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Relating resting-state hemodynamic changes to the variable language profiles in post-stroke aphasia

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ABSTRACT

Linking both structural lesions and the functional integrity of remaining brain tissue to patients' behavioural profile may be critical in discovering the limits of behavioural recovery post stroke. In the present study, we explored the relationship between temporal hemodynamic changes and language performance in chronic post-stroke aphasia. We collected detailed language and neuropsychological data for 66 patients with chronic (> 1 year) post-stroke aphasia. We used principal component analysis to extract their core language-neuropsychological features. From resting-state fMRI scans in 35 patients, we calculated the lag in the time-course of the intact brain voxels in each patient. Finally, variation across the language-cognitive factors was related to both the patients' structural damage and the time-course changes in each patient's intact tissue. Phonological abilities were correlated with the structural integrity of the left superior temporal, angular gyrus, supramarginal gyrus and arcuate fasciculus regions and hemodynamic advance in the left intra-parietal sulcus. Speech fluency related to integrity of premotor regions, plus hemodynamic advance in the left middle/superior temporal gyrus, left middle occipital gyrus, and right angular gyrus. Semantic performance reflected a combination of medial ventral temporal lobe status and hemodynamic delay in the left posterior middle temporal gyrus. Finally, executive abilities correlated with hemodynamic delay in the left middle/inferior frontal gyrus, right rolandic operculum, bilateral supplementary motor areas/middle cingulum areas, and bilateral thalamus/caudate. Following stroke, patients' patterns of chronic language abilities reflects a combination of structural and functional integrity across a distributed network of brain regions. The correlation between hemodynamic changes and behaviours may have clinical importance.

1. Introduction

Measuring changes in resting-state functional MRI (rs-fMRI) may provide insights into recovery mechanisms after brain damage (Carter et al., 2010; Carter et al., 2012; Grefkes and Fink, 2011, 2014; Ovadia-Caro et al., 2014). There are some advantages in collecting rs-fMRI data in patient populations as the technique can non-invasively measure hemodynamic responses of patients (Biswal et al., 1995) and the participant is simply asked to remain still in the scanner for around six minutes (Ovadia-Caro et al., 2014). These features suggest that the use of rs-fMRI might be one of the easiest and most feasible approaches to identifying functional networks in patient groups (Tie et al., 2014) and thus provide important information for possible recovery studies. Rs-fMRI studies have related changed functional connectivity (FC) to deficits and recovery mechanisms post-stroke, in motor deficits (Park et al., 2011) spatial neglect (He et al., 2007) and aphasia (Nair et al., 2015). There are, however, new ways to utilise rs-fMRI data, which might provide important insights about the relationship between patient's behavioural profile and the functional status of the remaining, intact brain regions.

Recently, rs-fMRI data were used to identify temporal hemodynamic changes in post-stroke populations (and proved crucial for understanding the true basis of altered FC) (Amemiya et al., 2014; Lv et al., 2013; Siegel et al., 2016). Intact brain regions had altered temporal hemodynamic flow, which either led or lagged behind the mean time course of intact grey matter. This finding was replicated in the acute and chronic stages of stroke, and steno-occlusive vessels disease (Amemiya et al., 2014; Siegel et al., 2016). Hemodynamic changes could emerge for at least two possible reasons. First, some brain regions share a vascular supply and therefore, if a common vascular supply is

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compromised, intact regions' hemodynamic response could be affected (Amemiya et al., 2014; Lv et al., 2013; Siegel et al., 2016). Secondly, remote regions can have structural and/or functional connections with the affected regions (Bullmore and Sporns, 2009) which could affect their functional integrity even if they have different vascular supplies. If temporal hemodynamic changes are caused by changes in blood flow to intact regions, it is interesting to explore which of these regions are related to behavioural performance.

There is a long history of relating patients' behavioural profiles to the underlying brain damage, both through classical lesion overlap mapping (Damasio et al., 1996) and more contemporary lesion-symptom analytic techniques (Bates et al., 2003). Whilst the location and extent of lesions are clearly a critical element in explaining patients' behavioural presentation, functional changes in the intact tissue may also be crucial. The core hypothesis of the current study is that patients' performance may reflect a combination of the direct effect of the lesion to the cognitive network-of-interest plus the functional status of the remaining cognitive networks. Accordingly, in this study we explored whether the structural lesion and hemodynamic lag in the intact regions (derived from rs-fMRI) could explain patient variation across four core components of language function. More specifically, there are two different kinds of change that might emerge after brain damage. First, it has become increasingly clear that many cognitive functions, including different aspects of language, are supported by distributed neural networks (e.g. Friederici and Gierhan, 2013). This network-based function may mean that when one or more of its nodes are damaged then the function of the entire network may become less efficient and time courses extended (Binney and Lambon Ralph, 2015) because there is reduced/inefficient activation propagation (Allendorfer et al., 2012; Geranmayeh et al., 2016; Skipper-Kallal et al., 2017). The second, additional possibility is that other cognitive functions (e.g. domain general executive control) become recruited in order to compensate or support the damaged system (Brownsett et al., 2013; Geranmayeh et al., 2014; Geranmayeh et al., 2017; Geranmayeh et al., 2016). To test the hypothesis, the current study determined the temporal hemodynamic changes in rs-fMRI data for a group of 35 patients with chronic post-stroke aphasia and related the results, alongside their structural lesions, to the pattern of their language and cognitive profiles.

