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Research Report

Damage to temporoparietal cortex is sufficient for impaired semantic control

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ABSTRACT

Semantic control allows us to focus semantic activation on currently relevant aspects of knowledge, even in the face of competition or when the required information is weakly encoded. Diverse cortical regions, including left prefrontal and posterior temporal cortex, are implicated in semantic control, however; the relative contribution of these regions is unclear. For the first time, we compared semantic aphasia (SA) patients with damage restricted to temporoparietal cortex (TPC; N = 8) to patients with infarcts encompassing prefrontal cortex (PF+; N = 22), to determine if prefrontal lesions are necessary for semantic control deficits. These SA groups were also compared with semantic dementia (SD; N = 10), characterised by degraded semantic representations. We asked whether TPC cases with semantic impairment show controlled retrieval deficits equivalent to PF+ cases or conceptual degradation similar to patients with SD. Independent of lesion location, the SA subgroups showed similarities, whereas SD patients showed a qualitatively distinct semantic impairment. Relative to SD, both TPC and PF+ SA subgroups: (1) showed few correlations in performance across tasks with differing control demands, but a strong relationship between tasks of similar difficulty; (2) exhibited attenuated effects of lexical frequency and concept familiarity, (3) showed evidence of poor semantic regulation in their verbal output – performance on picture naming was substantially improved when provided with a phonological cue, and (4) showed effects of control demands, such as retrieval difficulty, which were equivalent in severity across TPC and PF+ groups. These findings

Abbreviations: ATL, anterior temporal lobes; LIFG, left interior frontal gyrus; pMTG, posterior middle temporal gyrus; PF+, prefrontal cortex often with additional cortex; PFC, prefrontal cortex; SA, semantic aphasia; SD, semantic dementia; TPC, temporoparietal cortex.

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show that semantic impairment in SA is underpinned by damage to a distributed semantic control network, instantiated across anterior and posterior cortical areas.
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1. Introduction

Patients with distinct locations of brain damage show qualitative differences in their semantic impairment, suggesting that semantic cognition emerges from the interaction of multiple neurocognitive components, including (i) modality-specific 'spoke' regions; (ii) a heteromodal semantic 'hub' in the anterior temporal lobes (ATL) and (iii) semantic control processes that support the selection and controlled retrieval of conceptual information in a flexible and contextually-specific way (Jefferies et al., 2020; Jefferies & Lambon Ralph, 2006; Lambon Ralph et al., 2017). Patients with semantic dementia (SD), with atrophy centred on the ventrolateral ATL bilaterally, show degraded conceptual knowledge across both verbal and non-verbal tests (Bozeat et al., 2000; Ding et al., 2020). Other aspects of cognition are largely spared, including executive control (but see Chapman et al., 2020 for recent discussion on this topic). SD patients show strong correlations and item-specific consistency in their knowledge across different tasks, suggesting they have degradation of central semantic representations (Warrington & Cipolotti, 1996). In line with this characterisation, they are largely insensitive to cueing and highly sensitive to word frequency and familiarity – with more-frequent items degrading less rapidly than low frequency items that have less robust long-term memory representations (Jefferies et al., 2009).

Patients with semantic aphasia (SA) following left hemisphere stroke also show multimodal semantic deficits (Corbett et al., 2011; Gardner et al., 2012; Jefferies & Lambon Ralph, 2006). Most commonly, this impairment is associated with damage to left inferior frontal gyrus (LIFG), extending to posterior temporal and/or inferior parietal regions (PF+ patients). However, a minority of SA patients have lesions of posterior temporal and/or inferior parietal cortex, with left PFC spared (referred to here as temporoparietal cortex – TPC patients). The term SA was originally used by Head and Luria to describe patients with heteromodal and high-level conceptual and cognitive deficits, for example, affecting comprehension of reversible sentences and abstract thought (Head, 1926; Luria, 1976). In a series of studies of SA, we have selected patients with left-hemisphere stroke showing *heteromodal* semantic deficits (with impairment of both word and picture-based semantic tasks) and found that these individuals also showed impaired cognitive control, in line with Head/Luria's description. However, some of the patients in our sample had impaired semantic processing at the single-item level: consequently, they are more comparable to SD patients in terms of scores on semantic tasks (Jefferies & Lambon Ralph, 2006) and more severely impaired than other recent SA case series (Dragoy et al., 2017).

Our approach has allowed us to compare the nature of the heteromodal semantic deficit in SA and SD patients who fail the same range of semantic tasks. At the group level, SA patients show: (1) greater sensitivity than SD cases to the executive demands of semantic tests and correlations between semantic and executive performance (Thompson et al., 2018); (2) less consistency and weaker correlations in performance when the same items are probed using different tests (Jefferies & Lambon Ralph, 2006); (3) smaller effects of frequency/familiarity (Almaghyuli et al., 2012; Hoffman, Jefferies, et al., 2011; Hoffman, Rogers, et al., 2011) and (4) strong effects of cues on the ability to retrieve relevant knowledge (Jefferies et al., 2008; Lanzoni et al., 2019; Noonan et al., 2010). These findings suggest different underlying causes of semantic impairment in SA and SD: while SD cases have degraded conceptual knowledge, SA patients have difficulty shaping semantic retrieval to suit the circumstances. However, most previous studies of SA have primarily examined or deliberately focussed on patients who have left frontal lesions (Hallam et al., 2018; Stampacchia et al., 2018, 2019), and consequently it is not known whether damage to LIFG is *necessary* for semantic control deficits, or whether patients with TPC-only lesions can be equivalently impaired. In particular, it has not been established whether the multimodal semantic deficits in SA patients with TPC lesions resemble those reported for SA in general (i.e., following left prefrontal lesions) or if this group of SA patients has a pattern of impairment more similar to patients with SD, since both SD and TPC-only SA cases have temporal lobe damage that might impact conceptual representation.

The qualitative dissociation between SD and SA is also related to an earlier distinction between semantic 'storage' and 'access' cases described by Warrington and colleagues (McCarthy & Warrington, 2016; Warrington & Crutch, 2004; Warrington & McCarthy, 1983). Patients with deficits of semantic access have greater impairment when small sets of semantically related items must be retrieved in repeated cycles and in quick succession. This 'refractory' pattern is typically observed alongside inconsistent retrieval, absent frequency effects, and beneficial effects of cues – and many SA patients show all of these characteristics (Cogdell-Brooke et al., 2020; Hoffman, Jefferies, et al., 2011; Lanzoni et al., 2019; Thompson et al., 2015). Although Warrington and colleagues reported single cases who showed refractory access deficits specifically in the verbal domain, SA patients show semantic access deficits affecting judgements of words, sounds and pictures, in line with their heteromodal deficits of semantic control (Gardner et al., 2012; Thompson et al., 2015). Studies of semantic refractory effects have specifically associated this pattern with prefrontal and not temporo-parietal lesions: using voxel-lesion symptom mapping, Schnur et al.

