Mapping language and non-language cognitive deficits in post-stroke anomic aphasia

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Abstract

Background – While language impairment is the defining symptom of aphasia, the co-occurrence of non-language cognitive deficits and their importance in predicting rehabilitation and recovery outcomes is well documented. However, few studies have explored how individual cognitive domains contribute to patients' impairment and how this relates to underlying lesion pattern. A better understanding of this is essential for improving aphasia treatments.

Objectives – This study aimed to explore the brain-behaviour relationships between tests of individual cognitive skill, as well as language abilities, in patients with post-stroke aphasia. We predicted our analysis would reveal a latent (non-language specific) cognitive component, which would be driven by damage to left frontal cortices.

Methods – We analysed the behavioural and neural correlates of an extensive battery of language and non-language cognitive tests in a selective sample of 36 patients with post-stroke anomic aphasia, with relatively intact speech comprehension and repetition. The behavioural variables were analysed using Principle Component Analysis and their neural correlates were estimated using Voxel-Based Correlational Morphology.

Results – A significant number of anomia patients showed impaired performance on tests of non-language cognitive function. The variance underlying behavioural performance was best captured by four orthogonal components, two non-language cognitive components (executive function and verbal working memory) and two previously identified language components (phonology and semantics). Brain-behaviour relationships revealed separable neural correlates for each component in line with previous studies and a novel executive function correlate in the left inferior frontal cortex (LIFC).

Conclusion – Our findings suggest that in patients with chronic post-stroke anomia, non-language cognitive abilities explain more of the variance in language function than classical models of the condition imply. Additionally, lesions to the LIFC, including Broca's area, were associated with executive (dys)function, independent of language abilities, suggesting that lesions to this area might be primarily driving a (non-language specific) cognitive component in anomia.

1. Introduction

There is growing evidence that aphasia following a stroke can include deficits in non-language cognitive domains and that these are predictive of certain aspects of language function, recovery and rehabilitation. Despite compelling evidence for the influence of cognitive impairments on language abilities in post-stroke aphasia, patients rarely receive extensive cognitive assessment, meaning data on individual cognitive skills in these patients is scarce, and few studies have explored their relationship to underlying structural brain data.

Although language impairment is the defining consequence of post-stroke aphasia, the presence of co-occurring impairments in other cognitive domains has been well documented (Helm-Estabrooks, 2002; Murray, 2012; El Hachioui et al., 2014; Marinelli et al., 2017; Ramsey et al., 2017; Schumacher et al., 2019). Marinelli and colleagues (2017) examined language and cognitive function in 189 People with Aphasia (PWA) and found more severe language deficits to be associated with more severe cognitive impairments. Other studies have investigated executive functions in PWA and consistently found impaired inhibition, working memory or cognitive flexibility (Frankel et al., 2007; Fridriksson et al., 2006; Jefferies, Patterson and Ralph, 2008; Lee and Pyun, 2014; Murray, 2012; Vallila-Rohter and Kiran, 2013). This pattern of observation is important for clinical management and rehabilitation. In fact, a series of aphasia therapy studies emphasise that cognitive abilities, particularly executive function and verbal short-term memory, play an important role in driving recovery outcomes (Fillingham, Sage and Lambon Ralph, 2005a, 2005b, 2006; Conroy, Sage and Lambon Ralph, 2009; Lambon Ralph et al., 2010; Yeung and Law, 2010; Snell, Sage and Lambon Ralph, 2010, Sage, Snell and Lambon Ralph, 2011; Dignam et al., 2017).

While studies have highlighted the impact of cognition on aphasia rehabilitation and recovery, few have explored the contribution of individual cognitive skills and the relationship to underlying lesion pattern; a better understanding of this is essential for improving aphasia recovery outcomes. The neural basis of aphasia is commonly explored by linking behavioural assessment with brain lesion data. This has resulted in some distinct brain-behaviour relationships for various language domains, however studies have found it difficult to identify significant associations between tests of executive

function and lesion data, either because non-language assessments were not included (Kummerer et al., 2013; Mirman et al., 2015) or were only included in a limited scope (Butler et al., 2014; Halai et al., 2017; Tochadse et al., 2018; though see Lacey et al., 2017).

Executive function and language are closely linked in both brain and behaviour. Behaviourally, cognitive control and working memory have long been known to support language processing (Gordon et al., 2002; Novais-Santos et al., 2007; January et al., 2009; Fedorenko, 2014). Neurally, both executive function and language robustly engage regions within the left frontal cortex (Kaan and Swaab, 2002; Novick et al., 2005). This makes it challenging to functionally dissociate anatomical correlates of the two domains. Of particular relevance is the function of Broca's area and the left inferior frontal gyrus (LIFG). Damage to Broca's area, which encompasses cytoarchitecturally defined Brodmann's area BA 44 and BA 45 of the left posterior inferior frontal gyrus (LpIFG) (Ardila et al., 2016; Papitto et al., 2020) commonly results in anomia, which has led people to believe that Broca's area and the LpIFG play a causal role in language. However, research in more recent years challenges this notion; the current view is that long-term speech production outcome in patients with LIFG damage is best explained by a combination of damage to LIFG and neighbouring regions including the underlying white matter, which was also damaged in Paul Broca's two historic cases (Dronkers et al., 2007; Gajardo-Vidal and Lorca-Puls et al., 2021), and that Broca's area is not specialised for speech and language, but rather is part of a wider network of general cognitive processing that includes, but is not limited to language (Duncan, 2010; Duncan, 2013). Nevertheless, some argue that executive functions and language occupy nearby but distinct regions within the left frontal cortex (Fedorenko and Varley, 2016). To date, the brain areas required for speech production, and the type of aphasia that results from damage to the LIFG remains a topic of continued debate (Marie, 1906; Mohr et al., 1978; Alexander et al., 1990; Lorch, 2008; Fridriksson et al., 2015; Tremblay and Dick, 2016).

When assessing cognitive abilities, it is important to consider that cognition is a multidimensional construct broadly comprising five general domains, including language, attention, memory, executive function and visuo-spatial skills (Helm-Estabrooks, 2002), with each domain containing distinct components. Using composite or general scores risks reducing the sensitivity of the cognitive

measure. Shumacher and colleagues (2019) recently demonstrated the importance of this by using a detailed non-verbal neuropsychological assessment to show that brain regions involved in particular components of the attention and executive function domains contribute to the abilities of patients with a wide range of aphasia types. Another study used extensive assessments of attention to show that different aspects of attention differentially predict language function in aphasia (Murray, 2012). Finally, studies that have explored the role of cognition in aphasia have typically involved a sample of diverse aphasia types and severity. While this is pertinent to capturing the incidence of cognitive impairment in the general aphasic population, the wide variability of aphasia subtypes can confound analyses of the links between domain-general cognitive impairment and any particular aphasic subtype or symptom.

