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The role of the hippocampus in statistical learning and language recovery in persons with post stroke aphasia

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ABSTRACT

Although several studies have aimed for accurate predictions of language recovery in post stroke aphasia, individual language outcomes remain hard to predict. Large-scale prediction models are built using data from patients mainly in the chronic phase after stroke, although it is clinically more relevant to consider data from the acute phase. Previous research has mainly focused on deficits, i.e., behavioral deficits or specific brain damage, rather than compensatory mechanisms, i.e., intact cognitive skills or undamaged brain regions. One such unexplored brain region that might support language (re)learning in aphasia is the hippocampus, a region that has commonly been associated with an individual's learning potential, including statistical learning. This refers to a set of mechanisms upon which we rely heavily in daily life to learn a range of regularities across cognitive domains. Against this background, thirty-three patients with aphasia (22 males and 11 females, $M = 69.76$ years, $SD = 10.57$ years) were followed for 1 year in the acute (1–2 weeks), subacute (3–6 months) and chronic phase (9–12 months) post stroke. We evaluated the unique predictive value of early structural hippocampal measures for short-term and long-term language outcomes (measured by the ANELT). In addition, we investigated whether statistical learning abilities were intact in patients with aphasia using three different tasks: an auditory-linguistic and visual task based on the computation of transitional probabilities and a visuomotor serial reaction time task. Finally, we examined the association of individuals' statistical learning potential with acute measures of hippocampal gray and white matter. Using Bayesian statistics, we found moderate evidence for the contribution of left hippocampal gray matter in the acute phase to the prediction of long-term language outcomes, over and above information on the lesion and the initial language deficit (measured by the ScreeLing). Non-linguistic statistical learning in patients with aphasia, measured in the subacute phase, was intact at the group level compared to 23 healthy older controls (8 males and 15 females, $M = 74.09$ years, $SD = 6.76$ years). Visuomotor statistical learning correlated with acute hippocampal gray and white matter. These findings reveal that particularly left hippocampal gray matter in the acute phase is a potential marker of language recovery after stroke, possibly through its statistical learning ability.

Abbreviations: ANELT, Amsterdam-Nijmegen Everyday Language Test; BF, Bayes Factor; eTIV, estimated Total Intracranial Volume; FBC, Fibre Bundle Capacity; FLAIR, Fluid-Attenuated Inversion Recovery; NIHSS, National Institutes of Health Stroke Scale; RT, Reaction Time.

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1. Introduction

Approximately 15–45 percent of patients with acute stroke have a language impairment, or aphasia (Flowers et al., 2016; Inatomi et al., 2008). In the first months post stroke, there is often some spontaneous and intervention-induced recovery, but for 26–43 percent of patients a chronic language deficit remains (Laska et al., 2001; Maas et al., 2012). Several predictors of language recovery after stroke have been identified (Plowman et al., 2012; for reviews see Watila & Balarabe, 2015), yet there remains a considerable amount of unpredicted variance in individual language recovery patterns (Hope et al., 2013; Hope et al., 2018). Previous research has mainly focused on the influence of the brain damage and language deficits, but by focusing on what is damaged, one might forget an individual's learning potential (Dignam et al., 2016; Hoen et al., 2003) and the intact brain structures that support such cognitive abilities, such as the hippocampus (Tuomiranta et al., 2014). A specific set of learning mechanisms which is repeatedly assumed to rely on computations in the hippocampus is referred to as statistical learning (Batterink et al., 2019; Frost et al., 2015), i.e., the brain's ability to pick up and extract a wide variety of statistical properties inherent to the sensory input (Bogaerts et al., 2022; Conway, 2020). The present study aims to improve the prediction by assessing whether neuroanatomical measures of the hippocampus predict language recovery in patients with aphasia. In addition, we explore whether hippocampal measures are related to (intact) learning ability in patients with aphasia, measured via statistical learning tasks.

Predictors of language recovery after stroke can be subdivided into patient-related predictors, language-related behavioral predictors and lesion-related neural predictors. The evidence for the independent contribution of patient-related predictors such as age, gender, handedness and education is currently unclear (Hope et al., 2013; Plowman et al., 2012; Watila & Balarabe, 2015), but across all studied predictors, lesion size, lesion location and initial aphasia severity have most consistently been identified as best predictors of aphasia recovery (Hartwigsen & Saur, 2019; Plowman et al., 2012; Watila & Balarabe, 2015). However, the most influential prediction studies (Hope et al., 2013; Hope et al., 2018) have been conducted with patients (mainly) in the chronic phase post stroke, when the usefulness of the prognostication window has diminished, making it difficult to generalize to the clinically most relevant acute phase (Loughnan et al., 2019). In addition, a substantial proportion (20–70 %) of variance in language recovery remains unexplained (Benghanem et al., 2019; Blom-smink et al., 2017; Hope et al., 2013; Lazar et al., 2008; Osa García et al., 2020), implicating that we do not yet have a full picture of the factors driving recovery.

There is growing appreciation that the processing of linguistic information is mediated by other kinds of (non-linguistic) information, which redefines recovery from aphasia as a dynamic interplay between linguistic and non-linguistic cognitive processes (Cahana-Amitay & Albert, 2014). There is indeed evidence for the involvement of non-linguistic cognitive processes in aphasia treatment outcomes (Gilmore et al., 2019; Lambon Ralph et al., 2010; Seniów et al., 2009) as well as the compensatory value of learning potential in language recovery (Dignam et al., 2016; Hoen et al., 2003; Tuomiranta et al., 2014). At the neural level, studies have shown functional involvement as well as structural associations of the hippocampus with language learning tasks (Penaloza et al., 2022; Rodriguez-Fornells et al., 2009), and with successful language treatment outcomes after stroke (Goldenberg & Spatt, 1994; Meinzer et al., 2010; Menke et al., 2009). This evidence suggests that the hippocampus possibly constitutes a shared mechanism for both learning and language. Given that the hippocampus has the ability to rapidly encode relations ("binding") between arbitrary elements that consistently appear together in space and/or time (Cohen & Eichenbaum, 1993; Squire & Dede, 2015), the hippocampus is suggested to be specifically involved in statistical learning aspects (Shohamy & Turk-Browne, 2013). The link between hippocampus and language recovery in aphasia as well as whether this is mediated via statistical learning still awaits further investigation (Batterink et al., 2019; Covington et al., 2018).

In the domain of language, statistical learning is assumed to contribute to different aspects of language acquisition: Infants track the distribution of sounds in their language environment to discover phoneme categories, they identify transition probabilities of syllables to discover word boundaries, they use cross-situational statistics to learn word-object mappings, and they learn the order of word categories in sentences to acquire syntactic rules (for reviews see Arciuli et al., 2012; Kuhl, 2004; Romberg & Saffran, 2010; Saffran, 2003). Given the importance of statistical learning for the acquisition of the mother tongue and possibly also for second language learning (Frost et al., 2013; Hamrick, 2014; Kaufman et al., 2010; Onnis, 2012; Weiss et al., 2019), it could also constitute an important mechanism for language *re*learning in patients with aphasia after stroke. Previous studies have indeed shown substantial variation in statistical learning in patients with aphasia (Jarret et al., 2019; Peñaloza et al., 2017; Schuchard et al., 2017; Shaqiri et al., 2018; Vadinova et al., 2020; Vallila-Rohter & Kiran, 2015), hence individual differences in statistical learning might explain some variability in language recovery in aphasia.

In summary, a promising and relatively unexplored approach to improve early predictions of language recovery is to go beyond the lesion and expand the focus to properties of intact gray and white matter supporting cognitive abilities that are involved in (re)learning language. In addition, there is limited information on acute prognostic markers of language recovery. The present study aims to fill these gaps by (1) incorporating brain regions that were intact in most patients and reflect learning abilities, including statistical learning, and by (2) including these predictors in the acute phase to predict short and long-term language outcomes. More specifically, we aim to evaluate the unique predictive value of hippocampal gray and white matter in the acute phase (1–2 weeks post stroke) for short-term (3–6 months post stroke) and long-term (9–12 months post stroke) functional language outcomes closely representing daily life situations. The predictive value of the hippocampus is measured above and beyond known predictors which relate to the initial language impairment and lesion size. Next, we explore whether these structural hippocampal measures are related to statistical learning abilities. Given that it is debated (Bogaerts et al., 2022; Frost et al., 2015) whether statistical learning is one unitary learning system or whether the computations differ across domains, we evaluate statistical learning in this study using three different widely-used (linguistic and non-linguistic) tasks, in the domains of speech segmentation, visual object perception and visuospatial processing. We first investigate whether statistical learning abilities in the three different tasks are intact in patients with aphasia in the subacute phase by comparing them to healthy older controls, as this could indicate a potential protective learning mechanism. We then assess whether subacute statistical learning abilities correlate with structural properties of the hippocampus measured in the acute phase.