(2009) found an association between LIFG lesions and declining picture naming performance when semantically-related sets of items were repeated, while Thompson et al. (2015) found verbal perseverations were stronger in patients with left prefrontal as opposed to posterior infarcts. Indeed, there are numerous demonstrations of semantic control deficits following lesions largely restricted to LIFG (Corbett et al., 2009; Gardner et al., 2012; Jefferies & Lambon Ralph, 2006; Noonan et al., 2010). For example, Thompson-Schill et al. (1998) showed that focal inferior prefrontal damage impairs the ability to generate verbs for nouns, but only in 'high selection' conditions (e.g., when there are many potential verbs, see also Badre et al., 2005; Badre & Wagner, 2007; Moss et al., 2005; Thompson-Schill et al., 1997). These studies highlight the need to carefully evaluate the extent to which SA patients with TPC lesions show qualitatively-similar semantic deficits to those with PF+ lesions.

There is still debate about whether left temporoparietal regions support semantic control along with LIFG – or instead underpin specific aspects of semantic representation or lexical access to meaning. Neuroimaging studies of healthy participants have shown a stronger response in left posterior middle temporal gyrus (pMTG) to language versus non-language tasks (Obleser & Kotz, 2010; Rogalsky & Hickok, 2009), and to semantic tasks involving actions, events, verbs and thematic associations (Beauchamp et al., 2002; Kable et al., 2005; Kalénine et al., 2009; Martin et al., 1995). Lesion analysis has also identified a critical role of pMTG in lexical access (Hillis et al., 2002, 2005) and thematic understanding (Kalénine & Buxbaum, 2016). Nevertheless, neuroimaging and neurostimulation studies of healthy participants implicate *both* left inferior prefrontal and posterior temporal cortex in semantic control, as part of a network that responds to controlled retrieval demands – including increased activation in response to strong distractors and the presentation of weak or ambiguous target meanings (Hoffman, Pobric, et al., 2012; Jackson, 2021; Noonan et al., 2013; Whitney et al., 2011a, 2011b). Both lesions and inhibitory TMS to LIFG increase the engagement of left pMTG in tasks tapping semantic control (Hallam et al., 2016), suggesting that there is compensatory recruitment of posterior sites of this network when the function of LIFG is disrupted (Kwon et al., 2017). These sites also show strong intrinsic connectivity (Gonzalez Alam et al., 2019) and their structural disconnection predicts comprehension (Kwon et al., 2017; Souter et al., 2022). Yet within meta-analyses of neuroimaging studies of semantic control demands, some functional differences between left prefrontal and posterior regions have been observed (Noonan et al., 2013): while LIFG responded to semantic control demands across expressive and receptive tasks, control demands in speech production tasks only modulated activation in anterior parts of the semantic control network (although see Gauvin et al., 2021). If posterior nodes of the semantic control network are less critical for lexical selection, PF+ cases may show greater deficits in speech production that are ameliorated by providing external constraints on retrieval. In addition, the semantic control network lies in adjacent to a broader executive network referred to as the multiple demand network (Gao et al., 2021; Murphy et al., 2019). Regions within the multiple demand network have been shown to respond to manipulations of semantic as well as non-semantic control demands (Gao et al., 2021). Therefore, our analysis of SA cases, who have extensive lesions, does not aim to dissociate the role of these adjacent executive networks. Instead, we ask whether prefrontal lesions are *necessary* for semantic control deficits, or whether these can also follow TP-only lesions.

This study provides an analysis of the largest ever sample of SA patients with TPC lesions, to address two controversies in the literature. First, we compare this group with SD patients, to assess the claim that SA patients with TPC show a different pattern from SD, despite both groups showing multimodal semantic impairment following lesions within the temporal lobe. If anterior and posterior temporal lobe regions support long-term conceptual knowledge, we might expect TPC and SD patients to be qualitatively similar, and distinct from SA patients with left prefrontal damage. In contrast, if left temporoparietal regions primarily support semantic control, we would expect greater similarly between TPC and PF+ cases. Secondly, we present the first systematic comparison of TPC and PF+ patients on assessments of both semantic and non-semantic executive control to establish whether TPC-only cases can show semantic control deficits that are equivalent to those with PF+ lesions. If TPC-only cases can show equivalent deficits of semantic control, we can conclude that LIFG lesions are not necessary for semantic control deficits due to the distributed nature of the semantic control network.

2. Materials and methods

No part of the study procedures was pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. We analysed all available data which existed from the cohorts described below. This was restricted to subsets in some analyses (see Statistical analysis 2.4) due to the historic nature of some data, or where tasks required speech output.

2.1. *Participants*

Subjects' consent was obtained according to the Declaration of Helsinki and approval was provided by the relevant Local Ethics Committee in each case. We examined 30 SA patients – 22 with lesions affecting prefrontal cortex, usually with additional temporoparietal damage (PF+), and 8 with lesions only affecting temporoparietal regions (TPC). The SA sample was largely drawn from our previous studies of SA (between 2006 and 2018). A database of scanned stroke patients in Manchester, UK was used to identify additional TPC cases. Of 33 patients in this database who scored below the cut off for both verbal and non-verbal tasks, only 3 had damage which did not include prefrontal areas anterior to the precentral gyrus. The SA patients were compared with largely published data from patients with SD in order to establish if TPC-only cases more closely resemble SA cases with LIFG lesions or SD patients who also have temporal lobe lesions.

2.1.1. SA patients

SA patients were recruited from stroke clubs and speech and language therapy services in Manchester and York, UK. Patients were selected to show difficulties accessing semantic knowledge in both verbal and non-verbal tasks, in line with our earlier studies (Cogdell-Brooke et al., 2020; Jefferies & Lambon Ralph, 2006; Lanzoni et al., 2019; Stampacchia et al., 2018). The sample included moderate to severely impaired patients, who showed deficits on standard picture and word association tests (picture and word versions of the Camel and Cactus task; see below), and milder patients who were within normal limits on these assessments yet were impaired on both verbal and non-verbal assessments designed to tax semantic control processes (e.g., alternative object use and comprehension of ambiguous words; details below). All patients had chronic impairments resulting from a cerebrovascular accident at least one year prior to testing. The group included patients with fluent and less fluent language profiles (Supplementary Table 1 provides background diagnostic and demographic information).

2.1.2. SD patients

We used data from a total of 27 SD cases. 10 cases previously described were identified through the Memory and Cognitive Disorders Clinic at Addenbrooke's Hospital, Cambridge, UK (Bozeat et al., 2000; Jefferies & Lambon Ralph, 2006). Additional data was available from a cohort of 11 SD cases previously described (Jefferies et al., 2009) and for 6 SD cases previously described (Hoffman et al., 2014; Hoffman, Jones, et al., 2012). Available data is displayed in Supplementary Table 2. All patients contributed (where data was available), to general background neuropsychology analyses. Individual item-by-item semantic data was only available for the original cohort of 10 SD cases (Bozeat et al., 2000). The 96-item synonym task used data from the 11 SD cases (Jefferies et al., 2009), and the semantic distance task used 7 datasets, including 6 described in previous publications (Hoffman et al., 2014; Hoffman, Jones, et al., 2012) and one from the above cohort (GE, Jefferies et al., 2009). The different SD groups were matched for semantic impairment, with no differences in naming, picture Camel and Cactus and word-picture matching ($F < 1$). These patients fulfilled all of the published criteria for SD (Snowden et al., 1989): they had word-finding difficulties in the context of fluent speech and showed impaired semantic knowledge and single word comprehension; in contrast, phonology, syntax, visual-spatial abilities and day to day memory were relatively well preserved.