In this study, we investigated the behavioural and neural correlates of an extensive battery of language and domain-general cognitive functions in a selective population of patients with post-stroke anomic aphasia. Anomia is the most common symptom of post-stroke aphasia and manifests as difficulty in word retrieval when naming common objects (Laine and Martin, 2013). Crucially, patients with anomia have relatively preserved speech fluency, repetition, comprehension, and grammatical speech; as such anomia is seen as one of the 'purer' forms of language impairment (Goodglass et al., 2001). We collected a comprehensive behavioural battery containing language measures and an extensive assessment of individual cognitive domains, for 36 patients with anomia after stroke. The behavioural dataset was analysed using Principle Component Analysis (PCA). PCA is a useful exploratory tool that can extract the underlying latent structure of a set of correlated variables – like scores in standardised assessments of post-stroke cognitive impairment. Recently, there has been increasing interest in interpreting these latent variables in terms of the potentially separable cognitive sub-systems underlying (often strongly correlated) task scores. This is typically done by correlating latent variables with the original scores: those scores that correlate more strongly with the latent variable are said to load on that latent variable. Here, following recent results, we employ varimax rotation to encourage greater sparsity, and thus interpretability, in those loadings (Butler et al., 2014; Halai et al., 2017; Tochadse et al., 2018). The key aims of the study were: (i) to explore the underlying relationships between tests of individual cognitive skill, as well as patients'

language profiles; and (ii) to map the structural correlates for these underlying cognitive and language features. We predicted that our analysis would reveal a latent, (non-language specific) cognitive component to our patients' anomic symptoms, which would be driven by damage to left frontal cortices.

2. Materials and methods

2.1 Participants

Thirty-six English speakers with chronic aphasia following a single left-hemisphere stroke participated in the study (see fig. 1 for a lesion overlap map, table 1 for demographic and clinical data). All were at least 12 months post-stroke at the time of scanning and assessment, had normal hearing, normal or corrected-to-normal visual acuity and no previous history of neurological or psychiatric disease, as well as no contraindications to MRI scanning. Inclusion criteria were: (i) anomia as determined by the naming subtest of the Comprehensive Aphasia Test (Swinburn et al., 2005); (ii) good single word comprehension as assessed by the spoken words comprehension subtest of the Comprehensive Aphasia Test (Swinburn et al., 2005); (iii) relatively spared ability to repeat single monosyllabic words from the Psycholinguistic Assessments of Language Processing in Aphasia (Kay et al., 1992); (iv) absence of speech apraxia as determined by the Apraxia Battery for Adults (Dabul, 2000). Participants were excluded if they had any contraindications for scanning, had more than one stroke or had any other significant neurological or psychiatric conditions. Informed consent was obtained from all participants prior to participation under approval from Central London Research Ethics Committee, UK.

Table 1. Participant demographic and clinical data

ID	Gender	Age (years)	Education (years)	Handedness pre-stroke	Handedness post-stroke	Time post-stroke (years)	Lesion Volume (voxels)
RL	M	55	16	L	R	11	7691
AR	M	56	11	R	L	7	20100
WT	M	71	13	R	R	2	5345
AW	M	55	11	R	R	9	7155
RC	M	71	16	R	R	2	9795
LP	F	51	13	R	L	13	5427
SS	M	47	13	R	L	12	20226
YD	F	66	16	R	L	18	10398
KB	M	61	16	L	R	4	7945
PK	M	44	16	R	L	3	4768
DT	F	44	17	R	R	1	3686
NI	F	70	11	R	L	12	1116
TW	M	70	11	R	L	29	14694
TC	M	69	16	R	L	7	21464
AT	M	73	11	R	R	11	8914
KM	F	45	11	L	L	3	7941
RK	F	53	11	R	R	5	2781
MA	F	55	13	L	L	5	189
JB	M	40	17	R	L	8	20469
PD	M	64	13	R	L	24	38523
GG	M	42	17	R	R	1	8225
EM	M	74	16	R	R	11	20566
SM	M	63	16	R	R	25	19614
TH	M	64	16	R	R	10	43529
AS	M	60	16	R	L	11	11790
PS	F	60	11	R	L	6	27911
CB	M	75	11	R	R	12	14069
KV	F	50	16	R	L	3	16325
MK	M	64	11	R	R	8	30049
AM	M	29	13	R	R	6	9826
EA	F	81	10	R	R	16	12423
BH	M	60	13	R	L	20	50389
CB	M	65	13	R	L	14	48396
JB	M	82	13	R	R	34	19076
NH	M	58	16	R	L	8	29911
GM	M	39	17	L	L	2	11963

2.2 Neuropsychology

Behavioural assessment

A comprehensive battery of language and non-language tests was administered to assess participants' language and cognitive abilities (see supplementary material).

The language tests administered to assess speech production included the naming and repetition subtests of the CAT, the word/non-word repetition subtests from the Psycholinguistic Assessments of Language Processing in Aphasia subtests 8 and 9 (PALPA; Kay et al., 1992), the Boston Naming Test (BNT; Kaplan, Goodglass and Weintraub, 1983). The language assessments that captured other language functions included Pyramids and Palm Trees (PPT; Howard and Patterson, 1992), other subtests from the CAT, and the reading tasks from the PALPA8.

The non-language cognitive assessments included the Cattel Culture Fair IQ Test (Scale 2, Form A; Cattell and Cattell, 1963), Rey-Osterrieth Complex Figure Test (Osterrieth, 1944), Digit Span tasks from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008), the trail making and card sorting subtests from the Delis-Kaplan Executive Function System test (D-KEFS; Delis, Kaplan and Kramer, 2001), the Hopkins Verbal Learning Test (HVLT; Brandt and Benedict, 2001) and the Children's Sustained Attention to Response Task (cSART; Robertson et al., 1997).

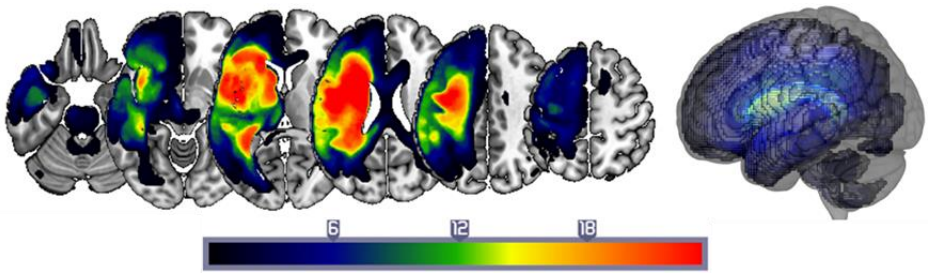

Figure 1. Lesion overlap map. A lesion overlap map for the 36 stroke anomic participants. Results are shown overlaid on the MNI template in MRIcro-GL (Rorden et al., 2007).

