups differences revealed better scores on the AO subtest compared to the MFG ($p < .001$) and the MLG ($p < .001$) subtests across all three groups (see *Figure 4B*).

4.2.4. Effects of aphasia on the principal WM tests

The linear mixed-effects model, which assessed performance differences between the groups of the LH stroke patients with no/minimal, mild, moderate and severe aphasia across the principal WM tasks (digit span (DS), block span (BS), and motor WM composite score (mWM)), indicated a significant APHASIA GROUP effect [$F_{(3,36.07)} = 8.59$, $p < .001$], a significant PRINCIPAL WM effect [$F_{(2,69.11)} = 32.14$, $p < .001$], as well as a significant interaction between APHASIA GROUP and PRINCIPAL WM [$F_{(6,68.99)} = 5.66$, $p < .001$]. The interaction indicated disparities in performance on the DS task by the different aphasia groups, while no significant differences in performance were observed in the BS and motor WM tests. Notably, both patients with no/minimal aphasia (*p* < .001) and patients with mild aphasia (*p* < .05) outperformed those with moderate and severe aphasia in the DS test. Subsequent pairwise comparisons examining within-group differences revealed significantly worse scores on the motor WM task compared to the scores on the DS test in LH stroke patients with no/minimal (*p* < .01) and mild aphasia (*p* < .01), and also compared to the scores on the BS test in LH stroke patients with moderate (*p* < .01) and severe (*p* < .01) aphasia. Moreover, patients with moderate (*p* = .09, here marginally significant) and severe (*p* < .05) aphasia exhibited better scores on the BS test compared to the DS test (see *Figure 5A*).

Figure 5. Effects of aphasia on working memory performance.



Panel ***A*** *illustrates the effects of aphasia on the principal WM performance, that is, comparisons between the BS, DS and motor WM (operationalized by the mWM composite score) tests. LH stroke patients showing no/minimal and mild aphasia scored significantly higher in the DS test in comparison to those LH stroke patients with moderate and severe aphasia. However, no significant performance differences were observed in the BS and motor WM test across the four aphasia groups. Panel* ***B*** *illustrates the effects of aphasia on the motor WM performance, that is, comparisons between the AO, MFG and MLG subtests. LH stroke patients with no/minimal aphasia scored differentially higher on the AO subtask in comparison to the groups of LH stroke patients with mild, moderate and severe aphasia. In contrast, no significant performance differences were detected in the MFG and MLG subtests across the four aphasia groups. Note that panel* ***B*** *depicts the adjusted mean span values after accounting for the scores on the DS and BS tests. Error bars indicate confidence intervals of 95%, and the asterisks indicate the level of significance of the post-hoc tests (Bonferroni-corrected at * p < .05, ** p < .01, *** p < .001).*

In addition, the linear mixed-effect model, which examined the influence of aphasia on the principal WM tests while accounting for concurrent apraxic deficits, corroborated the significant interaction observed between APHASIA GROUP and PRINCIPAL WM [$F_{(6,68.89)} = 5.47$, $p < .001$; see *Appendix 1A*]. In accordance with the previous analysis, this interaction effect was predominantly attributable to differences in performance in the DS test among the different aphasia groups. Consistent with the initial findings, the groups differentiated by aphasia severity did not exhibit significant disparities in their BS and motor WM scores. Furthermore, coherent with the previous analysis, patients with minimal aphasia outperformed patients with moderate and severe aphasia in the DS test ($p < .001$). However, the performance differences between patients with mild aphasia and those with moderate and severe aphasia was not significant in this subsequent analysis.

4.2.5. Effects of aphasia on the motor WM subtests

The linear mixed-effects model, which assessed performance differences between the groups of the LH stroke patients with no/minimal, mild, moderate and severe aphasia across the motor WM subtests (actions with objects (AO), meaningful gestures (MFG) and meaningless gestures (MLG)) while adjusting for deficits in verbal WM (DS) and visuospatial WM (BS), indicated a significant APHASIA GROUP effect [$F_{(3,33.55)} = 4.94$, $p < .01$], a significant MOTOR WM effect [$F_{(2,66.55)} = 21.82$, $p < .001$], as well as a significant interaction between APHASIA GROUP and MOTOR WM [$F_{(6,66.5)} = 2.73$, $p = .01$]. The group effect highlighted higher scores for patients with no/minimal aphasia across all three motor WM subtasks compared to patients with severe aphasia. Furthermore, the interaction effect indicated disparities in performance on the AO subtest by the different aphasia groups, while no significant differences in performance were observed in the MFG and MLG subtests. In particular, the patients with minimal aphasia exhibited higher scores on the AO subtest compared to those with mild ($p < .05$), moderate ($p < .05$) and severe aphasia ($p < .01$; see *Figure 5B*).

In contrast to the previous analysis, the linear mixed-effect model, which examined the influence of aphasia on the motor WM subtests while accounting for concurrent apraxic deficits, indicated no significant performance disparities among the aphasia severity groups across all motor WM subtests (see *Appendix 1B*). However, a marginally significant performance difference was noted in the AO subtest between patients with minimal aphasia and those with severe aphasia ($p = .08$).

4.2.6. Prediction of scores on clinical tests of apraxia using the principal WM tests

The regression analyses (see *Appendix 2, panels A, B and C*), which aimed at predicting the performance in Goldenberg's test of imitating hand positions, revealed that the three principal WM tests (DS, BS and motor WM test) accounted for 28% of the variance (adjusted $R^2 = .28$, $F_{(3,35)} = 5.8$, $p < .005$). Notably, the mWM composite score emerged as the sole significant predictor for the scores in the hand (position) imitation test ($\beta = 1.48$, $t(35) = 2.38$, $p < .05$). Likewise, these three principal WM tests accounted for 29% of the variance in Goldenberg's test of imitating finger configurations (adjusted $R^2 = .29$, $F_{(3,35)} = 6.06$, $p < .005$), with the mWM composite score ($\beta = 1.25$, $t(35) = 2.03$, $p < .05$) and, to a lesser extent, the BS score predicting performance ($\beta = 1.19$, $t(35) = 1.8$, $p = .08$). Furthermore, the combined influence of the principal WM tests was more pronounced in the object use (OU) test, explaining 49% of the variance (adjusted $R^2 = .49$, $F_{(3,35)} = 13.06$, $p < .001$), wherein, the BS scores ($\beta = 1.71$, $t(35) = 3.45$, $p < .005$) as well as the DS scores ($\beta = 0.63$, $t(35) = 2.51$, $p < .05$) significantly predicted performance on the OU test.

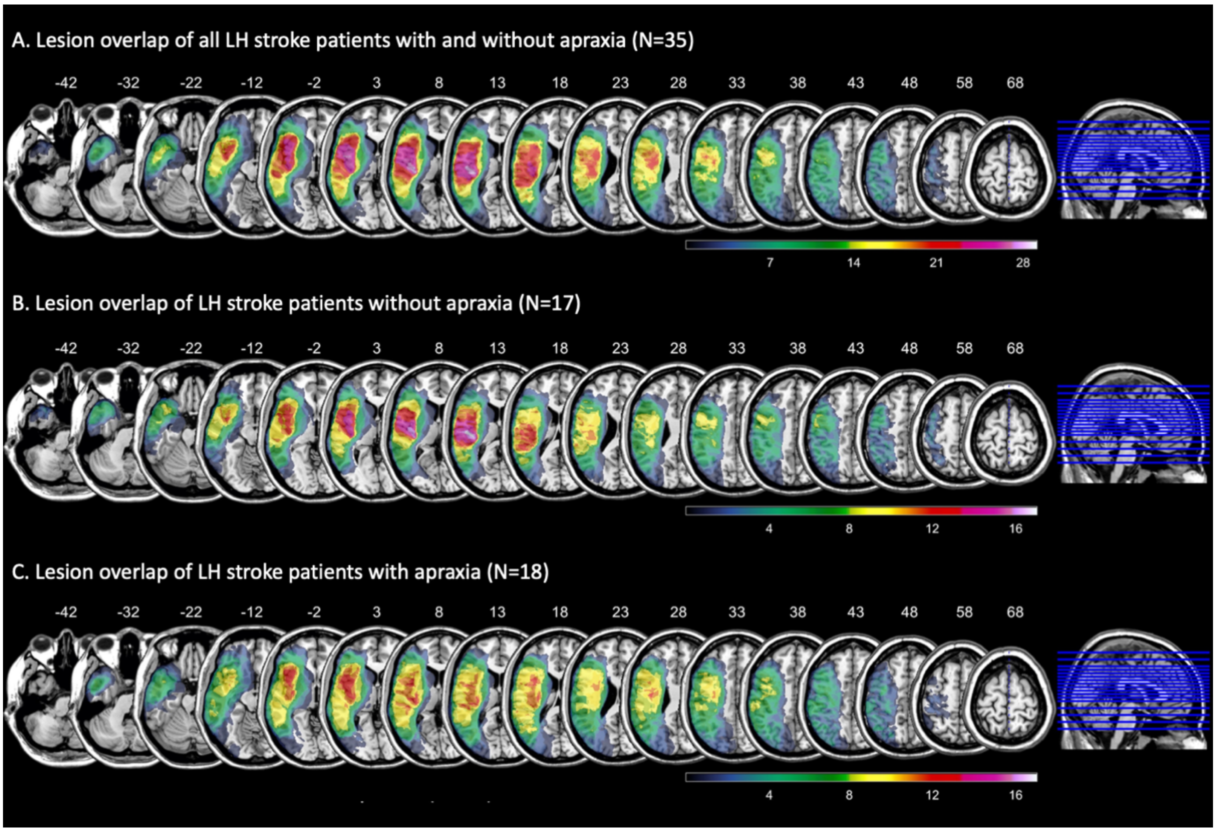
4.2.7. Prediction of scores on clinical tests of apraxia using the motor WM subtests

The regression models (see *Appendix 2, panels D, E and F*), which aimed at predicting performance on Goldenberg's gesture imitation tests revealed that the three motor WM subtests (AO, MFG and MLG) explained a significant portion of the variance. Specifically, the three subtests accounted for 32% of the variance in the hand (position) imitation test (adjusted $R^2 = .32$, $F_{(3,36)} = 7.03$, $p < .001$) and 26% of the variance in the finger (configuration) imitation test (adjusted $R^2 = .26$, $F_{(3,36)} = 5.52$, $p < .005$). Crucially, scores on the AO subtest emerged as a significant predictor for both hand ($\beta = 1.86$, $t(36) = 2.84$, $p < .01$) and finger ($\beta = 1.12$, $t(36) = 1.6$, $p < .01$) imitation tests. In addition, the model predicting scores on the object use test revealed an explanation of 32% of the variance by the three motor WM subtests (adjusted $R^2 = .32$, $F_{(3,36)} = 7.04$, $p < .001$), with the AO subtest again being the significant predictor of performance ($\beta = 1.38$, $t(36) = 2.39$, $p < .05$).

4.2.8. Lesion overlaps and voxel-based lesion-symptom mapping (VLSM)

Figure 6A, B and *C* display the lesion overlays of the whole sample of LH patients, with and without apraxia (N = 35), the LH patients without apraxia (N = 17), and the LH patients with apraxia (N = 18), respectively. The lesions predominantly affected the left middle cerebral artery (MCA) territory, with the maximum lesion overlap within the superior temporal gyrus (STG) observed in 29 of the 35 LH stroke patients (13 in the LH+ group and 16 in the LH- group).

Figure 6. Lesion overlap of the LH stroke patients with and without apraxia

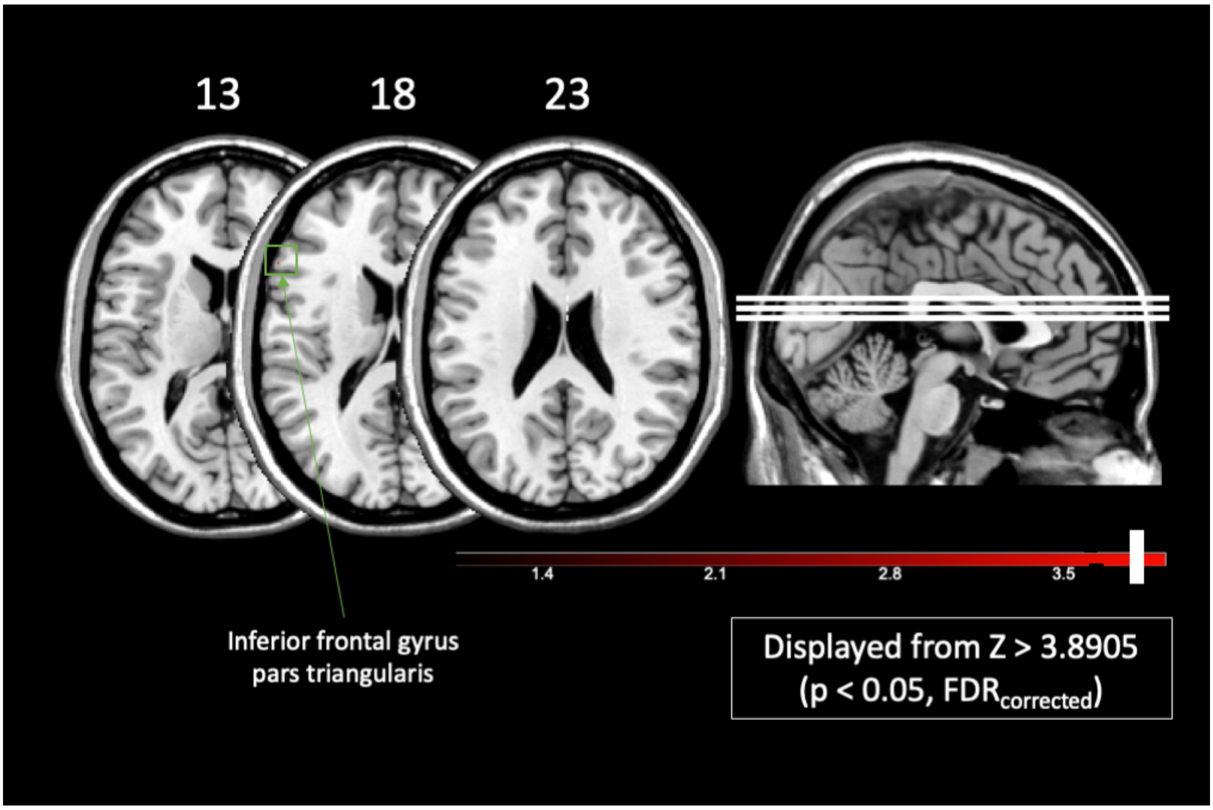


Lesion overlaps of the LH stroke patients for whom lesion maps were available. ***(A)*** *depicts the whole group of LH stroke patients with and without apraxia (N = 35),* ***(B)*** *depicts the LH- group (N = 17), and* ***(C)*** *depicts the LH+ group (N = 18). The number of overlapping lesions is indicated by color shades, with dark blue indicating the lowest overlap (one patient) and white indicating the highest overlap (28 in all LH stroke patients). Note that the highest overlap observed in the LH- and LH+ groups represents 17 and 13 patients, respectively.*

Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000)*. The depicted axial slices correspond to the z-coordinates from -42 to +68 in MNI space.*

The VLSM analysis for the whole sample of LH stroke patients (N = 35) using the scores on the actions with objects (AO) subtask revealed that lower scores on the AO subtask were associated with a single significant voxel in the par triangularis part of the IFG (max. *Z*-value = 3.891; MNI coordinates [x, y, z]: -59, +23, +18; see *Figure 7*). Note that these results were significant using the voxel-wise Brunner-Munzel statistical test (Brunner and Munzel, 2000), and not the t-test statistics. However, the remaining three VLSM analyses using the scores on the meaningful gestures (MFG) subtask, the meaningless gestures (MLG) subtask, and the motor WM composite score, yielded no significant results. For an illustration of the overlays of the statistical maps (with uncorrected voxels) produced by these three VLSM analyses, see *Appendix 3*.

Figure 7. VLSM results of the scores on the actions with objects subtask in the LH stroke patients.



Results of the VLSM analysis for the scores on the actions with objects (AO) subtask in the group of LH stroke patients (N = 35). Lesion correlates associated with lower scores on the AO subtask were found in the pars triangularis part of the IFG of the left hemisphere. Displayed voxels are above a Z-value of -3.8905, corresponding to a statistical threshold of p < .05, FDR-corrected. Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000)*. The depicted axial slices correspond to the z-coordinates from +13 to +23 in MNI space.*

5. Study II:

The second study involved a retrospective analysis of videos of patients with left hemisphere (LH) stroke and apraxia performing object-use pantomimes after visual presentation of 2D pictures of objects. Half of the patients (N = 49/96, 51%) showed an irregular approach behavior toward the presented object pictures before pantomime execution. The observed irregular behaviors with the left hand and fingers were categorized as ‘virtual grasping’, in which patients exhibited grasping movements directed toward the object picture, or ‘tracing’, in which patients traced the object’s contour on the picture.

Interestingly, these irregular pantomime behaviors bear partial resemblance to behaviors observed in patients with apraxia, primarily during gesture imitation tasks. Prominent among these phenomena are the ‘conduit d’approche’, in which patients exhibit multiple inaccurate spatial trajectories, progressively refining their movements, before finally reaching the intended gesture (Smania *et al.*, 2000; Luzzi *et al.*, 2010), and the ‘closing-in phenomenon’ characterized by the tendency of the patient’s hand to be drawn towards the examiner’s hand or target during imitation (Mayer-Gross, 1935; Kwon *et al.*, 2002; Ambron *et al.*, 2018). In contrast, the specific irregular behaviors of virtual grasping and tracing of object photographs that we observed during pantomiming of object-use have not been extensively reported or systematically assessed in the literature (Rohrbach *et al.*, 2021). Crucially, such irregular behaviors are often not captured by conventional scoring procedures that focus on the pantomime action itself (Goldenberg and Randerath, 2015; Rothi et al., 1997; Vanbellingen et al., 2011; Watson and Buxbaum, 2015; Weiss et al., 2013).

Accordingly, the current retrospective study focused on the following three primary objectives:

(i) To characterize the observed irregular behaviors of virtual grasping and tracing observed during the pantomime assessment in LH stroke patients with apraxia.

(ii) To elucidate the cognitive mechanisms and neuroanatomical substrates underlying these irregular behaviors.

(iii) To explore the association of these irregular behaviors with aphasia, a frequent concomitant deficit to apraxia following LH stroke.

Please note that the methods and results presented here are related to the following experimental study:

Barddakan, M., Schmidt CC., Kleineberg NN, Richter MK, Bolte K, Schloss N, Fink GR, & Weiss PH (in internal revision). Different strategies affecting pantomime performance in apraxia: virtual grasping and tracing of object-pictures.

5.1. Methods II

5.1.1. Patient sample

Study II included a retrospective analysis of neuropsychological and lesion data of 96 patients (59 men; μ_{age} = 70.2 years, range 32-90) who had suffered a single (first-ever) unilateral ischemic stroke in the left hemisphere (LH) and had no other concomitant neurological diseases affecting the central nervous system. The majority of the patients (N = 94) were assessed during the sub-acute phase post-stroke (*M* = 30, range 6-90 days post stroke); two patients were assessed during the chronic phase after stroke (time post stroke = 113 days and 145 days). All patients were diagnosed with apraxia using the Cologne Apraxia Screening (KAS, Weiss et al., 2013; see *Section 5.1.3*). Patients were recruited from the Neurological Rehabilitation Centre Godeshöhe, Bad Godesberg, Bonn (N = 32) and the neuro-rehabilitation ward of the MediClin hospital Rhein/Ruhr, Essen (N = 64) and were assessed by four trained physicians (KB, MRG, NS, NNK).

All patients (or their legal guardians) consented to the analyses of the patients' neuropsychological and clinical imaging data, including recorded videos of the patients' neuropsychological examination. The study was approved by the ethics committee of the Medical Faculty of the University of Cologne.

5.1.2. Clinical assessments

All patients were right-handed prior to their stroke as assessed by the Edinburg Handedness Questionnaire (EHI; (Oldfield, 1971)). The majority of the patients had unremarkable scores in the Hospital Anxiety and Depression Scale (HADS; (Zigmond and Snaith, 1983)); three patients showed mild anxiety (HADS anxiety scores of 11 or 12, cut-off-score ≥ 11) and five patients indicated mild depressive symptoms (HADS depression scores of

11 or 12, cut-off-score ≥ 11), and one patient indicated mild anxiety (score = 12) and moderate depressive symptoms (score = 17/21).