2. Method

2.1. Participants

This study makes use of our large neuropsychological and neuroimaging dataset, consisting of 66 patients with chronic aphasia post-stroke (either ischaemic or haemorrhagic). The full database was used in the behavioural factor analysis. For the brain–behaviour correlational analyses, we utilised a subset of 35 patients who had both rs-fMRI as well as T1 scans (see Table 1 for a summary of demographic details). Recruitment criteria were: (1) monolingual native English speakers, (2) normal or corrected-to-normal hearing and vision, (3) right-handed, (4) one stroke, (5) at least 12 months' post-stroke and (6) no other known neurological conditions. All participants gave informed consent under approval from the local ethics committee. Structural imaging data from a healthy age and education matched control group (8 female, 11 male) was used to determine the lesion outline in the patients using an automated lesion identification toolbox (Seghier et al., 2008). We obtained control resting-state scans on a control group (N = 30), however they were not age-matched (mean age: 30.5 years, standard deviation: 5, range: 25–43 years). We did not use freely available resting-state data as we collected dual-echo fMRI data in order to improve signal loss in magnetic susceptible regions such the anterior temporal lobe (Halai et al., 2015; Halai et al., 2014).

Table 1
Participants' background information. Abbreviations (Boston Diagnostic Aphasia Examination: BDAE)

ID	Age	Gender	Education years	Post months	BDAE classification
1	44	M	11	40	Anomia
2	61	M	11	16	Broca
3	73	M	11	23	Mixed Non-fluent
4	53	F	11	47	Anomia
5	51	F	11	66	Anomia
6	54	M	13	35	Broca
7	77	F	11	56	Anomia
8	52	F	11	99	Mixed Non-fluent
9	69	F	19	39	Anomia
10	78	M	13	36	Mixed Non-fluent
11	68	M	11	21	Anomia
12	68	F	16	22	Anomia
13	59	M	13	37	Broca
14	59	M	11	34	Anomia
15	58	M	13	57	Global
16	51	M	13	72	Anomia
17	46	F	16	21	Conduction
18	82	M	10	13	Broca
19	79	M	11	64	Global
20	68	M	11	37	Conduction
21	44	F	13	37	Anomia
22	73	F	11	46	Transcortical motor aphasia
23	75	F	11	160	Mixed Non-fluent
24	84	M	9	35	Anomia
25	74	M	11	18	Global
26	43	F	16	15	Anomia
27	64	M	11	29	Mixed Non-fluent
28	67	M	11	44	Mixed Non-fluent
29	79	M	11	63	Mixed Non-fluent
30	45	M	11	25	Anomia
31	58	F	11	278	Anomia
32	67	M	11	13	Conduction
33	52	M	11	73	Global
34	86	M	9	17	Anomia
35	73	M	11	114	Broca

2.2. Neuropsychological assessments and analysis

The neuropsychological battery was designed to assess input/output phonological processing, semantic processing and sentence comprehension, and general cognitive function. The battery included tasks from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) battery (Kay et al., 1992): (1) auditory discrimination using non-word minimal pairs, (2) auditory discrimination using word minimal pairs, (3) immediate repetition of non-words, (4) immediate repetition of words, (5) delayed repetition of non-words, and (6) delayed repetition of words. Tasks from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) included: (7) spoken word-to-picture matching, (8) written word-to-picture matching, (9) Camel and Cactus Test (picture), and (10) picture naming. Other language tasks included (11) the Boston Naming Test (BNT) (Kaplan et al., 1983) (12) written 96-trial synonym judgement (Jefferies et al., 2009) (13) the spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2005) and the ‘Cookie theft’ picture description task from the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1983) Patients' responses from this picture description were recorded and transcribed. The (14) number of word tokens (T), (15) type/token ratio (TTR), (16) mean length of utterance in morphemes (MLU), and (17) words-per-minute (WPM) were computed. Cognitive assessments included (18) forward and (19) backward digit span (Wechsler, 1987) (20) the Brixton Spatial Rule Anticipation Task (Burgess and Shallice, 1997) and (21) Raven's Coloured Progressive Matrices (Raven, 1962) All scores were converted into percentage based on the maximum score available; where no maximum was available, we used the max score in the group.

Following our previous studies (Butler et al., 2014; Halai et al.,