Principle Component Analysis

Participants' scores on all assessments were entered into a PCA with varimax rotation (conducted with SPSS 26.0). We had 55 variables and 36 cases. Factors with an eigenvalue ≥1.0 were extracted then rotated. After orthogonal rotation, the factor loadings of each test allowed interpretation of what cognitive-language primary process was represented by that factor (table 2). Individual participants' scores on each extracted factor were then used as behavioural covariates in the neuroimaging analysis.

2.3 Neuroimaging

MR Imaging acquisition and analysis

Whole-brain imaging was performed on a 3T Siemens TIM-Trio system (Siemens, Erlangen, Germany) at the Wellcome Centre for Human Neuroimaging. Structural (T1-weighted) MRI images were normalised using Statistical Parametric Mapping software (SPM12) running under Matlab 2015a (MathWorks, Natick, MA). Lesion images were defined by the Automatic Lesion Identification toolbox (ALI; Seghier et al., 2008), employing a variant of the unified segmentation algorithm (Ashburner and Friston, 2005), optimised for use in the focally damaged brain.

Structural MRI scans were pre-processed with Statistical Parametric Mapping software (SPM12: Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). The images were normalised into standard Montreal Neurological Institute (MNI) space using a modified unified segmentation–normalisation procedure optimised for focal lesioned brains (Seghier et al., 2008). Data from all participants were entered into the segmentation–normalisation. This procedure combines segmentation, bias correction and spatial normalisation through the inversion of a single unified model (see Ashburner and Friston, 2005 for more details). In brief, the unified model combines tissue class (with an additional tissue class for abnormal voxels), intensity bias and non-linear warping into the same probabilistic models that are assumed to generate subject-specific images. Images were then smoothed with an 8 mm full-width-half-maximum (FWHM) Gaussian kernel and used in the lesion analyses described below. The lesion of each patient was automatically identified using an outlier detection algorithm, compared to healthy controls, based on fuzzy clustering. Voxel values in these regions range from 0 to 1, with higher values indicating greater evidence that the voxel is damaged, and evidence is derived by comparing tissue intensity in each voxel to intensities from a population of neurologically normal controls. The default parameters were used. The images generated for each patient were individually checked and visually inspected with respect to the original scan, and were used to create the lesion overlap map in fig. 1. We selected the Seghier et al. (2008) method as it is objective and efficient for a large sample of patients (Wilke, de Haan, Juenger and Karnath, 2011), in comparison to a labour-intensive hand-traced lesion mask.

Lesion-Symptom Mapping

For lesion-symptom mapping, we used the fuzzy lesion images as described above and correlated these with PCA factor scores using a voxel-based correlational methodology (VBCM: Tyler, Marslen-Wilson and Stamatakis, 2005), a variant of voxel-lesion symptom mapping (VLSM: Bates et al., 2003). We used VBCM because this approach i) has the virtue of preserving the continuous nature of both behavioural and neural indices i.e., does not require a binary classification of the intact/lesioned brain to be marked, as in the case of VLSM, and ii) replicates previous methodology using varimax-rotated PCA in aphasia (e.g. Butler et al., 2014), aiding data comparisons within the field.

The VBCM analysis of PCA factors was conducted in SPM12 running on Matlab 2019b. The analysis used the four continuous multidimensional predictors of the PCA factor scores, which are necessarily uncorrelated (orthogonal) with one another; these were entered simultaneously as continuous behavioural covariates. The outcome of the analysis therefore denotes which voxels' variation in tissue concentration corresponds to the unique variance in a given principle component, while controlling for variation in the other components in the analysis. In order to ensure that the results were not merely attributable to lesion size, each participants' lesion volume was calculated from the lesion identified by the automated lesion identification method (Seghier et al., 2008) and this was entered as a covariate in the VBCM. All analyses were performed with and without a correction for lesion volume. All anatomical labels were based on the Harvard–Oxford atlas in MNI space.

3. Results

3.1 Neuropsychological profiles and principal language-cognitive factors

The rotated PCA produced a four-factor solution which accounted for 55% of variance in participants' performance (F1 = 28.6%; F2 = 10.6%; F3 = 8.3%; F4 = 7.1%). The loadings of each of the different behavioural assessments on each of the factors are given in table 2 (for individual participants' scores on each factor, see supplementary table 1). Tasks which tapped into input and output phonology (e.g. word and non-word repetition) loaded heavily on Factor 1, as such we refer to this

factor as ‘Phonology’. Factor 2 was interpreted as ‘Executive Function’, as assessments that loaded most heavily on it tapped into non-verbal cognitive processes (e.g. problem solving and concept formation). Assessments that loaded on Factor 3 were those requiring online maintenance and use of verbal inputs (e.g. digitspan, sentence repetition, spoken picture description), hence we refer to this factor as ‘verbal working memory’. Finally, Factor 4 was interpreted as ‘Semantics’, the assessments that loaded on this factor were more diverse but primarily required processing of meaning (e.g. picture naming and comprehension of written sentences).

3.2 The neural basis of performance in chronic stroke aphasia

<u>Voxel-based morphometry of principle component analysis factors</u>

The VBCM results are shown in fig. 2 and table 3. Each map displays where tissue concentration covaries uniquely with a given factor score, where the factors are necessarily uncorrelated with one another. Results are thresholded at $P < 0.05$ voxel-level and $P \leq 0.001$ FWE corrected cluster-level.

Performance on the phonological factor was uniquely correlated with a cluster of voxels in the left parietal lobe, with peak voxels in the left superior parietal lobe. The cluster also included voxels in the left inferior parietal lobule.

Performance on the executive function factor was uniquely related to a cluster of voxels in the left frontal lobe, with peak voxels in the left inferior frontal gyrus (pars orbitalis and pars triangularis) and the left dorsolateral prefrontal cortex.

Performance on the verbal working memory factor was uniquely related to a large cluster of voxels in the left hemisphere, with peak voxels in the posterior superior temporal gyrus, the superior longitudinal fasciculus and posterior thalamic radiation. The cluster also included voxels within left Werenicke’s area, Heschl’s gyrus and the hippocampus.

Performance on the semantic factor was uniquely related to two clusters in the left hemisphere with peak voxels in the superior/ middle temporal pole and superior/middle temporal gyrus. The clusters also included voxels across the left insula.