2. Materials and methods

2.1. Participants

This project was approved by the Medical Ethical Committee of the University Hospitals and University of Leuven (registration number B322201731747). Details on patient recruitment are provided in Supplementary Information and a flowchart of patient recruitment is shown in Supplementary Fig. 1. Informed consent was obtained from all patients and/or their relatives. Patients with a stroke lesion in the left hemisphere and a confirmed language deficit were followed from the acute phase (1–2 weeks post stroke, $n = 65$) to the chronic phase (9–12 months post stroke, $n = 43$), with an extra measurement in the subacute phase (3–6 months, $n = 42$). In the present longitudinal study, we included a subset of 33 patients with acute MRI data and at least one behavioral follow-up moment. Table 1 shows the participant

Table 1
Characteristics of the group of patients with aphasia under study.

Variable	N = 33[a]	Median (Range)	NA[b]
Age (years)	69.8 (10.6)	72.0 (41.0–86.0)	
Sex (female/male)	11/22		
Handedness (right-handed/other)	29/4		
Education (years)	13.7 (3.1)	14.0 (8.0–22.0)	1
Stroke type (ischemia/hemorrhage)	30/3		
Stroke laterality (left/bilateral)	28/5		
History of stroke (no/yes)	30/3		
Affected circulation area			
ACM/ACP/Avert/Abas/AchorA/ multifocal	22/5/1/1/ 1/3		
Acute lesion volume (cm^3)	43.16 (41.43)	27.72 (0.67–149.51)	
Old lesion load (cm^3)	20.33 (16.57)	15.27 (1.46–55.67)	
Acute NIHSS total score	7 (6)	4 (0–30)	
Acute volume left hippocampus (mm^3)	3,100 (459)	3,075 (2,368–4,185)	4
Acute volume right hippocampus (mm^3)	3,186 (376)	3,196 (2,312–3,989)	1
Acute FBC left hippocampus (a.u.)	2.97 (1.17)	2.76 (0.92–5.80)	5
Acute FBC right hippocampus (a.u.)	3.16 (1.06)	3.34 (0.65–5.87)	2
Initial language score (/72)[c]	46.05 (21.69)	54.50 (0.00–70.00)	2
Acute days post stroke	5 (6)	3 (0–29)	
Subacute functional language outcome (/50)[d]	38.46 (10.84)	42.50 (10.00–50.00)	1
Subacute days post stroke	117 (28)	108 (85–185)	1
Subacute auditory SL score (/32)	17.25 (3.56)	16.50 (12.00–25.00)	5
Subacute visual SL score (/32)	19.90 (4.72)	21.00 (12.00–32.00)	3
Subacute visuomotor SL score[e]	0.28 (0.32)	0.19 (-0.27–0.94)	1
Chronic functional language outcome (/50)[d]	39.77 (10.39)	44.50 (10.00–50.00)	3
Chronic days post stroke	288 (10)	286 (272–315)	

Note. ACM = arteria cerebri media, ACP = arteria cerebri posterior, Avert = arteria vertebralis, Abas = arteria basilaris, AchorA = anterior choroidal artery, NIHSS = National Institutes of Health Stroke Scale (a higher score corresponds to a more severe stroke), FBC = Fiber Bundle Capacity, SL = statistical learning.

[a] N is reported for categorical variables; M (SD) is reported for continuous variables.

[b] N indicates the number of participants for which the corresponding data are missing.

[c] as measured by the ScreeLing (Visch-Brink et al., 2010).

[d] as measured by the Amsterdam-Nijmegen Everyday Language Test, A-scale (Blomert et al., 1995).

[e] z-score difference sequence-random.

characteristics for this group and the number of missing data points per variable.

2.2. Procedure

In the acute phase, we administered the ScreeLing (Visch-Brink et al., 2010) and the Amsterdam-Nijmegen Everyday Language Test (ANELT, Blomert et al., 1995) to measure patients' language impairment and we acquired MRI data. The ScreeLing has been validated in an acute stroke population (Doesborgh et al., 2003; El Hachioui et al., 2012; El Hachioui et al., 2017) and assesses the three main linguistic components, i.e., semantics, phonology and syntax, and is thus mainly focused on the impairment level. For the purpose of this study, only the total ScreeLing score was considered, from now on referred to as "language score". In contrast, the ANELT (Blomert et al., 1995) assesses verbal communicative ability based on the informational content of utterances pertaining to ten everyday language scenarios (e.g., calling the doctor or talking to a friend). All scenarios were presented auditorily and patients were asked to respond verbally. All utterances were then rated on a 5-point scale for understandability of the message, from now on referred to as "functional language outcome". In the subacute phase, we readministered the ScreeLing (Visch-Brink et al., 2010) and the ANELT (Blomert et al., 1995). Patients were further assessed with statistical learning tasks in different modalities and completed a custom-made demographic questionnaire. Other measures were additionally collected but are outside the scope of this study and are not reported here. In the chronic phase, the ScreeLing (Visch-Brink et al., 2010) and the ANELT (Blomert et al., 1995) were repeated. Due to COVID-19, data collection in the acute phase was stopped prematurely, and follow-up moments were spread over a period of three months (subacute: 3–6 months post stroke, chronic: 9–12 months post stroke) instead of the foreseen one month (subacute: 3–4 months post stroke, chronic: 9–10 months post stroke).

3. Neuroimaging

3.1. Data acquisition

We acquired 3D T1-weighted images, multi-shell diffusion-weighted images and T2-weighted fluid-attenuated inversion recovery (FLAIR) data. Details regarding data acquisition can be found in the Supplementary Information. Other sequences were additionally acquired but are outside the scope of this study and are not reported here.

3.2. Lesion segmentation

Two different lesion masks were created per patient: an acute lesion map and a full lesion map. First, acute stroke lesions were manually delineated (by KS) on the FLAIR image (axial slices), with the diffusion-weighted image (*b*1000 and ADC [apparent diffusion coefficient]) as guidance for ischemic lesions. Manual delineations were drawn in MRIcron (v. 02092019, available via https://www.nitrc.org/projects/mricron) and visually checked twice by a resident in neurology. This lesion map was used to determine acute lesion volume (in cm^3) and to exclude recent lesioned tissue from the whole brain tractogram. A lesion overlay image for the acute lesion maps is presented in Fig. 1.

Second, a full lesion map covering all burden of cerebrovascular disease was created by segmenting all FLAIR hyperintense lesions (acute stroke lesions, old stroke lesions as well as leukoaraiosis) with the lesion prediction algorithm (Schmidt, 2017) as implemented in the Lesion Segmentation Toolbox (v. 3.0.0, available via https://www.statistical-modelling.de/lst.html) for Statistical Parametric Mapping. This map was then merged with the (manually drawn) acute lesions, as well as manual delineations of old (FLAIR) hypointense stroke lesions where necessary. Old lesion load (in cm^3) was calculated by subtracting the acute lesion map from the full lesion map.

3.3. MRI processing for gray matter volume of the hippocampus

Lesion free T1-weighted images were generated through Virtual Brain Grafting (available via https://github.com/KUL-Radneuron/KUL_VBG). These images were fed to FreeSurfer's recon-all (v. 6.0.0, available via https://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012), including the hippocampal subfields module for automated segmentation of the hippocampus (Iglesias & Sabuncu, 2015). Virtual Brain Grafting is a fully automated, open-source workflow aimed to reliably parcellate anatomical datasets in the presence of (bilateral) brain lesions (Radwan et al., 2021). This method was used to prevent FreeSurfer failure (Reid et al., 2016; Zhang et al., 2017) and ensure accuracy of the hippocampal parcellations in the presence of lesions and leukoaraiosis (Dadar et al., 2021). The whole-volume segmentations (shown in Fig. 2) of all bilateral hippocampi were visually inspected and were successfull in all patients without hippocampal lesions. Quantitative values for hippocampal volume (in mm^3) were extracted from FreeSurfer, as well as an individual's estimated total intracranial volume (eTIV; used to control for head size in statistical analyses).