2.2. Neuropsychological assessment

2.2.1. Non-semantic tasks

Non-semantic tasks included: (i) space perception tests from the Visual Object and Space Processing battery (tests 5–8, Warrington & James, 1991), (ii) forward and backward digit span (Wechsler, 1987), (iii) Elevator Counting, from the Test of Everyday Attention (Robertson et al., 1994), (iv) Ravens Coloured Progressive Matrices (Raven, 1962), (v) Wisconsin Card Sorting (Berg, 1948) and (vi) Brixton Spatial Rule Attainment (Burgess & Shallice, 1997). Legal copyright restrictions prevent public archiving of these tasks which can be obtained commercially from the copyright holders in the cited references.

2.2.2. Semantic tasks

Semantic tasks included: the Cambridge Semantic Battery (Bozeat et al., 2000), which comprised 64-items across four tasks, (i) picture naming, (ii) spoken word-to-picture matching, and (iii) word and picture versions of the Camel and Cactus test. Other tasks included (iv) the Boston Naming Test (Kaplan et al., 1983), including phonemic onset cues (e.g., /p/ for PARROT) for items not named spontaneously, (v) fluency tasks in which participants named as many items as they could in a minute, using six categories (ANIMALS, FRUIT, BIRDS, HOUSEHOLD OBJECTS, TOOLS, VEHICLES), and three letters (F, A, S), (vi) 96-item Synonym judgement (Jefferies et al., 2009) which manipulated word frequency, (vii) a 64-item Semantic Distance task (Noonan et al., 2010) which involved matching same-category items that were semantically-similar (e.g., HAT with CAP) and more distant (e.g., HAT with STOCKING), (viii) a 30-item ambiguity task (Noonan et al., 2010) in which participants were given polysemous word probes and identified targets relating to the dominant (e.g., LEAF and TREE) and subordinate (e.g., LEAF with PAGE) interpretations, and (ix) a 37-item alternative object use task (Corbett et al., 2011), which required selection of canonical and non-canonical object pictures which could be used to perform an action (e.g., "kill a fly" with FLYSWAT or NEWSPAPER; goals were depicted verbally and pictorially). For the Boston Naming Test, legal copyright restrictions prevent public archiving of these tasks which can be obtained commercially from the copyright holders in the cited references. All other semantic tasks can be found here: https://osf.io/v59dm/.

2.3. Neuroimaging data

Scans were available for 28/30 SA patients. Lesions were identified from T1 images using neighbourhood data analysis (LINDA v0.5.5, Pustina et al., 2016), see Supplementary Analysis 1 for details on the process, and Supplementary Table 3 for individual lesion breakdown by semantic region. Lesion overlap is displayed in Fig. 1 for the PF+ and TPC groups. Radiological reports were available for two further PF+ cases: patient 22's report indicated a left frontal lesion, while patient 25's lesion was described as affecting left frontal, temporal and parietal cortices.

2.4. Statistical analysis

We assessed the magnitude of impairment for non-semantic and semantic tasks across groups using ANOVA and t-tests. Pearson correlations in each group assessed consistency across tasks employing the same items with similar or different control demands. For the Camel and Cactus tests, we used logistic regression and ratings (Jefferies & Lambon Ralph, 2006) to characterise the impact of (a) co-occurrence of the probe and the target (e.g., *how often are camels and cacti thought of together?*) and (b) the difficulty of rejecting the distractors in each group. Within each logistic regression, we included familiarity, task (words or pictures) and individual participant ID. Concept familiarity ratings for these items were available from a previous study (Garrard et al., 2001).

Logistic regression and McNemar tests were also used to examine the impact of phonological cueing on the Boston Naming Task (Kaplan et al., 1983) in the subset of SA patients

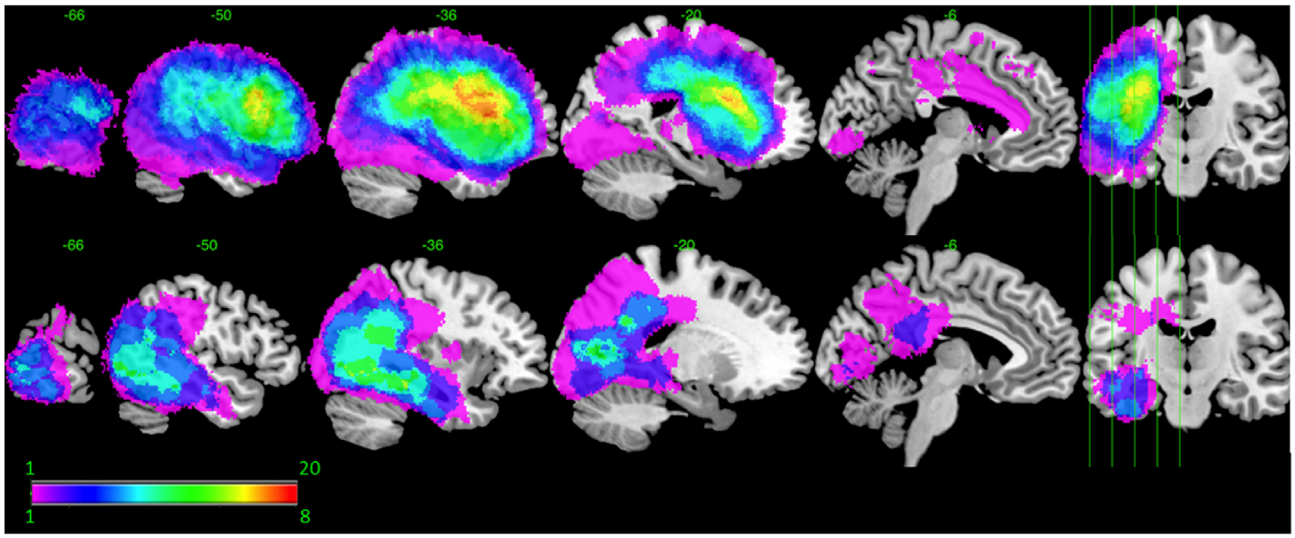

Fig. 1 – Lesion overlay for 20 PF+ patients (top row) and 8 TPC cases (bottom row).

(4 TPC and 6 PF+). Logistic regression included the variables: cueing condition, group (TPC, PF+), patient ID and the interactive term (group by cueing condition).

We assessed frequency effects in the 96-item synonym judgement task (Jefferies et al., 2009) using ANOVA. Concept familiarity ratings were also available for target items within the Cambridge Semantic Battery (Bozeat et al., 2000). Logistic regression was used to assess the effect of this variable on performance, with group, familiarity, participant, task and the familiarity by group interaction included in the model.