The severity of stroke symptoms was evaluated using the National Institute of Health Stroke Scale (NIHSS; score range 0-42, Goldstein et al., 1989) and the modified Rankin Scale (mRS; score range 0-6, Rankin, 1957; van Swieten et al., 1988) assessing the degree of disability and dependency on assistance. Higher scores on both scales indicate more severe impairments. In addition, ipsi- and contralesional grip force and limb paresis were measured using a vigorimeter and the Medical Research Council scale (MRC, score range 0-5, with lower scores indicating more severe paresis; O'Brien, 2000), respectively.

5.1.3. Neuropsychological assessments

The assessment of apraxic deficits in the LH stroke patients was conducted using a range of neuropsychological tests. Patients used their ipsilesional (i.e., left, non-paretic) hand in all apraxia tests. The Cologne Apraxia Screening (KAS), a validated and standardized diagnostic tool for apraxia that has high interrater reliability, was used to diagnose apraxia (Weiss *et al.*, 2013). The KAS consists of four subtests evaluating the performance in pantomiming object use and gesture imitation. In the pantomime tasks, patients are shown ten photographs of objects and asked to pantomime the typical use of the corresponding objects. One pantomime subtest assesses (i) pantomiming object-use that involves bucco-facial movements in addition to arm/hand movements (five object photographs: toothbrush, cup, comb, glass, tissue) and (ii) pantomiming object-use involving (only) arm/hand movements (five object photographs: whisk, dice, lighter, spinning top, and pair of scissors). Note that the first pantomime subtest involves (self)-reflexive movements, while the second pantomime subtest rather involves non-reflexive (arm/hand) movements (Bartolo *et al.*, 2019). In the imitation subtests, photographs of a woman performing gestures are shown and patients are asked to reproduce the gestures as ‘if seen in mirror’. The imitation tasks consist of two subtests: (i) imitating five bucco-facial gestures (e.g., sticking out the tongue) and (ii) imitating five arm/hand gestures (e.g., wiping the mouth). The maximum score for each item is four points, resulting in a maximum score of 20 points for a given subtest (five items per subtest) and a maximum score of 80 points for the KAS total score. Patients with a KAS total score of 76 points or less were classified as apraxic (Weiss *et al.*, 2013).

In addition to the KAS, three other standard neuropsychological tests were used to evaluate praxis deficits, namely the Goldenberg’s imitation tests of hand positions and finger configurations (Goldenberg, 1996) and an adapted version of the De Renzi test for actual object use (De Renzi *et al.*, 1968). Here, the scores of Goldenberg’s imitation test for finger configurations were transformed into percentages (i.e., a score of 100% is equivalent to the maximum possible score), since one of the included patients had a finger amputation that prevented a complete assessment of the patient on all the items of the finger imitation test. See *Section 4.1.2* in Study I for a detailed overview of the administration and scoring procedures of the three apraxia tests, and *Figure 2* for example stimuli from Goldenberg’s gesture imitation tests.

Moreover, putative concomitant aphasic deficits were evaluated using the short version of the Aphasia Check List (ACL-K; Kalbe et al., 2002). The ACL-K comprises four subtests: a reading aloud task (score range 0-9), a color-figure test tapping on auditory comprehension (score range 0-12; modified Token Test, for more details see *Section 4.1.2* in Study I), a semantic verbal fluency test (score range 0-10), and a rating of the patient’s verbal communication abilities by the examiner (score range 0-9). The total ACL-K score is the sum of the four subtest scores. Therefore, the maximal total ACL-K score is 40. A total ACL-K score below 33 indicates the presence of aphasia; scores between 26 and 32 points are classified as mild aphasia, scores between 15 and 25 points as moderate aphasia, and scores <15 points as severe aphasia (Kalbe *et al.*, 2005).

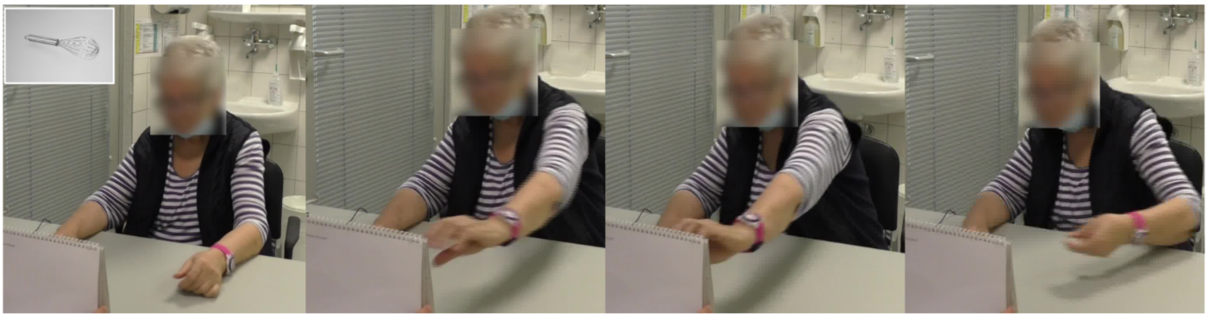
5.1.4. Classification of irregular pantomiming behaviors: virtual grasping and tracing

Data analysis was based on the videos recorded during the KAS pantomime assessments of the apraxic LH stroke patients, in which the patients were asked to pantomime the use of objects displayed on photographs presented by the examiner sitting in front of them. Two examiners reviewed the recorded videos and classified the pantomime behavior of each patient for the ten items (i.e., object pictures) of both KAS pantomime subtests for the presence or absence of irregular behaviors before or during pantomiming.

Approximately half of the patients with apraxia exhibited regular pantomiming behavior (N = 47; 49%), while the remaining patients (N = 49; 51%) showed an irregular approach behavior towards the presented object pictures prior to pantomiming object use. The observed irregular behaviors were categorized into two distinct strategies, hereafter referred to as ‘virtual grasping’ (GoP, grasping object pictures) and ‘tracing’ (ToP, tracing object pictures) of the object pictures. ‘Virtual grasping’ was defined as an object-directed grasping toward the object picture, mostly directed to the object part that is usually grasped when actually using this object (e.g., a whisk’s handle; see *Figure 8A*). ‘Tracing’ was defined as a continuous (or repetitive) tracing on the picture along the object’s contour or shape with the index finger or whole hand (see *Figure 8B*). Patients showing GoP behaviors at least in one test item and no ToP behavior were assigned to the ‘grasping’ group (LH+GoP). Patients were assigned to the ‘tracing’ group (LH+ToP) if they exhibited at least one instance of tracing behavior, regardless of whether they also showed virtual grasping. Due to the scarce observations of patients exhibiting exclusive ToP behaviors, we did not separate the patients showing only ToP behaviors and those showing both ToP and GoP behaviors into two separate groups (for more details see *Table 4* and *Section 5.2.2*).

Figure 8. Examples of virtual grasping and tracing of object pictures.

A Virtual grasping of object pictures (GoP)



B Tracing of object pictures (ToP)

Sequential frames illustrating the ***(A)*** *virtual grasping and* ***(B)*** *tracing behaviors observed in patients with apraxia before pantomiming the use of a whisk (presented as a photograph on a paper).* ***(A)*** *Virtual grasping of object pictures: the frames show a patient exhibiting virtual grasping, initially moving the hand towards the photograph with a grip configuration directed towards the handle (i.e., graspable part) of the whisk (second frame - A) proceeding to (virtually) grasp the whisk's handle (third frame - A) before demonstrating its typical use (fourth frame - A).* ***(B)*** *Tracing of object picture: the frames show a patient tracing the contour of the whisk photograph, beginning at the handle of the whisk photograph (first frame - B) following its contour through its functional end (second frame - B) and returning to the handle to repeat the tracing behavior (third frame - B) before demonstrating its typical use (fourth frame - B).*

The sequential frames were extracted from recorded videos of patients performing the KAS pantomime subtests. Note that the faces of the patients were blurred for the sake of anonymity.

5.1.5. Statistical analyses of behavioral data

All statistical analyses were performed using the software R (Version 4.0.5). Non-parametric independent Mann-Whitney *U* tests with continuity correction were applied to explore putative group differences in mean ranks in the demographical (age), clinical (time post-stroke, stroke severity, and basic motor functions), and neuropsychological (apraxia and aphasia) measures between patients showing regular pantomime behavior (LH+RPB; N = 47) and patients showing irregular pantomime behaviors (LH+IPB; N = 49). Similarly, non-parametric Mann-Whitney *U* tests investigated putative differences between the two groups of patients with irregular pantomime behaviors, i.e., between the patients showing 'virtual grasping' (LH+GoP, N = 32) and 'tracing' (LH+ToP, N = 17). A significance level of $p < .05$ was applied for all between-group comparisons. To account for multiple comparisons, Bonferroni's correction for multiple comparisons was used where applicable.

In addition, two generalized linear mixed-effects models (via the 'lme4' package in R; Bates et al., 2015) fit by maximum likelihood (Laplace approximation) were conducted to assess performance differences in the KAS subtests between the LH+GoP and the LH+ToP groups. Both mixed-effects models included the two-level between-subject fixed factor 'GROUP' (LH+GoP, LH+ToP) and the random factor 'PATIENT' (with random intercepts). For the mixed-effects model of interest, the within-subject fixed factor included the 'KAS PANTOMIME' subtests (KAS subtest of pantomiming bucco-facial-related objects, KAS subtest of pantomiming limb-related objects) to assess group differences in pantomiming object use with bucco-facial and arm/hand effectors. A complementary mixed-effects model was run with the within-subject fixed factor 'KAS IMITATION' subtests (KAS subtest of imitating bucco-facial gestures, KAS subtest of imitating arm/hand gestures) to assess group differences in imitating gestures with bucco-facial and arm/hand effectors. Independent samples Z-tests for generalized linear mixed-effects models (via the 'emmeans' package in R; Russell, 2021) were conducted to assess significant effects across the different levels of factors, Bonferroni-corrected for multiple comparisons and with a significance level set at $p < .05$.

Since praxis and language deficits are often concomitant following LH stroke (Goldenberg and Randerath, 2015; Weiss *et al.*, 2016), the association between the occurrence of the irregular pantomime behaviors and the severity of aphasic deficits as assessed by the ACL-K was also examined. A 'frequency score of GoP' was computed for each of the apraxic LH stroke patients showing irregular pantomime behaviors (LH+IPB; N = 49). The frequency score of GoP (ranging from zero to ten) corresponded to the number of observed GoP behavior showed across the ten items in the two pantomime subtests of the KAS. For instance, a patient who exhibited GoP on two items of the pantomime subtests was given a frequency score of 2 for GoP, while a patient exhibiting GoP on seven items was given a score of 7. Accordingly, the frequency score for GoP behaviors quantified the degree to which patients relied on the virtual grasping strategy during pantomiming object use in the KAS, with lower scores indicating lower reliance and higher scores indicating higher reliance on the virtual grasping strategy. Similarly, for the LH stroke patients in the LH+ToP group, a 'frequency score of ToP' was computed to quantify the degree of their reliance on the tracing strategy during pantomiming object use. Generalized linear regression analyses were then performed using the reliance on the virtual grasping strategy (as indexed by the frequency score of GoP) and the reliance on the tracing strategy (as indexed by the frequency score of ToP) to predict the total scores on the ACL-K using a significance level of $p < .05$. In particular, three separate analyses were conducted for the LH+IPB, LH+GoP and LH+ToP groups using the frequency score of GoP as a predictor. In addition, the frequency score of ToP was used to predict ACL-K scores in the LH+ToP group, both as a single predictor and in combination with the frequency score of GoP. Thus, a total of five distinct regression models were executed.

5.1.6. Lesion delineation

Lesion mapping was performed using the clinical MRI (N = 26) or CT (N = 18) scans that were available for the patients with apraxia exhibiting irregular pantomime behaviors (LH+IPB; N = 44; 28 patients of the LH+GoP group (87.5%) and 16 patients of the LH+ToP group, 94.1%). Five patients (four of the LH+GoP group and one of the LH+ToP patient) had no available imaging scans suitable for lesion mapping and were thus excluded from the lesion analysis.

Using the MRIcron software, all lesions were manually delineated on axial slices of a T1-weighted template MRI scan (ch2.nii) from the Montreal Neurological Institute (MNI). Lesions were drawn onto the axial slices of the ch2-template in increments of 5 mm in MNI space by matching or closely matching axial slices of the individual patient's CT or MRI scan. Lesion mapping was performed by three trained physicians (KB, NS or NNK) and confirmed by two independent examiners (CCS and PHW). The examiners had to agree upon the location and extent of the lesions in each patient and were blind to the neuropsychological test scores including the patient's group assignment (i.e., LH+GoP, LH+ToP) during lesion delineation.

5.1.7. Lesion subtraction analysis.

In order to qualitatively investigate the brain regions associated with the different pantomime strategies exhibited by the LH stroke patients with apraxia, a lesion subtraction analysis was conducted (Rorden and Karnath, 2004) using the MRIcron software (Version 30/04/2016, https://nitrc.org/projects/mricron). In particular, the analysis contrasted the available lesion maps of the patients in the LH+ToP group (16 out of 17) with those of the LH+GoP group (28 out of 32). In this context, the LH+ToP group constituted the group of patients exhibiting the ToP behavior of interest, while the LH+GoP group served as a control group (i.e., not exhibiting ToP). The ensuing subtraction images highlighted regions that were more frequently damaged in the LH+ToP group, but typically intact, in the LH+GoP group. Positive values on a lesion overlay represented regions more often damaged in the LH+ToP than in the LH+GoP group. Conversely, negative values indicated regions more frequently damaged in the LH+GoP group compared to the LH+ToP one. Note that regions not specifically associated with the ToP behavior will not appear in the subtraction plot, as these are (theoretically) similarly represented in both groups.

Given the discrepancy in sample sizes between the two groups, the subtraction analysis used restricted proportional values. In particular, the thresholds ranged from +10 to +50 for the LH+ToP group and from -50 to -10 for the LH+GoP group. These thresholds represented the frequency of voxel damage, with reported voxels being those more frequently damaged in 10% to 50% of patients in each group. Note that the selection of the upper threshold was informed by the maximum lesion overlap observed in both groups, which did not exceed 50% (see *Figure 10*). Moreover, to increase statistical power the analysis included voxels damaged in at least 10% (lower threshold) of the patients in each group.

5.1.8. Voxel-based lesion symptom mapping (VLSM)

Statistical lesion analysis was performed by means of voxel-based lesion-symptom mapping (VLSM, Bates et al., 2003) using the non-parametric mapping (NPM) software freely distributed with MRIcron (Version 30/04/2016, https://nitrc.org/projects/mricron). In particular, one VLSM was used for all LH+IPB patients with available lesion maps (N = 44) to determine the association between lesioned voxels and the patient's degree of reliance on virtual grasping strategy during pantomiming object use (as operationalized by frequency score of GoP). A complementary VLSM was conducted for the LH+ToP patients with available lesion maps (N = 16) using the patient's degree of reliance on the tracing strategy (as operationalized by a frequency score of ToP). Voxel-wise t-test statistics were performed on the frequency score of GoP and the frequency score of ToP, with groups categorized according to the presence or absence of damage in each voxel. Only voxels that were lesioned in at least 5% of the patients (i.e., two patients) were included in the VLSM analysis. The statistical threshold for significant voxels was set to $p < .05$, corrected for multiple comparisons using False Discovery Rate (FDR) correction (Benjamini and Hochberg, 1995). We report the voxel's maximum Z-value and corresponding MNI coordinates of the significant clusters (with a minimum size of 20 voxels). The brain regions associated with the significant voxels were identified using the Johns Hopkins University (JHU) atlas (Faria *et al.*, 2012) provided by MRIcron.

5.2. Results II

5.2.1. Comparative analysis of patients showing regular and irregular pantomime behaviors

The group of LH stroke patients with apraxia and irregular pantomime behaviors (LH+IPB; N = 49) was comparable to the LH stroke patients with apraxia and regular pantomime behavior (LH+RPB; N = 47) concerning age, time post-stroke, basic motor functions (i.e., grip force, MRC), overall disability (i.e., mRS), and stroke symptoms severity (i.e., NIHSS; all *p*-values > .15; all *z*-scores < 1.45; see *Table 2*).

Table 2. Demographic and clinical characteristics of the left hemisphere stroke patients with apraxia showing regular (LH+RPB; N=47) and irregular behaviors (LH+IPB; N=49) as well as of those left hemisphere stroke patients with apraxia showing grasping of pictures (LH+GoP; N=32) and tracing of pictures (LH+ToP; N=17) during pantomime assessment.

	Groups of left hemisphere stroke patients with apraxia showing					
	LH+RPB (*N*=47) Median (IQR)	**LH+IPB (*N*=49)** Median (IQR)	***p*-value**	**LH+GoP (*N*=32)** Median (IQR)	**LH+ToP (*N*=17)** Median (IQR)	***p*-value**
Age (years)	75 (61.5-80)	73 (63-80)	*.91*	72.5 (62.8-80.3)	73 (64-80)	*.85*
Time post-stroke (days)	30 (23-41.5)	29 (24-38)	*.69*	31.5 (24-37.3)	27 (17-42)	*.61*
National Institutes of Health Stroke Scale	4 (3-6.75)	4 (3-8)	*.95*	4 (2-7)	6 (3-8)	*.18*
Modified Ranking Scale	3 (2.5-4)	3 (2-4)	*.81*	3 (2-4)	3 (3-4)	*.51*
Grip force (left hand)	71 (53-88)	69 (52-100)	*.49*	78 (57.3-100)	66 (48-72)	*.25*
Grip force (right hand)	38 (9.5-70)	48 (10-61)	*.97*	52 (8.5-67.8)	40 (20-56)	*.4*
Medical Research Council (left hand)	5 (4.5-5)	5 (5-5)	*.15*	5 (5-5)	5 (5-5)	*.06*
Medical Research Council (right hand)	4.5 (3.5-5)	4.5 (3.5-5)	*.95*	4.5 (2.9-5)	4.5 (3.9-4.5)	*.45*

The group of left hemisphere (LH) stroke patients with apraxia showing irregular behaviors during pantomime assessment (LH+IPB; N=49) are comprised of two subgroups, i.e., apraxic LH stroke patients showing (virtual) grasping of pictures (LH+GoP, N=32) and those showing tracing of pictures (LH+ToP, N=17). Note that no significant group differences are observed for any of the demographic and clinical measures between stroke patients with apraxia showing regular (LH+RPB) and irregular (LH+IPB) behaviors and between stroke patients with apraxia showing grasping (LH+GoP) and tracing (LH+ToP) behaviors.

IQR: Interquartile range (Q1-Q3: lower quartile – upper quartile).

Further, similar overall performance scores in the neuropsychological tests assessing apraxic and aphasic deficits was revealed for the LH+RPB group compared to the LH+IPB group (i.e., the LH+GoP and LH+ToP groups combined; all *p*-values > .47; all *z*-scores < .37; see *Table 3*). Pantomime deficits according to the KAS (i.e., scores <39 out of 40 points in the KAS pantomime subtests) were present in most of the LH+RPB (N = 43, 91.5%) and LH+IPB (N = 45, 91.8%) groups. The remaining LH stroke patients suffered from imitation apraxia. Notably, the presence of pantomime deficits did not differ between the LH+RPB and LH+IPB groups ($\chi^2 < 0.0001$, $p = 1$).

Table 3. Neuropsychological characteristics of the left hemisphere stroke patients with apraxia showing regular (LH+RPB; N=47) and irregular behaviors (LH+IPB; N=49) as well as of those left hemisphere stroke patients with apraxia showing grasping of pictures (LH+GoP; N=32) and tracing of pictures (LH+ToP; N=17) during pantomime assessment.

	Groups of left hemisphere stroke patients with apraxia					
Aphasia and apraxia assessments	**LH+RPB (*N*=47)** Median (IQR)	**LH+IPB (*N*=49)** Median (IQR)	***p*-value**	**LH+GoP (*N*=32)** Median (IQR)	**LH+ToP (*N*=17)** Median (IQR)	***p*-value**
Aphasia Check List – Short version (ACL-K)	18.5 (10.8-27.8)	22 (10-30)	*.92*	22.8 (15.5-30.1)	14.5 (5-29.5)	*.08*
Cologne Apraxia Screening (KAS total)	59 (49.5-66.5)	61 (54-66)	*.81*	**63.5 (57.8-68)**	**53 (43-61)**	***.001***
KAS pantomime subtest: bucco-facial	16 (14.5-18)	18 (14-19)	*.47*	**18 (17-19)**	**14 (9-18)**	***.0003****
KAS pantomime subtest: arm/hand	14 (9-18)	14 (10-16)	*.92*	**16 (12-18)**	**10 (7-16)**	***.0003****
KAS imitation subtest: bucco-facial	18 (16-20)	20 (16-20)	*.88*	19 (16-20)	20 (18-20)	*1*
KAS imitation subtest: arm/hand	12 (9-16)	12 (8-14)	*.72*	**12 (10-16)**	**10 (6-12)**	***.015****
Goldenberg hand imitation test	15 (11.5-17.5)	15 (13-18)	*.77*	**16 (14-18.5)**	**13 (10-16)**	***.01***
Goldenberg finger imitation test (%)	80 (70-90)	80 (65-90)	*.72*	85 (74.5-95)	75 (55-90)	*.11*
De Renzi test of actual object use	31 (29.5-32)	31 (29-32)	*.92*	31 (30-32)	31 (27-32)	*.19*

Note that the apraxic patients of the virtual grasping (LH+GoP; N=32) and tracing (LH+ToP; N=17) groups are the two subgroups of the apraxic group of patients showing irregular behaviors during pantomiming object use (LH+IPB; N=49).

