Consistently inconsistent: Multimodal episodic deficits in Semantic Aphasia

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Running head: Inconsistent episodic memory retrieval in SA

Abstract

 Semantic Aphasia (SA) patients have difficulty accessing semantic knowledge in both verbal and non-verbal tasks appropriately for the current context. Automatically activated semantic knowledge overwhelms the system, because it is no longer able to inhibit interference from dominant meanings in order to select weaker alternatives. Episodic memory, like semantic memory, requires control to select relevant memories amongst competing episodes. For example, our memory for what we ate for breakfast last Saturday is affected by competition from numerous other breakfast meals eaten on other days. Where one is unable to guide retrieval, we may rely on automatically activated knowledge about “breakfast foods”, and therefore experience false memories. Brain systems that support semantic control are also implicated in episodic control, and therefore deficits in semantic control are likely to cause more widespread problems. Despite this, nearly all research to date focuses on semantic performance alone. This study explored the impact of this semantic impairment on episodic recall. We used a verbal and non-verbal episodic memory task: participants remembered nursery rhymes in the verbal condition and logos and their associated products in the visual condition (e.g. bowl of cereal and coco-pops*).* For both tasks, we manipulated a) congruency with pre-existing knowledge (e.g. expectancy of trials: baa baa black build– instead of sheep) and b) whether these trial types were blocked by congruency or mixed, as well as (c) distractor strength. If SA patients experience overwhelming automatic activation, they should find incongruent items more difficult to suppress, particularly when presented in an unpredictable task format. A total of 13 SA patients were compared to 33 controls across three experiments. In line with our predictions, SA patients found it more difficult to retrieve episodic memories which were in conflict with pre-existing semantic knowledge. This was true across modalities. Moreover, these deficits were accentuated when the congruency was presented in a mixed fashion, and so unpredictable across trials. Evidence of these episodic control impairments in SA cases supports the idea of a shared mechanism for semantic and episodic memory control.

Key words: episodic memory, semantic memory, controlled retrieval, stroke aphasia.

1. Introduction

Neuropsychological research has pointed to separable processes within the semantic system, and across memory systems. Patients with Semantic Dementia (SD) have degeneration of the database of knowledge across modalities, displaying poor comprehension in a wide range of semantic tasks (Hodges, Patterson, Oxbury, & Funnell, 1992). This is seen alongside relatively intact episodic memory, suggesting discrete memory processes that can function semi-independently of semantic knowledge (Graham, Simons, Pratt, Patterson, & Hodges, 2000; Hodges & Graham, 2001). These patients typically present with progressive atrophy within the interior and lateral anterior temporal lobes (Mummery et al., 2000). In contrast, episodic storage impairments are evident in anterograde amnesia, and thought to be caused by damage to the hippocampus and surrounding temporal lobes (Gilboa et al., 2006). Patients with damage to these regions have relatively normal semantic performance (Schmolck, Kensinger, Corkin, & Squire, 2002), which previously has been interpreted as suggesting the two memory systems are at least partially dissociable. However more recent work has provided evidence that counters this view. A meta-analysis by Eikelboom et al. (2018) discusses the presence of a widely distributed network underlying episodic memory, which spans beyond hippocampus and medial temporal lobe. Moreover, there are significant episodic memory deficits in patients with semantic variant primary progressive aphasia and these deficits can be explained by disrupted frontal and parietal regions rather than hippocampal damage (Irish et al., 2016; Win et al., 2017).