Table 2. Loadings of behavioural assessments on rotated PCA factors

	Factor 1 **Phonology**	Factor 2 **Executive Function**	Factor 3 **Verbal Working Memory**	Factor 4 **Semantics**
PALPA9 Repetition - Words (LILF)	**0.898**	0.089	0.064	0.190
PALPA9 Repetition - Words (LIHF)	**0.859**	-0.125	0.196	0.204
PALPA9 Repetition - Words (HILF)	**0.829**	0.189	0.054	0.055
PALPA9 Repetition Non-Words	**0.826**	0.045	0.299	0.135
PALPA8 Repetition Non-Words	**0.792**	-0.024	0.308	0.106
PALPA9 Repetition - Words (HIHF)	**0.778**	0.108	0.020	0.099
CAT Repetition - Words	**0.696**	0.075	0.003	0.404
CAT Repetition - Non-Words	**0.620**	0.227	0.180	0.019
CAT Comprehension - Spoken Words	**0.606**	0.269	-0.096	-0.099
CAT Repetition - Complex Words	**0.580**	0.042	0.252	0.265
DKEFS Card Sorting: Free Description	0.036	**0.892**	0.073	0.212
DKEFS Card Sorting: Correct Sorts	0.119	**0.888**	0.060	0.179
DKEFS Card Sorting: Recognition	0.089	**0.841**	0.207	0.219
DKEFS Card Sorting: Perceptual Sorts	0.073	**0.836**	0.178	0.225
DKEFS Card Sorting: Verbal Sorts	0.177	**0.599**	-0.052	0.141
WAIS Forward Digit Span	0.286	0.014	**0.870**	0.098
WAIS Backward Digit Span	0.013	0.014	**0.791**	0.000
CAT Repetition - Digit String	0.121	0.229	**0.776**	0.173
CAT Repetition - Sentences	0.233	-0.004	**0.650**	0.526
PALPA8 Reading - Non-Words	0.195	0.228	**0.628**	0.382
CAT Spoken Picture Description	0.276	0.241	**0.537**	0.330
CAT Reading - Non-Words	0.310	0.378	**0.506**	0.324
Boston Naming Test	0.123	0.440	-0.018	**0.771**
CAT Reading - Words	0.298	0.243	0.314	**0.748**
CAT Naming - Objects	0.400	0.055	0.099	**0.713**
CAT Naming - Actions	0.136	0.281	0.170	**0.646**
CAT Reading - Complex Words	0.273	0.049	0.568	**0.640**
CAT Reading - Function Words	0.088	0.265	0.268	**0.544**
CAT Writing to Dictation	0.161	0.290	0.399	**0.529**
CAT Comprehension -Written Sentences	0.138	0.139	0.372	**0.510**

Factor loadings >0.5 are given in bold. PALPA = Psycholinguistic Assessments of Language Processing in Aphasia; LILF = Low Intelligibility Low Frequency, LIHF = Low Intelligibility High Frequency, HIHF = High Intelligibility High Frequency, HILF = High Intelligibility Low Frequency. CAT = Comprehensive Aphasia Test. DKEFS = Delis-Kaplan Executive Function System. WAIS = Wechsler Adult Intelligence Scale.

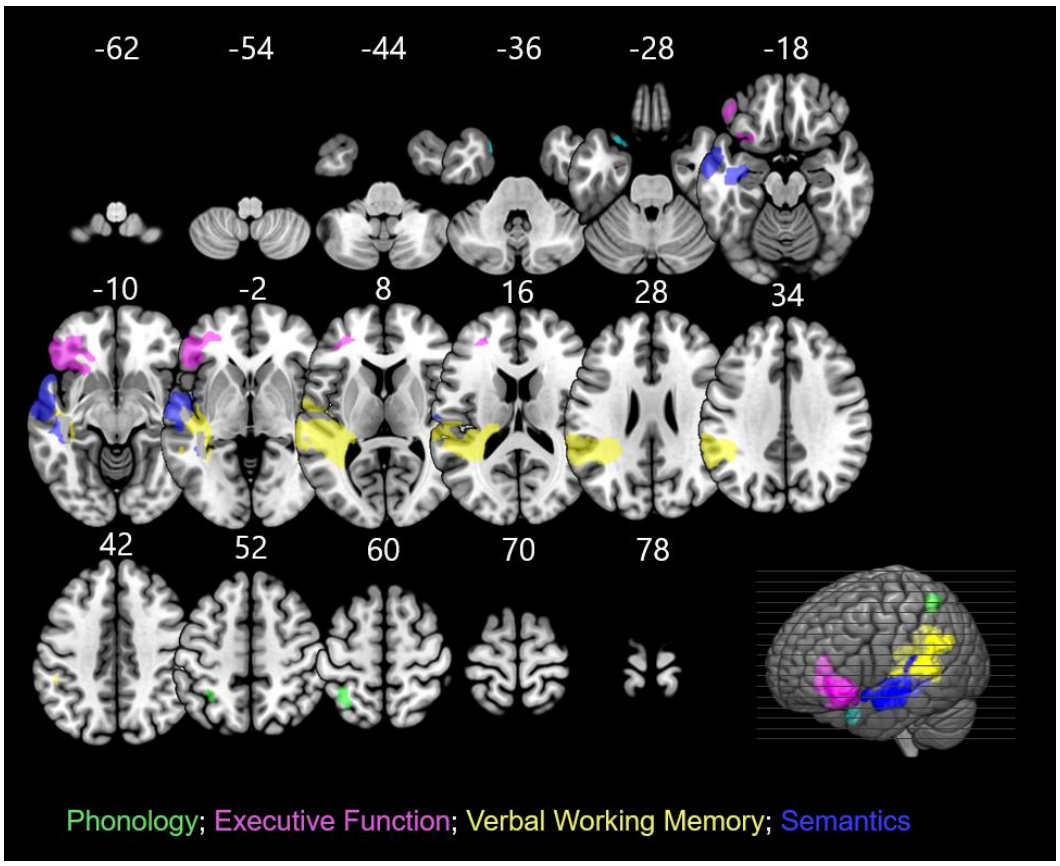

Figure 2. Structural correlates associated with each component from the combined PCA. Phonology: green; Executive Function: magenta; Verbal Working Memory: yellow; Semantics: two distinct clusters in cyan and indigo. Clusters were obtained by applying a voxel-level threshold at $P < 0.05$ and a FWE correction at cluster-level $P < 0.001$. The lower right corner displays a rendered brain showing clusters projected to the brain surface.