No significant differences are observed on neuropsychological tests between stroke patients with apraxia showing regular (LH+RPB) and irregular (LH+IPB) pantomime behaviors. Significant differences between LH+GoP and LH+ToP are highlighted in bold font for the Mann-Whitney U tests with continuity correction (p < .05 Bonferroni-corrected for the number of tests, N = 5), and with an additional asterisk sign for the generalized linear mixed-effects models.

Of note, the scores of the Goldenberg's finger imitation test were transformed into percentages (i.e., a score of 100% is equivalent to the maximum possible score), since one of the patients had a finger amputation that prevented a complete finger imitation assessment.

ACL-K: Aphasia Check List – Short Version, IQR: Interquartile range (Q1-Q3: lower quartile – upper quartile), KAS: Kölner (Cologne) Apraxia Screening.

5.2.2. Characterizing the patients exhibiting irregular pantomime behaviors: virtual grasping (LH+GoP) and tracing (LH+ToP) groups

Approximately half of the patients with apraxia exhibited irregular approach behavior towards the presented object pictures prior to pantomiming object use (LH+IPB; N = 49). Almost two-thirds (N = 32, 65.3%) of the patients showing irregular pantomime behavior were allocated to the 'virtual grasping' group (LH+GoP) and one-third (N = 17, 34.7%) of the patients were allocated to the 'tracing' group (LH+ToP). In the LH+GoP group, approximately half of the patients (N = 15, 46.9%) showed GoP in more than five items. In the LH+ToP group, most patients (N = 12, 70.6%) displayed ToP in up to five items. Note that 13 patients (76.5%) in the LH+ToP group also showed GoP for some items. Most of these LH+ToP patients (N = 10, 76.9%) displayed GoP behaviors for a maximum of five items, while only three patients showed GoP for more than five items (see *Table 4*).

Table 4. Distribution of the frequencies of virtual grasping (GoP) and tracing (ToP) behaviors exhibited during pantomime assessment across the left hemisphere stroke patients with apraxia showing irregular pantomime behaviors.

	Frequency of virtual grasping (GoP) and tracing (ToP) behaviors observed during pantomime assessment									
	1/10	***2/10***	***3/10***	***4/10***	***5/10***	***6/10***	***7/10***	***8/10***	***9/10***	***10/10***
LH+GoP showing GoP (N=32)	*5*	*2*	*5*	*3*	*2*	*0*	*2*	*0*	*4*	*9*
LH+ToP showing GoP (N=13)	*3*	*3*	*0*	*3*	*2*	*1*	*0*	*0*	*1*	*0*
LH+ToP showing ToP (N =17)	*5*	*3*	*0*	*2*	*2*	*3*	*0*	*1*	*0*	*1*

In the LH+GoP group, approximately half of the patients (N = 15, 46.9%) showed virtual grasping on more than 5 items (> 5/10). In the LH+ToP group, most patients (N = 11, 64.7%) showed virtual grasping on less than 5 items (< 5/10), and most patients (N=12, 70.6%) also displayed tracing on less than 5 items (<5/10).

Note that the number of patients in the LH+ToP group showing GoP is incomplete (13 out of 17) since four patients in the LH+ToP group showed no virtual grasping behaviors.

LH+GoP: left hemisphere stroke patients with apraxia in the virtual grasping of pictures group; LH+ToP: left hemisphere stroke patients with apraxia in the tracing of pictures group; GoP: virtual grasping of pictures; ToP: tracing of pictures.

5.2.3. Neuropsychological characteristics of the patients in the virtual grasping (LH+GoP) and tracing (LH+ToP) groups

Concerning additional praxis deficits in the current LH stroke patients with apraxia according to the KAS, 22% (7/32) of the apraxic patients in the LH+GoP group and 41% (7/17) of apraxic patients in the LH+ToP group showed also deficits in the De Renzi test for actual object use. Besides, two-thirds of the apraxic patients in the LH+GoP group (21/32, 66%) and most apraxic patients in the LH+ToP group (15/17, 88%) showed additional impairments in imitating Goldenberg's hand postures. Furthermore, about half of the patients in the LH+GoP (15/32, 47%) and almost two-thirds of the patients in the LH+ToP (11/17, 65%) had also deficits in imitating Goldenberg's finger configurations.

With regard to language performance, 28 of the 32 apraxic patients in the LH+GoP group (88%) were also aphasic according to the ACL-K, hereof 10 patients each showed mild and moderate aphasia and eight patients showed severe aphasia. Of the apraxic patients in the LH+ToP group, almost all patients (16/17, 94%) also suffered from aphasia, hereof four patients each suffered from mild and moderate aphasia and eight patients showed severe aphasia.

5.2.4. Comparative analysis of patients in the virtual grasping (LH+GoP) and tracing (LH+ToP) groups

There were no significant group differences between the apraxic patients in the LH+GoP and LH+ToP groups concerning age, time post-stroke, basic motor functions, overall disability, and stroke symptoms severity (all *p*-values > .06; all *z*-scores < 1.8; see *Table 2*). Besides, the LH+GoP and LH+ToP groups did not differ significantly in the Goldenberg test of imitating finger configurations, the De Renzi test of actual object use, and the ACL-K assessing aphasic deficits (all *p*-values > .08; all *z*-scores < 1.7; see *Table 3*). In contrast, the LH+GoP group performed significantly better than the LH+ToP group in the KAS (total score; *z* = 3.2, *p* = .001) and the Goldenberg test of imitating hand postures (*z* = 2.6, *p* = .01).

The generalized linear mixed-effects model assessing differences in performance between apraxic patients in the LH+GoP and LH+ToP groups across the two pantomime subtests of the KAS (pantomiming the use of bucco-facial-related objects and pantomiming the use of limb-related objects) revealed significant effects of GROUP (β = -.4, *SE* = .1, *z* = -3.6, *p* < .001) and EFFECTOR (β = .14, *SE* = .06, *z* = 2.3, *p* = .02), but no significant interaction effect between GROUP and EFFECTOR (β = .08, *SE* = .1, *z* = .8, *p* = .45). Apraxic patients in the LH+GoP group performed significantly better than patients in the LH+ToP group in both KAS subtests of pantomiming the use of bucco-facial-related objects (LH+GoP: $\mu = 17.3$, *SD* = 2.5, LH+ToP: $\mu = 13$, *SD* = 5.7) and of limb-related objects (LH+GoP: μ = 14.9, *SD* = 4.1, LH+ToP: $\mu = 10.3$, *SD* = 5.2; see *Table 3*). Interestingly, both apraxic groups of LH+GoP and LH+ToP scored worse in the subtest of pantomiming the use of limb-related objects compared to pantomiming the use of bucco-facial-related objects.

The generalized linear mixed-effects model assessing differences in performance between the apraxic patients in the LH+GoP and LH+ToP groups across the two imitation subtests of the KAS (imitating bucco-facial gestures and imitating limb-related gestures) revealed significant effects of GROUP(β = -.3, *SE* = .1, *z* = -2.9, *p* = .002) and EFFECTOR (β = .3, *SE* = .06, *z* = 4.9, *p* < .001) as well as a significant interaction effect between GROUP and EFFECTOR (β = .26, *SE* = .1, *z* = 2.2, *p* = .02). Patients of the LH+GoP group showed significantly better imitation performance in limb-related gestures ($\mu = 12.6$, *SD* = 4) than patients of the

LH+ToP group ($\mu = 9.3$, *SD* = 4.1; $\beta = .3$, *SE* = .1, *z* = 2.9, *p* = .015). However, no significant group difference was observed between the LH+GoP ($\mu = 17.4$, *SD* = 3.2) and LH+ToP ($\mu = 16.7$, *SD* = 5.9) groups for imitating bucco-facial gestures ($\beta = .04$, *SE* = .08, *z* = 0.5, *p* = .1; see *Table 3*).

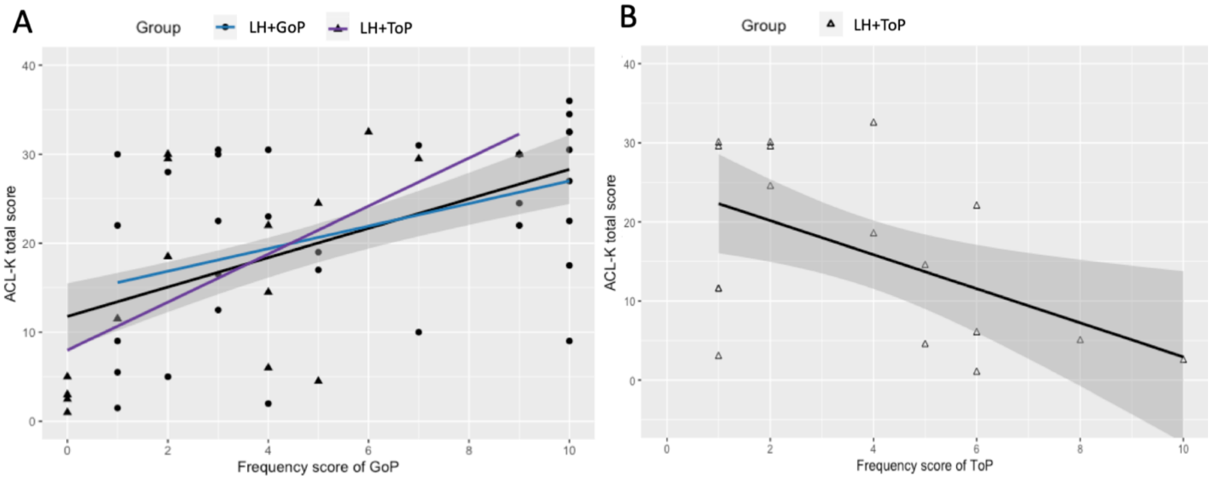
5.2.5. Association between aphasic deficits and the occurrence of irregular pantomime behaviors: virtual grasping (GoP) and tracing (ToP) behaviors

The regression model predicting performance on the ACL-K total score using the frequency score of GoP in all apraxic patients with irregular pantomime behavior (LH+IPB; N = 49) revealed a significant positive correlation ($\beta = 1.89$, *SE* = 1.02, $p < .001$) between the two dimensions (see *Figure 9A*), indicating that a higher frequency score of the virtual grasping strategy was associated with less severe aphasic deficits in the LH+IPB group. It is important to note that this positive prediction remains significant when running the model for the separate groups of LH+ToP ($\beta = 3$, *SE* = 1.8 , $p < .001$; see purple regression line in *Figure 9A*) and LH+GoP ($\beta = 1.6$, *SE* = 1.5 , $p < .001$; see blue regression line in *Figure 9A*).

In contrast, the regression model using the frequency score of ToP in the apraxic patients in the LH+ToP group (N = 17) revealed a significantly negative correlation ($\beta = -3.13$, *SE* = .88, $p < .01$) with the ACL-K total score (see *Figure 9B*), indicating that increased reliance on the tracing strategy was associated with more severe aphasic deficits in LH stroke patients. In addition, a separate regression model incorporating both frequency scores of GoP and ToP for predicting the ACL-K scores in the LH+ToP group showed no significant interaction between the two predictors. However, this model revealed a significant positive correlation of the frequency score of GoP ($\beta = 2.2$, *SE* = .8, $p < .05$) and a marginally negative correlation of the frequency score of ToP (β = -1.5, *SE* = .8, *p* = .09), with the ACL-K total scores (see *Appendix 4*).

Note that two equivalent regression models using the frequency scores of GoP and ToP behaviors to predict average pantomime performance across the two KAS pantomime subtests revealed a positive correlation with the frequency score of GoP and a negative correlation with the frequency score of ToP (see *Appendix 5*).

Figure 9. Prediction of aphasia severity using the frequency scores of GoP and ToP behaviors.



Prediction of aphasia severity (as assessed by the ACL-K total score) using ***(A)*** *the frequency of virtual grasping behaviour (GoP) in apraxic left hemisphere stroke patients that exhibited irregular behaviors during pantomime assessment (LH+IPB; N = 49), and* ***(B)*** *using the frequency of tracing behaviour (ToP) in apraxic left hemisphere stroke patients that exhibited tracing (LH+ToP; N = 17).*

The generalized linear regression models indicate that ***(A)*** *a higher frequency of GoP is significantly predictive (p < .001) of higher scores in the ACL-K (i.e., less severe aphasia deficits) in the LH+IPB group, whereas,* ***(B)*** *a higher frequency of ToP is significantly predictive (p < .01) of lower scores in the ACL-K (i.e., more severe aphasia deficits).*

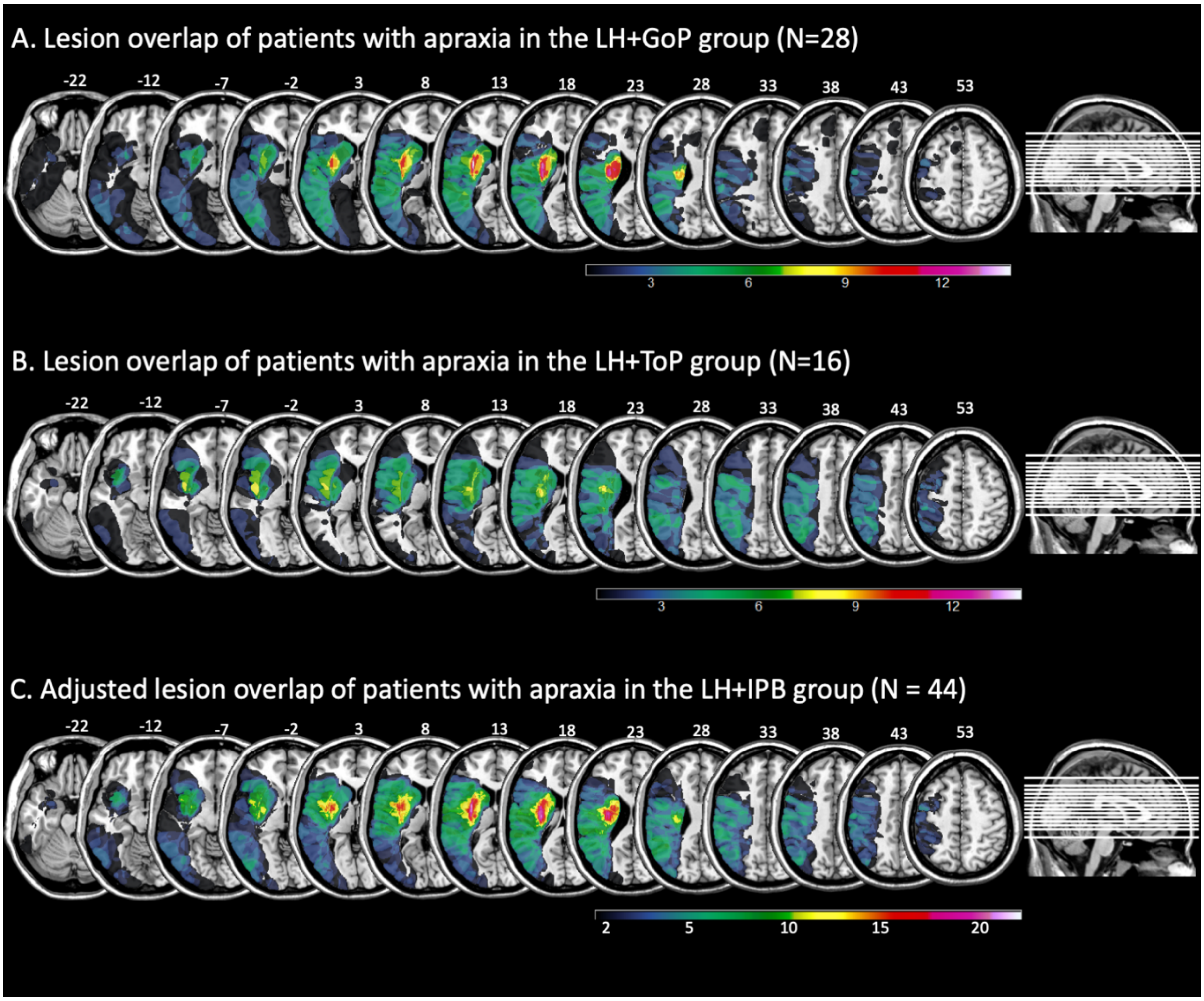
The regression lines indicate the linear trend and the 90% confidence interval (grey area surrounding the fitted lines) for ***(A)*** *the total group of apraxic left hemisphere stroke patients showing irregular pantomime behaviors (LH+IPB; N = 49, black line) and* ***(B)*** *the group of apraxic left hemisphere stroke patients showing tracing behaviors (LH+ToP; N = 17). Note that the blue and purple regression lines in graph (A) correspond to the regression lines of the separate models predicting ACL-K scores using the frequency of GoP in the LH+GoP group and the LH+ToP group, respectively.*

ACL-K: aphasia check list – short version, LH+GoP: left-hemisphere stroke patients with apraxia in the virtual grasping group, LH+ToP: left-hemisphere stroke patients with apraxia in the tracing group, GoP: virtual grasping of object pictures; ToP: tracing of object pictures.

5.2.6. Lesion distribution

Figure 10A and 10B display the lesion overlay of the patients with apraxia in the LH+GoP group (N = 28) and in the LH+ToP group (N = 16), respectively.

Figure 10. Lesion overlaps of the patients with apraxia in the LH+GoP, LH+ToP and LH+IPB groups.



Lesion overlaps of the LH stroke patients for whom lesion maps were available. ***(A)*** *Depicts the LH+GoP group (N = 28) and* ***(B)*** *the LH+ToP group (N = 16). The number of overlapping lesions is indicated by color shades, with dark blue indicating the lowest overlap (one patient) and white indicating the highest overlap (14 patients). Note that the highest overlap observed in the LH+ToP group is representing eight patients.*

(C) *Adjusted lesion overlaps of the left hemisphere (LH) stroke patients with apraxia who exhibited irregular behaviors during pantomime assessment and for whom lesion maps were available (LH+IPB; N = 44). Note that this group of apraxic LH stroke patients consisted of 28 patients in the LH+GoP and 16 patients in the LH+ToP group. Only those voxels damaged in at least 5% of the patients (i.e., at least 2 out of 44) and subjected to the voxel-based lesion-symptom mapping (VLSM) analysis are displayed.*

The number of overlapping lesions is indicated by color shades, with dark blue indicating the lowest overlap (2 patients) and white indicating the highest overlap (22 patients).

Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000)*. The depicted axial slices correspond to the z-coordinates from -22 to +53 in MNI space.*

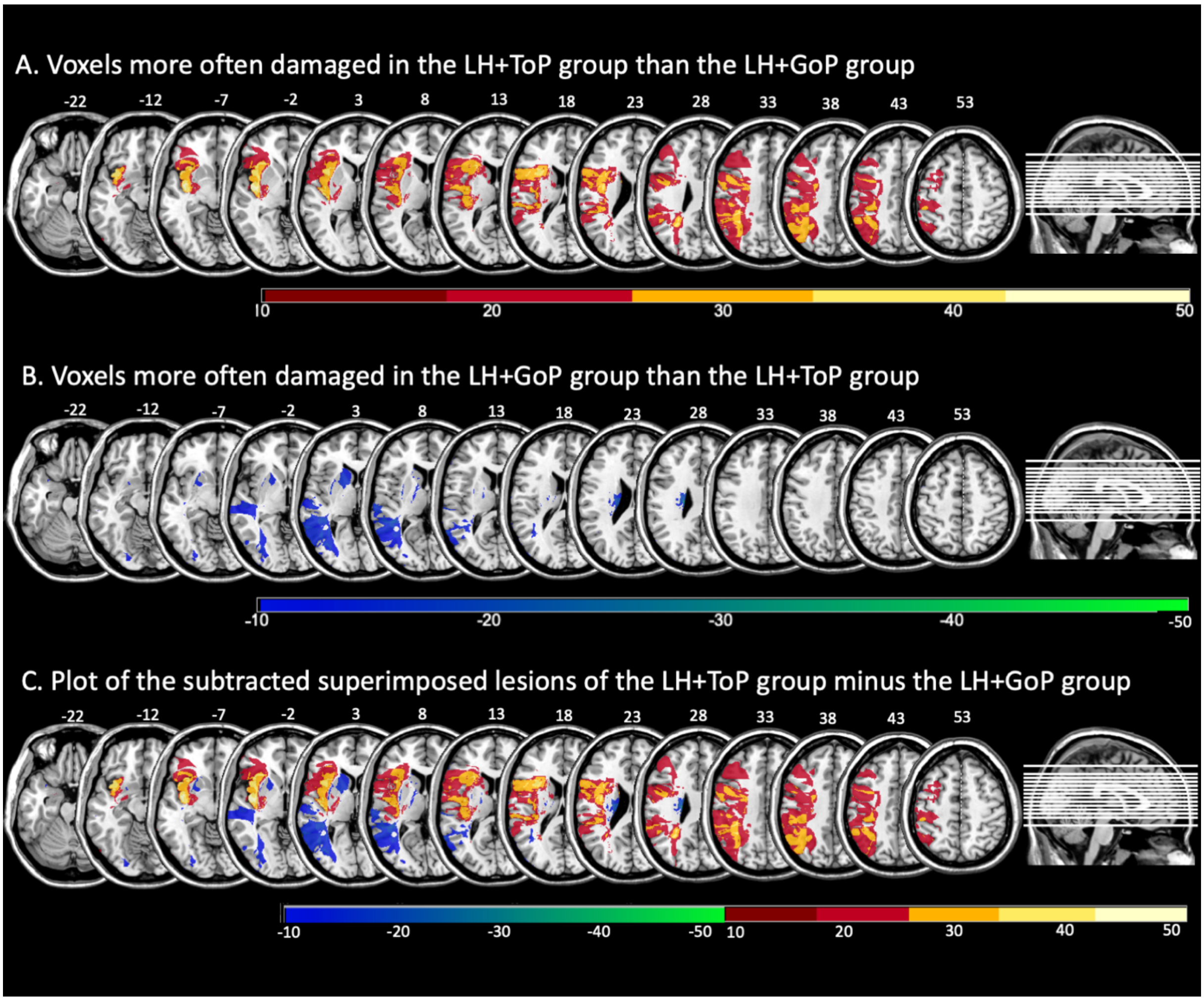
In addition, *Figure 10C* displays the adjusted lesion overlay of the patients with apraxia exhibiting irregular pantomime behaviors (LH+IPB; N = 44; 28 LH+GoP and 16 LH+ToP). The overlap displays only those voxels that were lesioned in at least 5% (i.e., 2/44) of the patients and thus included in the VLSM analysis using the frequency score of GoP behaviors as a predictor. The lesions predominantly affected the left middle cerebral artery (MCA) territory, with the maximum lesion overlap within the putamen observed in 22 of the 44 (14 in the LH+GoP group and 8 in the LH+ToP group) apraxic patients in the LH+IPB group.

5.2.7. Lesion subtraction analysis

The results of the lesion subtraction analysis of the LH+ToP and LH+GoP groups are shown in *Figure 11*. The analysis reveals an anatomical separation of the subtracted lesion overlaps of the LH+GoP and LH+ToP groups that matches the observed dissociation between patients who exhibit ToP behaviors and those who do not.

In patients with apraxia exhibiting ToP behaviors (LH+ToP), the most frequently damaged voxels were predominantly located in the superior temporal gyrus (STG, max. overlap of +46%; MNI coordinates [x, y, z]: -46, -7, -2) and in the posterior insula (max. overlap of +46%; MNI coordinates [x, y, z]: -41, -6, -7). Moreover, frequently damaged voxels were also observed in the par opercularis (max. overlap +37%; MNI coordinates [x, y, z]: -42, +13, +3) and par triangularis (max. overlap +38%; MNI coordinates [x, y, z]: -34, +17, +18) of the IFG extending to underlying parieto-frontal white matter, particularly the superior longitudinal fasciculus (SLF, max. overlap +38%; MNI coordinates [x, y, z]: -36, -5, +23) and anterior corona radiata (max. overlap +40%; MNI coordinates [x, y, z]: -25, +19, +13). The more frequently damaged voxels in the LH+ToP group extended posteriorly to the middle occipital gyrus (max. overlap +31%; MNI coordinates [x, y, z]: -29, -53, +28) and angular gyrus (max. overlap +38%; MNI coordinates [x, y, z]: -36, -39, +33).

Figure 11. Plots of the lesion subtraction analysis of the LH+ToP and LH+GoP groups



Plots of the subtracted lesions of the LH+ToP group (N = 16) showing ToP behaviors minus the LH+GoP group (N = 28) not exhibiting ToP behaviors. ***(A)*** *The subtracted lesions plot indicating voxels more frequently damaged in the LH+ToP group (N = 16) than in the LH+GoP group (N = 28).* ***(B)*** *The subtracted lesions plot indicating voxels more frequently damaged in the LH+GoP group than in the LH+ToP group.* ***(C)*** *The superimposed subtracted lesion plots for the LH+ToP group (warm colors) and the LH+GoP group (cold colors).*

The warm colors ranging from dark red (+10%) to bright yellow (+50%) represent the incremental increase in the percentage of voxels more damaged in the LH+ToP group. Whereas, the cold colors *ranging from dark blue (-10%) to bright green (-50%) represent the incremental increase in the percentage of voxels more frequently damaged in the LH+GoP group.*

In contrast, voxels more frequently damaged in patients with apraxia in the LH+GoP group were less extensive. These were primarily centered on the posterior middle temporal gyrus (max. overlap of -21%; MNI coordinates [x, y, z]: -42, -42, +8), extending to the inferior occipital gyrus (max. overlap -18%; MNI coordinates [x, y, z]: -45, -61, +3), with the highest overlap observed in the caudate nucleus (max. overlap -32%; MNI coordinates [x, y, z]: -18, -19, +23).

5.2.8. Voxel-lesion symptom mapping (VLSM) analyses

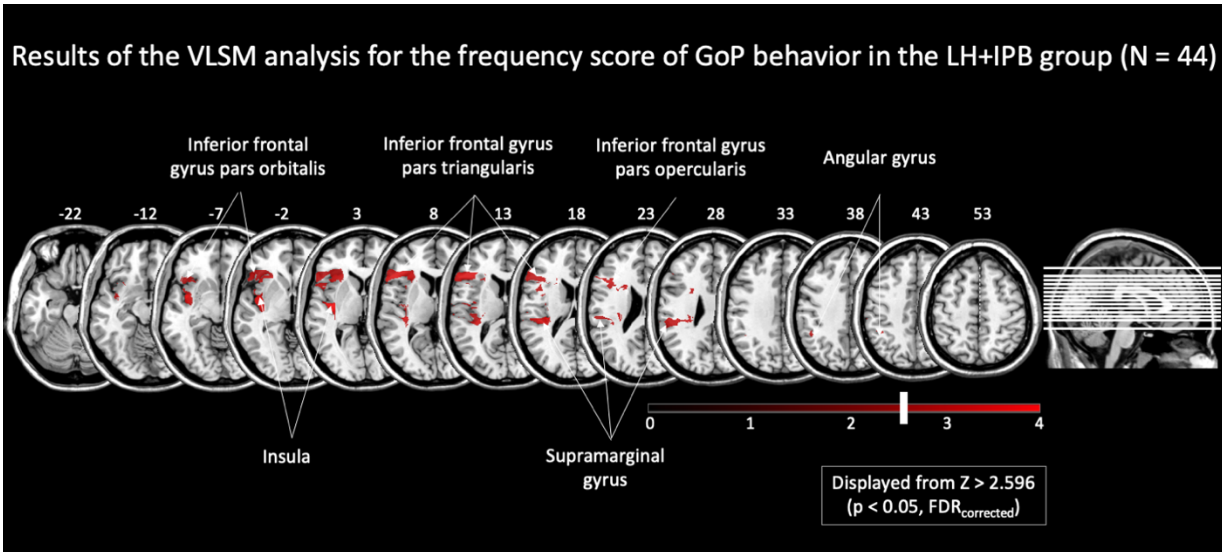
The results of the VLSM analysis with the frequency score of GoP in apraxic LH stroke patients exhibiting irregular pantomime behaviors are shown in *Figure 12*. A lower frequency score of GoP, i.e., a reduced application of the virtual grasping strategy, was associated with lesions of anterior brain regions including the insula (max. *Z*-value = 3.91; MNI coordinates [x, y, z]: -37, -14, -2) and all three parts of the inferior frontal gyrus (IFG; i.e., pars orbitalis (max. *Z*-value = 3.06; MNI coordinates [x, y, z]: -37, +20, -7), pars triangularis (max. *Z*-value = 3.33; MNI coordinates [x, y, z]: -41, +30, +8), and pars opercularis (max. *Z*-value = 3.06; MNI coordinates [x ,y, z]: -43, +13, +18)).

Furthermore, lower frequency scores of GoP were associated with lesions affecting posterior brain regions, with significant clusters found in the supramarginal gyrus (SMG; max. *Z*-value = 3.79; MNI coordinates [x, y, z]: -36, -27, +18) and angular gyrus (AG; max. *Z*-value = 3.29; MNI coordinates [x, y, z]: -43, -43, +43) of the inferior parietal lobule. Additional lesioned voxels significantly associated with a lower frequency score of GoP were observed in the posterior superior temporal gyrus (pSTG; max. *Z*-value = 3.39; MNI coordinates [x, y, z]: -35, -

32, +13), extending into the adjacent white matter, namely the posterior corona radiata (max. *Z*-value = 3.39; MNI coordinates [x, y, z]: -27, -28, +28).

Note that the clusters that remained significant following, a more conservative, permutation-based family-wise error (FWE) correction (at p < .05), included the insula and the supramarginal gyrus (see *Appendix 6*).

Figure 12. VLSM results of the frequency score of GoP behavior for the LH+IPB group.

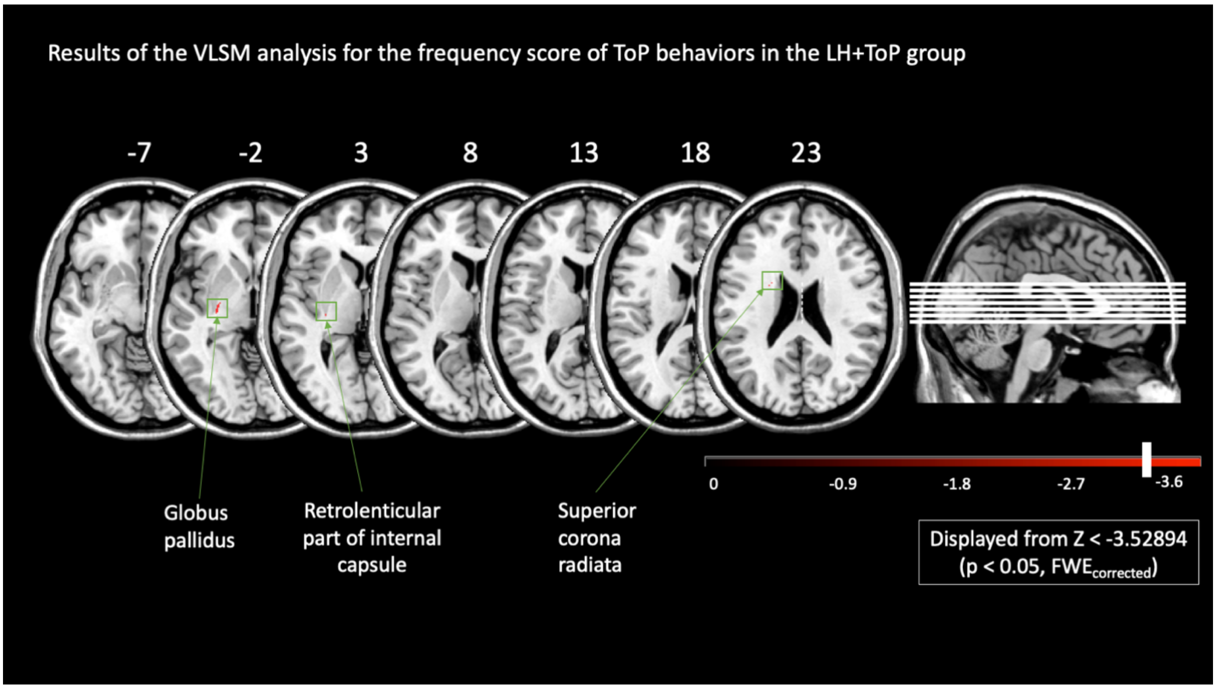


Results of the VLSM analysis for the frequency score of grasping behaviour (GoP) in apraxic LH stroke patients exhibiting irregular behaviors during pantomime assessment (LH+IPB; N = 44). Lesion correlates associated with lower frequency score of GoP behavior were found in the inferior frontal gyrus (pars orbitalis, triangularis, and opercularis), the insula, and the inferior parietal lobule (supramarginal and angular gyrus) of the left hemisphere. Displayed voxels surpassed a Z-value of 2.596, corresponding to a statistical threshold of p < .05, corrected for False Discovery Rate (FDR).

Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000). *The depicted axial slices correspond to the z-coordinates from -22 to +53 in MNI space.*

The results of the VLSM with the frequency score of ToP in the LH stroke patients with apraxia exhibiting tracing behaviors (LH+ToP) are shown in *Figure 13*. Note that due to the small sample size and consequently, lower statistical power, there were no significant voxels following FDR correction. Therefore, reported are clusters that remained significant following, a more conservative, permutation-based family-wise error (FWE) correction (at p < .05) regardless of the cluster size (Rorden *et al.*, 2007). A higher frequency score of ToP, i.e., an increased reliance on the tracing strategy, was associated with lesions affecting the globus pallidus (max. *Z*-value = -3.776 ; MNI coordinates [x, y, z]: -28, -16, -2), the retro-lenticular part of internal capsule (max. *Z*-value = -3.776; MNI coordinates [x, y, z]: -29, -18, -2), and the superior corona radiata (max. *Z*-value = -3.776 ; MNI coordinates [x, y, z]: -24, +4, +23).

Figure 13. VLSM results of the frequency score of ToP behaviors for the LH+ToP group.



Results of the VLSM analysis for the frequency score of ToP in the LH+ToP group (N = 16). Lesion correlates associated with higher frequency score of tracing behavior were found in the globus pallidus, superior corona radiata and the retro-lenticular part of internal capsule of the left hemisphere. Displayed voxels are below a Z-value of -3.52894, corresponding to a statistical threshold of p < .05, corrected for FWE.

Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000). *The depicted axial slices correspond to the z-coordinates from -7 to +23 in MNI space.*

6. General discussion

Apraxia is a complex and multifaceted higher motor disorder that arises from disruptions to various cognitive processes following stroke to the left hemisphere (LH). The main aim of this doctoral thesis is to provide insights about the complex cognitive mechanisms of motor-related memory and visuospatial processing, and their potential neuroanatomical underpinnings, which contribute substantially to apraxic deficits. This aim will be achieved through the discussion of findings from two distinct but complementary studies. The first study primarily focused on the contribution of impairments in working memory (WM) components to apraxia (Bartolo *et al.*, 2003), while the second study predominantly tackled the contribution of deficits in visuospatial processing mechanisms as postulated in the cognitive praxis model (Gonzalez Rothi *et al.*, 1991; Randerath, 2009). In order to align with the central objective of this thesis, the outcomes of both studies will be reexamined and integrated. To this aim, the findings of Study I will be reinterpreted in the context of visuospatial processing mechanisms, whereas the results of Study II will be revisited in relation to motor-related memory processes.

In the following discussion, the primary findings of Study I in conjunction with the secondary findings of Study II will be addressed, with an emphasis on the contribution of motor-related memory deficits. In particular, the discussion will encompass an examination of the contribution of motor WM deficits (from Study I) and long-term manipulation knowledge deficits (from Study II), alongside an exploration of their neuroanatomical correlates. Complementarily, the ensuing discussion will address the secondary findings of Study I alongside the primary results of Study II, with a focus on examining the impact of deficits in visuospatial WM (from Study I) and visuospatial processing mechanisms (from Study

II) on apraxia. This discussion will also include an in-depth analysis of the neuroanatomical underpinnings of visuospatial processing mechanisms associated with apraxia.

Subsequently, the thesis will explore the intricate relationship between aphasia and apraxic deficits following stroke to the LH. This section will concentrate on the insights gained from Study I about motor WM deficits and from Study II about visuospatial processing (and associated pantomime strategies), particularly exploring the independent contribution and/or interaction of these cognitive functions to both aphasia and apraxia. Furthermore, the potential clinical applications of the findings from Study I and Study II for improving current diagnostic tools and developing more effective treatment strategies for apraxia will be comprehensively discussed. Finally, the thesis will address the key methodological constraints encountered in both studies, suggesting potential avenues for future research on the topic.

6.1. Insights into motor-related memory deficits underlying apraxia

6.1.1. Motor working memory deficits in apraxia

The findings from Study I contribute significantly to the understanding of WM deficits in apraxia by underscoring that deficits in a distinct motor WM system play a substantial role in the manifestation of apraxia in patients with a stroke to the motor-dominant LH. The primary outcome of this study was that LH stroke patients with apraxia (LH+) exhibited pronounced deficits in the motor WM task, assessing their ability to maintain and recall action-related information, compared to both healthy controls and LH stroke patients without apraxia (LH-). This evident underperformance in the motor WM task among the LH+ patients remained significant even after accounting for potential influences from verbal and visuospatial WM deficits, evaluated by the forward digit span test (DS) and the block tapping test (BS), respectively (see *Figure 4*). Thus, the observed deficits in the motor WM task insinuate that deficiencies in a motor WM system in patients with apraxia is not merely a byproduct of broader cognitive impairments, but rather a distinct aspect of their neurological condition.

Further substantiating the link between motor WM and apraxic deficits, the findings of Study I revealed that the overall performance on the motor WM subtasks, as operationalized using the mWM composite score, was a predictive marker for the severity of apraxia on clinical tests assessing gesture imitation abilities, that is, tests of the imitation of hand positions and finger configurations. Interestingly, the performance on the 'actions with objects' subtask (AO) emerged as a key predictor of the severity of apraxia (both on clinical tests of gesture imitation and of actual object use) among the three motor WM subtasks (see *Appendix 2*). Despite being the least challenging among the three motor WM subtasks (as evidenced by higher scores on the AO compared to both the MFG and MLG subtasks across all studied groups, see *Figure 4B*), the AO subtask's predictive capacity insinuates that it is the complexity of the encoded action information, rather than the motor WM task's difficulty level, which drove the prediction observed for the performance on clinical tests of imitation by the mWM composite score. Thus, in parallel to the contribution of spatial WM deficits to the clinical symptoms of neglect following damage to the right hemisphere (Wojciulik *et al.*, 2001; Malhotra, 2004), the current findings similarly emphasize the significant impact of motor WM deficits on the clinical manifestations of apraxia following stroke to the LH.

The current neuropsychological findings corroborate earlier studies that introduced WM deficits as underpinning apraxic impairments of gesture imitation and pantomiming object use (Rumiati and Tessari, 2002; Bartolo *et al.*, 2003, Randerath *et al.*, 2011*b*) and further extend these studies by unravelling a more nuanced understanding of the specific contribution of different WM systems, particularly motor WM, to various apraxic deficits. In particular, the findings of Study I lend empirical support to the proposed link between WM deficits and apraxic deficits by demonstrating that motor WM deficits specifically contribute to impairments in gesture imitation, while verbal and visuospatial WM deficits play a broader role in actual object-use deficits among LH+ patients.

