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#### Neuropsychological evidence for a motor working memory 1 subsystem related to apraxia 2

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# Abstract

Recent evidence in healthy participants suggests that a motor subcomponent of working
memory (mWM) may exist. We investigated whether this mWM is impaired in patients with a
motor-dominant left hemisphere (LH) stroke and apraxia. Further, we hypothesized that a
deficient mWM contributes to deficits in motor cognition, i.e., apraxia, in LH stroke.
The study included 52 patients with LH stroke and 25 age-matched controls. Patients
were classified into LH stroke patients with and without apraxia based on deficits in gesture
imitation and object use. All participants were examined using the block span test (visuospatial
WM), the digit span test (verbal WM), and a novel mWM task. In the latter, participants were
presented with static pictures depicting three different actions: actions with objects,
meaningless actions, and meaningful actions.
In the mWM task, LH stroke patients with apraxia performed worse than age-matched
controls. Notably, LH stroke patients with apraxia showed more pronounced mWM deficits
than those without apraxia. These results remained significant even after controlling for
visuospatial and verbal WM deficits. Regression analyses revealed that LH stroke patients'
mWM deficits predicted deficits in imitation.
Data provide neuropsychological evidence for a motor subsystem of WM and suggest
that deficits in mWM contribute to the severity of apraxia in LH stroke patients.
Keywords: visuospatial working memory, verbal working memory, action observation, gesture

21 imitation, stroke.

# 1 Introduction

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The multicomponent model of working memory (WM) conceptualizes WM as a central executive system responsible for modulating attentional resources and manipulating information within two non-overlapping and modality-specific WM subsystems (Baddeley and Hitch, 1974; Baddeley, 1986). In particular, acoustic or semantic information is supposed to be mediated via the phonological loop (or verbal WM), whereas information on visual and spatial properties is mediated via the visuospatial sketchpad (or visuospatial WM) (Baddeley, 2012). Following the multicomponent WM model, recent evidence suggests the existence of an additional WM subsystem dedicated to processing motor information, e.g., static body configurations or dynamic goal-directed actions (for review, see Galvez-Pol et al., 2020). Here, the term 'motor WM' (mWM) delineates a WM subsystem responsible for temporarily encoding, retaining, and recalling visually perceived body- and action-related information. The behavioral evidence for a mWM subsystem mainly stems from dual-task studies. During the encoding phase, healthy participants had to memorize a sequence of body-related movements for later reproduction while performing either a verbal, spatial, or body-related secondary task. Across multiple experiments, implementing a verbal or spatial secondary task produced little to no interference in recalling meaningless body movements (Smyth et al., 1988; Smyth & Pendleton, 1990; Woodin & Heil, 1996) or object-related actions (Rumiati & Tessari, 2002). In contrast, a substantial decrease in the WM span for these motor actions was observed when the concomitant secondary task drew on sensorimotor functions such as hand tapping (Smyth et al., 1988; Woodin & Heil, 1996), tube squeezing (Rumiati & Tessari, 2002), or watching another person's body movements (Smyth & Pendleton, 1990). The 'enactment effect' provides further support for a specific mWM subsystem: Simple actions are recalled better when performed during the encoding phase than encoded using a verbal strategy (Russ et al., 2003). Taken together, these findings strongly suggest a specialized mWM subsystem

dedicated to processing body configurations and movements and dissociated from verbal and visuospatial WM.

A selective deficit of mWM in clinical populations (over and above verbal and visuospatial WM deficits) would further strengthen the concept of a specialized mWM. Given the motor dominance of the left hemisphere (LH), LH stroke patients constitute an ideal population to study specific deficits of mWM; especially if these patients suffer from apraxia, a deficit of motor cognition that cannot (solely) be explained by lower-level motor, sensory, or comprehension deficits (Dovern et al., 2012).

The present study examined an independent mWM subsystem by investigating the capacity of memorizing motor information in patients with a stroke affecting the motor-dominant LH. To explore this issue, we examined LH stroke patients (with and without apraxia) using standard visuospatial and verbal WM tests and a newly devised task tapping upon mWM. The latter included no relevant active motor component since lower-level motor deficits (e.g., paresis) of our patients with LH stroke precluded an efficient reproduction of the action stimuli. Similar paradigms relying on action recognition have been used in studies investigating a specialized mWM subsystem in healthy (Wood, 2007) and clinical populations (Vannuscorps & Caramazza, 2016). The action recognition paradigms used for studying mWM mechanisms are based on (i) the established link between action observation and action execution and (ii) the evidence that memorizing body-related actions is supported by the same motor and somatosensory areas that implement the execution of the respective actions (A. Galvez-Pol et al., 2018; Lu et al., 2016).

Given the deficits in motor cognition prevalent in patients with LH stroke *and* apraxia, we hypothesized that patients with a stroke to the motor-dominant LH and apraxia would exhibit deficits in mWM that are disproportionate to their visuospatial and verbal WM deficits and are more pronounced than mWM deficits in LH stroke patients without apraxia (and healthy controls). Finally, we assumed that deficits in the mWM task predict apraxia severity.

# 1 Methods

## **Participants**

The current sample consisted of 52 patients with a single, unilateral ischemic stroke of the left hemisphere (LH, mean age  $\pm$  SD:  $55.3 \pm 11.6$  years; see Figure 1A for the lesion overlay) and 25 age-matched ( $55.5 \pm 8.4$  years) control subjects (total sample size of 77 subjects).

A previously reported effect size (d = 1.42) of performance differences between patients and controls on an action WM task (Vannuscorps & Caramazza, 2016) suggests a relatively large effect size (Cohen, 1988). Power analysis for mixed models using the 'sjstats' package in R indicated that a total sample of about 56 subjects is required to detect a significant effect (d = 0.8; Cohen, 1988) in a linear mixed-effects model (with three groups and three measures for each group) with a power of 0.8 at an alpha-level of 0.05. Thus, our sample of 77 participants should be appropriate for the study's primary objective (i.e., to test for performance differences in mWM between LH stroke patients with and without apraxia and control subjects that exceed differences in visuospatial and verbal WM deficits).