Hippocampal blood supply is generally provided by collateral

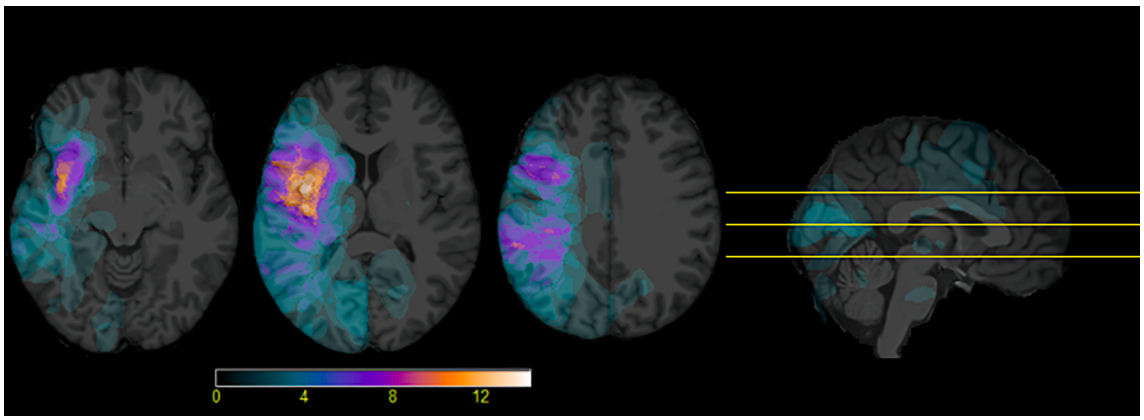

Fig. 1. Acute lesion overlay image (max overlap = 14) for the included participants (n = 33). Axial slices are shown in neurological orientation.

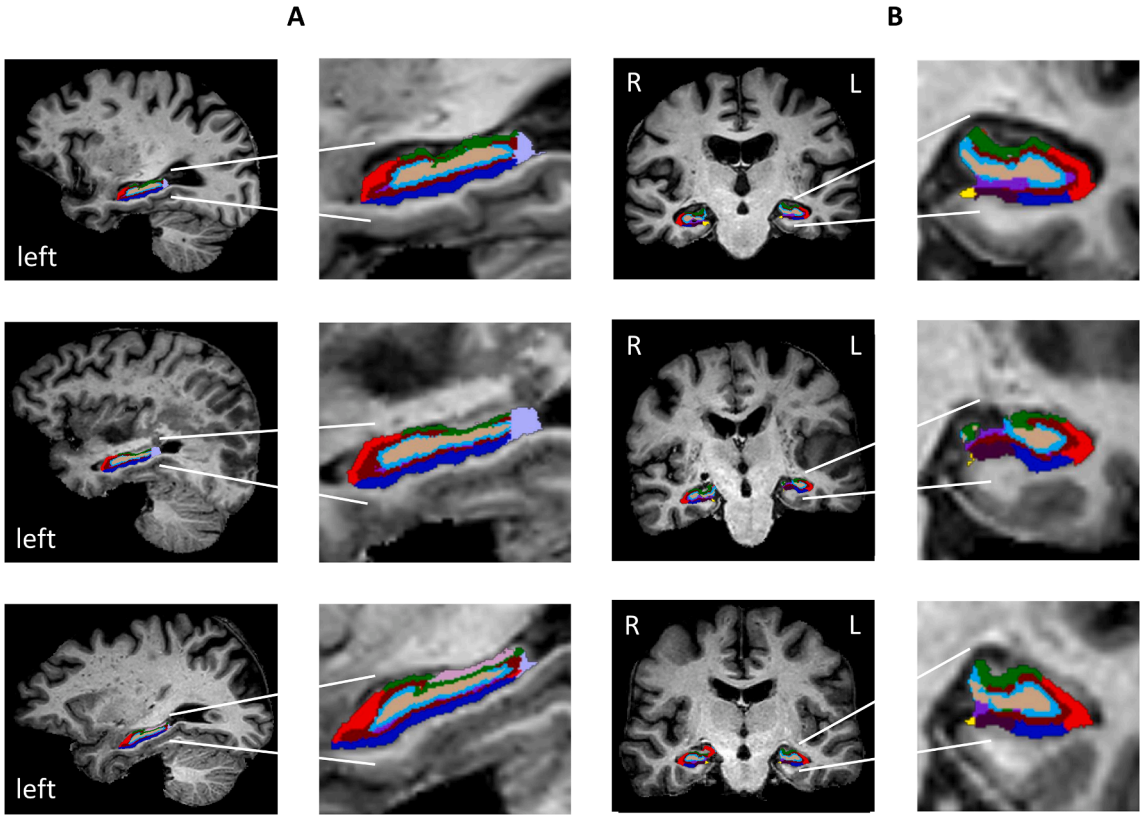

Fig. 2. Example hippocampal parcellations overlayed on the native T1 image for three patients (rows). **A** Sagittal view of the lateral left hippocampus with detail. **B** Coronal view of the anterior bilateral hippocampi with detail of the left hippocampus.

branches of the posterior cerebral artery and the anterior choroidal artery (Marinković et al., 1992; Spallazzi et al., 2019). As a consequence, vascular pathology in these arteries might cause direct damage to the hippocampus. To study the potential compensatory value of hippocampal integrity during aphasia recovery, hippocampal measures for patients with substantial (old or current) cerebrovascular disease in this region, i.e., more than 3 % overlap between hippocampal segmentations and the full lesion map, were excluded from the dataset. This threshold was defined based on visual inspection of the data. In our patient group, five patients had substantial hippocampal damage (left hippocampus: 4/33 patients; right hippocampus: 1/33 patient), including three patients with (previous) strokes in the posterior circulation and two patients with strokes in the vascular territory of the middle cerebral artery. Although the latter is more rare, proximal occlusion of the middle cerebral artery relative to the internal carotid artery can cause direct damage to the hippocampus in some patients due to individual variability in vascular anatomy (Meinzer et al., 2010). A few patients with damage in the vascular territory supplying the hippocampus did not show substantial hippocampal damage, possibly due to the high degree of anastomosing blood supply (Marinković et al., 1992).

3.4. MRI processing for white matter connectivity of the hippocampus

Diffusion images were denoised (Cordero-Grande et al., 2019; Veraart et al., 2016a; Veraart et al., 2016b) and unringed (Kellner et al., 2016) in MRtrix3 (Tournier et al., 2019) and subsequently corrected for (b0-paired) *EPI* distortions, B0-field inhomogeneities, eddy currents and inter-volume motion using topup and eddy tools in FMRIB Software

Library (FSL, v. 6.0.1) (Jenkinson et al., 2012; Smith et al., 2004) called by MRtrix3's preprocessing tool (Andersson et al., 2003; Andersson & Sotiropoulos, 2015; Bastiani et al., 2019; Holland et al., 2010; Smith et al., 2004). Finally, the images were corrected for bias fields (Tustison et al., 2010) and a brain mask was derived. The mean relative RMS value of the translational and rotational movement parameters ($M = 0.26$ mm, $SD = 0.07$ mm), as calculated by eddy (S)QUAD (Bastiani et al., 2019), did not exceed 0.55 mm for any patient, hence no diffusion data had to be excluded from the analysis (Satterthwaite et al., 2012).

Individual response functions were estimated in an unsupervised way (Dhollander et al., 2016; Dhollander et al., 2019) and averaged into group response functions. Fiber orientation distributions were estimated using multi-shell multi-tissue constrained spherical deconvolution (Jeurissen et al., 2014; Tournier et al., 2004) with default parameters. Intensity normalization was performed to correct for global intensity differences (Dhollander et al., 2021; Raffelt et al., 2017). To generate the whole-brain tractogram, 10 million streamlines were generated using the probabilistic Second-order Integration over Fiber Orientation Distributions (iFOD2) algorithm (Tournier et al., 2010), incorporating the anatomically-constrained tractography framework (Smith et al., 2012) (details in Supplementary Information) to improve biological plausibility of streamline generation with dynamic seeding and backtracking.