Semantic Aphasia (SA), a condition first described by Head (1926) and then adapted by Jefferies & Lambon Ralph, (2006), describes patients who display deregulated semantic cognition that does not affect knowledge, but instead leads to impairments of controlling semantic *access* following a left hemisphere stroke*.* These impairments manifest as a difficulty in manipulating retrieval mechanisms in order to appropriately respond to tasks. Performance is inconsistent across tasks, dependent not on the items themselves but rather on the level of control required (Jefferies & Lambon Ralph, 2006). There are a number of key characteristics found in SA. (a) Patients have difficulties inhibiting highly relevant but inappropriate information for the current task. Research suggests patients can be easily cued or miscued when words have multiple meanings. For example the sentence “the bank was slippery*”* can impair their capacity to retrieve the meaning of bank as a financial institution (Corbett, Jefferies, & Lambon Ralph, 2011; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010). This is in contrast to automatic semantic retrieval (such as the retrieval of fork from the semantic cue knife), which does not rely on semantic control (Hallam, Whitney, Hymers, Gouws, & Jefferies, 2016; Hoffman, Jefferies, & Lambon Ralph, 2010; Whitney, Kirk, O’Sullivan, Lambon Ralph, & Jefferies, 2011; Whitney et al., 2011). (b) Patients have difficulty selecting amongst competing items, such as a target and strongly related distractors (Saygın et al., 2003). For example, in synonym judgement tasks, SA patients find it difficult to select slice as a synonym of piece, when cake is presented as a distractor (Noonan et al., 2010). (c) Patients have difficulty maintaining focus towards the goal of a task, particularly if this goal changes during the task. For example in a refractory paradigm, the same items are presented repeatedly, but as the goal of the task changes the target is switched. Typically patients with prefrontal lesions display good performance initially and decline over time, when it is necessary to apply the current goal to select the target and overcome competition from previously selected items (Gardner et al., 2012; Thompson et al., 2015). (d) Patients deficits occur across modalities, with parallel deficits occurring in both verbal and non-verbal tasks, such as picture, sound and action understanding (Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009; Gardner et al., 2012). (e) Patients show highly inconsistent performance, where performance is driven by the task demands rather than the item itself (Jefferies & Lambon Ralph, 2006). Performance may be higher when distractors are weaker, or where items have been constrained by contextual cues, reflecting deficits in retrieval rather than storage of information.

Patients with SA typically have damage to left prefrontal and/or temporo-parietal regions (Jefferies & Lambon Ralph, 2006; Jefferies, Patterson, Jones, & Lambon Ralph, 2009; Jefferies, Patterson, & Lambon Ralph, 2008; Rogers, Patterson, Jefferies, & Ralph, 2015). The left temporo-parietal-occipital (TPO) regions were documented in a case of semantic aphasia by Lurii︠a︡, (1987) and this was later confirmed utilising contemporary neuroscientific methods such as in a review by Dragoy, Akinina, & Dronkers, (2017). In fMRI literature, these regions have been highlighted as important for semantic control. Regions in the frontal, temporal and parietal cortices are activated when engaging in semantically demanding tasks (Visser, Jefferies, & Lambon Ralph, 2009), as well as areas in the left PFC and temporo-parietal regions showing sensitivity to the control demands of semantic tasks (Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997; Wagner, Maril, Bjork, & Schacter, 2001) and the storage of semantic information (Binder, Desai, Graves, & Conant, 2009; Hodges et al., 1992; Patterson et al., 2007; Whitney et al., 2011). Additionally, a meta- analysis by Noonan, Jefferies, Visser, & Lambon Ralph (2013) implicates the left inferior frontal gyrus (LIFG; Brodmanns areas 44, 45, and 47) as a key site in semantic control. This region activates in fMRI studies when context cues are insufficient to elicit activation of target knowledge and additionally, it is important when multiple items are retrieved from memory but only a subset are appropriate for post-retrieval selection (Thompson, Robson, Lambon Ralph, & Jefferies, 2015). This bottom up selection is needed to resolve competition amongst numerous retrieved representations, when previously learned associations automatically elicits retrieval of information that competes with current retrieval task (Anderson & Neely, 1996; Nyhus & Badre, 2015; Postman & Underwood, 1973).