<u>Lesion size and age</u>

Given that some brain regions are more likely than others to be damaged after middle cerebral artery (MCA) stroke (Phan et al., 2005) and some regions are more susceptible to age-related atrophy, we controlled for lesion volume and age in subsequent lesion-symptom analyses.

Each participant's lesion volume was calculated from the lesion identified by the modified segmentation-normalization procedure (see 'Materials and methods' section). For the PCA factors, lesion volume correlated relatively weakly with the phonology factor (r=0.137, p=0.426), the auditory working memory factor (r= -0.318, p=0.059) and semantic factor (r= -0.313, p=0.063), and slightly more strongly with the executive-function factor (r= -0.426, p=0.10)

Including age in the VBCM model with the PCA factor scores did not alter the pattern of results obtained. However, including lesion volume in the model reduced the significance of the executive

function measure, but did not alter the pattern of results in the remaining 3 PCA factors. As previously mentioned, the executive function component correlated with tissue damage in the left inferior frontal cortex (LIFC); as a common region of damage in left MCA stroke (Phan et al., 2005), high covariance between LIFC tissue integrity and total lesion volume is expected.

Table 3. Neural correlates for omnibus PCA factors

Principle Component	Location	Extent (voxels)	Z	MNI co-ordinates		
				x	y	z
F1 (Phonology)	Left Superior Parietal Lobe	175	4.16	-34	-54	58
F2 (Executive Function)		1563				
	Left Inferior Frontal Gyrus (Pars Triangularis)		3.93	-44	36	2
	Left Inferior Frontal Gyrus (Pars Orbitalis)		3.59	-40	42	-8
	Left Middle Frontal Gyrus (Dorsolateral Prefrontal Cortex)		3.56	-30	44	4
F3 (Verbal Working Memory)		5262				
	Left Posterior Superior Temporal Gyrus		4.49	-58	-28	6
	Left Superior Longitudinal Fasciculus		4.94	-38	-44	18
	Left Posterior Thalamic Radiation		5.35	-36	-46	2
F4 (Semantics)		209				
	Left Superior Temporal Pole		4.82	-22	10	-24
	Left Middle Temporal Pole		4.47	-20	12	-34
		2343				
	Left Superior Temporal Gyrus		4.14	-64	-10	-4
	Left Middle Temporal Gyrus		4.14	-62	-14	-12

4. Discussion

The aim of the current study was to investigate the presence of latent cognitive factors that might explain the variance in aphasic language abilities and how this relates to underlying lesion pattern. We conducted an extensive language and non-language neuropsychological assessment in a selective sample of 36 patients with anomic aphasia, with relatively intact speech comprehension and repetition. Our study extended previous work on the importance of non-language cognitive function in aphasia and found that (i) a significant number of anomia patients showed impaired performance on tests of non-language cognitive function (see supplementary material); (ii) the variance underlying language and non-language test performance was best captured by four

orthogonal components, two previously identified language components (phonology and semantics) and two non-language cognitive components (executive function and verbal working memory) (table 2); (iii) brain-behaviour relationships revealed separable neural correlates for each component in line with previous studies and a novel executive function correlate in the left inferior frontal cortex (LIFC) (fig. 2, table 3).

The neural correlates associated with the two language components were in line with previous literature. The phonological component explained the largest proportion of behavioural variance. Scores on this component, which in our study loaded principally on tests of speech repetition, uniquely correlated with tissue damage in the left superior and inferior parietal lobule (fig. 2). This is in line with previous work showing impaired speech repetition is associated with left parietal lobe damage (Fridriksson et al., 2010). Previous studies that have used a similar approach of combined rotated PCA and VBCM in aphasia patients report a phonology component in left temporo-parietal regions (Butler et al.,2014; Halai et al., 2017; Shumacher et al., 2019). It is important to note that the phonology component in those studies loaded on tests of naming and verbal working memory, as well as repetition. This differentiation may be due to a more extensive neuropsychological assessment in our study resulting in more discrete PCA components, or a result of our selective patient sample. The semantic component explained the least amount of behavioural variance in our sample. Scores on this factor loaded on tests of naming, reading and written comprehension and uniquely correlated with regions in the left superior/ medial temporal pole and the left superior/ medial temporal gyrus (fig. 2). This supports recent work extending the temporal region implicated in semantic control (Jackson, 2021).

Importantly, higher cognitive functions, namely executive function and verbal working memory, explain a significant amount of variance in language abilities in our population of anomic aphasics. As mentioned previously, both executive function and verbal working memory are robust predictors of aphasia recovery outcomes (Fillingham, Sage and Lambon Ralph, 2005a, 2005b, 2006; Conroy, Sage and Lambon Ralph, 2009; Lambon Ralph et al., 2010; Yeung and Law, 2010; Snell, Sage and Lambon Ralph, 2010, Sage, Snell and Lambon Ralph, 2011; Dignam et al., 2017). During aphasia recovery, executive function is important for the generation of semantic and phonological concepts

to aid with word retrieval (Dignam et al, 2017) and to navigate other complex dynamics of human communication, while the integrity of general memory processes enables learning and retention of linguistic knowledge during rehabilitation. In our study, the verbal working memory component uniquely correlated with regions of tissue damage in the left posterior superior temporal gyrus, left superior longitudinal fasciculus, as well as Heschl's gyrus, Werenicke's area and the hippocampus (fig. 2). This component captured abilities in online maintenance and use of verbal inputs (e.g. digit-span, sentence repetition, spoken picture description). This replicates findings from Tochadse et al., (2019) who report a similar neural correlate associated with a novel auditory working memory component in aphasia patients.

Scores on the executive function factor uniquely correlated with tissue damage in the left inferior frontal cortex (LIFC), including pars orbitalis and pars triangularis (fig. 2). These findings support the role of Broca's area, here pars triangularis in particular, in domain-general cognition and extend our understanding of the neural correlates of anomia. We show that in these patients, lesions to the LIFC, including Broca's area, are principally associated with executive (dys)function, independent of language abilities. This suggests that, while damage to the LIFC commonly coincides with language impairment after stroke, lesions to this area might be primarily driving a (non-language specific) cognitive component of anomia. We speculate that lesions to Broca's area result in cognitive deficits which can indirectly contribute to varying levels of long-term language impairment, and the nature of these impairments will vary depending on the pattern of damage to neighbouring regions of grey and white matter (Kimberg et al., 2007; Richardson et al., 2012; Inoue et al., 2014; Mah et al., 2014; Sperber and Karnath et al., 2017; Gajardo-Vidal and Lorca-Puls et al., 2021).