To make sure that streamline counts reflected the underlying anatomical fiber density information, we performed Spherical deconvolution Informed Filtering of Tracts, resulting in a weight for every streamline (Smith et al., 2015). To quantify connectivity from the hippocampus, the whole-brain tractogram (and its associated weights) was filtered using the hippocampus segmentations from FreeSurfer (left and right) as inclusion regions and the acute lesion as an exclusion region (see Fig. 3, details in Supplementary Information). The latter was done because at the time of scanning, the patients varied in time post stroke from 1 to 31 days, implying that there was some variability in whether damaged fibers already had degenerated. Notably, the pattern of results remained similar using hippocampal connectivity measures obtained without excluding the acute stroke lesion. Finally, the summed streamline weights of the filtered tractograms were scaled by the (individually determined) proportionality coefficient μ, which enabled comparison across patients. We will refer to this derived measure of connectivity throughout the paper as Fiber Bundle Capacity (FBC) (Smith, 2022). In short, FBC is highly correlated with the number of streamlines (r 0.90), but addresses the limitations of raw streamline count as a metric of connectivity in the context of quantitative tractography. Ideally, FBC provides an estimate of the total cross-sectional area of the white matter pathway of interest, which should represent its information transfer capacity (Smith, 2022). We included two FBC measures per patient, i.e., one for the left and one for the right hippocampus.

3.5. Statistical learning

Statistical learning was assessed in the auditory, visual and visuomotor modality in the subacute phase (except for one patient who refused subacute follow-up, for which the tests were administered in the chronic phase instead). These tasks were not administered in the acute phase because behavioral testing immediately after stroke is challenging (Wade et al., 1986). Existing tasks in the literature (Lum et al., 2012; Siegelman et al., 2017b; Siegelman & Frost, 2015) were adapted to increase feasibility in difficult-to-test populations and implemented in a tablet-based version (Schevenels et al., 2021). We provide a short explanation of the three tasks here, however, full details can be found in Schevenels et al. (2021) (Experiment 2, shortened task versions). From the same study (Schevenels et al., 2021), data from a healthy older

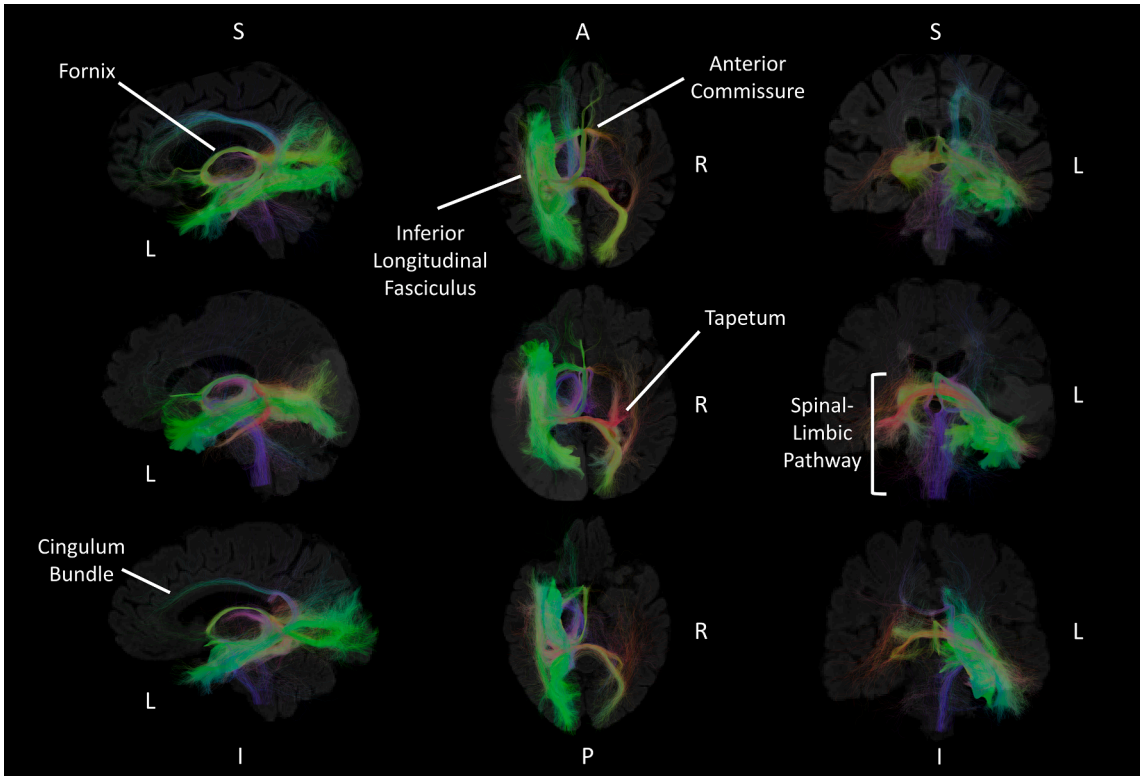

Fig. 3. Example tractograms showing whole-brain left hippocampal connectivity overlayed on the native FLAIR image for three patients (rows). First column: left sagittal view, second column: superior axial view, third column: anterior coronal view. Definition of the tracts is guided by the findings in the study by Maller et al. (2019), in which in-vivo ultra-high angular resolution (1150 directions) diffusion tractography was performed in humans to describe whole-brain macroscopic extra-hippocampal structural connectivity. In this study, in total, 96% of all the streamlines were part of one out of six pathways: the inferior longitudinal fasciculus, the spinal-limbic pathway, the anterior commissure, the cingulate bundle, the fornix, or the tapetum (Maller et al., 2019).

control group were available, which served as a comparison group for the patients with aphasia in the current study. The selected healthy older control group ($N = 23$) did not significantly differ in age ($Median_{HC} = 75$, $Median_{PWA} = 72$, $W = 468.5$, $p = .140$), or years of education ($Median_{HC} = 14$, $Median_{PWA} = 14$, $W = 405.5$, $p = .522$) from the group of patients with aphasia under study ($N = 33$). On the other hand, the gender distribution was significantly different between both groups (healthy control group: 8 males, 15 females, PWA: 22 males, 11 females, $\chi^2(1) = 4.33$, $p = .037$). Information on handedness was not available for the healthy control group.

In the auditory modality, statistical learning was measured by exposing patients to an "artificial language" consisting of a continuous syllable stream (Saffran et al., 1996). Unknown to the patients, four predefined disyllabic words ("timu", "segi", "bode" and "vofa", transitional probability = 1) were each repeated 96 times. Foils ("bomu", "tide", "vogi" and "sefa", transitional probability = 0) were constructed by combining the first syllable of one of the words with the second syllable of a different word. In a two-alternative forced choice test following the passive listening phase, each of the words was combined with each of the foils twice, and patients were instructed to pick the word belonging to the language they had just heard. For each of the 32 test trials, we recorded whether the answer was correct or not. Prior to the administration of this task, a short hearing screening (pure tone audiometry) was performed in order to determine the necessary stimulus intensity (for details see Schevenels et al., 2021).

In the visual modality, the task was very similar as in the auditory modality. Patients were exposed to a stream of sequentially presented abstract shapes (on average 1.75 s per stimulus). Unknown to the patients, four predefined shape pairs (transitional probability = 1) were each repeated 24 times. Foils were constructed by combining the first shape of one of the pairs with the second shape of a different pair. In a two-alternative forced choice test following the passive viewing phase, patients were instructed to choose the pair that appeared in that order in the post test. For each of the 32 test trials, we recorded whether the answer was correct or not. The total score was used in subsequent analyses. Due to a technical mistake, one pair appeared only twice in the post test, while the other pairs were presented 10 times and all 4 foils appeared 8 times.

In the visuomotor modality, statistical learning was measured using a variant of the classic Serial Reaction Time task (Nissen & Bullemer, 1987). Patients were asked to press on a visual cue, the location of which followed a predefined (predictable) 6-item sequence (right-left-down-up-left-down), which was repeated 6 times across 4 blocks, for a total of 24 presentations. Learning of the sequence was expected to result in a decrease in reaction time (RT). In the last block, pseudorandom trials were introduced, for which we expected an increased RT if learning had occurred. To correct for an individual's baseline processing speed, patients' raw RTs were transformed into *z*-scores referenced to the median and standard deviation (*SD*) across trials for that patient. Data points with RTs that were 3 *SD* or more above individual's mean RTs were dismissed, in total 1.85 % of the data. Due to a logging problem in 11 patients specific to the logging of accuracy, incorrect trials were not discarded from the dataset, however, analyses on the subset of patients whose incorrect trials could be dismissed lead to similar results as the ones reported here.