Furthermore, although rarely studied within the same paradigm, the neuroimaging literature of controlled retrieval in episodic tasks suggests a highly overlapping network (see Figure 1). These tasks require recall of episodic memories, which are specific to a place or time and not held in our short or working memory (Schacter, Addis, & Buckner, 2007). Regions such as the left inferior frontal gyrus (LIFG) have been shown to be critical in semantic retrieval, for instance when recalling weakly rather than strongly encoded memories (Hayes, Buchler, Stokes, Kragel, and Cabeza, 2011), however, they are also engaged in controlling episodic retrieval (Barredo, Öztekin, & Badre, 2013). Wimber, Rutschmann, Greenlee, & Bäuml, (2008) demonstrated that the LIFG was activated during retrieval tasks where inhibitory mechanisms, used to prevent interference from strongly associated competitors, were controlling episodic retrieval and resolving inferences from competing sources. The anterior LIFG lies outside the ‘multiple demand cortex’ and appears to support control of memory, suggesting a shared mechanism for episodic and semantic control. Damage to these regions in SA patients may lead to difficulties in episodic as well as semantic control.

The effect of semantic deficits on episodic performance has been rarely studied, and the potential shared role of control in these two systems understudied. Only two studies to our knowledge have focussed on episodic memory functioning in patients with SA (Stampacchia et al., 2019, 2018). Stampacchia and colleagues reported that SA patients have episodic memory deficits when a) the learnt material is not supported by existing knowledge, b) there is competition from distractors, and c) retrieval is not supported by contextual cues. This suggests that parallel deficits can occur and supports the hypothesis that there are common control processes for episodic and semantic memory retrieval. These deficits were found in both verbal and non-verbal tasks in both semantic and episodic domains, although, these studies did not explore whether some of the common traits of SA, like inconsistent performance, are found in the episodic domain. Additionally, contrary to the exploration of SA in semantic memory, there was a difference in performance of verbal and non-verbal tasks, with the effect strongest in the verbal conditions. This is somewhat surprising, given their matched performance in the semantic domain. Stampacchia et al. (2018) suggest it may be the nature of stimuli (being concrete exemplars of an item) leading to more superficial visual matching rather than deeper semantic processing. The current study aims to explore this further.

1. Overlap of Semantic and episodic networks (b) Lesion overlap mask

 *Figure 1.* (a) Overlap of semantic control network and episodic network reproduced with kind permission from Stampacchia et al. (2018). Semantic control network map was produced utilising Activation Likelihood Estimation technique in a meta-analysis by Noonan et al. (2013) and episodic network maps were produced utilising Neurosynth software (<https://neurosynth.org/>). Both overlap masks were created using MRIcroGL. For more detailed information please see original papers. Areas of overlap include a cluster which corresponds to mid-to-post LIFG extending to middle frontal gyrus. (b) Lesion overlap mask across 7 patients scanned. Colour bar indicates amount of overlap from 1 to 7 patients.

 This present study will examine whether SA patients are influenced by pre-existing knowledge when performing an episodic memory task. We manipulated four variables: (1) modality, predicting the same pattern of performance in verbal and non-verbal domains as seen in the semantic domain, (2) distractor strength, predicting degraded performance on high competition trials, (3) expectedness of rhymes (whether or not items are congruent with pre-existing – or expected – knowledge), predicting patients will be more accurate on trials which are congruent with pre-existing knowledge, and (4) whether these items are presented in a blocked or mixed condition. We predicted that patients will be worse when they cannot rely on the task to cue the retrieval demands. Finally, because items were repeated across tasks (blocked vs. mixed) we were able to assess (5) consistency. We expected to see inconsistency between trials on an item-by-item basis. Theses variables have been shown to impact SA patients within the semantic domain, but it is unclear whether the deficits will be paralleled in the episodic domain. Results supporting these predictions would not only provide support for an overlap in the mechanisms used in semantic and episodic retrieval, but also provide novel contributions to the nature of deficit in SA.