In addition, the pattern of findings from Study I suggest a substantial role of the LH's fronto-parietal praxis network not only in the manifestation of apraxia following lesions to this network but also in subserving motor WM functions. Notably, this association between apraxic deficits and motor WM deficits is in alignment with recent neuroimaging findings in healthy participants, which demonstrated the activation of regions within the fronto-parietal praxis network during action-related memory processes, particularly, during the encoding and maintenance stages. For example, the retention of biological motion has been linked to activity in the left middle frontal gyrus, IFG and the inferior and superior parietal lobules of the LH (Lu *et al.*, 2016). Additionally, as the memory load of action sequences increased, a corresponding increase in the activation of the MTG was observed, along with increased functional connectivity between the latter and a fronto-parietal network (Cai *et al.*, 2018). Similar neuroimaging results were observed when recalling manipulable objects that are implicated in goal-directed actions. Specifically, the encoding and recall of manipulable objects, in contrast to the response to non-manipulable objects, triggered the activation of the left ventral premotor cortex as well as the IFG (Chao and Martin, 2000; Mecklinger, 2002). In addition, the ventral region of the premotor cortex, which is anatomically adjacent to the IFG, was shown to play a crucial role in the planning and execution of multi-step or hierarchical object use actions in healthy participants (Grafton *et al.*, 1997; Garcea and Buxbaum, 2019), as well as in the sequencing of complex movements in patients with apraxia (De Renzi *et al.*, 1983; Harington and Haaland, 1992). Note that the processing of such complex action plans necessitates sophisticated cognitive mechanisms capable of effectively chunking and temporally parsing the individual subcomponents of an action sequence (Seidler *et al.*, 2012), mechanisms that are likely to be mediated by a specialized motor WM system. Importantly, a substantial portion of the reported neural substrates implicated in the encoding, retention and recall of action-related stimuli encompass regions within the motor-dominant LH.

In accordance with these findings, the VLSM results from Study I revealed a significant association between performance in the 'actions with objects' (AO) subtask – the sole significant predictor of apraxia severity among the three motor WM subtasks – and a lesion in the IFG in LH+ patients (see *Figure 7*). Likewise, the results of the lesion analysis that were uncorrected for multiple comparisons revealed that a pattern of large lesion clusters in the IFG was associated with the performance on the motor WM composite score and the MFG subtask, along with a relatively small lesion cluster in the IFG linked to scores on the MLG subtask (see *Appendix 3*). Together these insights from neurologically healthy participants and the Study I's sample of LH stroke patients with apraxia converge on the assumption that the IFG may serve as a key node in motor WM processes necessary for praxis abilities, particularly those crucial for executing meaningful gestures, and to a lesser extent, meaningless gestures. It is important to note that for further elucidating the potential left hemispheric lateralization of motor WM processes, comparative studies are warranted that undertake direct comparisons between LH stroke patients and those with RH stroke.

6.1.2. Manipulation knowledge and pantomime strategies

Pantomiming the use of objects comprises two sequential phases (Niessen et al., 2014; Roy and Hall, 1992). First, a 'trigger phase' encompassing the activation of a stored motor schema (i.e., manipulation knowledge) that serves as a valid proxy for actual object use. This motor schema contains the long-term stored specification of spatio-temporal characteristics that are pertinent for the use of a given object (Gonzalez Rothi *et al.*, 1991; Buxbaum, 2001). Second, an ‘execution phase’ that involves the transformation of this motor schema into an explicit motor command for pantomiming the use of objects, including the successive and anatomically dissociable components of pretending to (i) reach for and transport the hand towards the object, (ii) configure the hand to grasp the object, and (iii) the use of the object accordingly (Vingerhoets, 2014).

The observations of irregular approach behaviors in patients with apraxia in Study II provide insights into two distinct strategies – namely, virtual grasping and tracing of object pictures – with disparate outcomes that were potentially implemented either to facilitate or even to alleviate difficulties in retrieving the manipulation knowledge necessary to execute an accurate pantomime of object use. Note that the difficulties exhibited by patients with apraxia during pantomiming object use at the level of triggering and retrieving stored manipulation knowledge is partially attributed to the absence of tactile and visual feedback (here for 3D shapes) that are inherently afforded by physically holding and manipulating an object (Canzano *et al.*, 2016). These feedback mechanisms play a supportive role in eliciting accurate object-use pantomimes, as evidenced by the improved performance of pantomiming object use in the presence of proprioceptive cues received from holding an object in hand (De Renzi *et al.*, 1982; Goldenberg *et al.*, 2004; Hermsdörfer *et al.*, 2013), as well as following visual perception of object affordances in real objects and pictures of objects (Buxbaum *et al.*, 2005; Jax *et al.*, 2006, Randerath *et al.*, 2011*b*; Bartolo *et al.*, 2020). In accordance with the latter reported benefits of online visuomotor feedback, the virtual grasping behavior, predominantly observed in the patients with apraxia exhibiting virtual grasping (LH+GoP), appears to be instrumental in efficiently triggering the accurate retrieval of the motor schema associated with the presented objects, leading to a better pantomime performance in this group. This assertion is corroborated by the better performance of the LH+GoP patients on the KAS pantomime subtests in comparison to the patients with apraxia exhibiting tracing (LH+ToP; see *Table 3*), as well as the positive correlation between the frequency of the virtual grasping (GoP) behavior and pantomime performance (see *Appendix 5*).

In addition, this compensatory recruitment of the virtual grasping strategy is likely to have been mediated via a relatively intact bilateral dorso-dorsal stream. The latter has been shown to be crucial in compensating for difficulties in retrieving manipulation knowledge, posited to be stored in the ventro-dorsal stream, through relaying real-time proprioceptive and tactile information to activate motor schemas in patients with apraxia (for an overview see Buxbaum, 2017). Notably, the subtraction analyses qualitatively differentiating between the patients in the LH+GoP and LH+ToP groups revealed that the LH+GoP patients exhibited no relevant lesions affecting areas within the dorso-dorsal stream of the LH (compared to the LH+ToP patients; see *Figure 11*). These findings suggest a relatively preserved left dorso-dorsal stream in the LH+GoP in contrast to the LH+ToP patients. It is possible that the compensatory recruitment of the virtual grasping strategy might have relied upon the established complex interplay of feedforward and feedback mechanisms across the neural action streams of the object processing network, namely, the ventral, ventro-dorsal and dorso-dorsal streams (Mahon *et al.*, 2013; van Polanen and Davare, 2015; Fabbri *et al.*, 2016). In particular, the neural processes underlying the implementation of the virtual grasping strategy may have incorporated an initial transfer of functional knowledge (pertaining to what an object is used for and assumed to be preserved in LH+GoP patients; see *Section 6.3.2.*) from the ventral stream to the dorso-dorsal stream following the visual perception of the object-picture. Consecutively leading to an initiation of an appropriate grip posture for (virtually) grasping the object by the dorso-dorsal stream, which in turn might have provided online feedback to the ventro-dorsal stream, thereby, facilitating the activation of the motor schema necessary for executing the object use pantomime.

Within this complex neural interplay, the IFG, through its connectivity with the SMG, is hypothesized to serve as a hub integrating and coordinating the information flow across the different streams (Randerath *et al.*, 2010; Garcea and Buxbaum, 2019). This role is in accordance with the IFG's previously observed involvement in working memory (WM) functions (see *Section 6.1.1.*). Interestingly, the VLSM analysis using the frequency of GoP behaviors revealed a notable association between a reduced reliance on the virtual grasping strategy and lesions to the IFG and SMG (see *Figure 12*). In light of the previous claims, the diminished ability of the patients with apraxia to implement the virtual grasping strategy may be attributed to combined lesions in the IFG and SMG, which likely disrupted an efficient coordination of information flow across the action processing streams. This disruption is potentially centered on a compromised WM subsystem that is supported by the IFG – supposedly the motor WM subsystem – and which plays a crucial role in monitoring and fine-tuning action outputs in conjunction with the SMG.

6.1.2.1 Tracing and the technical reasoning hypothesis

In contrast to the virtual grasping strategy, the implementation of tracing behaviors prior to pantomiming object use appears to be less effective in triggering the required motor schema. This is substantiated by the lower pantomime performance in the LH+ToP group compared to the LH+GoP group (see *Table 3*) and the negative correlation between the frequency of ToP behaviors and pantomime scores (see *Appendix 5*). Furthermore, the LH+ToP patients exhibited more lesions affecting the left dorso-dorsal stream compared to the

LH+GoP patients (see *Figure 11*), suggesting a potentially compromised capacity in the LH+ToP group to effectively recruit this stream for compensating their deficits in accessing manipulation knowledge. Notably, the LH+ToP patients exhibited a prolonged and atypical engagement in the initial phase of pantomiming object use, here characterized by reaching for and persistently tracing the contour of object pictures. Crucially, this behavior indicates an unwarranted lingering in this phase, accompanied by prominent difficulties and delays in smoothly transitioning to the subsequent phase of pretending to grasp the object. Such a pattern of disruption in the hierarchical flow of execution phases, implies that the LH+ToP patients may have had specific impairments in the lateral part of the dorso-dorsal stream – putatively involving the anterior IPS and posterior part of the IFG (pars opercularis) – primarily associated with the grasping phase (Binkofski *et al.*, 1999; Culham *et al.*, 2003; Frey *et al.*, 2005). In contrast, the medial part of the dorso-dorsal stream – putatively involving the SPL, medial IPS and dorsal premotor cortex – supporting the reaching stage (Johnson, 2002; Karnath and Perenin, 2005; Blangero *et al.*, 2009), appears to be relatively intact in the LH+ToP patients. In accordance with these claims, it is possible to postulate that the previously discussed effectiveness of the virtual grasping strategy in accessing manipulation knowledge in the LH+GoP patients might be primarily driven by a preserved functionality specifically in the grasp system within the dorso-dorsal stream.

In addition, the behavior of tracing the object's contour with the fingers or hands in the LH+ToP group can be interpreted as an attempt to extract the object's physical visuomotor properties – particularly its shape and spatial details – that are essential for grasping and using it (Graham *et al.*, 1999; Valenza, 2001). Notably, among several stereotypical haptic strategies used by healthy participants to identify objects, 'contour following' – akin to the observed tracing strategy – was shown to be the most efficient in extracting ‘precise spatial details concerning an object’s shape’, despite being the most time-consuming (Klatzky and Lederman, 1992; Lederman and Klatzky, 1993). The ability of the LH+ToP patients to recruit such structural processing mechanisms is also apparent in the absence of significant differences in performance between them and LH+GoP patients on the apraxia tests strongly requiring structural processing, namely, Goldenberg’s finger imitation test and De Renzi’s test for actual object use (see *Table 3*; Schwoebel and Coslett, 2005; Goldenberg and Karnath, 2006; Matheson *et al.*, 2017; Tamè *et al.*, 2017; Schmidt *et al.*, 2022).

Importantly, mechanisms for extracting visuomotor properties are argued to draw upon mechanical knowledge, which delineates the capacity to discern *de novo* possible conventional (or non-conventional) uses of familiar objects, as well as potential uses of novel objects, through an analysis of their structural properties (Goldenberg and Spatt, 2009; Goldenberg, 2014). Deficits in mechanical knowledge have been associated with impaired object use in patients with a stroke to the LH (Goldenberg and Hagmann, 1998; Lesourd *et al.*, 2019). In contrast to the manipulation knowledge hypothesis that posits pantomiming (and actual) object use to rely on retrieving stored motor representations, the technical reasoning hypothesis posits that pantomiming (and actual) object use is primarily contingent upon online mental simulations about potential mechanical actions afforded by the physical properties of an object (Osiurak *et al.*, 2009, 2011, 2021). Although beyond the scope of the current PhD dissertation, briefly addressing the ongoing debate between these two hypotheses (Jarry *et al.*, 2013; Osiurak and Badets, 2016; Buxbaum, 2017; Kleineberg *et al.*, 2023) is instructive for the improvement of the praxis model. Within this framework, the current observations in the LH+ToP group insinuate that relying on mechanical problem solving, as evidenced by the attempt of extracting the objects’ visuomotor properties via the tracing behaviour, is inadequate for triggering accurate pantomiming of object use. Thus, the findings of Study II lend partial support to the manipulation hypothesis, suggesting that accurate pantomiming of object use may depend more on accessing and retrieving stored motor schemas than on real-time mechanical problem solving and structural processing based on objects' physical properties.

6.2. Insights into visuospatial deficits underlying apraxia

6.2.1. Visuospatial working memory deficits and object use

The prediction models of apraxic deficits in Study I have elucidated the crucial contribution of visuospatial WM to the manifestation of apraxic deficits during actual object use. While deficits in visuospatial WM were not shown to significantly influence performance in gesture imitation in patients with apraxia, performance on the De Renzi test of actual object use was positively correlated with both visuospatial and verbal WM, as measured using the block span (BS) and digit span (DS) tests, respectively (see *Appendix 2*). This outcome aligns with existing evidence underscoring the involvement of these two WM subsystems in object use tasks (Baumard *et al.*, 2014). On the one hand, the contribution of verbal WM is particularly pronounced in tasks of pantomiming object use (Bartolo *et al.*, 2003) and may relate to the processing of stored semantic representations pertaining to the conventional use of objects (i.e., functional knowledge; Postle *et al.*, 2005). On the other hand, the analysis of object affordances during both pantomiming object use and actual object use has been demonstrated to require the processing of spatial relationships between the hand/fingers and the object (Randerath *et al.*, 2011*a*). The latter potentially involves the short-term storage and manipulation of spatial relationships within visuospatial WM as the (pantomime of) object use unfolds, thereby enabling continuous updating and coordination of movements with respect to the changing position and orientation of the object.

In addition, the assessment of object use implemented in this study required the single use of objects (e.g., hammering), which may have been adequately supported by preserved visuospatial WM processes (in conjunction with preserved verbal WM) in patients with apraxia. However, these processes are likely not to be sufficient in more complex object use tasks that involve multiple action steps to achieve the intended action goal (e.g., preparing toast and coffee; Schwartz *et al.*, 2002), which more closely resemble activities of daily living. Notably, patients with apraxia were shown to commit more errors during the execution of increasingly complex sequences of hand (Harrington and Haaland, 1992) or arm (Weiss *et al.*, 2001) movements. For such complex sequences of actions, a more specialized motor WM subsystem might be necessary in order to effectively maintain and manipulate the representations of multiple action units constituting the complete action sequence. In fact, if stroke patients relied exclusively on spatial WM strategies for processing the stimuli in the novel motor WM task, involving sequences of static body images, one would expect their performance in this task to be comparable to that in the BS task. However, Study I revealed a distinct differentiation in WM performance across these tasks between the stroke patients with (LH+) and without apraxia (LH-). While there were no significant differences observed between the two groups on the BS task, significant differences were evident across the motor WM subtasks (see *Figure 4*). These findings further imply that the (sole) implementation of visuospatial WM processes may be inadequate for storing and manipulating complex action sequences.

6.2.2. Visuospatial processing and pantomime strategies

The main findings of Study II indicated that the use of the virtual grasping strategy during pantomime assessment serves as a compensatory mechanism that improves pantomime performance in LH stroke patients with apraxia; potentially by facilitating the retrieval of stored manipulation knowledge (see *Section 6.1.2*). In particular, the apraxic LH stroke patients exclusively employing the virtual grasping strategy (LH+GoP) showed better pantomime performance (both for objects involving bucco-facial movements and for objects involving arm/hand movements) compared to the apraxic LH stroke patients using the tracing strategy (LH+ToP; *see Table 3*). Moreover, the frequency of virtual grasping (GoP) behaviors positively correlated with overall pantomime performance in both LH+GoP and LH+ToP groups (see *Appendix 5*). In addition, albeit non-significant, a discernable trend insinuates that the LH+GoP group outperformed the apraxic patients exhibiting regular pantomime behaviors (LH+RPB) in the KAS pantomime tests (see *Table 3*). It is important to note that no significant differences in performance were found across the different clinical and neuropsychological measures when comparing apraxic LH stroke patients showing regular behaviors (LH+RPB) with those showing irregular behaviors (LH+IPB) during pantomime assessment.

Interestingly, in a recent study investigating the effect of using holograms on pantomime performance in stroke patients with apraxia (Rohrbach *et al.*, 2021), an ‘interaction scale’ assessed the presence or absence of an interaction with different object representations (holograms or pictures on a screen that were presented in a static or dynamic state) before pantomime execution. In corroboration to the current observation of better pantomime performance in LH+GoP patients, Rohrbach et al. (2021) also found that a more pronounced interaction with dynamic object cues correlated with better pantomime performance in their stroke patients with apraxia. Notably, in Rohrbach et al.'s (2021) study, approach behaviors (“interaction”) were mostly directed towards animated objects on a screen or holograms, whereas in Study II, approach behaviors were directed towards static pictures of objects in the KAS stimulus folder. Furthermore, the method of Study II consisted of contrasting two different types of irregular approach behaviors (GoP, ToP), whereas

Rohrbach and colleagues performed correlation analyses with the amount of observed object interactions, independently of the type of interaction, i.e., reaching to and grasping or following the object.

In addition to an improved pantomime performance, the LH+GoP patients differentially outperformed the LH+ToP patients on two apraxia tests assessing the imitation of arm/hand gestures, namely Goldenberg's test for imitating hand positions and the KAS subtest for imitating arm/hand gestures. In contrast, no significant differences were observed between the LH+GoP and LH+ToP patients on other apraxia assessments, including actual object use, imitation of finger configurations and imitation of bucco-facial gestures. Similarly, no significant differences were observed between the LH+GoP and LH+ToP groups on clinical assessments of basic motor parameters, overall disability, and stroke symptoms severity (see *Table 3*). These findings further suggest that the compensatory virtual grasping strategy might highly rely on motor-cognitive mechanisms specifically employed during the imitation of arm/hand gestures.

Notably, in a previous sample of 91 LH stroke patients (with and without apraxia), Goldenberg's test for imitating hand positions as well as the KAS subtest for imitating arm/hand gestures highly loaded on a PCA component representing the processing of intrinsic spatial relationships between different body parts and/or extrinsic spatial relationships between external objects and the body (see component #2 in Schmidt et al., 2022). Therefore, the current pattern of the neuropsychological test results suggests that the virtual grasping behavior (GoP) and the imitation of arm/hand gestures are both reliant on visuo-spatial processing mechanisms, damage to which was shown to contribute extensively to apraxic deficits (see *Section 1.6.1.*; Randerath *et al.*, 2011*a*). Furthermore, the processing of spatial relationships (represented by the component #2 of Schmidt *et al.*, 2022) was associated with lesions to the supramarginal gyrus (SMG) and the angular gyrus (AG). In the VLSM analysis of Study II, a lower reliance on the virtual grasping strategy was associated with lesions in the SMG and AG (see *Figure 12*), i.e., the two brain regions associated with the cognitive component representing spatial processing mechanisms (Schmidt et al., 2022). These VLSM findings further corroborate the hypothesized link between the reliance on the virtual grasping strategy and the cognitive mechanisms subserving visuo-spatial processing in the context of pantomime actions.

In addition to the IPL's well known role in gesture imitation (Goldenberg and Karnath, 2006; Kleineberg et al., 2023; Lesourd et al., 2018), it plays a crucial role in processing intrinsic and extrinsic spatial relationships during the planning and execution of object-directed grasping (Goldenberg, 2009). Particularly, the AG was implicated in the planning of appropriate hand configurations for object use (Randerath *et al.*, 2010), while the SMG was involved in processing contextually relevant spatial parameters during the execution of object-directed grasping actions (Vingerhoets, 2014; Reynaud *et al.*, 2016). These previous findings are consistent with the current observation that IPL lesions result in a reduced frequency of the virtual grasping behavior.

In addition to lesion correlates in the IPL, reduced reliance on the virtual grasping strategy was also associated with multiple brain regions consistently related to pantomime deficits in patients with apraxia. These regions encompassed the IFG (Goldenberg et al., 2007), the insula (Hermsdörfer *et al.*, 2013), and the STG (Malfatti and Turella, 2021). Especially the IFG, through its connection with the SMG, contributes to the selection of functional grasping actions for subsequent object use (Randerath *et al.*, 2010; Kleineberg *et al.*, 2018), particularly in the presence of conflict arising from selecting among multiple competing responses (e.g., different hand configurations) triggered by the same object (Miller and Cohen, 2001; Thompson-Schill and Botvinick, 2006; Watson and Buxbaum, 2015). Furthermore, the current dissertation posited a central role of the IFG in motor working memory functions (see *Section 6.1.1.*) and in coordinating the interactions between the ventro-dorsal and dorso-dorsal action streams for the purpose of efficiently retrieving stored motor representations related to object manipulation (see *Section 6.1.2.*). Both of these functions considered to be highly pertinent for the production of an accurate pantomiming of object use (Bartolo *et al.*, 2003; Buxbaum, 2017).