Behaviourally, the executive function component loaded on tests of problem solving and concept formation as measured by the D-KEFS Card Sorting assessment. Card sorting assessments, including the D-KEFS and Wisconsin (Berg, 1948) tasks, appear to reliably engage executive function and the left inferior frontal gyrus (LIFG) in aphasia patients. The neural correlates associated with our executive function component show some overlap with a PCA component identified by Schumacher and colleagues (2019), which the authors refer to as 'inhibit-generate'. The 'inhibit-generate' component captured abilities of idea generation, reasoning, problem solving and response

inhibition in aphasia patients and loaded on, amongst others, the D-KEFS card sorting test. Additionally, using the Wisconsin Card Sorting Task, Baldo et al. (2005) reported impairments in aphasic individuals, but not in patients with left-hemisphere damage but without aphasia, suggesting that the card sorting task taps into executive function abilities that are necessary for language function. Another study showed that the D-KEFS Card Sorting assessment is predicative of successful anomia therapy outcomes (Dignam et al., 2017). Collectively, these findings suggest that in aphasia patients, D-KEFS is a sensitive measure of executive function and associated neural correlates in the LIFG that support language function. Not including assessments of concept formation and problem solving, such as card sorting tasks, might be why previous studies in aphasia have struggled to find associations between tests of executive function and brain tissue integrity (Kummerer et al., 2013; Butler et al., 2014; Mirman et al., 2015; Halai et al., 2017; Tochadse et al., 2018).

In conclusion, our findings suggest that in patients with chronic post-stroke anomia, cognitive abilities and in particular executive function and verbal working memory, explain more of the variance in language function than classical models of the condition imply. Moreover, lesions to the LIFG, including Broca's area, determine whether patients suffer worse executive (dys)function, independent of their language abilities, suggesting that damage to Broca's area is primarily associated with outcomes in cognitive domains outside of language. This highlights the importance of higher-order cognitive domains and their neural correlates in aphasia (Helm-Estabrooks, 2002; Fucetola et al., 2009), but does not imply that all aphasics will have additional cognitive impairments. A better understanding of the covariance between language and non-language deficits and their underlying neural correlates will inform more targeted aphasia treatment, tailored to an individual's pattern of impairments. This may be in the form of neurostimulation targeting regions of domain-general cognition or by incorporating measures of higher-order cognitive function, such as concept formation and verbal working memory, to improve the accuracy of aphasia prediction models (Price et al., 2010; Hope et al., 2013, 2018; Yourganov et al., 2015).

References

Alexander, M. P., Naeser, M. A. and Palumbo, C. (1990) ' Brocas area aphasias - aphasia after lesions including the frontal operculum', *Neurology,* 40 (2), pp.353-362.

Ardila, A., Bernal, B. and Rosselli, M. (2016) 'How Localized are Language Brain Areas? A Review of Brodmann Areas Involvement in Oral Language', *Archives of Clinical Neuropsychology,* 31(1), pp. 112-122.

Ashburner, J. and Friston, K. J. (2005) 'Unified segmentation', *Neuroimage,* 26(3), pp. 839-851.

Baldo, J., Dronkers, N., Wilkins, D., Ludy, C., Raskin, P. and Kim, J. (2005) 'Is problem solving dependent on language?', *Brain and Language,* 92(3), pp. 240-250.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T. and Dronkers, N. F. (2003) 'Voxel-based lesion–symptom mapping', *Nature Neuroscience,* 6(5), pp. 448-450.

Berg, E. A. (1948) 'A Simple Objective Technique for Measuring Flexibility in Thinking', *The Journal of General Psychology,* 39(1), pp. 15-22.

Brandt J, Benedict R. Verbal Learning Test-Revised Professional Manual. Lutz, FL: Psychological Assessment Resources, Inc (2001).

Butler, R. A., Lambon Ralph, M. A. and Woollams, A. M. (2014) 'Capturing multidimensionality in stroke aphasia: mapping principal behavioural components to neural structures', *Brain,* 137(12), pp. 3248-3266.

Cattell, R. B. and Cattell, A. K. S. (1963). Culture fair intelligence test. Champaign, IL: Institute for Personality and Ability Testing

Conroy, P., Sage, K. and Lambon Ralph, M. A. (2009) 'The effects of decreasing and increasing cue therapy on improving naming speed and accuracy for verbs and nouns in aphasia', *Aphasiology,* 23(6), pp. 707-730.

Dabul, B. (2000). Apraxia battery for adults (second ed.). Austin, Tx: Pro-Ed.

Delis, D. C., Kaplan, E., and Kramer, J. H. (2001). D-KEFS Executive Function System: Examiners manual. *San Antonio, TX: Psychological Corporation.*

Dignam, J., Copland, D., O'Brien, K., Burfein, P., Khan, A. and Rodriguez, A. D. (2017) 'Influence of Cognitive Ability on Therapy Outcomes for Anomia in Adults With Chronic Poststroke Aphasia', *Journal of Speech, Language, and Hearing Research,* 60(2), pp. 406-421.

Dronkers, N. F., Plaisant, O., Iba-Zizen, M. T. and Cabanis, E. A. (2007) 'Paul Broca's historic cases: high resolution MR imaging of the brains of Leborgne and Lelong', *Brain,* 130(5), pp. 1432-1441.

Duncan, J. (2010) 'The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour', *Trends in Cognitive Sciences,* 14(4), pp. 172-179.

Duncan, J. (2013) 'The Structure of Cognition: Attentional Episodes in Mind and Brain', *Neuron,* 80(1), pp. 35-50.

El Hachioui, H., Visch-Brink, E. G., Lingsma, H. F., Van De Sandt-Koenderman, M. W. M. E., Dippel,

D. W. J., Koudstaal, P. J. and Middelkoop, H. A. M. (2014) 'Nonlinguistic Cognitive Impairment in Poststroke Aphasia', *Neurorehabilitation and Neural Repair,* 28(3), pp. 273-281.

Fedorenko, E. (2014) 'The role of domain-general cognitive control in language comprehension', *Frontiers in Psychology,* 5.

Fedorenko, E. and Varley, R. (2016) 'Language and thought are not the same thing: evidence from neuroimaging and neurological patients', *Annals of the New York Academy of Sciences,* 1369(1), pp. 132-153.

Fillingham, J., Sage, K. and Lambon Ralph, M. (2005a) 'Further explorations and an overview of errorless and errorful therapy for aphasic word-finding difficulties: The number of naming attempts during therapy affects outcome', *Aphasiology,* 19(7), pp. 597-614.

Fillingham, J. K., Sage, K. and Lambon Ralph, M. A. (2005b) 'Treatment of anomia using errorless versus errorful learning: are frontal executive skills and feedback important?', *International Journal of Language & Communication Disorders,* 40(4), pp. 505-523.