3.6. Statistical analysis

All statistical analyses were performed in R (v. 4.1.1) (R Core Team, 2021), with both frequentist and Bayesian statistics. First, we evaluated Bayesian regression models to assess the predictive value (1–2 weeks) of acute hippocampal gray matter and white matter for short-term (3–6 months) and long-term (9–12 months) functional language outcome (measured by the ANELT). Bayesian multiple linear regression models were built in several steps. In step 1, we defined a basic model predicting functional language outcomes using traditional predictors. Given the heterogeneity in our group of patients, we considered in step 2 eight other predictors that might potentially influence language outcomes. Specifically, we calculated inclusion Bayes factors (*BF* inclusion) for each of these other predictors separately on top of the original model defined in step 1. *BF* inclusion reflects the change from prior to posterior inclusion odds combined across models that include a particular effect. Other predictors with an associated *BF* inclusion larger than 3, reflecting substantial evidence for inclusion, were added to the original model defined in step 1, and this resulted in our updated model. In step 3, we assessed in the same way whether we could further improve this updated model with hippocampal volume and FBC. For the regression analysis, missing data were imputed for six variables: years of education (1 data point), initial ScreeLing score (2 data points), initial ANELT score (2 data points), subacute ScreeLing score (1 data point), subacute ANELT score (1 data point) and chronic ANELT score (3 data points). Data were considered to be Missing At Random and imputed using multivariate imputation by chained equations (MICE) (Azur et al., 2011; van Buuren and Groothuis-Oudshoorn, 2011). Further details on the missing data imputation and the Bayesian regression analyses are provided in Supplementary Information.

In addition to the regression analyses, we explored the role of statistical learning. We started by investigating whether patients' statistical learning ability was intact, by comparing them to healthy older controls from a previous study using a two-sample Wilcoxon or *t*-test (Schevenels et al., 2021). Then, to investigate a potential role of the hippocampus in statistical learning, we examined whether there was an association between the subacute statistical learning measures and the acute hippocampal measures using Holm's corrected pairwise Pearson correlations.

Data availability

The pseudonymized study data and code to reproduce the figures and findings of this study are publicly available at https://github.com/kschevenels/pwasl. Please note that the MRI data cannot be shared under any circumstance, as lesioned MRI data are person-specific and therefore cannot be considered anonymous.

4. Results

A matrix representing pairwise correlations between all (dependent and independent) variables under study is provided in Supplementary Fig. 3.

4.1. Prediction of short-term functional language outcome

Table 2 shows the process of model building for short-term (i.e., subacute: 3–6 months post stroke) prediction of language outcomes. In step 1, we established our original model that predicted short-term functional language outcome and included traditional measures, i.e., initial language score and acute lesion volume. Initial language score was the most critical predictor of later performance, as a model including this predictor is more than 100 times more likely than a model without. The average R^2 (*SD* across imputed datasets) for the original short-term model was 0.69 (0.02). Given the heterogeneity in our group of patients, in step 2 we considered eight other predictors that potentially influenced later language outcomes. Predictors on the received language treatment were not considered as this information is not available immediately post stroke, i.e., when we intend to use the model (Moons et al., 2009). As none of the other predictors had an associated *BF* inclusion larger than 3, the original model was not updated. In step 3, we assessed whether we could improve the traditional model with our hippocampal predictors. Note that, as explained in the methods, hippocampal measures for patients with substantial (old or current) cerebrovascular damage in this region were excluded from the dataset and consequently did not influence the *BF*s. For all hippocampal predictors, on average, models with the specific effect were less likely (*BF* inclusion < 1) to have produced the observed data than models without the effect. Therefore, none of the hippocampal predictors were added to the

Table 2
Building a model to predict short-term functional language outcome (subacute: 3–6 months post stroke).

Step 1: Traditional predictors	**BF inclusion: mean (SD)**
Initial language score	202,254.94 (68,632.76)
Acute lesion volume	0.26 (0.04)
Step 2: Adding other predictors	**BF inclusion: mean (SD)**
Subacute days post stroke	0.48 (0.02)
Old lesion load	0.21 (0.02)
Age	0.20 (0.03)
Sex	0.53 (0.06)
Education	0.57 (0.55)
Acute NIHSS total score	0.19 (0.01)
Acute NIHSS language score	0.19 (0.04)
Estimated total intracranial volume	0.16 (0.00)
Step 3: Adding hippocampal predictors	**BF inclusion: mean (SD)**
Volume left hippocampus	0.19 (0.01)
Volume right hippocampus	0.18 (0.02)
FBC left hippocampus	0.24 (0.01)
FBC right hippocampus	0.18 (0.01)

Note. *BF* inclusion indicates, given the data, how many times more likely a model is including a specific predictor than a model without that specific predictor.

original model. In summary, in our sample, short-term functional language outcome could best be predicted by initial language score alone (model parameters of the final model are given in Supplementary Table 1).

4.2. Prediction of long-term functional language outcome

Table 3 shows the process of model building for long-term (i.e., chronic: 9–12 months post stroke) prediction of language outcomes. In step 1, similar to the short-term model, we found extreme evidence for the effect of initial language score on long-term language outcome: the observed data are more than 100 times more probable under models that include this predictor than under models that exclude it. In addition, there is anecdotal evidence for the role of acute lesion volume. The average R^2 (*SD* across imputed datasets) for the original long-term model was 0.69 (0.10). In step 2, none of the other predictors had an associated *BF* inclusion larger than 3. Therefore, the original model was not updated. In step 3, we found substantial evidence for the inclusion of left hippocampal volume in the original model. Importantly, its associated model parameter was positive, which indicates that a larger volume of the left hippocampus was beneficial for later language outcome (visualisation in Supplementary Fig. 4). In addition, the *BF* inclusion of the hippocampal predictor remained stable (*M* (*SD* across imputed datasets) = 5.52 (9.13)) over and above the effect of eTIV (*M* (*SD* across imputed datasets) = 0.22 (0.04)). The average R^2 (*SD* across imputed datasets) for the final long-term model was 0.75 (0.12) (model parameters of the final model are given in Supplementary Table 2). In summary, in our sample, long-term functional language outcome could best be predicted by a combination of initial language score, acute lesion volume and acute left hippocampal volume.

Table 3
Building a model to predict long-term functional language outcome (chronic: 9–12 months post stroke).

Step 1: Traditional predictors	BF inclusion: mean (SD)
Initial language score	251,585.29 (447,453.33)
Acute lesion volume	2.16 (1.23)
Step 2: Adding other predictors	**BF inclusion: mean (SD)**
Chronic days post stroke	0.25 (0.06)
Old lesion load	1.94 (1.48)
Age	1.33 (1.24)
Sex	0.52 (0.07)
Education	0.48 (0.22)
Acute NIHSS total score	1.40 (0.69)
Acute NIHSS language score	0.23 (0.03)
Estimated total intracranial volume	0.35 (0.35)
Step 3: Adding hippocampal predictors	**BF inclusion: mean (SD)**
Volume left hippocampus*	8.45 (17.89)
Volume right hippocampus	0.60 (0.24)
FBC left hippocampus	1.27 (0.50)
FBC right hippocampus	0.29 (0.11)

* BF inclusion >3, providing moderate evidence for the predictor of interest.

4.3. Statistical learning results and comparison with healthy older controls

To explore the potential role of statistical learning in the observed relation between hippocampal measures and long-term language outcomes, we examined whether statistical learning was intact in patients with aphasia and related to hippocampal measures. We assessed three statistical learning tasks, covering the auditory, visual and visuomotor modality. To determine whether statistical learning was induced in the auditory and visual tasks, we performed one-sided one-sample *t*-tests or Wilcoxon tests (when the assumption of normality was violated) against the group chance level (50 % correct or a score of 16/32) and the individual chance level (66 % correct or a score of 21/32). The latter reflects the number of trials a certain individual needs to successfully answer, in order to have a probability of 0.95 to reject the null hypothesis of random guessing (50 % correct), determined on the basis of a binomial distribution (Siegelman et al., 2016).

For the auditory task (Fig. 4, panel A), we found that 14 out of 28 patients scored above the group chance level ($M = 17.25$, $W = 253$, $p = .062$, Wilcoxon effect size $r = 0.28$) and 4 out of 28 patients scored above the individual chance level ($W = 16.5$, $p > .999$, Wilcoxon effect size $r = 0.72$). There was no significant difference in auditory statistical learning between the patient group and the group of healthy controls ($M_{PWA} = 17.25$, $M_{controls} = 17.00$, $W = 324$, $p = .977$, Wilcoxon effect size $r = 0.01$). Due to the absence of statistical learning in both the older healthy control group (Schevenels et al., 2021) and the patient group, this task was not considered for the correlational analysis with hippocampal measures.