Finally, ANOVA and t-tests examined the impact of semantic control demands in a subset of patients where data was available. For the semantic distance task (Noonan et al., 2010), 10 PF+ and 6 TPC patients were compared with 7 SD patients. For the ambiguity task (Noonan et al., 2010), data was available for 21 PF+ and 7 TPC patients. For the alternative object use task (Corbett et al., 2011), there were 18 PF+ and 6 TPC cases. To assess whether the effect of control was equivalent across modalities and tasks in PF+ versus TPC patients, we used omnibus ANOVA to compare semantic distance, ambiguity and alternative object use tasks.

2.5. *Data availability*

The conditions of our ethics approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the lead author or the ethics committee at the Department of Psychology, University of York. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Access will be granted when this is possible under the terms of the GDPR.

3. Results

No part of the study analysis was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

3.1. *Non-semantic tasks*

Both SA groups were more impaired than SD patients on non-semantic assessments requiring executive control, including cube analysis, backward digit span and Raven's coloured progressive matrices ($t > 2.4$; $p < .05$; statistical comparisons are provided in full in Supplementary Table 4). PF+ cases were consistently poorer than TPC cases on executive tasks involving verbal output – digit span and elevator counting – as well as on the Wisconsin card sorting test ($t > 2.5$; $p < .05$; see Supplementary Table 4). There were no differences in the magnitude of the impairment of PF+ and TPC cases as measured by Brixton spatial anticipation or Raven's coloured progressive matrices. These results confirm that there is a deficit of cognitive control in both SA groups beyond the semantic domain.

3.2. *Semantic tasks*

All patients showed impairment on the majority of verbal and non-verbal semantic tasks (Supplementary Table 2). These tasks are thought to have somewhat differing control demands. For example, the Camel and Cactus task involves retrieving weak associations and establishing from semantic information what might link two concepts together (and therefore what to focus on in the absence of an explicit goal for retrieval); this task is known to activate the semantic control network (e.g., Davey et al., 2015; Hallam et al., 2016). Identity matching tasks, such as word-picture matching, are often less impaired in SA cases with deregulated semantic retrieval, since the conceptual information that should be the focus of retrieval at a given point in time is specified by the task itself and does not depend on identifying a context in which concepts can co-occur (c.f., Thompson et al., 2017) – nevertheless, control was needed in the task presented here to select target concepts from a set of nine semantically-related distractors. Picture naming and semantic fluency tasks also have a requirement to generate an appropriate response

rather than simply recognising the target concept from a set of prescribed alternatives, and fluency tasks are considered to be especially demanding as they involve adopting an appropriate semantic search strategy and constraining a series of responses to avoid repetition (c.f., Rogers et al., 2015). Given this task analysis, both PF+ and TPC-only SA patients might be expected to show some degree of impairment across all of these assessments if they have deficient semantic control. If SA cases with both PF+ and TPC lesions are more sensitive to task demands than SD patients, they might also show more variation in performance across these assessments.

Patients in all three groups commonly made semantic errors and omissions on the picture naming task from the Cambridge semantic battery (see Supplementary Table 5), with no difference in accuracy between groups: $F(2,31) = 1.698$, $p = .200$. SD patients showed larger deficits in word-picture matching than both SA groups ($t \geq 2.540$; $p \leq .016$; Supplementary Table 6), potentially reflecting better performance on identity matching tasks in SA cases when the goal for retrieval is specified by the instructions (Thompson et al., 2017). Conversely, on the letter fluency task, the SD group showed significantly better performance than the PF+ group ($t = 6.087$; $p < .001$; Supplementary Table 6). SA patients with PF+ and TPC lesions showed equivalent impairment on verbal and non-verbal tests of semantic association, as well as on naming and word-picture matching.

Next, we assessed correlations between the comprehension tasks in each group. The SD patients ranged from mildly to more severely semantically impaired and showed substantial variation in test scores. Previous studies have suggested that SD patients' deficits reflect degradation of heteromodal conceptual knowledge, explaining why they show strong correlations between tasks with different demands that probe the same concepts (Bozeat et al., 2000; Jefferies & Lambon Ralph, 2006). In contrast, if SA patients' difficulties following PF+ and/or TPC lesions reflect poor semantic control, they should show correlations between tasks with similar control requirements but also a heightened sensitivity to task demands even when the same concepts are presented, and potentially ceiling effects on tests which do not have substantial control demands that align with the control impairment. This pattern was observed: SD patients showed significant correlations between all pairwise combinations of tasks ($r > .78$, $p < .001$), while both SA groups showed stronger correlations between word and picture versions of the Camel and Cactus test (i.e., within-task comparisons; $r > .82$, $p < .001$), and fewer and weaker correlations between association and identity matching tasks (i.e., between-task comparisons; see Fig. 2; full details are in Supplementary Table 7). Fisher r-to-z transformation (Fisher, 1915) confirmed that between-task correlations (comparing word-picture matching with the word and picture versions of the Camel and Cactus test) were weaker for both SA groups than the SD group ($z > 2.28$, $p < .005$); however, within-task correlations were equivalent across these groups. There were no differences between the strength of correlations between PF+ and TPC cases on any comparison, with the exception of letter and category fluency ($z = 3.05$, $p = .002$). The reduced range of scores on the word-picture matching task in both SA groups reflects the number of patients who were at or near ceiling on this assessment, despite relatively poor performance on the Camel and Cactus test. While this pattern is consistent with the proposal that identity matching tests are relatively impervious to semantic control processes (since the information that needs to be retrieved is well-specified by the task; Thompson et al., 2017), it should also be noted that the correlations we report here are reduced in magnitude for both SA groups for this reason.

3.3. *Factors which affect performance on tests of semantic association*

The next analysis examined the impact of several ratings of difficulty on Camel and Cactus performance, including (i) co-occurrence of the probe and target and (ii) ease of rejecting the distractor. Logistic regressions compared pairs of groups and also examined each group separately (Table 1). Both SA and SD patients were sensitive to the frequency of co-occurrence of the probe and target concepts (showing higher performance when the probe and target were strongly associated), even when item familiarity was included in the model. This measure of long-term associative strength was larger in the SD than in PF+ cases, suggesting representations of frequently-occurring associations are more robust in the face of semantic degradation (Jefferies et al., 2020). Only SA groups showed a significant impact of distractor strength on performance and both SA groups were more impacted by distractor strength than SD cases. There were no group interactions for PF+ and TPC cases, suggesting the two SA groups responded equivalently to these variables.

3.4. *The impact of familiarity and word frequency*

Effects of item familiarity were examined using logistic regression for the tasks in the Cambridge Semantic Battery (see Supplementary Table 8). Familiarity was a significant predictor of accuracy for SD cases (Wald = 19.875, $p < .001$), but not for either group of SA patients (Wald $\leq$ 1.386, $p \geq .239$). There was a significant interaction between familiarity and group for PF+ and SD cases (Wald = 18.744, $p < .001$), although this effect did not reach significance for the comparison of TPC and SD (Wald = 1.685, $p = .194$). The PF+ cases were also less sensitive to familiarity than the TPC cases (Wald = 3.903, $p = .048$).