All subjects were right-handed. The LH stroke patients were divided into patients with  $(n = 28, LH+, 56.5 \pm 12.5 \text{ years})$  and without apraxia  $(n = 24, LH-, 53.8 \pm 10.5 \text{ years})$ ; see Figure 1B and 1C for the lesion overlays) based upon clinical tests of gesture imitation and object use (Dovern et al., 2012). In the imitation tests, patients were asked to imitate ten meaningless hand positions and ten meaningless finger configurations with the ipsilesional (i.e., left) hand. The maximum score in both imitation tests is 20 points. A score below 18 (for hand positions) and 17 (for finger configurations) indicates an apraxic imitation deficit (Goldenberg, 1999). For the object use test, patients should demonstrate using a hammer, a toothbrush, a pair of scissors, a toy gun, an eraser, a key with a padlock, and a match with a candle (De Renzi et al., 1968). The maximum score is 32 points, with a cut-off score of 29 for apraxic performance (Ant et al.,

2019). Patients performing below the respective cut-off scores in at least one of the three apraxia tests (hand imitation, finger imitation, object use) were considered apraxic.

Besides, stroke patients were administered the Token test (De Renzi & Vignolo, 1962), 3 a valid measure of aphasia in LH stroke patients irrespective of their clinical type of aphasia 4 (Orgass & Poeck, 1966). Consistent with clinical experience, patients with apraxia (LH+) 5 scored significantly lower on the Token test assessing language comprehension (T-score (mean 6  $\pm$  SD): 47.7  $\pm$  8.2) than patients without apraxia (LH-; T-score (mean  $\pm$  SD): 60.7  $\pm$  10.8, p <7 0.001). Note that the Token test aims to assess deficits in verbal comprehension and, thus, 8 cannot specify whether the observed aphasic deficits are related to semantic or phonological 9 10 impairments. The time interval between stroke and testing did not differ between LH- patients (median  $\pm$  standard error of the mean (SEM): 415.5  $\pm$  128.3 days, range from 4 to 2563) and 11 LH+ patients (335  $\pm$  148.6 days, range from 3 to 2581). In the LH stroke patients, the time post-12 13 stroke correlated with performance in the digit span (DS) task (r = -0.35, p = 0.02, n = 44), i.e., the longer the time post-stroke, the worse the DS performance. A recent systematic review 14 15 revealed that stroke patients showed more severe deficits in (verbal and visuospatial) WM functions in the chronic phase than in the subacute phase post-stroke compared to healthy 16 controls (Lugtmeijer et al., 2021). Note that we assessed patients during their subacute to 17 chronic phase post-stroke. Consistent with the review by Lugtmeijer et al. (2021), we have 18 divided our stroke patients into 'subacute' patients (when assessed within 90 days after stroke) 19 and 'chronic' patients (when assessed after 90 days post-stroke). The correlation tests revealed 20 a positive, albeit non-significant, correlation between the DS and time post-stroke in the 21 'subacute' stroke patients (r = 0.11, p = 0.7, n = 14; time post-stroke < 90 days; see 22 supplementary Figure S1 panel A). In contrast, a negative, although non-significant, correlation 23 between the DS and time post-stroke was observed in the 'chronic' stroke patients. (r = -0.21,24 p = 0.26, n = 30; time post-stroke > 90 days; see supplementary Figure S1 panel B). Although 25 the correlations in the subsamples of 'subacute' and 'chronic' stroke patients were insignificant, 26

- they suggest that the negative correlation between the digit span and time post-stroke observed
- 2 in the whole sample of LH stroke patients was driven by the chronic stroke patients. No other
- 3 significant correlations were observed between time-post stroke and performance in the other
- 4 WM tests.
- Moreover, a negative correlation was observed between age and performance on the
- block span (tapping on visuospatial WM) for all three groups: healthy controls (r = -0.43, p =
- 7 0.03), patients without apraxia ((LH-), r = -0.65, p < 0.001) and patients with apraxia ((LH+),
- 8 r = -0.48, p = 0.009).
- 9 Informed written consent was obtained from all subjects. The study was approved by
- the local ethics committee and was conducted under the Declaration of Helsinki.

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#### **Testing Procedure**

Participants were assessed using a block tapping test and a forward digit span test, which are standard assessment tools for visuospatial and verbal working memory (WM), respectively,

and a novel mWM task. The three tests were applied in randomized order.

The German version of the Corsi block span test (Corsi, 1972) was administered as described in the manual (block tapping test, (Schellig, 1997)), with the modification that patients used their ipsilesional, i.e., left arm to execute the movements. In short, participants were instructed to repeat a sequence of blocks in the correct serial order by tapping on the respective blocks of an asymmetric grid of nine blocks after the examiner had demonstrated the sequence of blocks. The sequence length was gradually increased, and the block span was defined as the maximum number (sequence) of blocks correctly repeated by the subject. The

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forward digit span test was taken from the Wechsler Memory Scale - Revised (WMS-R, (Wechsler, 1987)) and required participants to reproduce a verbally presented sequence of digits correctly. For the stroke patients with language comprehension deficits (as assessed by the Token test, see above), the sequence of digits was presented visually, and patients were not required to respond verbally, but they had to point - with their ipsilesional hand - to the numbers presented on paper cards in front of them. Again, the length of the sequence was progressively increased, and the digit span was defined as the maximum sequence of digits correctly recalled. In the mWM task, participants were presented with static pictures displaying three different categories of action-related stimuli demonstrated by two actresses sitting at a table: (i) actions with objects (AO), (ii) meaningful actions without objects (MFA), and (iii) meaningless actions without objects (MLA). The order of the three mWM subtasks was randomized across subjects. The items of the category AO included the following: peel an apple, open a bottle, light a candle, deal out cards, hammer a nail into a woodblock, file a sheet of paper, sharpen a pencil, polish one's shoes, and apply toothpaste on a toothbrush (nine items in total). The MFA subtask included nine items that consisted of three meaningful finger movements (lure someone, OK sign, and victory sign), three meaningful unimanual hand movements (box, show physical power by flexing one's biceps muscles, and threaten someone with one's fist), and three meaningful bimanual hand movements (clap, hands up, and pray; nine items in total). Finally, the MLA items consisted of a similar arrangement of meaningless gestures adopted

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from those initially devised by Goldenberg (Goldenberg, 1999) for his imitation tests (nine

items in total). See Figure 2 for an example stimulus of each category.