For the visual task (Fig. 4, panel B), we found that 23 out of 30 patients scored above the group chance level ($M = 19.90$, $t(29) = 4.52$, $p < .001$, Cohen's $d = 0.83$) and 11 out of 30 patients scored above the individual chance level ($t(29) = -1.28$, $p = .894$, Cohen's $d = 0.23$). There was no significant difference in visual statistical learning between the patient group and the group of healthy controls ($M_{PWA} = 19.90$, $M_{controls} = 21.00$, $t(48.37) = -0.86$, $p = .395$, Cohen's $d = 0.24$). A Bayesian two-sample *t*-test indicated that the data were 2.66 times more likely under H_0 (no difference between healthy older controls and patients with aphasia), providing anecdotal evidence that statistical learning was age-appropriate in our group of patients.

For the visuomotor task (Fig. 4, panel C), we found that 27 out of 32 patients showed slower *z*-standardized RTs in the pseudorandom block compared to the last sequence block. The mean difference between both blocks across patients was significantly above 0, indicating statistical learning on the group level ($M = 0.28$, $t(31) = 4.91$, $p < .001$, Cohen's $d = 0.87$). There was no significant difference in statistical learning between the patient group and the group of healthy controls ($M_{PWA} = 0.28$, $M_{controls} = 0.30$, $t(39.68) = -0.22$, $p = .828$, Cohen's $d = 0.06$). A Bayesian two-sample *t*-test indicated that the data were 3.56 times more likely under H_0 (no difference between healthy older controls and patients with aphasia), providing substantial evidence that statistical learning was age-appropriate in our group of patients.

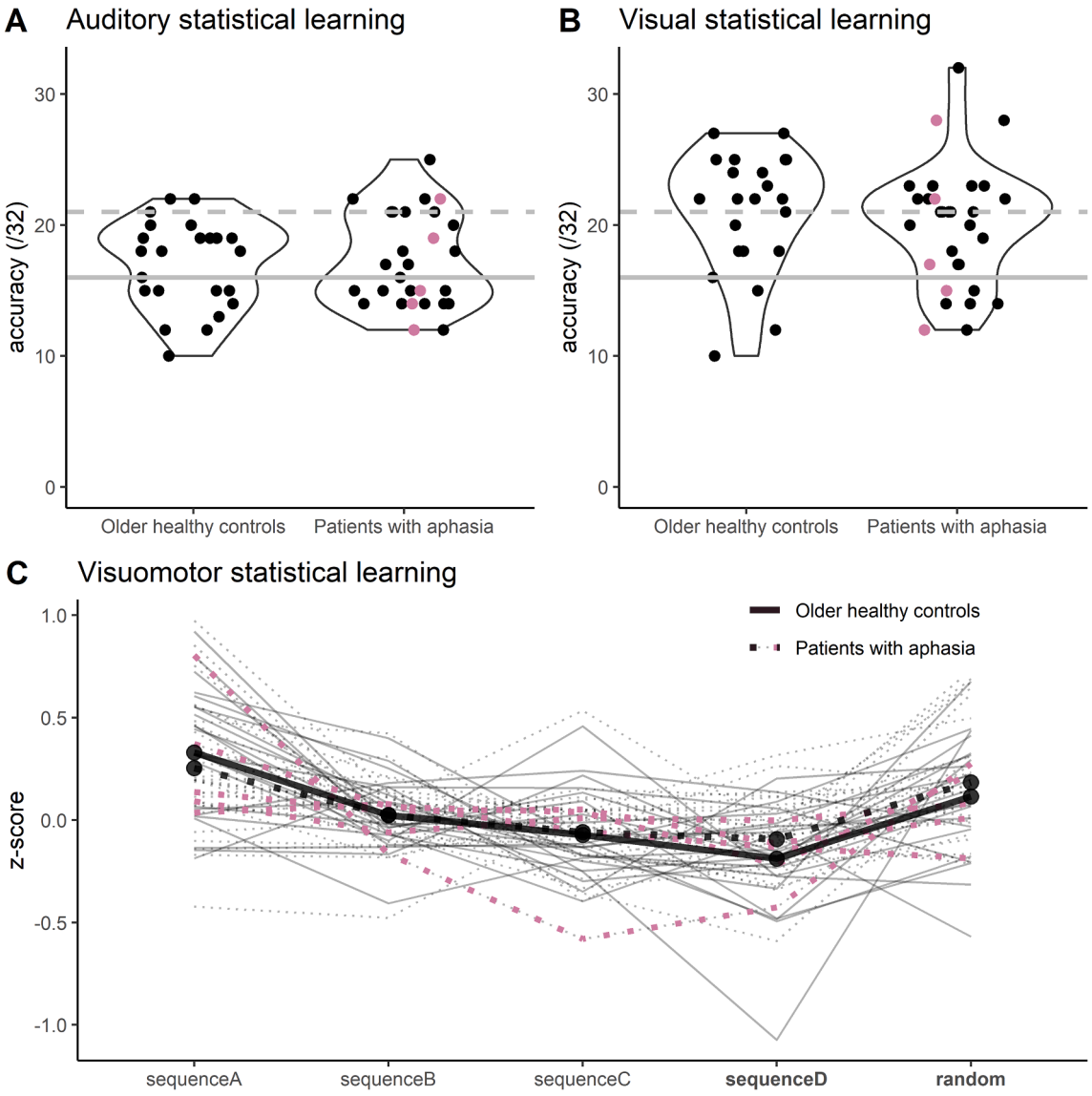

Fig. 4. Comparison of the statistical learning results with the performance of the healthy older control group. **A** and **B** show the individual results in the auditory and visual SL task. The group and individual chance levels are indicated with a solid and dashed line, respectively. Data points from patients with hippocampal damage are shown in pink. **C** shows the mean *z*-transformed RTs in each block of the visuomotor task. In this panel, the results of older healthy controls are represented with solid lines, and the results of patients with aphasia are represented with dashed lines (in pink in case of hippocampal damage). Overall (thick lines), we see the expected decrease in RTs across the sequence blocks indicating learning, followed by a RT increase when the pseudorandom block is introduced. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.4. Association between statistical learning results and hippocampal measures

To determine whether patients' statistical learning ability, measured in the subacute phase, was correlated with structural properties of the hippocampus, measured in the acute phase, we calculated Holm's corrected pairwise Pearson correlations (Fig. 5). For the visual task, none of the correlations between derived hippocampal measures and statistical learning results were significant. In contrast, visuomotor statistical learning results were significantly positively related to almost all derived hippocampal measures. The latter correlations remained similar when controlling for eTIV and age (left volume: $r_p = .55$, $t(24) = 3.20$, $p_{cor} = 0.015$, *95 % CI* = [0.09, 0.81]; right volume: $r_p = .37$, $t(27) = 2.06$, $p_{cor} = 0.053$, *95 % CI* = [0.00, 0.65]; left FBC: $r_p = .51$, $t(23) = 2.85$, $p_{cor} = 0.027$, *95 % CI* = [0.05, 0.79]; right FBC: $r_p = .42$, $t(26) = 2.35$, $p_{cor} = 0.053$, *95 % CI* = [-0.002, 0.71]).

5. Discussion

The present study examined acute (1–2 weeks) predictors of short-term (3–6 months) and long-term (9–12 months) functional language outcome after stroke. We were interested in the early prognostic value (over and above traditional predictors) of the intact hippocampus – because of its potential role in learning, including statistical learning – and its structural connectivity to the rest of the brain. To this end, stroke patients with aphasia were recruited from a large-scale screening in the stroke unit, and followed up longitudinally from this acute stage to the subacute (i.e., short-term) and chronic (i.e., long-term) phase post stroke. In our group of patients, analyses revealed that, while short-term functional language outcome was best predicted by initial language score alone, long-term prognostication of functional language outcome could be improved by considering left hippocampal volume. In addition, we did not find impairments in non-linguistic statistical learning in our group of patients, and, we found evidence for associations between