In contrast to the LH+GoP patients, those who implemented the tracing strategy (LH+ToP) exhibited notable deficits in recruiting visuospatial processing mechanisms to improve their pantomiming performance, which was shown to be significantly worse than in the LH+GoP patients (see *Table 3*). This was corroborated not only by their underperformance on tests that rely heavily on visuospatial processing (i.e., Goldenberg's imitation of hand positions and the KAS subtest of imitating arm/hand gestures), but also by the VLSM outcomes using the frequency of ToP behaviors. In particular, a higher frequency of ToP behaviors was associated with lesions in the globus pallidus (GP) and adjacent white matter structures, namely, the internal capsule and corona radiata (see *Figure 13*). Although research focusing on the contribution of subcortical lesions to apraxic deficits are relatively scarce, several studies have highlighted the significance of lesions to the basal ganglia (BG) in the manifestation of specific apraxic deficits. The BG, through its function as a subcortical junction for parieto-frontal circuits (Rizzolatti *et al.*, 1998), were implicated in apraxic impairments in the sensorimotor transformations of visually perceived spatial object locations relative to body parts into an appropriate hand posture and grip configuration for grasping (Della Sala *et al.*, 1992; Leiguarda and Marsden, 2000). Notably, the BG were shown to be involved in the spatiotemporal coordination of object-oriented movements related to pre-learned motor schemas, such as reaching and grasping, in patients with apraxia (Hanna-Pladdy, 2001) and healthy participants (Deiber *et al.*, 1991; Rushworth *et al.*, 1998). Supporting these observations, the GP was also shown to be activated during grasping in healthy participants (Matsumura *et al.*, 1996; Rizzolatti *et al.*, 1996), and its dysfunction in Parkinson's disease patients was associated with deficits in memory-guided reaching (Jackson *et al.*, 1995) and with delays in transitioning from reaching to manipulating objects (Bennett *et al.*, 1995). These previous reports suggest that the GP is a key structure within the BG for visuospatial computations necessary for object-directed reaching and grasping. Thus, the current VLSM results corroborate the claim that a higher reliance on the tracing strategy in LH+ToP patients is indicative of impairments in effectively recruiting visuospatial processing mechanisms. Note that a recent study highlighted the importance of lesions in the caudate nucleus, rather than in the GB, in the manifestation of apraxic deficits in patients with subcortical LH stroke (Schmidt *et al.*, 2023). The discrepancy between this study's outcome and the current findings of Study II can be attributed to differences in the studied samples of LH stroke patients. In particular, Schmidt *et al.* (2023) investigated patients with exclusively subcortical lesions while excluding those with combined cortical and subcortical lesions; whereas, the patients in the LH+ToP group had lesions encompassing both cortical and subcortical areas. Therefore, the observed association of lesions in the GP with the degree of reliance on the tracing strategy might be attributed to the crucial interaction of the GB with cortical areas in coordinating complex actions. Particularly, the VLSM results may point to a disruption in the effective communication between the GP and the parieto-frontal circuits during pantomiming object use.

Together, the VLSM results of Study II indicate that apraxic LH stroke patients, who exhibited a reduced reliance on the virtual grasping strategy and those who exhibited an increased reliance on the tracing strategy during pantomime assessments, were more likely to have damage to brain regions subserving spatial processing mechanisms. These VLSM results complement the behavioral findings, emphasizing that apraxic patients with preserved or less damaged brain regions associated with visuospatial processing mechanisms may be able to effectively recruit the virtual grasping strategy, resulting in improved pantomime performance.

Importantly, the findings of Study II lend additional support to Randerath's (2009) proposal regarding the key role of a visuospatial component in reducing the cognitive load on WM processes prior to action execution (see *Figure 1* and *Section 1.4.3.*). In particular, the implementation of the virtual grasping strategy, shown to be highly dependent on robust visuospatial processing mechanisms, is likely instrumental in minimizing the cognitive burden on WM typically inherent in pantomiming object use, primarily by providing online visuomotor feedback. Importantly, by leveraging intact visuospatial abilities to support WM mechanisms, the application of the virtual grasping strategy facilitated an efficient retrieval and integration of manipulation knowledge into the ongoing action plan, and consequently, contributed to more accurate pantomime performance in patients with apraxia (see *Section 6.1.2.*). Furthermore, the observation of reduced virtual grasping in apraxia patients with more pronounced lesions in the IFG further suggest that these visuospatial processing mechanisms specifically support motor WM processes, shown to be essential for planning and executing actions. Thus, current findings not only support but also extend Randerath's (2009) proposal by elucidating a distinct interplay between visuospatial processes and a specialized motor WM system.

6.3. Contribution of concomitant aphasia to apraxic deficits

6.3.1. Concomitant aphasia and motor working memory

The results of the complementary analysis examining the impact of aphasic deficits on the performance of the LH stroke patients in the motor WM subtests suggest that language-related impairments do not modulate motor-related WM mechanisms. In corroboration with existing research on the relationship between aphasia and distinct WM deficits (Christensen *et al.*, 2018), the results of Study I indicated that aphasic deficits negatively affected performance in verbal WM (as measured by the digit span (DS) task), but had no discernable effect on performance in visuospatial WM (as measured by the block span (BS) task). In particular, LH stroke patients with no/minimal and mild aphasia performed significantly better on the DS task in comparison to the LH stroke patients with moderate and severe aphasia, while no significant differences in performance across the four aphasia groups were observed in the BS task. Importantly, concomitant aphasic deficits showed no significant impact on the motor WM composite score as well as the three motor WM subtasks: actions with objects (AO), meaningful gestures (MFG), and meaningless gestures (MLG). Specifically, LH stroke patients with various aphasia severity levels (i.e., mild, moderate and severe) exhibited no substantial differences in performance across these tasks (see *Figure 5*). Note that even the higher scores of patients with no/minimal aphasia (considered to be equivalent to a control group) on the AO subtask compared to the patients with varying aphasia severity was no longer significant compared to patients with mild and moderate aphasia after controlling for apraxia severity (see *Appendix 1*). Therefore, after adjusting for apraxic impairments, LH stroke patients with varying aphasia severity displayed a relatively similar performance in motor-related WM tasks, further supporting the claim that the observed deficits in motor WM in the Study I's cohort of LH stroke patients with apraxia (LH+) are more likely to be related to apraxic deficits rather than aphasic impairments.

In alignment with this notion, the LH+ patients did not exhibit specific impairments in the motor WM subtasks that involved semantically meaningful stimuli, namely, the AO and MFG subtasks. It is noteworthy that these tasks are associated with corresponding action-semantic representations and are typically processed via the indirect (semantic) action route (see *Figure 1*). Actually, the LH+ patients' impairments extended to the MLG subtask involving the encoding and retrieval of meaningless stimuli that are not typically associated with semantic representations (see *Figure 4*), and which are presumably processed via the direct (non-semantic) action route (see *Figure 1*). These observations insinuate that the functional scope of motor WM is not restricted to processing actions linked to action-semantic representations, but rather suggest that the encoding of actions in motor WM might occur independently of, or at least might not necessarily require, an understanding of the action's semantic content. Notably, this comprehensive nature of motor WM reconciles the theoretical claims posited within the cognitive model of apraxia, namely, the proposed function of WM in processing information along the indirect route (Bartolo *et al.*, 2003; represented by the orange dashed lines in *Figure 1*) as well as direct route (Cubelli *et al.*, 2000; represented by the green dashed lines in *Figure 1*). It is important to note that the aphasia assessment in Study I was confined to the Token Test, which focuses solely on assessing verbal comprehension without any distinct evaluation of semantic and/or phonological deficits. Therefore, the findings of the analyses considering aphasia severity should be taken with caution, as this limited aphasia assessment cannot conclusively determine whether any impairments in processing action-semantic information that are typically related to long-term memory processes (e.g., functional knowledge), had any impact on the processing and retrieval of the displayed action stimuli in the motor WM subtasks.

6.3.2. Concomitant aphasia and pantomime strategies

At the group level, no significant differences were observed between the patients of Study II exhibiting the virtual grasping strategy (LH+GoP) and those employing the tracing strategy (LH+ToP) in their performance across the ACL-K test, assessing concomitant aphasia (see *Table 3*), nor were there any significant disparities between the two groups in their aphasia severity profiles (i.e., frequencies of patients classified as having mild, moderate or severe aphasia; see *Section 5.2.3.*). However, an intriguing pattern of disparate predictions emerged in the investigation of the relationship between the two pantomime strategies prior to pantomiming object use and the severity of aphasia, as assessed by the ACL-K. On the one hand, a more pronounced reliance on the virtual grasping strategy during pantomime assessment (as operationalized by the frequency score of GoP behaviors) was positively correlated with the ACL-K scores (i.e., with less severe aphasic deficits) in the sample of apraxic LH stroke patients showing irregular behaviors (LH+IPB). This significant pattern was consistently observed across both LH+GoP and LH+ToP groups (see *Figure 9A*). On the other hand, a greater reliance on the tracing strategy (as operationalized by the frequency score of ToP behaviors) was negatively correlated with the ACL-K scores (i.e., with more severe aphasic deficits) in the LH+ToP patients (see *Figure 9B*). These findings suggest that the degree to which patients with apraxia relied on the virtual grasping and tracing strategies was indicative of disparate aphasic deficits, namely, a reduced severity of aphasia was associated with a higher implementation of the grasping strategy, whereas an increased severity of aphasia was associated with a greater dependence on the tracing strategy. Notably, these observations resonate with the proposed communicative function of pantomiming, namely, that pantomimes serve to convey conceptual information about the properties and usage of objects, which heavily relies on the extraction and integration of stored functional knowledge from semantic memory (Goldenberg and Randerath, 2015; Goldenberg, 2017; Finkel *et al.*, 2018).

Importantly, the observed object-directed grasping movements were predominantly directed towards the object part that is usually grasped when using the corresponding object (e.g., the handle of a cup), implying an accurate recognition of the presented object and its functional elements, particularly its graspable part, following visual processing (Goodale and Milner, 1992; Creem and Proffitt, 2001). In contrast, the tracing behaviors were not directed towards the functional parts of the object pictures, such as the handle (i.e., graspable element) or the head (i.e., the element through which an object interacts with the external environment), but these behaviors rather involved random tracing along the object's contours. This pattern of behavior likely indicates a failure in visually recognizing the action-relevant object properties through the retrieval of stored semantic representations, leading to an attempt to alternatively recognize it via structural processing and mechanical problem solving (see *Section 6.1.2.1.*). Thus, based on this qualitative analysis of the two pantomime strategies, it is conceivable to postulate that a greater reliance on the virtual grasping strategy might be associated with more preserved access to and integration of functional knowledge into the motor plan, whereas the increased recruitment of the tracing strategy could suggest a rather disturbed and/or limited access to this functional knowledge. As previously discussed, preserved functional knowledge, which is hypothesized to be supported by ventral stream areas in the left temporal lobe (Canessa *et al.*, 2008; Goldenberg and Spatt, 2009), is likely to provide pivotal feedforward information about what an object is used for towards the ventro-dorsal and dorso-dorsal streams, thereby potentially initiating the observed (virtual) grasping behaviors that can boost pantomime performance in patients with apraxia (see *Section 6.1.2.*).

Together these findings insinuate that the observed association between more severe aphasic deficits and an increased reliance on tracing behaviors on the one hand as well as a decreased reliance on virtual grasping behaviors on the other hand, may relate to specific deficits in retrieving and integrating functional knowledge into the pantomime of object use. It is important to note that while functional knowledge is deemed pivotal for producing an accurate pantomime of object use, it is not considered sufficient on its own, but rather requires a complementary interplay with manipulation knowledge and/or technical reasoning (Buxbaum and Saffran, 2002; Buxbaum, 2017; Osiurak *et al.*, 2021).

6.4. Clinical applications and future prospects

6.4.1. Clinical implications of a specialized motor WM subsystem

The findings from Study I underscore the apraxia-specific nature of motor WM deficits and their potential prognostic relevance for post-stroke apraxia, especially gesture imitation, in LH stroke patients. In particular, the observed impairments in motor WM among LH+ patients were independent of concomitant aphasia (see *Figure 5*) and distinct from deficiencies in other WM domains, namely, verbal and visuospatial WM (see *Figure 4*). Therefore, motor WM impairments in LH stroke patients with apraxia do not merely result from general stroke-related cognitive deficits (El Husseini *et al.*, 2023), but rather constitute a fundamental component contributing to post-stroke apraxia, paralleling the pivotal roles of verbal WM in aphasia following LH damage (Christensen *et al.*, 2018) and visuospatial WM in neglect following RH damage (Wojciulik *et al.*, 2001; Malhotra, 2004).

This specificity and sensitivity of motor WM in detecting and predicting apraxia highlight the added value of incorporating motor WM assessments into the standardized neurobehavioral batteries used in clinical settings to evaluate apraxia. Although current apraxia screening batteries evaluate a broad range of apraxic deficits, including object use, pantomiming of object use, and gesture imitation (Weiss *et al.*, 2013; Goldenberg and Randerath, 2015; Watson and Buxbaum, 2015), integrating an additional neuropsychological test for motor WM would improve the comprehensiveness of these batteries. However, an additional test would also make the screening process more time-consuming and potentially increase the cognitive and physical demands on stroke patients (Rothi *et al.*, 1997).

In light of these considerations, the current research advocates the use of a simple and short action recognition paradigm, namely, the novel motor WM task, as an adequate and effective tool for evaluating motor WM in stroke patients. The implementation of this paradigm closely resembles the commonly used Corsi Block tapping test for assessing visuospatial WM deficits post-stroke (Corsi, 1972; Ronchi *et al.*, 2009), thus making it highly suitable for clinical application. A key advantage of the novel motor WM task is its ability to circumvent the physical constraints inherent in alternative action production paradigms of motor WM (Smyth and Pendleton, 1989, Woodin and Heil, 1996*b*; Rumiati and Tessari, 2002), the results of which might be affected by lower-level motor deficits in stroke patients. In addition, the novel motor WM paradigm permits an evaluation of a broader range of actions, including the retrieval of both unimanual and bimanual actions (see *Figure 3*), whereas the scope of stimuli presented in action production paradigms would be restricted to unimanual actions, due to the requirement for patients to use their ipsilesional, non-paretic hand to reproduce actions during apraxia assessments.

The importance of motor WM functions in predicting apraxia severity suggests that rehabilitative approaches targeting motor WM deficits could effectively translate into the recovery or improvement of praxis functions following stroke, particularly those pertaining to gesture imitation. Crucially, similar treatment approaches targeting verbal WM deficits were shown to significantly improve aphasia symptoms (for a review see Salis *et al.*, 2015). Moreover, WM training strategies were proven to be effective in increasing WM capacity in stroke patients (Westerberg *et al.*, 2007). Following these findings, clinicians are encouraged to implement treatment strategies that specifically concentrate on training or restoring motor WM functions in patients with apraxia. Such strategies could involve training patients to produce sequences of actions that progressively increase in complexity, mirroring those typically encountered in activities of daily living. For instance, treatment strategies such as the 'naturalistic action therapy' (Randerath and Buchmann, 2019; Buchmann *et al.*, 2020), in which patients with apraxia are guided in performing a series of movements to achieve an end goal (e.g., preparing an envelope with a letter), could be particularly promising in restoring motor WM functionality. Note that a specialized motor WM subsystem could play a crucial role in effectively organizing and parsing sub-actions that make up complex action sequences, thus enabling stroke patients to break down such complex tasks into manageable steps.

In addition, the non-invasive brain stimulation method of transcranial direct current stimulation (tDCS) has been proven to be effective in restoring cognitive functions that are compromised in several brain disorders (for reviews see Hill *et al.*, 2016; Begemann *et al.*, 2020), particularly in enhancing WM functions. Notably, tDCS applied over the DLPFC has been associated with improved verbal WM performance in RH stroke patients (Jo *et al.*, 2009) and patients with Parkinson's disease (Boggio *et al.*, 2006). Furthermore, tDCS targeting the posterior parietal cortex of the LH in patients with apraxia was particularly linked with improvements in gesture imitation deficits (Bolognini *et al.*, 2015; Ant *et al.*, 2019), which were found to be associated with motor WM scores in Study I (see *Section 4.2.6*). Accordingly, the application of tDCS provides a promising avenue for improving the efficacy of therapeutic strategies aimed at rehabilitating motor WM deficits in patients with apraxia. The VLSM outcomes using the motor WM scores indicate that the left IFG might be a prospective key target for neuromodulatory interventions using tDCS (see *Figure 7*). Note that a recent study revealed an improved verbal WM performance in healthy participants following tDCS over the left IFG (Zhu *et al.*, 2020). Importantly, combining non-invasive brain stimulation with WM training strategies could offer a holistic and comprehensive treatment approach, in which the restored motor WM functions via brain stimulation would be further consolidated with targeted motor WM training, thus potentially leading to substantial and enduring improvements in motor WM functions (Burton *et al.*, 2023).

6.4.2. Clinical implications of irregular pantomime behaviors

Tests of pantomiming the use of objects are widely implemented in the diagnostic inventory of apraxia due to their high sensitivity in detecting apraxic deficits (Goldenberg and Randerath, 2015; Rothi et al., 1997; Vanbellingen et al., 2011; Watson and Buxbaum, 2015; Weiss et al., 2013). Notably, diverse instruction modes are adopted for the different neuropsychological tests assessing object-use pantomimes in apraxia, including the presentation of two-dimensional (2D) images (i.e., photos of objects; (Goldenberg and Randerath, 2015; Randerath et al., 2017; Watson and Buxbaum, 2015; Weiss et al., 2013)) or virtual holograms of objects (Rohrbach *et al.*, 2021), verbal commands (e.g., naming the object) without visual cues (Vanbellingen *et al.*, 2011), or a combination of multiple instruction modes (Rothi *et al.*, 1997).

Despite the differences in the instruction modes, the scoring schemes used by different pantomime tests share some common criteria. Qualitative analyses of pantomime execution primarily focus on three error types: content errors (e.g., pantomiming actions that are semantically unrelated to the intended use of the object), spatial errors (e.g., deficient grip and finger configurations or deficient position and movement of the hand and arm), and temporal errors (e.g., inaccurate timing or ordering of sequenced movements). Another commonly observed error in pantomiming object-use is the 'body part as tool/object' error (Haaland and Flaherty, 1984), in which a body part is moved as if it were the object itself (e.g., using the index and middle fingers as scissors or index finger as toothbrush). However, the irregular behaviors of virtual grasping and tracing as observed in Study II in the context of pantomiming the use of objects have scarcely been reported in the literature (Rohrbach *et al.*, 2021).

The findings of Study II underscore the importance of identifying and classifying irregular behaviors during the assessment of pantomiming object use in LH stroke patients with apraxia (LH+), since the specific strategies adopted by LH+ patients can provide valuable insights into their cognitive profiles, shedding light on both their primary apraxic deficits as well as their secondary and concomitant aphasic deficits. Consequently, current pantomime assessment tools would benefit amply from including in their scoring protocol a systematic assessment of any irregular approach behaviors exhibited by patients towards the presented object stimuli. Note that a general binary scoring system documenting the 'presence' or ‘absence’ of irregular approach behaviors, such as the one implemented in Rohrbach *et al.*, (2021), may limit the insights clinicians can gain into the patients’ cognitive profiles. Although no differences were detected in neuropsychological measures between the patients showing regular (LH+RPB) and irregular (LH+IPB, here not distinguishing the type of irregular behavior) pantomime behaviors, the two qualitatively distinct irregular behaviors detected within the LH+IPB subgroups (i.e., LH+GoP and LH+ToP) were associated with disparate levels of pantomime performance and cognitive deficits. Thus, a more nuanced classification of the type of irregular approach behaviors is crucial for a more accurate clinical assessment.

In addition, the setup of the pantomime assessment should enable the execution of reaching and grasping movements towards the presented object (actual, photograph or hologram) to increase the sensitivity of observing the patients’ potential reliance or lack thereof on irregular pantomime behaviors. Particularly, by ensuring that the location of the object is within a reachable distance from the patient. It is noteworthy that the presence of paresis in LH stroke patients would not preclude the observation of these behaviors since patients are instructed to perform the pantomime using their ipsilesional, non-paretic hand. Importantly, the detection of such irregular approach behaviors would not be possible in pantomime assessments that rely on presenting the object solely through verbal instructions without any additional visual feedback (Vanbellingen *et al.*, 2011). This limitation points to the potential diagnostic shortcomings of using such verbal instruction modes and further emphasizes the established beneficiary effects of visually presenting objects during tests of pantomiming object use (Jax *et al.*, 2006; Bartolo *et al.*, 2020).

Furthermore, the identification of the specific strategy predominantly implemented by apraxic LH stroke patients to compensate for their pantomime deficits can help in tailoring personalized therapeutic interventions that specifically address the patients' individual cognitive deficits and leverage their intact cognitive abilities, consequently, optimizing their rehabilitation outcomes. For instance, apraxia patients who demonstrate a predominant reliance on the virtual grasping strategy, and thus exhibiting more preserved visuospatial processing mechanisms, may benefit from therapeutic interventions that rely on integrating visuospatial information into motor planning and execution to mitigate apraxic deficits, such as the restorative 'gesture training' approach (Smania *et al.*, 2000, 2006). Whereas, apraxia patients exhibiting the tracing strategy, and thus exhibiting more preserved structural processing and potentially more damaged access to functional knowledge, may benefit from treatment approaches that emphasize analyzing the structure of objects, such as the 'explorative training' of Goldenberg and colleagues (2001) for the purpose of restoring the patient's ability to access and integrate action-semantic information about what an object is used for.