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In analogy to the above-mentioned verbal and visuospatial WM tests, subjects were first shown two items (pictures) of a given mWM subtask (actions with objects (AO), meaningful

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actions (MFA), or meaningless actions (MLA)). The pictures were displayed on a computer monitor for three seconds with a one-second inter-stimulus interval. Note that the action pictures were presented for a relatively long duration of three seconds (compared to one second in the digit span and block span) to allow sufficient processing time of the respective stimulus. Previous studies investigating WM for actions also presented (static and dynamic) action stimuli for three seconds (Vannuscorps & Caramazza, 2016; Vicary et al., 2014) or even four seconds (Lu et al., 2016). Subjects were then asked to recall the just presented pictures and their sequence by selecting them in the correct order from the nine items/pictures of the respective mWM subtask. The set of nine pictures was laid on a table next to the computer in a fixed spatial arrangement (3 x 3 matrix) and uncovered immediately after presenting the last picture in a sequence. Participants were instructed to respond by pointing with their left (ipsilesional) hand to the correct pictures in the correct order as they pointed to the blocks in the block span task. If the subject's response was correct (i.e., correct pictures and order), a sequence of three pictures was presented, followed by a sequence of four pictures etc. If the subject's response was incorrect (i.e., wrong picture or incorrect order), then a second trial was presented with the same number of pictures of the same category, albeit different ones. If the subject erred again, the subtest was terminated. The mWM span for a given category was defined as the maximum number of pictures correctly retrieved by the subject.

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### Analysis of Behavioral Data

A motor WM (mWM) compound score was computed for each participant as the mean span score across the three mWM subtasks. Note that the three mWM subtasks were highly correlated in the LH stroke patients. The performance on the 'actions with objects' (AO) subtask was positively correlated with the performance on the 'meaningful actions' (MFA) and 'meaningless actions' (MLA) subtasks in the patients with apraxia LH+ (r = 0.71, p < 0.001)

and r = 0.75, p < 0.001, respectively) and the patients without apraxia LH- (r = 0.53, p < 0.011 2 and r = 0.53, p < 0.05, respectively). Moreover, there was a positive correlation between the MFA and MLA subtasks in LH+ (r = 0.48, p < 0.05) and LH- (r = 0.59, p < 0.05). For the age-3 matched controls, marginally significant correlations were observed between the MFA and 4 MLA subtasks (r = 0.52, p = 0.05) and between the MFA and AO subtasks (r = 0.35, p = 0.05). 5 Statistical analyses were performed using the software R (version 4.0.5). Data were 6 7 analyzed using linear mixed-effects models via the lme4 package (version 1.1-27.1; (Bates et al., 2015)) to analyze putative performance differences between the healthy control participants 8 and LH stroke patients with and without apraxia on all administered WM tasks. To select the 9 10 optimal model, we used the 'performance' package in R (Lüdecke et al., 2021) to rate and assess the performance of different linear mixed-effects models. Accordingly, we (only) report the 11 results of the model that fit the data best (i.e., the model with the most favorable BIC/AIC 12 13 values compared to the other models' performances). We report F statistics for significant effects and the degrees of freedom as estimated by Satterthwaite's approximation. Significant 14 effects were followed by pairwise comparisons across the factors' levels using paired samples 15 t-tests for linear mixed-effects models (using the 'emmeans' package in R; (Russell, 2021) with 16 post-hoc Bonferroni corrections for multiple comparisons and a significance level of p < 0.05. 17 The mixed models always included the three-level between-subject factor group (age-18 matched controls, patients with apraxia (LH+), and patients without apraxia (LH-)). The within-19 subject factors of interest included the main WM task (block span (BS), digit span (DS), and 20 motor WM compound score (mWM)) to assess group differences across the main WM tasks, 21 as well as the motor WM subtasks (actions with objects (AO), meaningful actions (MFA), 22 meaningless actions (MLA)) in order to assess group differences in performance on the three 23 mWM subtasks. In the model considering mWM subtasks, we also included the DS and BS 24 scores as covariates to control for the effects of verbal and visuospatial WM deficits, 25 respectively. To further investigate the effects of age and stroke severity (as operationalized by 26

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1 lesion size in voxels), we conducted a separate linear mixed-effects model with the sample of

2 35 LH stroke patients (18 LH+ patients and 17 LH- patients) for whom lesion maps were

available (see Figure 1). This model assessed performance differences between the LH+ and

LH- on the main WM tasks (BS, DS, and mWM) while controlling for age and lesion size

(number of affected voxels).