2. Participants

2.1. Patients

 Thirteen aphasic stroke patients [nine male, four female; M (SD): age= 61.5(8.58); age left education= 19.4(3.44)] with semantic aphasia from a left-hemisphere cerebrovascular accident (CVA) were recruited via support groups in Surrey, West Sussex and North Yorkshire (UK). All patients had chronic impairments from a CVA happened at least a year previously and – on the basis of their aphasic symptomatology – they could be classified as follows: three global, one Wernicke’s, two Anomia, two transcortical sensory, one Broca’s, two conduction, one motor and one mixed transcortical, (see Supplementary Table S1 and S2).There were 10 patients in Experiment 1, nine in Experiment 2 and eight in Experiment 3. Patients were recruited in line with the inclusion criteria for Semantic Aphasia proposed by Jefferies & Lambon Ralph, (2006) i.e. patients were selected to show difficulties accessing semantic knowledge in both verbal and non-verbal tasks.

We previously found that such multimodal semantic deficits in stroke aphasia reflect difficulties with controlled access to semantic information (Corbett, et al., 2009a; Corbett et al., 2011; Gardner et al., 2012; Noonan et al., 2010; Thompson et al., 2015, Stampacchia et al., 2018,2019), and this pattern was reproduced in this sample (see Background Neuropsychological Testing Table S2). All the patients showed greater difficulty on semantic tasks when control demands were high. In line with our previous results, we expected patients to show (i) a strong influence of word ambiguity, with poorer performance for subordinate meanings (assessed using the Ambiguity task below); (ii) strong effects of cueing and miscuing (in the Ambiguity task); (iii) poor inhibition of strong competitors (assessed using the Synonym judgment task with distractors); (iv) difficulty accessing non- canonical functions and uses of objects (assessed using the Object Use task). We also expected inconsistent performance at the group level e on semantic tasks probing the same concepts with different control demands (assessed using the Cambridge semantic battery).2.2. Lesion analysis

 We manually defined abnormal brain tissue utilising T1, T2 and FLAIR MRI images for each available patient that met the scanning criteria (7 of 13 patients; Fiez, Damasio, & Grabowski, 2000; Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). We aligned each modality in subject space, and performed lesion tracing using an image segmentation tool developed in collaboration with Imperial College London (ImSeg). When in doubt, brain tissue was visually compared between patients and controls.T1 images from each patient were pre-processed using the FMRI Expert Analysis tool (FEAT Version 6.00) from the FMRIB Software Library (FSL; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). We performed brain extraction to remove non-brain tissue (BET; Smith, 2002). When required, BET parameters were manually adjusted to ensure that brain extraction was optimal and only removed non-brain tissue. This was followed by normalising T1 and brain lesion masks to Montreal Neurological Institute (MNI) 152 standard space using FMRIB Linear Image Registration tool (FLIRT). Lesion masks from all patients were combined and Mango viewing software was used to identify areas of overlap as shown in Figure 1. The lesion overlap for the patient group centred within the left temporal lobe, with severe damage in six out of seven patients to area in the IFG (BA 44 & 45) and partial damage in four patients across the middle and pre-central gyrus (BA 9, 10, 46, 4 & 6). Six patients also had severe damage to superior portions of the temporal lobe (BA 38 & 41) with five patients displaying at least some damage to brain regions commonly known as Wernicke’s area (BA 21 & 22). The insula was damage in all patients (BA 13) however the lesions were often extensive and 1-2 patients showed damage in areas extending into the basal ganglia as well as some damage to the middle occipital gyrus (although vision was not impaired; Supplementary Table S3).

2.3. Controls

Healthy controls were recruited from the general population via an advertisement [17 males, 16 females; M (SD): age = 64.06 (10.64); age left education = 19.14 (2.78)]. 10 took part in Experiment 1, and seven of these took part in Experiment 2, with an additional four recruited for this Experiment. Experiment 3 recruited 19 new participants. For each experiment groups were statistically matched to ensure there were no age, gender or education differences between patients and controls (t<1). All controls had normal results in the mini mental state exam (MMSE; Folstein, Robins, & Helzer, 1983).