6.5. Limitations

While offering various insights into the cognitive mechanisms contributing to apraxia following stroke to the LH, this dissertation was not exempt from several methodological constraints, particularly related to the neuropsychological inventories used in the two studies. A notable limitation is the use of two different aphasia assessment tools in the two studies – the Token test was used in Study I while the more comprehensive ACL-K was used in Study II – that led to inconsistencies in the ensuing classification of patients into groups with different aphasia severity, which in turn affected the comparability of the results across the studies. In addition, the omission of an assessment of object use pantomimes in the inventory of Study I is particularly critical, as it limits the ability to draw direct conclusions about the specific association between motor WM deficits and apraxic impairments in pantomiming object use, a relationship that is postulated to be highly relevant in apraxia (Bartolo *et al.*, 2003). Another issue pertains to the potential contribution of body structural description deficits to the lower performance in the motor WM task as well as to the observed discrepancies in pantomime performance between the LH+GoP and LH+ToP groups. Note that deficits in body structural description are known to contribute to apraxic deficits in both gesture imitation and object-related actions (Cardinali *et al.*, 2009; Carlson *et al.*, 2010; Dafsari *et al.*, 2019). However, including a neuropsychological test to evaluate this function (Semenza, 1988; Cash *et al.*, 2004) was not feasible, given time limitations and the reduced capacity of patients to endure extensive assessments.

In addition, the novel motor WM paradigm proposed in Study I might be more cognitively demanding than the block tapping and forward digit span tests since processing action-related information appears to be more complex than memorizing spatial and/or verbal information. Notably, the relatively shorter motor WM span (i.e., in comparison to the block span and digit span) was observed not only in the LH stroke patients with apraxia (LH+), but also in patients without apraxia (LH-) as well as healthy controls (see *Figure 4A*). This finding aligns with existing literature that converges on the notion that the motor WM system in healthy participants has somewhat of a limited capacity (Smyth and Pendleton, 1990; Wood, 2007; Wu and Coulson, 2014). Nevertheless, LH+ patients exhibited a consistently lower performance in both the hypothetically simpler ‘actions with object’ subtask and the supposedly more difficult ‘meaningless gestures’ (MLG) subtask in comparison to the LH- patients (see *Figure 4B*), thus suggesting that the lower performance of the LH+ patients on the motor WM task is not solely attributable to task difficulty.

Furthermore, a more comprehensive investigation of the pantomime strategies of virtual grasping and tracing was partially hindered by the presence of overlapping behaviors within the LH+ToP patients during the pantomime assessment. In particular, 13 out of the 17 patients assigned to the LH+ToP group exhibited instances of both virtual grasping and tracing, while only four patients consistently exhibited tracing behaviors alone (see *Table 4*). This limited number of patients exclusively displaying tracing behaviors rendered it impractical to categorically divide the sample of LH+ patients into three different groups: patients exhibiting solely virtual grasping, patients exhibiting solely tracing, and patients exhibiting a combination of both strategies. Consequently, this overlap within the LH+ToP patients restricted the capacity of Study II to produce a clearer delineation and more detailed conclusions about the distinct cognitive mechanisms and neuroanatomical substrates associated with each of the two pantomime strategies. Future studies with larger cohorts are warranted to provide sample sizes sufficient for dividing patients into three distinct groups based on their pantomime strategies, thereby facilitating a more nuanced exploration of these pantomime strategies in apraxia.

The validity of the structure-function inferences drawn from the VLSM analysis of the neuroanatomical correlates of motor WM in the Study I's sample of LH stroke patients encounters several methodological challenges. A critical issue is the wide variation in time post-stroke among the included LH stroke patients, which ranged from the subacute phase (< 28 days after stroke) to the chronic phase (> 28 days after stroke) post-stroke (Bernhardt *et al.*, 2017). This variability in the time post stroke complicates the interpretation of the VLSM outcomes since the reliability of the VLSM results is influenced by the elapsed time between stroke occurrence and clinical assessment. In particular, the correlation between a cognitive deficit and its underlying brain lesions is putatively the most robust during the subacute phase post-stroke and is assumed to weaken during the chronic phase post-stroke due to potential recovery of the cognitive function as well as reorganization of brain functions (Karnath and Rennig, 2017). However, in Study I, no significant correlation was observed between the time post stroke and motor WM, i.e., the primary cognitive function of interest. The only notable correlation was between time post stroke and visuospatial WM scores, which falls outside the scope of the current research's focus.

Another problematic issue arises from the observation that the significant result of Study I's VLSM analysis was restricted to the association of deficits in the 'actions with objects' (AO) subtask with damage to a single voxel within the IFG (see *Figure 7*). The identification of a single significant voxel, as opposed to a more compelling cluster of voxels, might constitute a potential false positive within the VLSM analysis (Mirman *et al.*, 2018). Nevertheless, the absence of significant voxels in the VLSM analyses conducted on other WM scores (i.e., motor WM composite, MFG, MLG, BS, and DS) suggests that this singularly significant voxel may indeed be functionally relevant for WM processes involved in actions with objects. Supporting this observation, several meta-analyses have highlighted the potential role of the left IFG as a neural substrate for WM processes (Liakakis *et al.*, 2011; Emch *et al.*, 2019). Future studies with larger samples of LH stroke patients, particularly those in the subacute phase post-stroke, are warranted for a more accurate investigation of the neural correlates of motor WM. Furthermore, to further validate the proposal of a left hemispheric lateralization of motor WM functions, comparative paradigms investigating motor WM deficits in both LH and RH stroke patients are necessary.

For the lesion-mapping findings of Study II, the main outcome of the subtraction analysis, which indicated that patients in the LH+ToP group had a relatively more damaged dorso-dorsal stream (particularly the grasp system) compared to the LH+GoP group, should be interpreted with caution (see *Figure 11*). The subtraction analysis method primarily serves as a descriptive tool and, as such, does not allow systematic statistical inferences (de Haan and Karnath, 2018). However, the outcome of this analysis was partially corroborated by the qualitative analysis of the observed pantomime strategies. In particular, the LH+GoP patients displayed an efficient use of grasping movements in triggering pantomiming of object use, whereas the LH+ToP patients exhibited difficulties in smoothly transitioning from the reaching phase to the grasping one.

In addition, the VLSM outcomes using the frequency score of ToP behaviors should also be interpreted cautiously, since the detected significant lesion correlates were confined to subcortical structures (see *Figure 13*). In the LH+ToP group, lesions predominantly affected the territory of the left middle cerebral artery (MCA), damage to which commonly results in significant lesions of the putamen, the caudate nucleus, and adjacent white matter tracts (Kumral *et al.*, 1999). While the highest lesion overlap in the LH+ToP patients was observed in the putamen, the VLSM analysis using the frequency score of ToP behaviors revealed a significant association with lesions to the globus pallidus and adjacent white matter tracts. This result suggests that the lesions in the globus pallidus might specifically relate to the tracing strategy rather than just being an unspecific by-product of MCA stroke. Nevertheless, the increased reliance on the (less efficient) tracing strategy in the LH+ToP group might not be directly attributable to focal damage in the globus pallidus and adjacent white matter. Instead, it could be related to indirect dysfunctions stemming from these subcortical lesions, affecting cortical and connected brain regions that remained structurally intact following stroke. The latter phenomenon, often referred to as the diaschisis (Feeney and Baron, 1986), is recognized for its contribution to various clinical motor impairments following subcortical lesions (Grefkes *et al.*, 2008; Carrera and Tononi, 2014). Thus, the higher reliance on the tracing strategy might reflect broader neural network disruptions rather than isolated damage to the globus pallidus *per se*.

7. Summary

This dissertation delves into the cognitive mechanisms underlying apraxia after left hemisphere (LH) stroke, focusing on motor working memory (WM, Study I) and visuospatial processing (Study II). The thesis aims to elucidate the specific contribution of these cognitive components to apraxic deficits, explore their neuroanatomical correlates, and examine how aphasia, often concomitant with apraxia, modulates these processes. The revealed insights are thereafter leveraged to inform clinical improvements in diagnostic tools and rehabilitation approaches within the context of apraxia.

Study I's investigation of the motor WM in LH stroke patients underscored the apraxia-specific nature of motor WM deficits and their potential prognostic relevance for post-stroke apraxia impairments, especially in gesture imitation. Crucially, motor WM deficits in LH stroke patients were independent of concomitant aphasia and were disproportional to deficiencies in verbal and visuospatial WM. These results align with previous research highlighting the role of WM deficits in apraxia (Bartolo *et al.*, 2003), and further extend this field by revealing a more nuanced understanding of the specific contribution of distinct WM systems to apraxic deficits, notably emphasizing the pivotal role of motor WM in gesture imitation and highlighting the broader implications of verbal and visuospatial WM in object use.

Study II's retrospective analysis of the irregular pantomime behaviors of virtual grasping and tracing revealed that LH stroke patients with apraxia who relied more extensively on virtual grasping exhibited better pantomime performance and less severe aphasic deficits, while the opposite pattern was observed in those patients favoring tracing. Behavioral analyses indicated that the compensatory reliance on virtual grasping may be associated with more preserved visuospatial processing mechanisms. Lesion mapping analyses further revealed that a higher reliance on virtual grasping and (to a lesser extent) a lower reliance on tracing were associated with damage to regions involved in visuospatial processing and pantomiming object use, notably, the inferior parietal lobule and the inferior frontal gyrus. These findings corroborate the importance of visuospatial processing in reducing the cognitive load during pantomiming (Randerath, 2009) by showing that virtual grasping, which is dependent on visuospatial processing of action-relevant object properties, facilitates the retrieval and integration of motor schemas into action plans, thus enhancing pantomime performance.

Collectively, the dissertation advances the understanding of the cognitive underpinnings of apraxia following LH stroke and provides empirical support for the cognitive praxis model by delineating the contributions of a specialized motor WM system and visuospatial processing to this disorder. Importantly, the thesis advocates a more nuanced approach in diagnosing apraxia and emphasizes the need for tailored rehabilitative strategies that specifically target these cognitive components to improve recovery outcomes.

8. Zusammenfassung

Diese Dissertation untersucht die kognitiven Mechanismen, die der Apraxie nach einem Schlaganfall in der linken Hemisphäre (LH) zugrunde liegen, und konzentriert sich dabei auf das motorische Arbeitsgedächtnis (WM, Studie I) und die visuell-räumliche Verarbeitung (Studie II). Ziel der Arbeit ist es, den spezifischen Beitrag dieser kognitiven Komponenten bei schlaganfall-bedingter Apraxie aufzuklären, ihre neuroanatomischen Korrelate zu erforschen und zu untersuchen, wie aphasische Defizite, welche oft mit einer Apraxie einhergehen, diese Prozesse modulieren. Die gewonnenen Erkenntnisse werden anschließend genutzt, um umfassendere klinisch-neuropsychologische Assessments für apraktische Defizite und neuartige Rehabilitationsansätze bei Apraxie vorzuschlagen.

Die Untersuchung der Arbeitsgedächtnisprozesse in Studie I unterstrich die enge Assoziation von Apraxie und motorischen WM-Defizite bei Patienten mit Schlaganfällen in der LH und deren potenzielle prognostische Relevanz für apraktische Defizite nach Schlaganfall, insbesondere bei der Gestenimitation. Hervorzuheben ist, dass die motorischen WM-Defizite bei Patienten mit Schlaganfällen in der LH unabhängig von einer begleitenden Aphasie waren und in keinem Verhältnis zu den Defiziten im verbalen und visuell-räumlichen WM standen. Diese Ergebnisse unterstützen frühere Untersuchungen, welche schon die Rolle von WM-Defiziten bei Apraxie hervorgehoben haben (Bartolo et al., 2003). Zudem erweitern die aktuellen Ergebnisse die bisherigen Erkenntnisse, indem sie ein differenzierteres Verständnis des spezifischen Beitrags verschiedener WM-Systeme zu den verschiedenen apraktischen Defiziten aufzeigen, insbesondere die zentrale Rolle des motorischen WM bei der Gestenimitation betonen und die Bedeutung des verbalen und visuell-räumlichen WM beim Objektgebrauch hervorheben.

Die retrospektive Analyse der irregulären Verhaltensweisen des virtuellen Greifens und Nachzeichnens (Tracing) bei der klinischen Untersuchung von Pantomimen in Studie II ergab, dass apraktische Patienten mit einem Schlaganfall in der LH, die sich stärker auf das virtuelle Greifen verließen, eine bessere pantomimische Leistung und weniger schwere aphasische Defizite aufwiesen, während bei denjenigen Patienten, die das Tracing bevorzugten, das umgekehrte Muster beobachtet wurde. Die durchgeführten Verhaltensanalysen deuteten darauf hin, dass das kompensatorische Nutzen des virtuellen Greifens mit besser erhaltenen visuell-räumlichen Verarbeitungsmechanismen verbunden sein könnte. Statistische Läsionsanalysen ergaben ferner, dass eine stärkere Abhängigkeit vom virtuellen Greifen und (in geringerem Maße) eine geringere Abhängigkeit vom Nachzeichnen (Tracing) mit einer Schädigung von Regionen verbunden waren, die bei der visuell-räumlichen Verarbeitung handlungsrelevanter Objekteigenschaften und bei Objektgebrauchspantomimen genutzt werden, nämlich mit einer Schädigung des inferioren Parietallappens und des inferioren frontalen Gyrus. Diese Ergebnisse bestätigen die Bedeutung der visuell-räumlichen Verarbeitung bei der Verringerung der kognitiven Belastung während der Pantomime des Objektgebrauchs (Randerath, 2009), indem sie zeigen, dass das virtuelle Greifen, welches von der visuell-räumlichen Verarbeitung abhängt, den Abruf und die Integration von motorischen Schemata in Handlungspläne erleichtert und somit die pantomimische Leistung verbessert.

Insgesamt trägt die Dissertation zum Verständnis der kognitiven Grundlagen der Apraxie nach einem Schlaganfall in der LH bei und unterstützt das kognitive Praxismodell mit empirischen Daten, indem die aktuellen Untersuchungen die Beiträge eines spezialisierten motorischen WM-Systems und der visuell-räumlichen Verarbeitung zu den verschiedenen apraktischen Defiziten präzise charakterisiert. Die Arbeit plädiert für einen differenzierteren

Ansatz bei der Diagnose von Apraxie und unterstreicht die Notwendigkeit maßgeschneiderter therapeutischer Strategien, die speziell auf die untersuchten kognitiven Komponenten abzielen, um die Rehabilitation von apraktischen Defiziten nach einem Schlaganfall zu verbessern.

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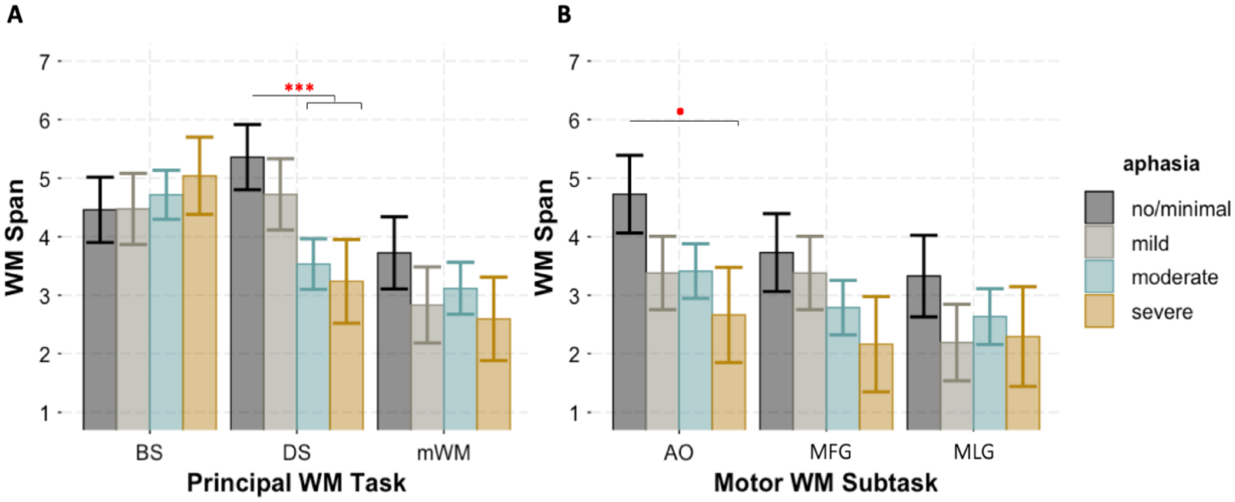
10. Appendices

10.1. Appendix 1

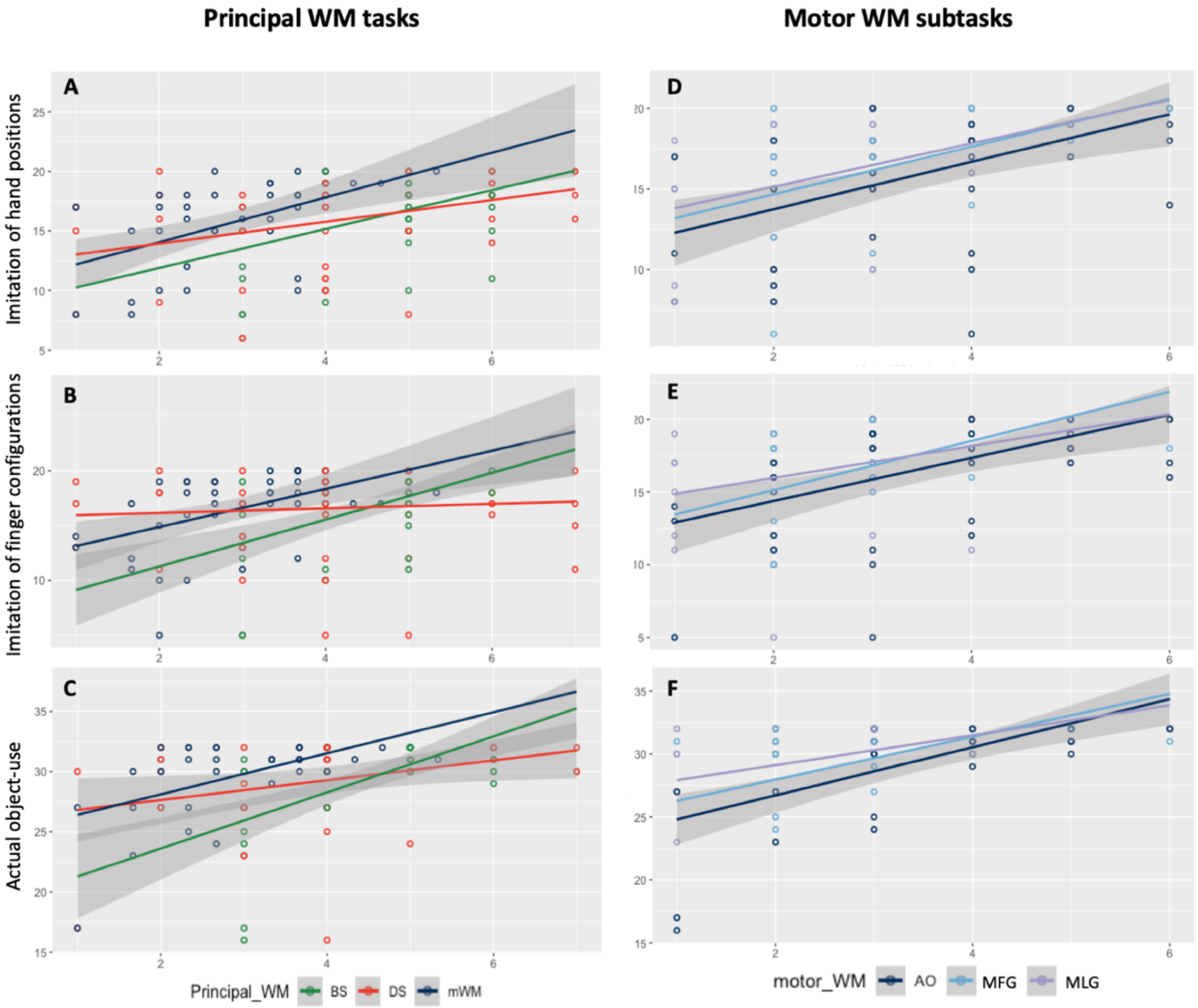
Effects of aphasia on working memory performance while accounting for concomitant apraxic deficits