Fillingham, J. K., Sage, K. and Lambon Ralph †, M. A. (2006) 'The treatment of anomia using errorless learning', *Neuropsychological Rehabilitation,* 16(2), pp. 129-154.

Frankel, T., Penn, C. and Ormond-Brown, D. (2007) 'Executive dysfunction as an explanatory basis for conversation symptoms of aphasia: A pilot study', *Aphasiology,* 21(6-8), pp. 814-828.

Fridriksson, J., Fillmore, P., Guo, D. and Rorden, C. (2015) 'Chronic Broca's Aphasia Is Caused by Damage to Broca's and Wernicke's Areas', *Cerebral Cortex,* 25(12), pp. 4689-4696.

Fridriksson, J., Kjartansson, O., Morgan, P. S., Hjaltason, H., Magnusdottir, S., Bonilha, L. and Rorden, C. (2010) 'Impaired Speech Repetition and Left Parietal Lobe Damage', *Journal of Neuroscience,* 30(33), pp. 11057-11061.

Fridriksson, J., Nettles, C., Davis, M., Morrow, L. and Montgomery, A. (2006) 'Functional communication and executive function in aphasia', *Clinical Linguistics & Phonetics,* 20(6), pp. 401-410.

Fucetola, R., Connor, L. T., Strube, M. J. and Corbetta, M. (2009) 'Unravelling nonverbal cognitive performance in acquired aphasia', *Aphasiology,* 23(12), pp. 1418-1426.

Gajardo-Vidal, A., Lorca-Puls, D. L., Team, P., Warner, H., Pshdary, B., Crinion, J. T., Leff, A. P., Hope, T. M. H., Geva, S., Seghier, M. L., Green, D. W., Bowman, H. and Price, C. J. (2021) 'Damage to Broca’s area does not contribute to long-term speech production outcome after stroke', *Brain*.

Goodglass, H., Kaplan, E., and Barresi, B. (2001) The assessment of aphasia and related disorders (3rd ed.). *Philadelphia: Lippincott, Williams, & Wilkins*.

Gordon, P. C., Hendrick, R. and Levine, W. H. (2002) 'Memory-Load Interference in Syntactic Processing', *Psychological Science,* 13(5), pp. 425-430.

Halai, A. D., Woollams, A. M. and Lambon Ralph, M. A. (2017) 'Using principal component analysis to capture individual differences within a unified neuropsychological model of chronic post-stroke aphasia: Revealing the unique neural correlates of speech fluency, phonology and semantics', *Cortex,* 86, pp. 275-289.

Helm-Estabrooks, N. (2002) 'Cognition and aphasia: a discussion and a study', *Journal of*

Communication Disorders, 35(2), pp. 171-186.

Hope, T. M. H., Leff, A. P. and Price, C. J. (2018) 'Predicting language outcomes after stroke: Is structural disconnection a useful predictor?', *NeuroImage: Clinical,* 19, pp. 22-29.

Hope, T. M. H., Seghier, M. L., Leff, A. P. and Price, C. J. (2013) 'Predicting outcome and recovery after stroke with lesions extracted from MRI images', *NeuroImage: Clinical,* 2, pp. 424-433.

Howard, D., and Patterson, K. (1992) Pyramids and Palm Trees: A test of semantic access from pictures and words. *Bury St. Edmunds, UK: Thames Valley Test Company.*

Inoue, K., Madhyastha, T., Rudrauf, D., Mehta, S. and Grabowski, T. (2014) 'What affects detectability of lesion–deficit relationships in lesion studies?', *NeuroImage: Clinical,* 6, pp. 388-397.

Jackson, R. L. (2021) 'The neural correlates of semantic control revisited', *NeuroImage,* 224, pp. 117444.

January, D., Trueswell, J. C. and Thompson-Schill, S. L. (2009) 'Co-localization of Stroop and Syntactic Ambiguity Resolution in Broca's Area: Implications for the Neural Basis of Sentence Processing', *Journal of Cognitive Neuroscience,* 21(12), pp. 2434-2444.

Jefferies, E., Patterson, K. and Ralph, M. A. L. (2008) 'Deficits of knowledge versus executive control in semantic cognition: Insights from cued naming', *Neuropsychologia,* 46(2), pp. 649-658.

Kaan, E. and Swaab, T. Y. (2002) 'The brain circuitry of syntactic comprehension', *Trends in Cognitive Sciences,* 6(8), pp. 350-356.

Kaplan, E., Goodglass, H., Weintraub, S (1983) Boston Naming Test. *Philadelphia: Lea & Febiger.*

Kay, J., Lesser, R., & Coltheart, M. (1992) Psycholinguistic Assessments of Language Processing in Aphasia (PALPA). *Hove: Erlbaum.*

Kimberg, D. Y., Coslett, H. B. and Schwartz, M. F. (2007) 'Power in Voxel-based Lesion-Symptom Mapping', *Journal of Cognitive Neuroscience,* 19(7), pp. 1067-1080.

Kümmerer, D., Hartwigsen, G., Kellmeyer, P., Glauche, V., Mader, I., Klöppel, S., Suchan, J., Karnath, H.-O., Weiller, C. and Saur, D. (2013) 'Damage to ventral and dorsal language pathways in acute aphasia', *Brain,* 136(2), pp. 619-629.

Lacey, E. H., Skipper-Kallal, L. M., Xing, S., Fama, M. E. and Turkeltaub, P. E. (2017) 'Mapping Common Aphasia Assessments to Underlying Cognitive Processes and Their Neural Substrates', *Neurorehabilitation and Neural Repair,* 31(5), pp. 442-450.

Laine, M. and Martin, N. (2013) Anomia: Theoretical and clinical aspects. *Psychology Press.*

Lambon Ralph, M. A., Snell, C., Fillingham, J. K., Conroy, P. and Sage, K. (2010) 'Predicting the outcome of anomia therapy for people with aphasia post CVA: Both language and cognitive status are key predictors', *Neuropsychological Rehabilitation,* 20(2), pp. 289-305.

Lee, B. and Pyun, S.-B. (2014) 'Characteristics of Cognitive Impairment in Patients With Post-stroke Aphasia', *Annals of Rehabilitation Medicine,* 38(6), pp. 759.

Lorch, M. P. (2008) 'The merest Logomachy: The 1868 Norwich discussion of aphasia by Hughlings Jackson and Broca', *Brain,* 131, pp. 1658-1670.

Mah, Y.-H., Husain, M., Rees, G. and Nachev, P. (2014) 'Human brain lesion-deficit inference

remapped', *Brain,* 137(9), pp. 2522-2531.