Since LH stroke often leads to concomitant language and praxis deficits, we also assessed the effect of aphasia on WM performance. For that purpose, we re-classified the LH stroke patients into four groups of differing degrees of aphasia severity based on their T-values in the Token test (for a similar allocation of patients into groups of different aphasia severity, see (Achilles et al., 2016)). The 42 LH stroke patients with complete Token test scores (22 patients with apraxia (LH+), 20 patients without apraxia, (LH-)) were divided into patients with no/minimal aphasia (n = 10, 1 LH+, T-values = 73-63), mild aphasia (n = 8, 3 LH+, T-values = 62-54), moderate aphasia (n = 17, 11 LH+, T-values = 53-44), and severe aphasia (n = 7, 7) LH+, T-values = 43-29). Following the analysis considering the effect of apraxia on WM performance, we conducted two linear mixed-effects models using the four-level group factor aphasia (minimal, mild, moderate, severe) as between-subject to assess the effect of aphasia on the performance across the main WM tasks (block span (BS), digit span (DS), and motor WM compound score (mWM)) as well as across the mWM subtasks (actions with objects (AO), meaningful actions (MFA), meaningless actions (MLA)). The latter model again included the scores on the DS and BS as covariates to control for the effects of verbal and visuospatial WM deficits, respectively. Note that the healthy age-matched controls were not included in this analysis, but the patients with no/minimal aphasia were considered a control group since their performance on the Token test was comparable to that of healthy controls.

To further investigate the interaction between aphasia and apraxia on WM performance, we conducted two additional linear mixed-effects models assessing the effect of aphasia on WM performance while controlling for apraxic deficits. For these analyses, we converted the

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stroke patients' raw scores in the apraxia tests into standardized z-scores to account for the different score ranges. We then included the mean z-score of the three apraxia tests (i.e., an overall apraxia score) as a covariate of interest in the aphasia models assessing the effect of aphasia on the performance across the main WM tasks as well as across the motor WM subtasks. Comparable to the original analysis, the latter model included the DS and BS scores

as covariates to control for verbal and visuospatial WM deficits, respectively.

Furthermore, multiple linear regression analyses were performed on the LH stroke patients to predict the scores of the three apraxia tests (imitation of hand postures, imitation of finger configurations, object use) using as predictors (i) the three main WM tasks (block span (BS), digit span (DS), motor WM compound score (mWM)) and (ii) the three mWM subtasks (actions with objects (AO), meaningful actions (MFA), meaningless actions (MLA)). The six multiple linear regression models included all LH stroke patients for whom complete scores on all the WM tasks were available (n = 39, 22 patients with apraxia (LH+) and 17 patients without apraxia (LH-)). The samples of apraxic and non-apraxic stroke patients included in the regression model did not significantly differ concerning age [mean  $\pm$  standard deviation (years): LH+ =  $56 \pm 13$ ; LH- =  $53 \pm 9.6$ ] and time-post stroke [median  $\pm$  SEM (days): LH+ =  $487.5 \pm 10^{-2}$ 174.3; LH- =  $619 \pm 157.9$ ]. Due to technical and organizational issues, 12 patients (seven LHpatients and five LH+ patients) had missing values for the MLA subtask, and one apraxic patient had a missing value for the DS. Since linear regression analyses require a complete data set of each patient, these 13 patients could not be included in these analyses. Given the sample size of 39 LH stroke patients for whom complete scores were available, we detected significant results with a minimum effect size of  $f^2 = 0.31$ , which is considered a large effect (Cohen, 1988), using a multiple linear regression analysis with three predictors at an alpha-level of 0.05 and a power of 0.8.

# Results

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- 2 Effects of apraxia on working memory performance
- 3 Effects of apraxia: Comparisons between the three working memory (WM) tasks
- 4 The linear mixed-effects model assessing differences in performance across the main WM tasks (block span (BS), digit span (DS), motor WM compound score (mWM)) revealed 5 significant effects of group  $[F_{(2,70.39)} = 39.6, p < 0.001]$  and task  $[F_{(2,125.98)} = 33.05, p < 0.001]$ 6 and a significant interaction between task and group  $[F_{(4.125.78)} = 5.76, p < 0.001]$ . In particular, 7 age-matched controls performed better than patients with apraxia (LH+) on the three WM tasks: 8 the BS (p < 0.05), the DS (p < 0.001), and the mWM (p < 0.001). Follow-up pairwise 9 comparisons for between-group differences showed that healthy controls performed better on 10 the DS than LH- patients (p < 0.001), and LH+ patients performed worse than LH- patients on 11 the mWM task (p < 0.01). Notably, the performance on the mWM task was worse than on the 12 DS for all three groups: age-matched controls (mean scores: 4.88 vs. 6.44, p < 0.001), LH-13 patients (3.75 vs. 4.79, p < 0.01), and LH+ patients (2.46 vs. 3.81, p < 0.001). In addition, 14 15 follow-up pairwise comparisons for within-groups differences showed that controls performed 16 better on the DS than the BS (6.44 vs. 5.32, p = 0.001), and that the performance on the mWM task was lower than on the BS only for the LH+ patients (2.46 vs. 4.25, p < 0.001) and LH-17 18 patients (3.75 vs. 4.86, p = 0.01) groups, but not for the controls (see Figure 3A). A Bayesian analysis was conducted to support the absence of significant differences 19 between patients without apraxia (LH-) and patients with apraxia (LH+) on the block span (BS) 20 and digit span (DS). The corresponding Bayes factors (BF) are reported. Partially consistent 21 with the reported Frequentist statistics, the Bayesian analysis indicated anecdotal evidence for 22 the absence of differences between LH+ and LH- patients on the BS (BF<sub>10</sub> = 0.86) and anecdotal 23 evidence for the presence of differences between LH+ and LH- patients on the DS (BF<sub>10</sub> = 24

1.94). Note that a BF<sub>10</sub> between 1/3 and 1 indicates anecdotal evidence for the null hypothesis

over the alternative hypothesis. Likewise, a BF<sub>10</sub> between 1 and 3 indicates anecdotal evidence

for the alternative hypothesis over the null hypothesis (here: for a difference between groups,

3 (Raftery, 1995)).

4 Besides, the separate linear mixed-effects model conducted on the subsample of 35 LH

stroke patients with lesion maps revealed no significant effects for age and lesion size.

Following the analysis of the whole patient sample, patients with apraxia (LH+) and without

apraxia (LH-) showed no significant differences in performance on the BS and DS tests.