There was a similar pattern in a synonym judgement task which manipulated word frequency. Overall, there was a main effect of frequency: $F(1,35) = 46.390$, $p < .001$, group: $F(2,35) = 3.994$, $p = .027$, and an interaction: $F(2,35) = 19.916$, $p < .001$. In paired group comparisons, there was a significant frequency and group interaction for PF+ and SD patients [$F(1,29) = 35.507$, $p < .001$], and TPC and SD patients [$F(1,16) = 14.520$, $p = .002$]. However, there were no differences between the two SA groups [TPC and PF+ patients: $F(1,25) = 2.090$, $p = .161$], see Fig. 3.

3.5. *Effects of cues in picture naming*

The two SA groups were tested on a cued naming paradigm to assess whether they could retrieve more concept names when

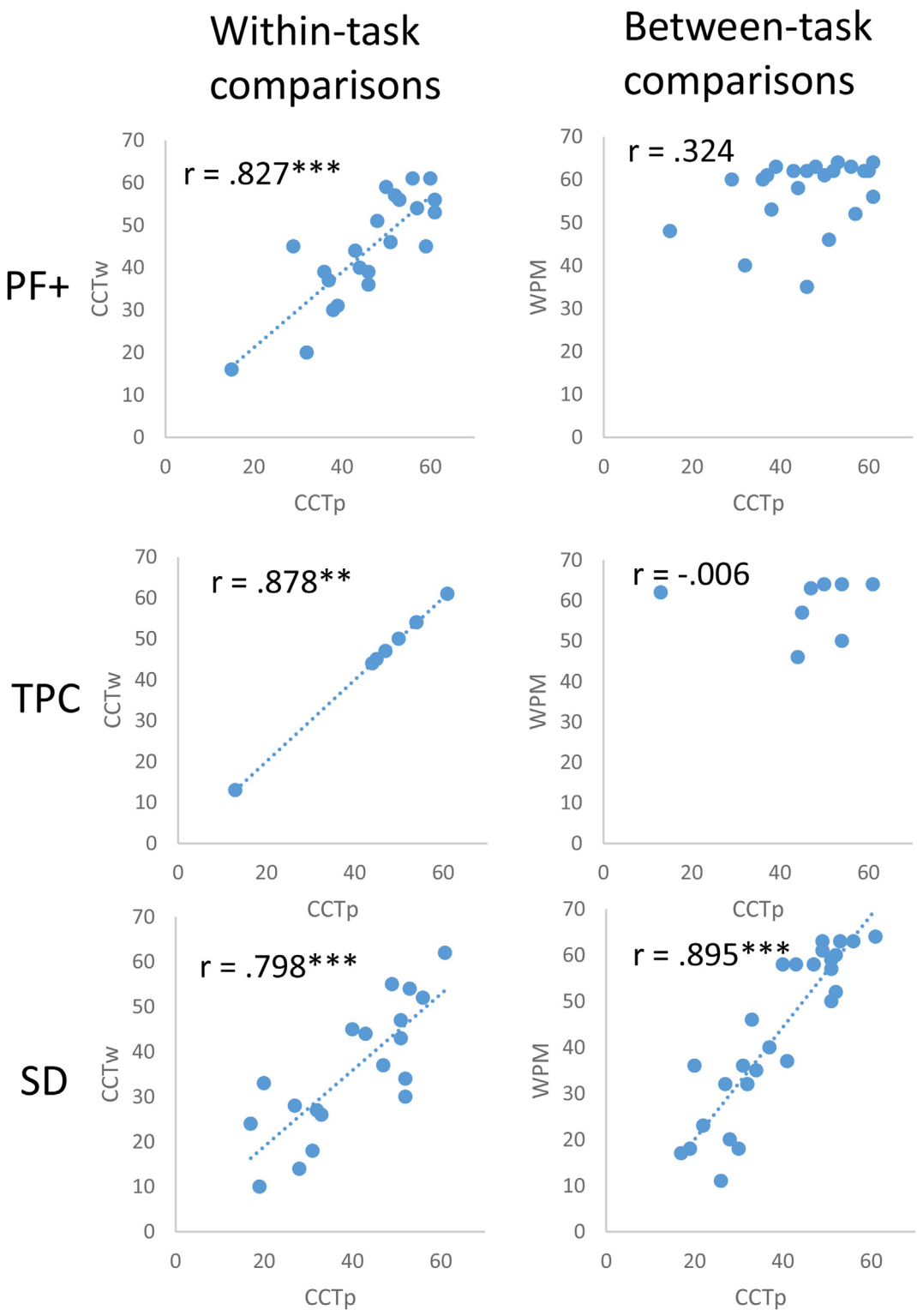

Fig. 2 – Correlations between and within tasks per group. CCTp = picture Camel and Cactus test; CCTw = word Camel and Cactus test; WPM = word-picture matching.

retrieval was constrained (Fig. 4). McNemar tests revealed that all individual SA patients showed significant positive effects of cueing ($p \leq .031$). Logistic regression revealed a cue effect (Wald = 84.469, $p < .001$), which did not interact with group (Wald < 1), indicating that PF+ and TPC cases benefited equivalently from cues. There was higher performance in the TPC group overall (Wald = 29.141, $p < .001$) and an effect of patient ID (Wald = 168.237, $p < .001$).

Table 1 – Factors affecting performance on the Camel and Cactus test of semantic association.

Variables in the model	PF+	TPC	SD	PF+ and SD	TPC and SD	PF+ and TPC
Co-occurrence probe-target	15.8***	12.4***	20.2***	26.7***	23.3***	13.4***
Rejecting distractor	40.4***	18.9***	n.s.	n.s.	n.s.	19.0***
Familiarity	n.s.	n.s.	10.0**	3.7~	7.0**	n.s.
Participant	351.8***	119.3***	192.6***	542.5***	302.8***	467.9***
Task	6.2	7.9**	16.7***	18.3***	n.s.	n.s.
Group	–	–	–	10.0**	9.5**	n.s.
Group*co-occurrence	–	–	–	5.2*	n.s.	n.s.
Group*distractor	–	–	–	16.9***	14.2***	n.s.

Numbers are Wald values. * = $p < .05$; ** = $p < .01$; *** = $p < .001$, ~ = $p < .1$. Participant = the individual participant ID. Task = CCT word or CCT pictures.