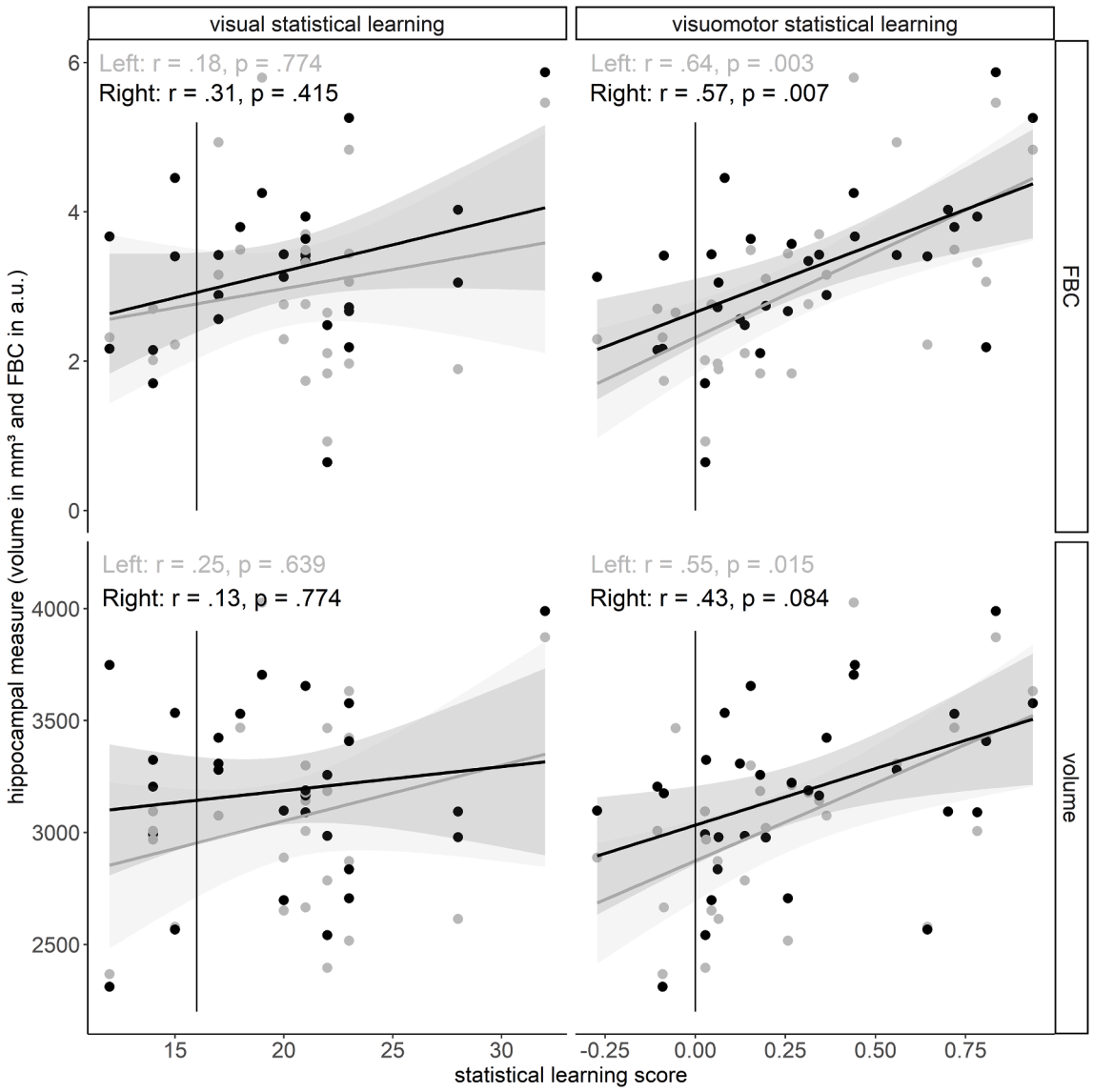

Fig. 5. Scatterplots of the statistical learning results in both tasks versus both hippocampal measurements. Results for the visual statistical learning task are shown on the left side (accuracy), results for the visuomotor statistical learning task are shown on the right side (z(RT) difference between the last sequence block and the pseudorandom block). Vertical lines indicate the cut-off for statistical learning on the group level. Hippocampal FBC (in arbitrary units) is shown on top, hippocampal volume (in mm^3) is shown on the bottom with gray representing values for the left hemisphere and black representing values for the right hemisphere. Corresponding regression lines with 95% confidence intervals are shown on the plot. The plots are annotated with pairwise Pearson correlations and corresponding significance test results (*p*-values are corrected for multiple comparisons using Holm's method).

visuomotor statistical learning and hippocampal volume and connectivity. Together, these findings suggest that hippocampal measures could reflect a potential protective mechanism in patients with aphasia. These findings also indirectly support our hypothesis that statistical learning abilities could have the potential to support functional language (re)learning in aphasia, with the hippocampus as an important measurable proxy early post stroke.

5.1. *The role of the hippocampus*

We specifically focused on the hippocampus in predicting language recovery because a growing body of literature suggests that the hippocampus constitutes a shared neural mechanism for non-linguistic cognition, such as memory but potentially also statistical learning, and language (Covington & Duff, 2016). In terms of the predicted language outcomes, we chose an outcome measure of communication effectiveness (i.e., the ANELT), which assesses the informational content of utterances in relation to ten everyday language scenarios (e.g., calling the doctor). This measures increases the ecological validity of our study (Blom-smink et al., 2017), but also allows to test flexible use of language at the sentence or discourse level, which is expected to reply more on the hippocampus than constrained test settings (e.g., such as the ScreeLing) (Duff & Brown-Schmidt, 2012).

Our regression results demonstrated the potential value of left hippocampal volume as an acute predictor of long-term everyday oral communication after stroke, above and beyond initial aphasia severity and lesion size. For the prediction of short-term outcomes, initial aphasia severity was identified as a strong predictor, which is in accordance with previous literature (Blom-smink et al., 2017; Osa García et al., 2020), but a predictive role of acute hippocampal measures or lesion size was not found. This suggests that the best predictor combination for language outcomes seems to be dependent on the time post stroke. As suggested by Osa García and colleagues and corresponding with our results, lesion-related variables might have a more prominent

role in the prediction of long-term than for short-term language outcome (Osa García et al., 2020). Our results suggest that the same might hold for predictors related to intact structures, such as the hippocampus.

In contrast to hippocampal volume which was predictive for long-term language recovery, structural connections linked to hippocampus, measured via FBC, were not retained neither in the short-term nor in the long-term model. Our FBC measure is a quantitative measure of streamline count and we might find different results with measures more attuned to the quality of the underlying connections. Another possibility is that a measure specific to connections between the hippocampus and certain language areas is more informative than the broad connections considered in this study (see Fig. 3). Alternatively, the FBC measure might provide less unique information on top of lesion-related predictors relative to the volume predictor, given that hippocampal measures of patients with hippocampal damage were excluded from the dataset, while the surrounding white matter connections might still be damaged.

The interpretation of the role of the left hippocampus in the prediction of long-term language outcomes is not straightforward. One interpretation could be that the mediating factor for the association between hippocampal measures and language recovery is a person's general cognitive health. Previous studies have indeed consistently linked decreases in hippocampal volume and connectivity strength to (subtle) cognitive decline (e.g., memory decline) in aging individuals (Bettio et al., 2017; Lazarczyk et al., 2012; Stark et al., 2021; Zanchi et al., 2017), even over and above the presence of brain infarcts (Blum et al., 2012; Kliper et al., 2016). In a similar vein, genetic studies on the apolipoprotein E ε4 allele, which is quite widely present (15 % in the general population and 65 % in Alzheimer dementia), have found associations between memory decline, smaller hippocampi and worse recovery after stroke (Mattsson et al., 2018; Rajan et al., 2016; Tang et al., 2015). However, the laterality of our finding (i.e., the left and not the right hippocampus was related to language outcomes) and its unique contribution over and above information on the initial language impairment (see Supplementary Fig. 3), suggests a role for the left hippocampus in language *relearning*. This neatly complements previous research on hippocampal involvement in language (learning) in healthy adults (Bonhage et al., 2015; Breitenstein et al., 2005; Hocking et al., 2009; Kepinska et al., 2018; Maguire & Frith, 2004; Mårtensson et al., 2012; Opitz & Friederici, 2003; Piai et al., 2016; Whitney et al., 2009) and suggests that language recovery post stroke might rely upon similar neural mechanisms as language learning in healthy adults (Menke et al., 2009). A central component of language learning is *statistical learning* (for reviews see Arciuli et al., 2012; Kuhl, 2004; Romberg & Saffran, 2010; Saffran, 2003), which has also been linked to the hippocampus (Shohamy & Turk-Browne, 2013), hence statistical learning could mediate the association between the left hippocampus and language recovery.

5.2. The role of statistical learning

In our study, we examined whether statistical learning is intact in patients with aphasia, allowing it to serve as a protective mechanism in relearning language, and whether statistical learning ability was related to hippocampal measures.