2.4. Open access and declarations

Public archiving of brain data was not possible due to consent restrictions, therefore researchers who wish to access this data should contact the corresponding author and all data to replicate results will be released, when this is possible under the terms of GDPR (General Data Protection Regulation EU 2016/2017) and subject to approval from the Research Ethics and Committee of the University of Surrey. Behavioural data is provided in the Open Science Framework (OSF; <https://osf.io/cxubp/>). Digital materials where possible are also available in the OSF (<https://osf.io/6s7fg/>) and any that are inaccessible due to the programme used can be released by contacting the corresponding author. The background neuropsychological materials are not provided on OSF since these included published and copyrighted tests, and because they were administrated as ‘paper and pencil tests’. Researchers who wish to access these materials should contact the corresponding author. The study procedures and analyses were not pre-registered prior to the research; all manipulation and measure of this study are reported in the following sections.

1. Background neuropsychological tasks

Patients were tested on as many of the background neuropsychological tasks as they were able to complete. In some instances, due to verbal fluency, patients may have been unable to complete tasks and these were abandoned.

3.1. Language, Executive and Working Memory Tasks

 Data for individual patients are shown in Supplementary Table S2. Two language tasks were conducted. (1) Word repetition (PALPA9; Kay, Lesser, & Coltheart, 1996) with nine of the 12 patients tested displayed impairments with three achieving above the threshold for severe impairment. (2) The ‘cookie theft’ scene description task (Goodglass & Kaplan, 1972) revealed non-fluent speech for three out of 10 patients. In line with previous studies showing that deregulated semantic cognition is associated with executive dysfunction (Jefferies & Lambon Ralph, 2006; Noonan et al., 2010; Stampacchia et al., 2018; Thompson et al., 2018), the majority of patients were impaired on at least one of the tasks used: Ravens Coloured Progressive Matrices (Raven, 1962) and Trail Making Test (Reitan, 1958). Working memory was assessed verbally using forward digit span (Wechsler, 1945) with eight of the 10 patients tested being below the normal cut off, and visually using the Symbol Span task where five of the seven patients tested were impaired. The Brief Cognitive Status Exam (BSCE) was also completed that assesses Orientation, Time Estimation, Mental Control, Organisation, Recall, Inhibitory Control and Verbal production. Eight of the nine patients tested were below average.

3.2. Semantic tasks

Firstly, four shortened semantic tasks were selected, from the Cambridge Semantic Memory Test Battery (Bozeat, Ralph, Patterson, Garrard, & Hodges, 2000) as well as other tasks: (1) the 25 items Camel and Cactus test assesses semantic association for both pictures and words. (2) The 16-item picture naming task was conducted (from the Cambridge Semantic Battery; Bozeat et al., 2000) and (3) the 16 item word-picture matching, a subset from the CAT (Howard, Swinburn, & Porter, 2010). (4) Category and Letter fluency tasks were completed to assess fluency, with seven of the 11 patients tested displaying impairments across these tasks, and the remaining four displaying impairments in only the letter fluency task. Additionally the 96-item synonym judgement task was completed (Jefferies et al., 2009) with seven of the nine patients tested displaying impairments in this task.

Pairwise correlations between all semantic tasks revealed a lack of correlation across tasks that required different control demands, which replicates findings in previous studies (p ≥ .13; Jefferies & Lambon Ralph, 2006; Stampacchia et al., 2018). The only significant correlations were between category and letter fluency (r = .50, p = .018) and the word and picture association judgements which probe the same association in different modalities (see above).