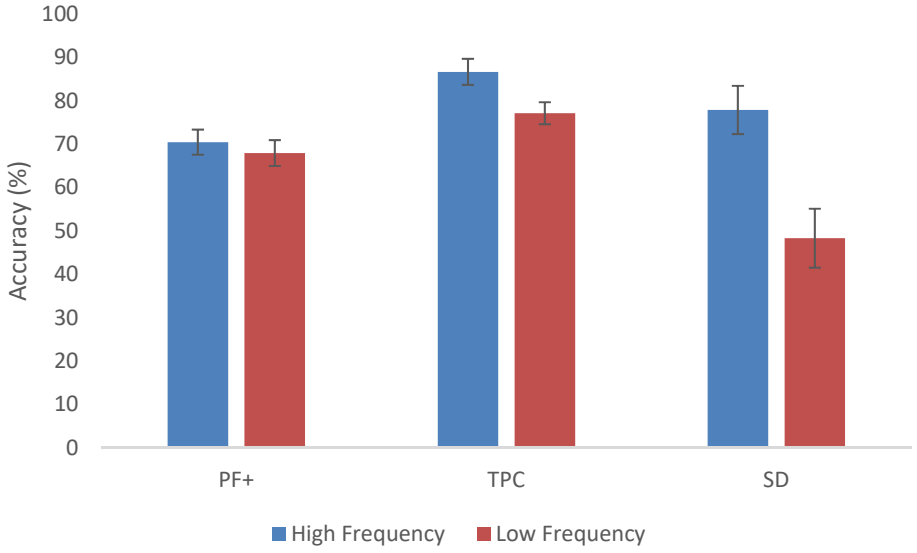

Fig. 3 – The impact of frequency on accuracy across groups. Error bars show standard error of mean.

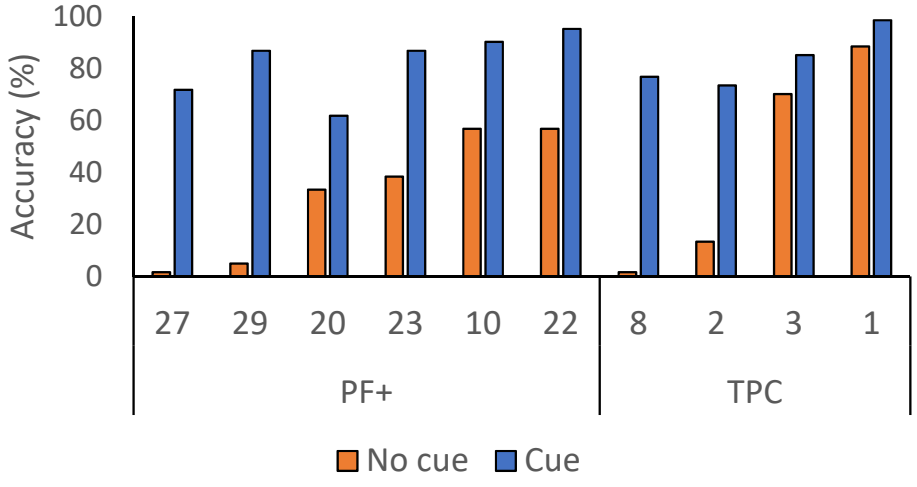

Fig. 4 – The impact of cueing on picture naming.

3.6. Manipulations of semantic control

3.6.1. Semantic distance

When assessing all patients (SD, PF+ and TPC), there were main effects of semantic distance: $F(1,20) = 55.686$, $p < .001$; group: $F(2,20) = 3.523$, $p = .049$; and a marginal interaction: $F(2,20) = 3.478$, $p = .051$; shown in Fig. 5. Both SA groups showed larger effects of semantic distance than the SD cases: there was an interaction between group and distance for PF+ and SD cases: $F(1,15) = 6.325$, $p = .024$, as well as for TPC and SD cases: $F(1,11) = 5.803$, $p = .035$. There was no interaction between PF+ and TPC cases: $F < 1$.

3.6.2. Semantic ambiguity

The remaining semantic control tasks were only tested on PF+ and TPC groups. ANOVA revealed a main effect of semantic ambiguity: $F(1,26) = 93.737$, $p < .001$. There was a marginal effect of group: $F(1,26) = 3.378$, $p = .078$, but no interaction ($F < 1$). PF+ and TPC cases were equally impaired at retrieving the subordinate meanings of ambiguous words (see Fig. 6).

3.6.3. Alternative object use task

We examined the ability of PF+ and TPC cases to identify non-canonical as well as canonical uses of objects, to establish if both groups of SA cases had equivalent semantic control deficits in a non-verbal task. ANOVA revealed a main effect of canonicity [$F(1,22) = 108.512$, $p < .001$], but no effect of group ($F < 1$) or interaction ($F < 1$), showing that PF+ and TPC patients were equally impaired at non-canonical object use (see Fig. 6).

We compared the verbal and non-verbal manipulations of semantic control demands (object use, ambiguous words, semantic distance) in SA subgroups using an omnibus ANOVA. There was a significant main effect of control demands [$F(1,12) = 104.220$, $p < .001$] but no interaction with group ($F < 1$) or main effect of group [$F(1,12) = 2.994$, $p = .109$]. There was additionally a main effect of task [$F(1,12) = 91.942$, $p < .001$], and an interaction of task and control demands [$F(1,12) = 15.385$, $p = .002$], but no interaction of task and group ($F < 1$), or three way interaction ($F < 1$). Consequently, PF+ and TPC cases showed equivalent verbal and non-verbal deficits.

3.7. Category effects

Finally, we asked if TPC cases show category-specific semantic deficits for tools, since fMRI studies have shown category-selective responses in TPC (Beauchamp & Martin, 2007; Kalénine et al., 2009). Contrary to this hypothesis, TPC patients performed significantly better than PF+ and SD cases on tools (see Supplementary Analysis 2 for further details).

4. Discussion

We asked whether SA patients with damage restricted to left temporoparietal cortex (TPC cases) show controlled retrieval deficits that are equivalent to those seen in individuals with damage to left prefrontal cortex (PF+ cases), or instead show hallmarks of semantic degradation similar to patients with SD. Since previous studies of SA included very few TPC cases, this novel neuropsychological comparison addresses key debates about the contribution of temporoparietal regions to semantic cognition. We tested a key prediction of the Controlled Semantic Cognition framework (Lambon Ralph et al., 2017) – namely that individuals with lesions to posterior parts of the semantic control network will struggle to constrain semantic retrieval like people with SA following infarcts affecting left inferior frontal cortex, demonstrating that damage to LIFG is not necessary for semantic control deficits. We also tested alternative predictions that temporoparietal regions support verbal semantic access (Hickok & Poeppel, 2007; Turken & Dronkers, 2011) or specific aspects of semantic representation relevant to knowledge of events and tools (Binder & Desai, 2011; Martin, 2007). Finally, we compared the individuals with TPC lesions to SD patients, to establish whether multimodal semantic deficits following TPC lesions resemble the conceptual degradation seen following