8 However, LH+ patients performed significantly worse than LH- patients on the mWM task (p

< 0.04). These findings suggest that the worse performance of LH+ patients on the mWM task

remains significant even after controlling for stroke severity and age.

#### Effects of apraxia: Comparisons between the three motor working memory (mWM) subtasks

The linear mixed-effects model assessing differences in performance between the three groups (controls, patients with apraxia (LH+), patients without apraxia (LH-)) across the three mWM subtasks (actions with objects (AO), meaningful actions (MFA), meaningless actions (MLA)) while controlling for visuospatial WM (block span) and verbal WM (digit span) deficits revealed significant effects of group [ $F_{(2,67.66)} = 13.38$ , p < 0.001] and subtask [ $F_{(2,127.57)} = 26.67$ , p < 0.001], but no significant interaction effect. Follow-up pairwise comparisons for between-groups differences showed that LH+ patients performed worse than healthy controls (p < 0.001) and LH- patients (p < 0.01) on all three mWM subtasks, whereas no significant differences were observed between controls and LH- patients. Across the three groups, the performance on the AO subtask was better than on the MFA (p < 0.001) and MLA (p < 0.001) subtasks. However, no significant differences in performance were observed between the MLA and MFA subtasks across the three groups (see Figure 3B).

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- Effects of aphasia on working memory performance
- Effects of aphasia: Comparisons between the three working memory (WM) tasks

The linear mixed-effects model assessing differences in performance between the four 5 aphasia groups (no/minimal, mild, moderate, severe) across the main WM tasks (block span 6 7 (BS), digit span (DS), motor WM compound score (mWM)) revealed significant effects of group  $[F_{(3,36.07)} = 8.59, p < 0.001]$  and task  $[F_{(2,69.11)} = 32.14, p < 0.001]$  and a significant 8 interaction between task and group  $[F_{(6,68.99)} = 5.66, p < 0.001]$ . The interaction effect revealed 9 10 a differential group performance on the DS, while the patient groups classified by the degree of aphasia did not show significant differences in their performance in the BS and mWM task. 11 In particular, in the DS the patients with no/minimal aphasia performed better than the patients 12 with moderate (p < 0.001) and severe aphasia (p < 0.001). Similarly, patients with mild aphasia 13 performed better in the DS task than the patients with moderate (p < 0.05) and severe aphasia 14 (p < 0.05). Post-hoc comparisons of within-group differences showed that performance on the 15 mWM task was worse than the performance on the DS in patients with minimal (p < 0.01) and 16 mild (p < 0.005) aphasia, as well as worse than the performance on the BS in patients with 17 moderate (p < 0.005) and severe (p < 0.005) aphasia. Also, the performance on the BS was 18 better than on the DS for the patients with moderate (p = 0.09) and severe (p < 0.05) aphasia 19 (see Figure 4A). 20

Besides, the separate linear mixed-effects model assessing the effect of aphasia on the main WM tasks while controlling for concomitant apraxia revealed again a significant interaction between task and group [ $F_{(6,68.89)} = 5.47$ , p < 0.001; see supplementary Figure S2, panel A]. Following the original analysis, the interaction effect was driven by a differential group performance in the DS task. In contrast, the stroke patient groups classified by the degree

- of aphasia did not show significant differences in their performance in the BS and motor WM
- 2 compound scores. As in the initial linear mixed-effects model, patients with no/minimal aphasia
- 3 performed better in the DS task than patients with moderate and severe aphasia (p < 0.001).
- 4 Notably, the previously observed difference in DS performance between the mild aphasia group
- 5 and the moderate and severe aphasia groups was no longer significant.

# Effects of aphasia: Comparisons between the three motor working memory (mWM) subtasks

The linear mixed-effects model assessing differences in performance between the four aphasia groups (no/minimal, mild, moderate, severe) across the motor WM subtasks (actions with objects (AO), meaningful actions (MFA), meaningless actions (MLA)) while controlling for visuospatial WM (block span) and verbal WM (digit span) deficits revealed significant effects of group [ $F_{(3,33.55)} = 4.94$ , p < 0.01] and subtask [ $F_{(2,66.55)} = 21.82$ , p < 0.001] and a significant interaction between group and subtask [ $F_{(6,66.5)} = 2.73$ , p = 0.01]. The group effect indicated that patients with no/minimal aphasia performed better than patients with severe aphasia on all mWM subtasks. Moreover, the interaction effect revealed a differential group performance in the AO subtask, while the patient groups classified by the degree of aphasia did not show significant differences in their performance on the MFA and MLA subtasks. Specifically, the patients with no/minimal aphasia performed better on the AO subtask than the other three patient groups with mild (p < 0.05), moderate (p < 0.05), and severe aphasia (p < 0.01; see Figure 4B).

Furthermore, the linear mixed-effects model assessing the effect of aphasia on the motor WM subtasks while controlling for concomitant apraxia revealed no significant differences between the patient groups with different aphasia severity for all motor WM subtasks (see supplementary Figure S2, panel B). In the combined analysis, only a marginally significant

1 difference was observed between patients with no/minimal and severe aphasia on the AO

2 subtask (p = 0.08).