*Panel **A** illustrates the effects of aphasia on the principal WM performance, that is, comparisons between the BS, DS and motor WM (operationalized by the mWM composite score) tests. LH stroke patients showing no/minimal aphasia scored significantly higher in the DS test in comparison to those LH stroke patients with moderate and severe aphasia. However, no significant performance differences were observed in the BS and motor WM test across the four aphasia groups. Note that panel **A** depicts the adjusted mean span values after accounting for apraxia severity. Panel **B** illustrates the effects of aphasia on the motor WM performance, that is, comparisons between the AO, MFG and MLG subtests. LH stroke patients with no/minimal aphasia scored marginally higher (p = .08) on the AO subtask in comparison to the group of LH stroke patients with severe aphasia. In contrast, no significant performance differences were detected in the MFG and MLG subtests across the four aphasia groups. Note that panel **B** depicts the adjusted mean span values after accounting for the scores on the DS and the BS tests, as well as for apraxia severity. Error bars indicate confidence intervals of 95%, and the asterisks indicate the level of significance of the post-hoc tests (Bonferroni-corrected at *** p < .001).*

10.2. Appendix 2

Prediction of scores on clinical tests of apraxia: principal WM tasks and motor WM subtasks

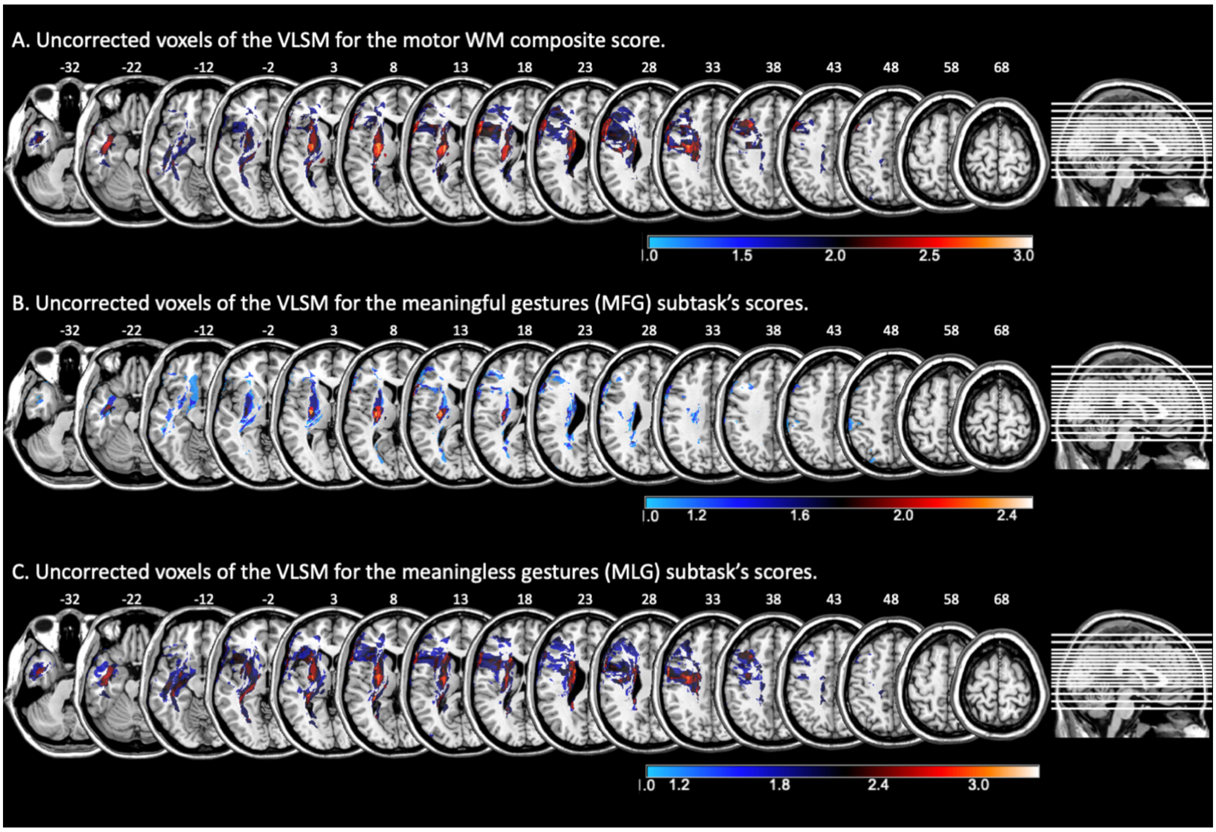


*Panels **A**, **B** and **C** illustrate the use of the principal WM tasks (BS, DS and mWM) as predictors of the scores on the clinical tests of imitation of hand positions, imitation of finger configurations, and actual object use, respectively. Panels **D**, **E** and **F** illustrate the use of the motor WM subtasks (AO, MFG and MLG) as predictors of the scores on the clinical tests of imitation of hand positions, imitation of finger configurations, and actual object use, respectively. On the one hand, the regression models using the principal WM tasks as predictors indicated that the motor WM was a significant predictor of scores on the test of imitating hand positions (panel **A**), and that the motor WM and the BS (to a lesser extent) were significant predictors of scores on the test of imitating finger configurations (panel **B**), while both the BS and DS were significant predictors of scores on the test of actual object-use (panel **C**). On the other hand, the regression models using the motor WM subtasks as predictors indicated that the AO subtask was the only significant predictor for the three apraxia tests of imitation of hand positions (panel **D**), imitation of finger configurations (panel **E**), and actual object use (panel **F**).*

The regression lines indicate the linear trend of each predictor. The 95% confidence interval (grey area surrounding the fitted lines) is depicted only for the predictors that were found to be significant in the multiple linear regression models.

10.3. Appendix 3

Uncorrected voxels of the VLSM for the motor WM subtasks.


A. Uncorrected voxels of the VLSM for the motor WM composite score.

B. Uncorrected voxels of the VLSM for the meaningful gestures (MFG) subtask's scores.

C. Uncorrected voxels of the VLSM for the meaningless gestures (MLG) subtask's scores.

Illustration of the uncorrected voxels of the VLSM conducted for ***(A)*** *the motor WM composite score (LH = 29),* ***(B)*** *the meaningful gestures (MFG) subtask (LH = 35), and* ***(C)*** *the meaningless gestures (MLG) subtask (LH = 29).*

(A) *For the VLSM using the motor WM composite score, the highest Z-value was observed in the external capsule (max. Z-value = 3.026; MNI coordinates [x,y,z]: -28, + 16, +3), and the biggest cluster was in the superior corona radiata (max. Z-value = 2.813; [x,y,z]: -18, +2, +28). Other big clusters (above 200 voxels in size and arranged from bigger to smaller clusters) with high Z-values were observed in the hippocampus (max. Z-value = 1.863; [x,y,z]: -33, -28, -7), the posterior internal capsule (max. Z-value = 2.91; [x,y,z]: -24, -13, +8), the caudate nucleus (max. Z-value = 2.597; [x,y,z]: -16, -10, +23), the middle frontal gyrus (max. Z-value = 2.503; [x,y,z]: -28, +20, +38), the STG (max. Z-value = 2.246; [x,y,z]: -38, -4, -17), the ITG (max. Z-value = 2.521; [x,y,z]: -42, -16, -22), and the IFG par triangularis (max. Z-value = 2.359; [x,y,z]: -57, + 26, + 23).*

(B) *For the VLSM using the scores on the MFG subtask, the highest Z-value was observed in the posterior internal capsule (max. Z-value = 2.484; [x,y,z]: -24, -13, +8), and the biggest cluster was in the globus pallidus (max. Z-value = 1.829; [x,y,z]: -30, -16, -2). Other big clusters (above 200 voxels in size and arranged from bigger to smaller clusters) with high Z-values were observed in the IFG par triangularis (max. Z-value = 1.939; [x,y,z]: -57, +26, +23), the putamen (max. Z-value = 2.347; [x,y,z]: -28, -14, +3), the superior corona radiata (max. Z-value = 2.077; [x,y,z]: -18, +2, +28), the STJ (max. Z-value = 2.235; [x,y,z]: -38, -4, -17), the ITG (max. Z-value = 1.619; [x,y,z]: -40, -10, -27), the superior occipital gyrus (max. Z-value = 1.684; [x,y,z]: -23, -63, +18), and the SMG (max. Z-value = 1.119; [x,y,z]: -63, -24, +43).*

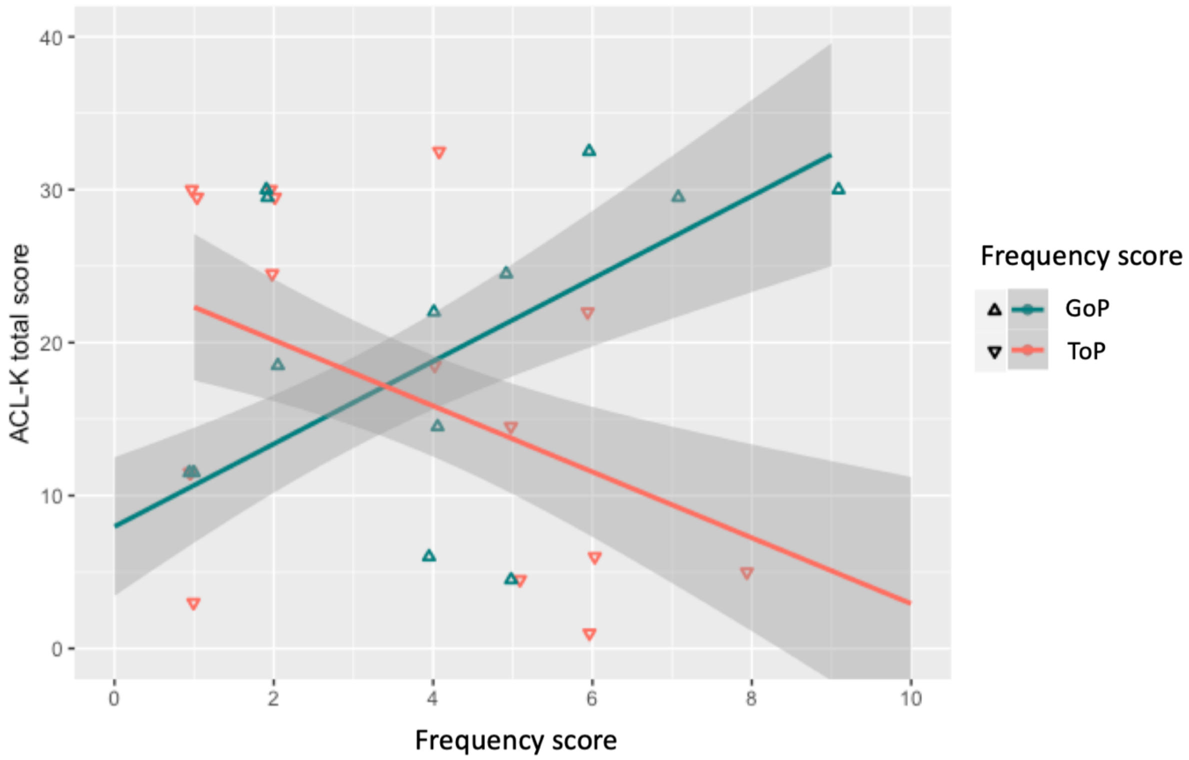
(C) *For the VLSM using the scores on the MLG subtask, the highest Z-value as well as the biggest cluster was observed in the external capsule (max. Z-value = 3.338; [x,y,z]: -28, +16, +3). Other big clusters (above 200 voxels in size and arranged from bigger to smaller clusters) with high Z-values were observed in the precentral gyrus (max. Z-value = 2.888; [x,y,z]: -58, +2, +33), the posterior thalamic radiation (max. Z-value = 2.218; [x,y,z]: -37, -39, -2), the inferior longitudinal fasciculus (max. Z-value = 2.218; [x,y,z]: -38, -33, -12), the hippocampus (max. Z-value = 2.218; [x,y,z]: -33, -28, -7), the caudate nucleus (max. Z-value = 2.766; [x,y,z]: -16, -10, +23), the STJ (max. Z-value = 2.322; [x,y,z]: -39, -9, -17), the putamen (max. Z-value = 2.776; [x,y,z]: -25, -12, +8), the posterior internal capsule (max. Z-value = 2.7; [x,y,z]: -24, -13, +13), the ITJ (max. Z-value = 2.767; [x,y,z]: -42, -16, -22), the middle frontal gyrus (max. Z-value = 2.322; [x,y,z]: -28, +20, +38), and the IFG par triangularis (max. Z-value = 2.248; [x,y,z]: -41, +20, +8).*

Displayed are the uncorrected voxels surpassing a Z-value of one, the latter was arbitrarily chosen in order to avoid displaying voxels with relatively lower Z-values (i.e., those ranging between 0 and 1). Note that the maximum Z-value is different for each of the three VLSM tests, and corresponds to the maximum Z-value detected by the voxel wise t-test statistics for the motor WM composite score (max. Z-value = 3.026), MFG subtask (max. Z-value = 2.484) and MLG subtask (max. Z-value = 3.338). Cold colors indicate voxels with lower Z-values while warm colors indicate voxels with higher Z-values.

Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000)*. The depicted axial slices correspond to the z-coordinates from -32 to +68 in MNI space.*

10.4. Appendix 4

Prediction of aphasia severity using the frequency score of GoP and ToP in the LH+ToP group



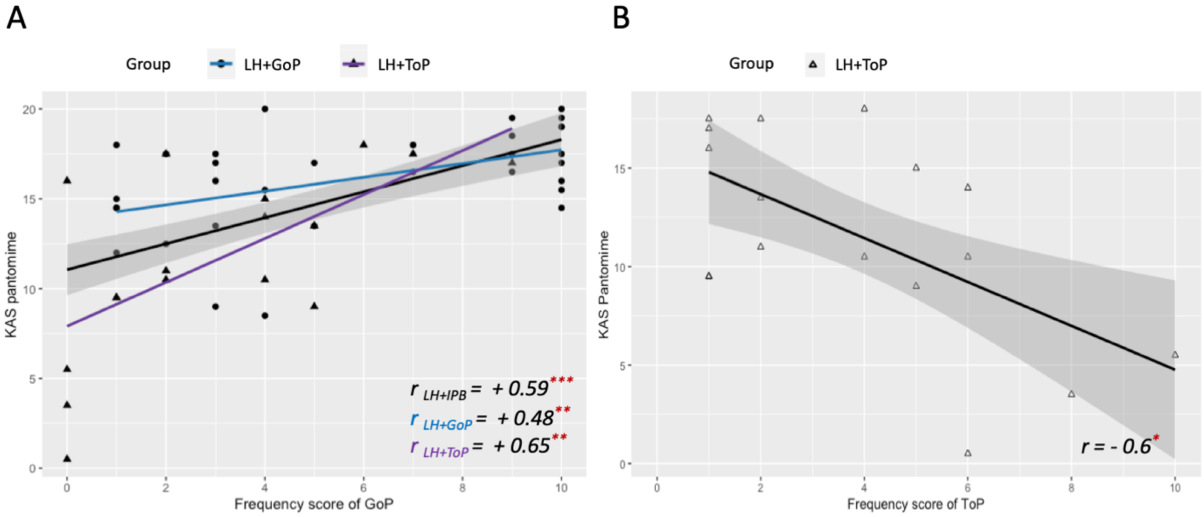
Prediction of aphasia severity (as assessed by the ACL-K total score) using the frequency scores of ToP and GoP in apraxic left hemisphere stroke patients in the LH+ToP group (N = 17). The generalized linear regression model indicates no significant interaction between the frequency scores of GoP and ToP in predicting the ACL-K score. However, the frequency score of GoP was positively correlated (p < .05) with ACL-K (green regression line) and the frequency of ToP was marginally negatively correlated (p = .09) with ACL-K (orange regression line) in the LH+ToP group.

The regression lines indicate the linear trends and their 90% confidence interval (grey area surrounding the fitted lines) for the frequency scores of GoP (green regression line) and ToP (orange regression line).

ACL-K: aphasia check list – short version, GoP: virtual grasping of object pictures, ToP: tracing of object pictures.

10.5. Appendix 5

Prediction of KAS pantomime using the frequency scores of GoP and ToP behaviors



Prediction of KAS pantomime (computed as the average of scores on the KAS pantomime subtests of pantomiming buccofacial-related and limb-related actions) using ***(A)*** *the frequency of virtual grasping behaviour (GoP) in apraxic left hemisphere stroke patients that exhibited irregular behaviors during pantomime assessment (LH+IPB; N = 49), and* ***(B)*** *using the frequency of tracing behaviour (ToP) in apraxic left hemisphere stroke patients that exhibited tracing (LH+ToP; N = 17).*

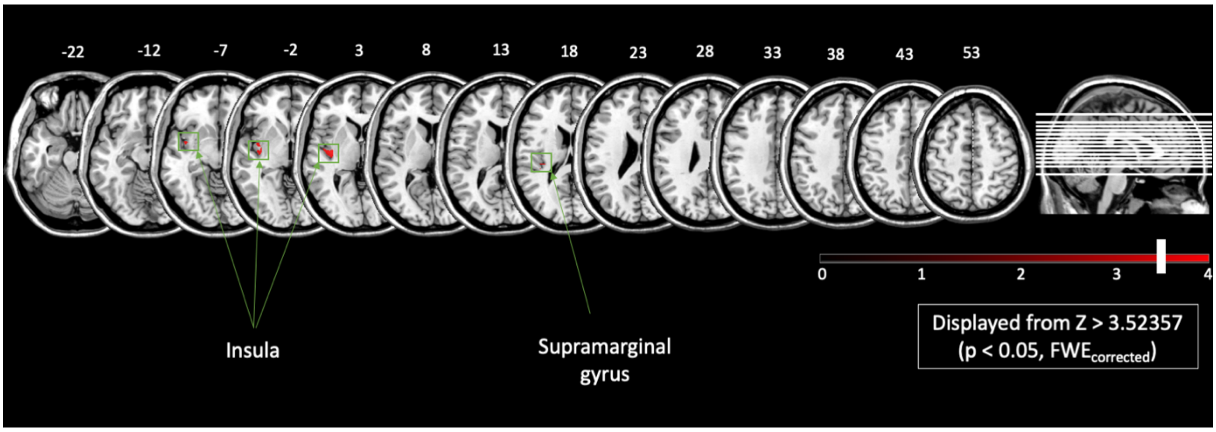
The generalized linear regression models indicate that ***(A)*** *a higher frequency of GoP is significantly predictive (p < .001) of higher KAS pantomime scores in the LH+IPB group, whereas* ***(B)*** *a higher frequency of ToP is significantly predictive (p < .05) of lower KAS pantomime scores.*

The regression lines indicate the linear trend and the 90% confidence interval (grey area surrounding the fitted lines) for ***(A)*** *the total group of apraxic left hemisphere stroke patients showing irregular pantomime behaviors (LH+IPB; N = 49, black line) and* ***(B)*** *the group of apraxic left hemisphere stroke patients showing tracing behaviors (LH+ToP; N = 17). Note that the blue and purple regression lines in graph* ***(A)*** *correspond to the regression lines of the separate models predicting KAS pantomime scores using the frequency of GoP in the LH+GoP group and the LH+ToP group, respectively. The correlation coefficient for each group, along with its statistical significance (* p < .05, ** p < .01, *** p < .001), is presented in each graph.*

KAS: Kölner (Cologne) Apraxia Screening, LH+GoP: left-hemisphere stroke patients with apraxia in the virtual grasping group, LH+ToP: left-hemisphere stroke patients with apraxia in the tracing group, GoP: virtual grasping of object pictures; ToP: tracing of object pictures.

10.6. Appendix 6

FWE-corrected VLSM results of the frequency score of GoP behavior for the left hemisphere stroke patients with apraxia exhibiting irregular behaviors (LH+IPB) during pantomime assessment.



Results of the VLSM analysis for the frequency score of grasping behaviour (GoP) in apraxic LH stroke patients exhibiting irregular behaviors during pantomime assessment (LH+IPB; N = 44). Lesion correlates associated with lower frequency score of GoP behavior were found in the insula and the supramarginal gyrus of the left hemisphere. Displayed voxels surpassed a Z-value of 3.524, corresponding to a statistical threshold of p < .05, corrected for family-wise error (FWE).

Lesions are plotted on the ch2-template provided by MRIcron (Rorden and Brett, 2000). *The depicted axial slices correspond to the z-coordinates from -22 to +53 in MNI space.*

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