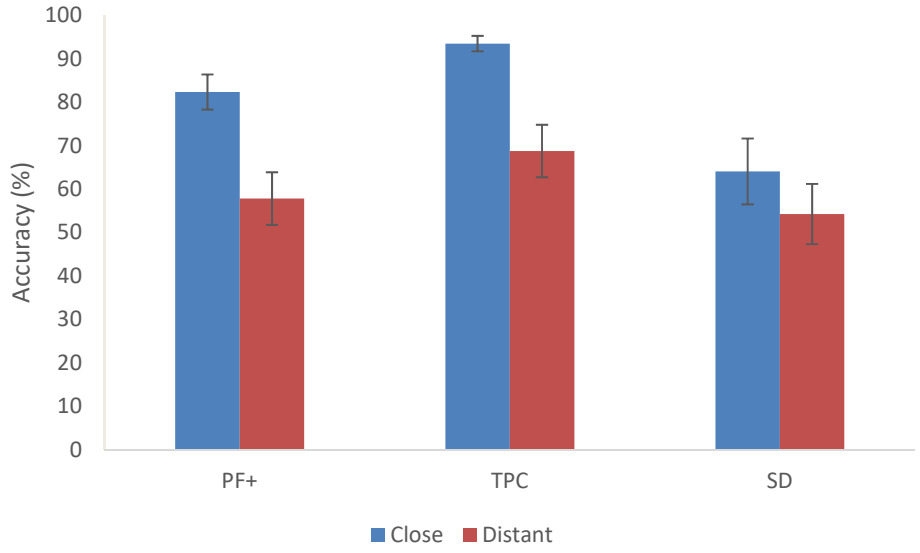

Fig. 5 – The impact of semantic distance on performance across groups. Error bars show standard error of mean.

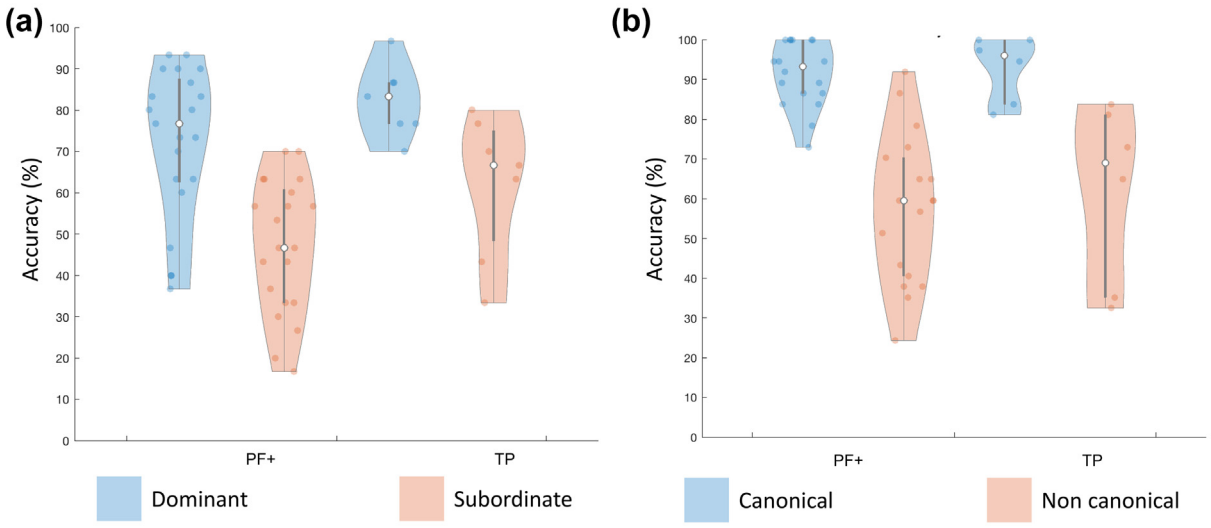

Fig. 6 – The impact of semantic control manipulations on (a) retrieval of dominant and subordinate meaning of ambiguous words, and (b) canonical and non-canonical use of objects. The white dot in these violin plots shows the median, with the line representing the interquartile range, and individual participants shown in red/blue dots, surrounded by kernel density.

anterior temporal cortex damage in SD, or the semantic control deficits associated with LIFG lesions. We observed striking similarity across the two SA groups, and common differences to the pattern observed in SD, consistent with a critical role for TPC in semantic control across modalities and tasks probing different types of knowledge. Our key findings are summarised below:

- PF+ and TPC cases had poorer cognitive control than SD cases. A relationship between executive functions and semantic performance in stroke aphasia has been found in previous studies (Schumacher et al., 2019), with SA patients showing correlations between executive and semantic deficits (Jefferies & Lambon Ralph, 2006; Thompson et al., 2018). PF+ cases had additional difficulties on tasks involving spoken output.
- While SD cases showed strong correlations between all semantic tasks consistent with conceptual degradation of a central semantic store (Bozeat et al., 2000), PF+ and TPC cases had fewer and weaker correlations between identity and association matching tasks, suggesting larger effects of task demands (Jefferies & Lambon Ralph, 2006). This pattern was linked to ceiling effects in both SA groups in the identity matching but not the association matching task; this might reflect the way that the target for conceptual retrieval is specified in the instructions during identity matching but must be established on the basis of weak meaning overlap in association matching (Thompson et al., 2017).
- SD cases were highly sensitive to word frequency and familiarity, in line with the expected pattern for semantic 'storage' deficits. PF+ cases were insensitive to these factors, as expected for patients with semantic 'access' deficits, while TPC cases were intermediate between these two groups. High frequency words have stronger representations, but they are also more semantically diverse – FIRE can mean losing your job, triggering a gun or a warming hearth (Hoffman, Jefferies, et al., 2011; Hoffman, Rogers, et al., 2011). This increases the requirement to select appropriate information, which may explain attenuated frequency effects in SA cases with PF+ lesions (Almaghyuli et al., 2012).
- Both PF+ and TPC cases were more affected than SD patients by manipulations of semantic control demands, showing larger effects of distractor strength in association matching and of semantic distance between probes and targets. This further demonstrates a neurocognitive dissociation between long-term semantic storage and controlled retrieval processes, in line with the Controlled Semantic Cognition framework (Lambon Ralph et al., 2017).
- PF+ and TPC cases showed equivalent effects of cueing in picture naming. Phonemic cues are thought to direct activation towards targets and away from potential competitors (Jefferies et al., 2008; Soni et al., 2009, 2011), benefitting patients with deficient semantic control who have difficulty constraining retrieval.
- TPC cases did not appear to show specific impairment of lexical access, or poorer knowledge of tools, actions or associations. Instead, PF+ and TPC patients showed common deficits of semantic control across verbal and non-verbal tasks. Both groups had equivalent difficulty retrieving less frequent interpretations of words and goals for action.

This pattern of results indicates that damage to either anterior or posterior nodes of the semantic control network is sufficient for the emergence of highly-similar deficits of semantic control. These sites may play a comparable role in constraining retrieval when weakly-represented aspects of knowledge need to be brought to the fore, in line with

functional meta-analyses and patterns of intrinsic connectivity in healthy participants that have revealed that LIFG is strongly co-activated with regions in left pMTG and pre-supplementary motor area (Gonzalez Alam et al., 2019; Jackson, 2021; Noonan et al., 2013; Wang et al., 2018).