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- Prediction of performance on the clinical tests of apraxia
- 7 Multiple linear regression models using the three WM tasks as predictors

8 The results of the regression model predicting the performance in the hand (position)

9 imitation test indicated that the three main WM tasks (block span (BS), digit span (DS), motor

WM compound score (mWM)) explained 28% of the variance (adjusted  $R^2 = .28$ ,  $F_{(3,35)} = 5.8$ ,

p < 0.005). Importantly, the mWM compound score was the only significant predictor of the

hand imitation scores ( $\beta = 1.48$ , t(35) = 2.38, p < 0.05). Similarly, the three main WM tasks

explained 29% of the variance in the finger (configuration) imitation test (adjusted  $R^2 = .29$ ,

 $F_{(3.35)} = 6.06$ , p < 0.005). Performance in the finger imitation test was significantly predicted

by the mWM compound score ( $\beta = 1.25$ , t(35) = 2.03, p < 0.05) and marginally by the BS score

 $(\beta = 1.19, t(35) = 1.8, p = 0.08)$ . Moreover, the three WM tasks explained 49% of the variance

in the object use scores (adjusted  $R^2 = .49$ ,  $F_{(3.35)} = 13.06$ , p < 0.001). Performance in the object

use test was significantly predicted by the BS scores ( $\beta = 1.71$ , t(35) = 3.45, p < 0.005) and the

19 DS scores ( $\beta = 0.63$ , t(35) = 2.51, p < 0.05).

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### Multiple linear regression models using the three motor WM subtasks as predictors

The results of the regression models predicting the performance in the imitation tests indicated that the three mWM subtasks (actions with objects (AO), meaningful actions (MFA),

meaningless actions (MLA)) explained 32% of the variance in the test of imitating hand

positions (adjusted  $R^2 = .32$ ,  $F_{(3,36)} = 7.03$ , p < 0.001) and 26% of the variance in the test of

imitating finger configurations (adjusted  $R^2$  =.26,  $F_{(3,36)}$  = 5.52, p < 0.005). Importantly, the performance on the AO (mWM) subtask was the only significant predictor of the scores in the hand imitation test ( $\beta$  = 1.86, t(36) = 2.84, p < 0.01) and the finger imitation test ( $\beta$  = 1.12, t(36) = 1.6, p < 0.01). Besides, the regression model predicting the performance in the object use test indicated that the three mWM subtasks explained 32% of the variance (adjusted  $R^2$  =.32,  $F_{(3,36)}$  = 7.04, p < 0.001). Again, the AO (mWM) subtask was the only significant predictor of object

# Discussion

use scores ( $\beta = 1.38$ , t(36) = 2.39, p < 0.05).

The study's primary outcome that patients with a stroke to the motor-dominant LH and apraxia showed specific deficits in motor working memory (mWM, even when controlled for their concurrent visuospatial and verbal working memory (WM) deficits) strongly supports the notion of a WM subsystem dedicated to the processing of action-related information. Moreover, a compound score reflecting performance in the mWM subtasks predicted the severity of apraxic deficits in gesture imitation. These findings suggest that mWM deficits contribute to apraxia in LH stroke patients.

Our data provide neuropsychological evidence for a distinct mWM subsystem and point to a relevant association between mWM deficits and apraxia. Compared to healthy control participants and non-apraxic LH stroke patients, apraxic LH patients exhibited severe deficits in maintaining and retrieving action-related information. The worse performance observed in patients with apraxia (LH+) in the mWM task remained significant after controlling for visuospatial and verbal WM deficits (as assessed by the block tapping test (BS) and the forward

digit span test (DS), respectively). Notably, if patients had relied (solely) on spatial WM

strategies to process the static body images, one would expect their performance on the mWM

subtasks and the BS to be comparable. However, our data show a clear differentiation in the

motor subcomponent of WM.

pattern of performance between the LH stroke patients with (LH+) and without apraxia (LH-)
on the two tasks; no significant differences were observed between the LH+ and LH- patients
on the BS, but significant differences occurred between these two patient groups in the mWM
subtasks. Thus, apraxic LH stroke patients showed differential mWM deficits over and above
their deficits in verbal and visuospatial WM, further supporting the notion of a specialized

A separate analysis indicating that aphasic deficits (i.e., language deficits) were unlikely to modulate performance in the mWM subtasks further corroborated these findings. Following the literature on aphasia and WM (Christensen et al., 2018), we observed that aphasic deficits were associated with poorer performance on verbal WM (as assessed by the DS) but did not affect the performance of visuospatial WM (as assessed by the BS). Importantly, no relevant effects of aphasic deficits were found on the mWM compound score and the mWM subtasks, as LH stroke patients with mild, moderate, and severe aphasia showed no significant differences. Thus, even after controlling for apraxic deficits, patients with different degrees of aphasia severity exhibited no differential group performance across all motor WM subtasks. These findings further corroborate the notion that the observed deficits in the motor WM task in our sample of LH stroke patients with apraxia are more likely to be associated with apraxic deficits rather than with concomitant aphasia.

Besides, LH+ stroke patients did not show specific deficits on the mWM subtasks with meaningful stimuli (i.e., actions with objects (AO) and meaningful actions (MFA) subtasks) that relate to respective action-semantic representations. Their deficits extended to the encoding and retrieval of 'meaningless actions' (MLA) stimuli not considered to relate to semantic representations. Given that our aphasia assessment was restricted to the Token test (i.e., assessing verbal comprehension with no differential evaluation of semantic or phonological impairments), we cannot ascertain whether deficits in the processing of (action-)semantic

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information (processes related to long-term memory) did or did not affect the processing and recall of the presented action stimuli in the current mWM subtasks.

The contribution of mWM deficits to apraxia after LH stroke was further substantiated by the finding that the overall performance in the mWM tasks (operationalized by the mWM compound score) predicted the severity of apraxic deficits in clinical tests of gesture imitation (imitation of hand positions and finger configurations). Note that the additional contribution – albeit to a lesser degree – of visuospatial WM to the finger imitation test scores is consistent with the notion that visuospatial processing contributes to the imitation of finger configurations (Goldenberg & Strauss, 2002; Goldenberg, 1999). Moreover, memorizing motor stimuli depicting 'actions with objects' (AO) was shown to drive the prediction of apraxia severity as assessed by clinical tests of gesture imitation (as well as object use). Notably, the AO subtask was the easiest among the three subtasks (given the better performance on this task than the MFA and MLA subtasks across all studied groups). This finding suggests that it is not the difficulty level of the mWM task but presumably the complexity of the encoded action stimuli that drove the prediction of the scores on the tests of imitating finger configurations and hand positions by the mWM compound score. Thus, our findings on the contribution of mWM deficits to apraxic deficits parallel the observation that spatial WM deficits contribute to the clinical symptoms of neglect due to right hemisphere damage (Malhotra, 2004; Wojciulik et al., 2001). As the current apraxia assessment focused on imitating single movements and using single objects, future studies are warranted that examine the contribution of mWM deficits after LH stroke to motor sequencing deficits prevalent in LH stroke patients with apraxia (LH+). Note that LH+ patients exhibit increased error rates when performing increasingly complex sequences of arm (Weiss et al., 2001) or hand movements (Harrington & Haaland, 1992).