Marie P. (1906) Aphasia from 1861 to 1866. Essay of historical criticism on the genesis of the doctrine of aphasia. *Sem Méd. 26:565–571.*

Marinelli, C. V., Spaccavento, S., Craca, A., Marangolo, P. and Angelelli, P. (2017) 'Different Cognitive Profiles of Patients with Severe Aphasia', *Behavioural Neurology,* 2017, pp. 15.

Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B. and Schwartz, M. F. (2015) 'Neural organization of spoken language revealed by lesion–symptom mapping', *Nature Communications,* 6(1), pp. 6762.

Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W. and Davis, K. R. (1978) 'BROCA APHASIA - PATHOLOGIC AND CLINICAL', *Neurology,* 28(4), pp. 311-324.

Murray, L. L. (2012) 'Attention and Other Cognitive Deficits in Aphasia: Presence and Relation to Language and Communication Measures', *American Journal of Speech-Language Pathology,* 21(2), pp. S51-S64.

Nicholas, L. E., Brookshire, R. H., Maclennan, D. L., Schumacher, J. G. and Porrazzo, S. A. (1989) 'Revised administration and scoring procedures for the Boston Naming test and norms for non-brain-damaged adults', *Aphasiology,* 3(6), pp. 569-580.

Novais-Santos, S., Gee, J., Shah, M., Troiani, V., Work, M. and Grossman, M. (2007) 'Resolving sentence ambiguity with planning and working memory resources: Evidence from fMRI', *NeuroImage,* 37(1), pp. 361-378.

Novick, J. M., Trueswell, J. C. and Thompson-Schill, S. L. (2005) 'Cognitive control and parsing: Reexamining the role of Broca's area in sentence comprehension', *Cognitive, Affective, & Behavioral Neuroscience,* 5(3), pp. 263-281.

Osterrieth, P.A. (1944) Le test de copie d'une figure complexe. *Arch. Psychol. 30, 206–356.*

Papitto, G., Friederici, A. D. and Zaccarella, E. (2020) 'The topographical organization of motor processing: An ALE meta-analysis on six action domains and the relevance of Broca's region', *NeuroImage,* 206, pp. 116321.

Phan, T. G., Donnan, G. A., Wright, P. M. and Reutens, D. C. (2005) 'A Digital Map of Middle Cerebral Artery Infarcts Associated With Middle Cerebral Artery Trunk and Branch Occlusion', *Stroke,* 36(5), pp. 986-991.

Price, C. J., Seghier, M. L. and Leff, A. P. (2010) 'Predicting language outcome and recovery after stroke: the PLORAS system', *Nature Reviews Neurology,* 6(4), pp. 202-210.

Ramsey, L. E., Siegel, J. S., Lang, C. E., Strube, M., Shulman, G. L. and Corbetta, M. (2017) 'Behavioural clusters and predictors of performance during recovery from stroke', *Nature Human Behaviour,* 1(3), pp. 0038.

Richardson, J. D., Fillmore, P., Rorden, C., Lapointe, L. L. and Fridriksson, J. (2012) 'Re-establishing Broca's initial findings', *Brain and Language,* 123(2), pp. 125-130.

Robertson, I. H., Manly, T., Andrade, J., Baddeley, B. T. and Yiend, J. (1997) '`Oops!': Performance correlates of everyday attentional failures in traumatic brain injured and normal subjects',

Neuropsychologia, 35(6), pp. 747-758.

Sage, K., Snell, C. and Lambon Ralph, M. A. (2011) 'How intensive does anomia therapy for people with aphasia need to be?', *Neuropsychological Rehabilitation,* 21(1), pp. 26-41.

Schumacher, R., Halai, A. D. and Lambon Ralph, M. A. (2019) 'Assessing and mapping language, attention and executive multidimensional deficits in stroke aphasia', *Brain,* 142(10), pp. 3202-3216.

Seghier, M. L., Ramlackhansingh, A., Crinion, J., Leff, A. P. and Price, C. J. (2008) 'Lesion identification using unified segmentation-normalisation models and fuzzy clustering', *Neuroimage,* 41(4), pp. 1253-1266.

Snell, C., Sage, K. and Lambon Ralph, M. A. (2010) 'How many words should we provide in anomia therapy? A meta-analysis and a case series study', *Aphasiology,* 24(9), pp. 1064-1094.

Sperber, C. and Karnath, H.-O. (2017) 'Impact of correction factors in human brain lesion-behavior inference', *Human Brain Mapping,* 38(3), pp. 1692-1701.

Swinburn K, Porter G, Howard D. (2005) The Comprehensive Aphasia Test. *Hove, UK: Psychology Press*.

Tochadse, M., Halai, A. D., Ralph, M. A. L. and Abel, S. (2018) 'Unification of behavioural, computational and neural accounts of word production errors in post-stroke aphasia', *Neuroimage-Clinical,* 18, pp. 952-962.

Tranter, L. J. and Koutstaal, W. (2008) 'Age and Flexible Thinking: An Experimental Demonstration of the Beneficial Effects of Increased Cognitively Stimulating Activity on Fluid Intelligence in Healthy Older Adults', *Aging, Neuropsychology, and Cognition,* 15(2), pp. 184-207.

Tremblay, P. and Dick, A. S. (2016) 'Broca and Wernicke are dead, or moving past the classic model of language neurobiology', *Brain and Language,* 162, pp. 60-71.

Tyler, L. K., Marslen-Wilson, W. and Stamatakis, E. A. (2005) 'Dissociating neuro-cognitive component processes: voxel-based correlational methodology', *Neuropsychologia,* 43(5), pp. 771-778.

Vallila-Rohter, S. and Kiran, S. (2013) 'Non-linguistic learning and aphasia: Evidence from a paired associate and feedback-based task', *Neuropsychologia,* 51(1), pp. 79-90.

Wechsler, D. (2008) Wechsler Adult Intelligence Scale (4th ed.). *San Antonio, TX: Pearson Assessment.*

Wilke, M., de Haan, B., Juenger, H. and Karnath, H. O. (2011) 'Manual, semi-automated, and automated delineation of chronic brain lesions: A comparison of methods', *Neuroimage,* 56(4), pp. 2038-2046.

Yeung, O. and Law, S.-P. (2010) 'Executive functions and aphasia treatment outcomes: Data from an ortho-phonological cueing therapy for anomia in Chinese', *International Journal of Speech-Language Pathology,* 12(6), pp. 529-544.

Yourganov, G., Smith, K. G., Fridriksson, J. and Rorden, C. (2015) 'Predicting aphasia type from brain damage measured with structural MRI', *Cortex,* 73, pp. 203-215.