Group comparisons on the statistical learning tasks showed that performance in patients with aphasia across modalities was not different from a healthy older control group, which suggests that the cognitive processes upon which these statistical learning tasks rely are intact in our group of patients. Although our auditory-linguistic task was not able to evoke statistical learning in the healthy older control group (for in depth discussion see Schevenels et al. (2021)) and in patients with aphasia, we did observe significant statistical learning on the group level in the non-linguistic visual and visuomotor conditions. Previous research has demonstrated that also non-linguistic statistical learning can be associated with language behavior in healthy adults and patients with aphasia (Conway & Pisoni, 2010; Daltrozzo et al., 2017; Misyak & Christiansen, 2012; Vadinova et al., 2020). Our findings of intact statistical learning abilities are consistent with previous evidence reporting intact statistical learning in chronic aphasia (Goschke et al., 2001; Jarret et al., 2019; Penaloza et al., 2015; Schuchard et al., 2017; Schuchard & Thompson, 2014; Schuchard & Thompson, 2017), and therefore extend existing evidence for the first time to subacute aphasia. On the other hand, other studies have demonstrated statistical learning impairments in patients with aphasia compared to a healthy control group (Basirat et al., 2019; Christiansen et al., 2010; Goschke et al., 2001; Peñaloza et al., 2017; Schuchard & Thompson, 2014; Vadinova et al., 2020; Vallila-Rohter and Kiran, 2013b; Vallila-Rohter and Kiran, 2013a; Vallila-Rohter and Kiran, 2015; Zimmerer et al., 2014), although this does not necessarily imply absence of statistical learning (Peñaloza et al., 2017; Vadinova et al., 2020). This variability in statistical learning performance across studies is likely due to differences in the assessed modality, the testing paradigm with corresponding evoked learning processes, the difficulty of the embedded regularities, individual differences and heterogeneity in patients with aphasia and the extent to which the used stimuli require linguistic processing. Nevertheless, our study provides unique (group and individual level) data on the statistical learning capacity of patients with post stroke subacute aphasia in the visual and visuomotor modality. However, in the context of prognostic modelling, the use of neuroanatomical markers of statistical learning is more interesting, as behavioral testing immediately post stroke is not feasible in one third of patients (Wade et al., 1986) and structural imaging is unequivocally part of the standard clinical stroke protocol (Boyd et al., 2017; Vilela & Rowley, 2017; Warren et al., 2010).

To examine whether the hippocampus could be a neuroanatomical correlate for statistical learning ability, we related performance on statistical learning tasks to hippocampal volume and connectivity in patients with aphasia. Note that due to limitations in the feasibility to test statistical learning in the acute phase, hippocampal measures (acute) and statistical learning measures (subacute) were not collected at the same time point and therefore we can only make statements about lagged associations. Our results indicated that statistical learning was associated with hippocampal metrics in patients with aphasia. This positive correlation was observed for statistical learning with local hippocampal structure as well as with hippocampal connectivity (Maller et al., 2019). An assocation between the hippocampus and statistical learning was expected based on functional studies in healthy adults and hippocampal lesion studies (Covington et al., 2018; Gheysen et al., 2011; Jablonowski et al., 2018; Schapiro et al., 2014, 2016; Schendan et al., 2003; Turk-Browne et al., 2009), but we extended it to structural measures and to patients with aphasia. There is one other structural MRI study in infants showing that earlier in life the association between hippocampal volume and statistical learning is negative (Schlichting et al., 2016), suggesting that this association might change in elderly. The found correlations in our study did not represent a general brain size or age effect as they remained relatively stable when controlling for eTIV and age, respectively. The association we observed between the hippocampus and statistical learning was only significant for the visuomotor statistical learning task. This task is assumed to tap on implicit statistical learning mechanisms because learning is tested while performing the task ("online"). In contrast, in the visual task, patients had to make explicit judgments about the test items after the exposure ("offline") (Schevenels et al., 2021). Although hippocampal involvement in statistical learning has been shown under both implicit and explicit learning conditions and across modalities (Jablonowski et al., 2018; Karuza et al., 2017; Rose et al., 2011; Schendan et al., 2003), several other cognitive processes (e.g., decision making) (Siegelman et al., 2017a) in the posttest of the visual task might have blurred associations with the hippocampal measures. Alternatively, the integration of temporally ordered (i.e., sequential) and spatially structured information with motor output in the visuomotor task might have required a higher level of hippocampal recruitment for the development of

representations necessary for statistical learning compared to the temporal information in the visual task. The latter argument converges with the general idea that the hippocampus is specialized for the rapid, incidental binding of multimodal information (O'Reilly & Rudy, 2001).

To conclude, given that the correlational results demonstrate a link between statistical learning and the hippocampus, this could mean that a person's statistical learning ability shapes long-term changes in language performance observed in patients with aphasia. However, it is important to note that our research design does not allow us to determine whether the predictive contribution of the hippocampal volume to aphasia recovery is mediated by and/or specific to statistical learning. Other cognitive mechanisms (e.g., memory decline, explicit associative learning, imagination and prediction of future events) similarly rely on the hippocampus and might be relevant for language recovery (Buckner, 2010; Dignam et al., 2016; Tuomiranta et al., 2014). Thus, the specificity of the role of the hippocampus in aphasia recovery to statistical learning remains to be tested in future research. Nevertheless, our results suggest an interconnectedness of language functions with non-linguistic domains of cognition supported by the hippocampus during aphasia recovery (Cahana-Amitay & Albert, 2015).

6. Limitations and future directions

Although an intensive collaboration with the university hospital was set up through a large-scale screening of every incoming patient (n = 787 screened patients), the number of included patients with aphasia with early MRI and behavioral follow-up over a 1 year period was relatively small. Consequently, some of the null effects in the correlational and regression analyses might be the result of a lack of statistical power (Brysbaert, 2019) and mediation analyses to directly test whether the relation between hippocampus and language recovery was mediated by statistical learning could not be performed. In addition, due to the onset of the COVID-19 pandemic during testing, the subacute and chronic follow up moments took place spread over a period of 3 months (i.e., respectively 3–6 months and 9–12 months post stroke) instead of 1 month as initially planned. Moreover, compared to other studies, we did not exclude patients with a history of stroke or other conditions, or left handers, patients with bilateral stroke, brain hemorrhage, or severe stroke/aphasia. We contend that this variability is important as studies with highly specific inclusion criteria have limited generalizability, and hence they might have little clinical relevance. Crucially, external validation of our findings in independent datasets is needed before our results can be generalized to other patients with aphasia (Poldrack et al., 2020). Nonetheless, our findings encourage future research to consider an individual's potential for compensation in the prediction of a person's later communicative ability.

Importantly, since the start of this longitudinal study, several improved measures of statistical learning have been proposed in the literature. Although widely used, the current statistical learning tasks have been criticized for their relatively low reliability as measures of individual differences in statistical learning (compared to group level estimates) (Siegelman & Frost, 2015; West et al., 2018). In the study by Siegelman & Frost (2015), test-retest reliability of the auditory statistical learning task was highest, with r = 0.63, followed by the visual statistical learning task, with r = 0.58, and the (probabilistic) SRT task, with r = 0.47 (Siegelman & Frost, 2015). Future (patient) studies might benefit from more recent measures of statistical learning, including psychometrically optimized tasks (Siegelman et al., 2016; Siegelman et al., 2018), tasks with more implicit offline tests (Isbilen et al., 2020; Turk-Browne et al., 2005), tasks with online measures that track learning during familiarization (Siegelman et al., 2017b) and/or neural measures of statistical learning that do not require overt responses (Batterink & Paller, 2017; Bogaerts et al., 2020). Especially the latter are promising for acute patient populations (Xu et al., 2022).

7. Conclusion

Our longitudinal acute-to-chronic investigation of aphasia recovery provides support for a role of left hippocampal volume as an acute predictor of long-term everyday oral communication after stroke and thus confirms a link between hippocampal integrity and successful language outcomes. Furthermore, given that we find that statistical learning ability is intact in our group of patients and that statistical learning is related to hippocampal measures, the hippocampus has the potential to serve as a neural correlate of a protective learning mechanism in patients with aphasia. Future large-scale studies should examine whether the predictive role of acute hippocampal measures for language recovery can be confirmed and should directly test the mediating role of statistical learning in this association. Early and more accurate predictions of aphasia recovery would bring us one step closer to a reliable individual prognosis in the clinic, with a positive impact on quality of life of patients and their relatives, and with the potential to lead to individualized treatment plans that maximize the available recovery potential of the patient.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The pseudonymized study data and code to reproduce the figures and findings are publicly available at https://github.com/kschevenels/pwasl. MRI data cannot be shared (lesions are person-specific and therefore cannot be considered anonymous).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103243.

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