While the mWM compound score was the main significant predictor of the LH stroke patients' imitation performance, the scores in the object use test were significantly predicted by the visuospatial WM and verbal WM scores, as assessed by the block span and digit span,

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respectively. This outcome is consistent with visuospatial and verbal WM processes contributing to object/tool use (Baumard et al., 2014). The role of verbal WM processes is especially evident in pantomiming the use of objects (Bartolo et al., 2003). Moreover, processing object affordances in pantomimed and actual object use entails action-related WM and the processing of spatial relationships (Randerath et al., 2011).

The current neuropsychological results extend previous findings in LH stroke patients with apraxia (LH+), implying a potential link between apraxic and WM deficits. In particular, the notion of a specific WM deficit related to apraxic deficits was initially proposed in a case study conducted by Bartolo et al. (2003). Here, the authors reported an apraxic patient with pantomiming deficits correlated with verbal WM deficits. The patient did not show any other executive deficits. Moreover, WM deficits were suggested to underlie deficits in pantomiming the use of objects and deficits in actual object use (Randerath et al., 2011). Notably, short-term memory/WM was not only considered a mediating buffer that integrates the goal of action with the relevant knowledge about how to use a specific tool into a successful action plan in object use tasks (Randerath et al., 2011), but also integrates the perception of (meaningless) gestures with a successful production plan in imitation tasks (Rumiati & Tessari, 2002). Thus, previous studies investigating patients with apraxic deficits in (pantomiming) object use and imitating gestures imply a potential contribution of WM deficits to the observed apraxic deficits. In contrast to these previous studies, the current study aimed to directly assess the contribution of different WM subsystems, particularly mWM, to apraxic deficits in patients with LH stroke. Our findings support the proposed link between apraxic deficits and WM deficits by suggesting a specific contribution of mWM deficits to deficits in gesture imitation and a general contribution of verbal and visuospatial WM deficits to deficits in object use in LH+ patients.

Further, the notion that apraxic deficits are associated with mWM deficits converges with recent functional imaging findings in healthy participants, which revealed the recruitment of structures in fronto-parietal praxis networks during the encoding and maintenance of action-

related information. For instance, the maintenance of biological motion was shown to rely on the left middle and right inferior frontal gyri and the superior and inferior parietal lobule of the LH (Lu et al., 2016). Likewise, with an increasing memory load of action stimuli, the middle temporal cortex showed increased activation and functional connectivity with a fronto-parietal network (Cai et al., 2018). Similar findings were observed for the recall of tools (objects used in goal-oriented actions). In particular, memorizing manipulable objects was associated with cortical activations in the left ventral premotor cortex and the left inferior frontal gyrus when compared to non-manipulable objects (Mecklinger, 2002). Most of the reported neural correlates of memorizing action-related information involve structures in the motor-dominant LH. Future studies are warranted that directly compare patients with stroke to the left hemisphere and patients with stroke to the right hemisphere to further investigate a potential left hemispheric lateralization of mWM functions.

### Limitations

A potential limitation of the current study is that processing action-related information presented in our mWM task seems more demanding than memorizing verbal and spatial information. However, the reported shorter mWM span was found in LH stroke patients with apraxia (LH+), patients without apraxia (LH-), and healthy controls. This observation is in line with previous literature on mWM in healthy participants that converge on the notion that this system is characterized by a somewhat limited capacity (Smyth & Pendleton, 1990; Wood, 2007; Wu & Coulson, 2014). Importantly, LH+ patients showed a significant performance difference compared to the LH- patients in the supposedly difficult 'meaningless actions' (MLA) subtask and the supposedly easier 'actions with objects' (AO) subtask. Therefore, it is unlikely that the lower performance on the mWM task of the LH+ patients is solely due to task difficulty.

Another potential contributing factor to the lower performance on the mWM task in patients with apraxia might be deficits in the body structural description that have been shown to contribute to apraxia (Dafsari et al., 2019). Body structural description (or body schema) is essential in processing gestures without objects but is also relevant for object-related actions (Cardinali et al., 2009; Carlson et al., 2010; Iriki et al., 1996). Due to time constraints and the reduced resilience of the LH stroke patients, the applied neuropsychological test battery did not include additional neuropsychological tests to assess deficits in body structural description (Semenza, 1988) or body image (Cash et al., 2004) in our sample of LH stroke patients. Future studies further characterizing motor WM functions in stroke patients with apraxic deficits should control for potential concomitant deficits in the body structural description.

Another critical factor to consider is the single motor WM compound score computed to devise a standardized measure of the WM motor domain, which can be equivalently compared to the standardized digit span and block span scores of the verbal and visuospatial WM domains. Nevertheless, it is essential to note that using the motor WM compound score in the regression analyses can be problematic given the observed high correlations between its three sub-scores (i.e., actions with objects (AO), meaningful actions (MFA), and meaningless actions (MLA)). These high correlations make it challenging to determine which of the three subcomponents drives the observed prediction effects by the motor WM compound score. However, the consistent observation that the AO subtask predicts the apraxia test scores suggests that performance on the AO subtask drives the observed significant prediction of imitation test scores by the motor WM compound score.