Our conclusions are well-aligned with recent observations that the networks that underpin memory and cognitive control are highly distributed, in contrast to primary sensory-motor systems that are localised to a specific part of cortex (Margulies et al., 2016; Yeo et al., 2011). Recent perspectives on cortical organisation highlight the way in which transmodal regions of the brain (including semantic and cognitive regions) are located at a distance along the cortical mantle from primary systems (Margulies et al., 2016); the distributed nature of these networks may allow them to support representations that are not strongly influenced by any one sensory-motor code and to integrate information from different sources. The multiple-demand network, implicated in cognitive control across domains, shows a highly-distributed topographical organisation, including inferior frontal and intraparietal sulcus (Assem et al., 2020; Duncan, 2010); the default mode network implicated in memory similarly draws together frontal, parietal and temporal regions (Buckner et al., 2008; Smallwood et al., 2021; Spreng et al., 2013; Yeo et al., 2011). Moreover, the anterior and posterior nodes of the semantic control network are unique in showing positive connectivity with both multiple-demand regions (inferior frontal sulcus) and anterior temporal lobe regions associated with semantic memory, which are normally anti-correlated at rest (Davey et al., 2016). In a recent study, we found that the semantic control network was located in between multiple-demand and default mode regions linked to memory, both on the cortical surface and in terms of functional recruitment (Wang et al., 2020). Since the semantic control network is physically adjacent to default mode and multiple-demand regions in the left hemisphere, this network will also be distributed across frontal, parietal and temporal areas.

An unresolved issue in cognitive neuroscience concerns the extent to which the distributed nodes of large-scale networks are functionally dissociable. The connectivity patterns and functional tuning of individual cortical regions are likely to be dominated by areas that are adjacent to them: for this reason, anterior portions of the semantic control network might be expected to support tasks drawing strongly on complex motor codes (e.g., speech production), while posterior nodes might be more important for semantic control in visual and auditory paradigms. On the other hand, patterns of intrinsic connectivity within large-scale functional networks are maximally similar across the distant brain regions that comprise each network (Yeo et al., 2011). This might help to explain why PF+ and TPC cases were indistinguishable on the majority of semantic tasks we used, yet showed some differences in speech output tasks. These might reflect a more critical role for LIFG in controlling speech production (Noonan et al., 2013) or alternatively damage to motor speech regions in many PF+ patients (Halai et al., 2017). The distributed nature of higher-order cognition might also explain why lesion size and location are not always reliable predictors of cognitive deficits in stroke aphasia (Geranmayeh et al., 2016; Price et al., 2017; Seghier et al., 2016), although they could be more reliable predictors of sensory and motor deficits. Cognitive impairment should be associated with global network alteration, reflecting white matter disconnection, the proportion of network nodes that are damaged and individual differences in premorbid organisation, on top of lesion location and size.

There are some important limitations of the current study. Our PF+ and TPC cases had large lesions which likely extended across adjacent default mode, semantic control and multiple-demand cortex, making it difficult to separate the effects of these networks. Even though recent studies point to partial segregation of semantic control and multiple demand cortex (Gao et al., 2021; Gonzalez Alam et al., 2022; Wang et al., 2020), the spatial proximity of these networks in the left-hemisphere can explain the commonly-observed association between semantic and executive deficits in aphasia. Our results might also reflect disconnection of the anterior temporal lobe 'hub' from control regions within the multiple demand network. Future studies could potentially distinguish between the contribution of these networks to semantic cognition by comparing similar lesion groups in left and right hemisphere, since the multiple-demand and semantic ATL regions are largely bilateral, while the semantic control network is highly left-lateralised (Gonzalez Alam et al., 2019, 2022). In addition, it is highly likely that damage to one node of a network will have distributed effects through disrupted connectivity; for example, previous work has shown that anterior lesions can have behavioural impairments which directly relate to the functional disconnection of posterior regions within the same network (Kwon et al., 2017). Assessing patterns of structural and functional connectivity in PF+ and TPC patients would establish whether local damage to left frontal and posterior temporal cortex is always sufficient for deficient semantic control or whether these behavioural deficits reflect disconnection of the broader network. In a recent study, we found that semantic impairment in SA was correlated with structural disconnection within the left hemisphere semantic control network, while executive impairment on a non-semantic task was correlated with cross-hemispheric disconnection (Souter et al., 2022). This might reflect the highly lateralised nature of the semantic control network, contrasting with the bilateral nature of multiple-demand cortex; however, there were insufficient TPC cases in this study to permit lesion-symptom mapping for these cases specifically. In sum, while the importance of connectivity is consistent with our hypothesis that controlled semantic cognition draws on a distributed network including left prefrontal and posterior temporal cortex, it remains unclear whether TPC lesions necessarily cause this profile of impairment.

Multimodal semantic deficits were more commonly observed following PF+ than TPC lesions in this study – yet if all nodes of the semantic control network are equally important, it is unclear why this pattern would be observed. Further research could examine patients specifically selected to show damage to anterior and posterior components of the semantic control network, irrespective of their neuropsychological deficits – it would then be possible to properly quantify the likelihood of semantic control deficits in these lesion groups. In addition, while we did not observe selective semantic deficits for tools, action understanding or semantic associations

and events in this sample of TPC patients, we cannot rule out category or task-based dissociations within TPC more generally (for example, within more specific regions), given the prevalence of category sensitivity in these regions in fMRI studies (Beauchamp & Martin, 2007; Kalénine et al., 2009; Martin, 2007). Finally, the prefrontal SA patients often had phonological deficits which would have contributed to their poorer performance on naming tasks, which might have accounted for stronger correlations between category and letter fluency, and significantly lower performance for letter fluency than in the other two groups (Baldo et al., 2010). It is not possible to rule out the hypothesis that a lower level dysfunction, such as impaired lexical access or phonological retrieval, or damage to the link between semantic and lexical representations (Schwartz et al., 2009) contributed to some of the patterns in the PF+ group, such as improved naming following cueing (however, see McCall et al., 2021, for a recent exploration of this hypothesis).

In conclusion, we confirm, for the first time, that the semantic impairment in patients with SA following TPC lesions resembles that in PF+ cases and is distinct from SD patients with degraded knowledge. TPC cases were impaired at regulating their semantic knowledge in a task-appropriate fashion – to the same extent as patients with prefrontal lesions.

Credit author statement

Hannah E. Thompson: Formal analysis Investigation Data curation Roles/Writing - original draft Writing - review & editing. **Krist A. Noonan**: Formal analysis Roles/Writing - original draft Investigation. **Ajay D. Halai**: Formal analysis Writing - review & editing Investigation Visualization. **Paul Hoffman**: Writing - review & editing Investigation. **Sara Stampacchia**: Writing - review & editing Investigation. **Glyn Hallam**: Writing - review & editing Investigation. **Grace E Rice**: Investigation. **Blanca De Dios Perez**: Investigation. **Matthew A. Lambon Ralph**: Conceptualization Funding acquisition Supervision Writing - review & editing. **Elizabeth Jefferies**: Conceptualization Funding acquisition Supervision Project administration Writing - review & editing.

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Declaration of competing interest

The authors report no competing interests.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2022.05.022.

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