Finally, it is essential to note that there was a (partial) overlap between the stimuli presented in the mWM subtasks and the items used in the clinical tests of apraxia. However, only three items from the object use test were similar to those presented in the AO subtask, and only three (out of ten) items from the tests of imitating hand positions and finger configurations were similar to the stimuli used in the MLA subtask. Moreover, the administration and

1 reproduction of the individual items differed across tasks. In the imitation tests, patients

2 reproduced a single meaningless gesture immediately after its presentation, whereas in the

MLA (mWM) subtask, they had to recognize a sequence of meaningless gestures from an array

of nine pictures.

### Conclusion

Using a novel mWM task in LH stroke patients with and without apraxia (and age-matched healthy controls), we found neuropsychological evidence for a specialized mWM subsystem dedicated to the encoding, maintenance, and retrieval of action- and body-related information. The current mWM task revealed that patients with a stroke to the motor-dominant LH and apraxia exhibited specific deficits in mWM that were disproportionate to their visuospatial and verbal WM deficits. Importantly, since the mWM deficits of the LH stroke patients predicted their deficient performance in apraxia tests assessing imitation, we established a contribution of mWM deficits to apraxia after LH stroke.

Thus, the performance of LH stroke patients on the three WM tasks provides neuropsychological evidence for a domain-specific mWM subsystem that is specifically impaired in apraxic patients. This pattern of results suggests that the fronto-parietal praxis networks of the LH, which, when lesioned, cause apraxia, may also support mWM functions.

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# 1 Figure legends

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- Figure 1. Lesion overlays for left hemisphere stroke patients with and without
- 4 apraxia.
- 5 Lesion overlay plots of the LH stroke patients with available lesion maps and complete
- 6 neuropsychological test scores. (A) Lesion overlay of all LH stroke patients with available
- 7 lesion maps (n = 35), (**B**) lesion overlay of the subgroup of LH stroke patients without apraxia
- 8 (and available lesion maps, n = 17), and (C) lesion overlay of the subgroup of LH stroke patients
- 9 with apraxia (and available lesion maps, n = 18).
- Lesions are plotted on the ch2-template provided by MRIcron (Rorden & Brett, 2000). The
- depicted slices correspond to the z-coordinates ranging from -42 to 68 mm in MNI space. The
- amount of lesion overlap across patients is indicated by the color shades, with the black color
- indicating the lowest degree of overlap and the white color indicating the highest degree of
- overlap. *LH*: left hemisphere.

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- Figure 2. Example stimuli of the novel motor working memory (WM) task.
- 17 The motor WM paradigm presented participants with action-related pictures depicting three
- categories of actions: actions with objects (here, for example, peeling an apple), meaningful
- 19 actions (here, for example, showing physical power by flexing one's biceps muscles), and
- 20 meaningless actions. Note that neither the actress nor her clothing changed within a given
- 21 category. Thus, the same actress performed all items for the 'actions with objects' subtask,
- 22 while another actress performed all items for the 'meaningful actions' (wearing an orange T-
- shirt) and 'meaningless actions' (wearing a red T-shirt) subtests. Participants were presented
- 24 with a sequence of pictures from each of the three categories. Subjects were then asked to recall
- 25 the correct pictures in the correct order from a sample of nine pictures of the same category.
- The sequence length of the displayed pictures increased incrementally by a single item on each

- successive trial with a correct answer (starting with two pictures, up to a maximum of nine
- 2 pictures), and the task was terminated after two consecutive errors in reproducing the displayed
- 3 sequence on the same trial.

- 5 Figure 3. Effects of apraxia on working memory (WM) performance.
- 6 (A) Effects of apraxia: comparisons between the three working memory (WM) tasks. Compared
- 7 to the age-matched controls, LH stroke patients with apraxia (LH+) performed significantly
- 8 worse on the three tasks: block span (BS), digit span (DS) and motor WM compound score
- 9 (mWM). In contrast, the LH stroke patients without apraxia (LH-) performed worse than the
- 10 controls only in the DS test. Importantly, patients with apraxia (LH+) showed more pronounced
- deficits in the mWM task than patients without apraxia (LH-); however, the performance of the
- two patient groups did not differ significantly in the BS and DS tasks.
- 13 (B) Effects of apraxia: comparisons between the three motor WM subtasks. In comparison to
- 14 healthy controls and patients without apraxia (LH-), patients with apraxia (LH+) showed
- significantly worse performance on all three mWM subtasks: the 'actions with objects' (AO),
- 16 'meaningful actions' (MFA), and 'meaningless actions' (MLA) subtasks. No significant
- differences were observed between the controls and patients without apraxia. Panel B illustrates
- the adjusted mean values after controlling for the scores on the BS and DS. Error bars indicate
- 19 95% confidence intervals. Asterisks indicate the Bonferroni-corrected level of significance for
- 20 post-hoc tests (\* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001).

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- Figure 4. Effects of aphasia on working memory (WM) performance.
- 23 (A) Effects of aphasia: comparisons between the three working memory (WM) tasks. On the
- 24 digit span (DS) task, patients with no/minimal aphasia and mild aphasia performed better than
- 25 patients with moderate and severe aphasia. No significant differences were observed between

- the four aphasia groups (minimal, mild, moderate, and severe) in the block span (BS) and motor
- 2 WM compound score (mWM).
- 3 (B) Effects of aphasia: comparisons between the three motor WM subtasks. Patients with
- 4 no/minimal aphasia performed better than patients with mild, moderate, and severe aphasia on
- 5 the actions with objects (AO) subtask. No other significant differences between the aphasia
- 6 groups were observed in the meaningful actions (MFA) and meaningless actions (MLA)
- 7 subtasks. Panel B illustrates the adjusted mean values after controlling for the scores on the BS
- 8 and DS. Error bars indicate 95% confidence intervals. Asterisks indicate the Bonferroni-
- 9 corrected level of significance for post-hoc tests (\* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001).