3.3. Episodic Tasks.

Episodic tasks were selected from the Wechsler Memory Scale (Wechsler, 1945) and are briefly described below. All patients showed some impairments on at least one element of this battery. (1) Verbal Paired Associates I and Verbal Paired Associates II tasks assess verbal memory for word pairs for immediate and delayed recall respectively, the Verbal Paired recognition task tests recognition for the same word-pairs. The majority of patients were impaired on the more difficult elements of the task (recall more than recognition). (2) Visual Reproduction I and Visual Reproduction II tasks assess immediate and delayed recall for non-verbal visual stimuli (symbols) with Visual Reproduction Recognition task confirming recognition of the symbols presented. Additional tasks from the battery were tested such as Logical Memory I, II and recognition however these draw heavily on language and are therefore difficult to interpret in aphasia. Pairwise correlation revealed a similar pattern to that of the semantic tasks, with no significant correlation between all episodic tasks with different retrieval requirements (p ≥ .07). Within the tasks themselves, Verbal Pair 1 and 2 were correlated (r = .79, p = .018), and performance was correlated across modalities, with the strongest correlation between Verbal pair 1 and Visual reproduction 3 (r = .93, p = .008).

4. Methods and Results for Experimental Tasks

 Three experiments were conducted across this study. In Experiment 1, 2 and 3, the effect of expectedness of the stimuli/target pairing was manipulated (expected versus unexpected). In Experiment 1, distractors were manipulated (strong versus weak) within a verbal blocked experiment. Pattern of presentation was manipulated in Experiment 2 (blocked versus mixed). Experiment 3 was a non-verbal task to investigate the manipulation of modality [nursery rhymes (verbal) versus logo and image (non-verbal)].

4.1. Experiment 1: Verbal blocked

4.1.1. Method

 Experiment 1 consisted of 20 nursery rhymes, repeated in four conditions in a two by two design (80 presentations in total; See Table 2), presented via E-Prime 2 in separate sessions (Schneider, Eschman, & Zuccolotto, 2002). Each participant completed a learning and a recognition portion of each condition: Expected or Unexpected and Strong or Weak distractor (S or W). In the learning phase, rhymes appeared for five seconds, with the target separated by a fixation cross. A recognition portion followed, with participants instructed to identify the target words in a four alternative fixed choice (AFC) design. Conditions were counterbalanced across participants, and categories within conditions also counterbalanced. Upon completion of all conditions, participants took part in a recognition task to ensure prior knowledge of each rhyme. To do this, participants were presented with different lines from the same nursery rhymes tested, and asked whether they recognised those. Both patients and controls reported being familiar with 100% of the items. Accuracy, reaction time (RT) and response efficacy (RE) were recorded. Analysis focused on accuracy as there were no significant results other than overall slower RT from patients relative to controls (F = 5.232, p = .035).

4.1.2. Material

Familiar nursery rhymes were chosen according to pilot testing in 10 age matched individuals who did not take part in the final experiment. Rhymes were selected when at least 75% of those tested felt the rhyme was highly familiar. The final word in each rhymes was the target word, which was manipulated and presented alongside three distractors. In the expected condition, target words were the original rhyme (e.g. baa baa black sheep) and in the unexpected condition they were unrelated to the target word e.g. baa baa black build). We used 20 rhymes in each condition. In the strong distractor condition there were two semantic and one episodic distractors; semantic distractors were based on associative strength using Latent Semantic Analysis (see Supplementary Table S4; <http://lsa.colorado.edu/>; e.g. goat for sheep) and episodic distractors were previously presented target words. These distractors were selected by the researcher, controlling for imageability, frequency and phonology. In the weak distractor condition, three unrelated distractors were presented alongside the target word (see Table 1 for example).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Condition | Expected Strong | Expected Weak | Unexpected Strong | Unexpected Weak |
| Learning | Ba Ba Black …Sheep | Ba Ba Black …Sheep | Ba Ba Black …Build | Ba Ba Black …Build |
| Recognition  | Ba Ba Black …**Sheep**, Goat, Cattle, Graze | Ba Ba Black …**Sheep**, Bottle Weight, String | Ba Ba Black …**Build**, Sheep,Goat, Plug | Ba Ba Black …**Build**, Down, Fish, Hermit |

*Table 1.* Example of each condition learning and recognition block.

4.1.3. Data analysis

T-tests were conducted to investigate group differences. ANOVAs and logistic regression were used to assess the effect of the condition and hypotheses of accuracy. Given the heterogeneous nature of SA patients individual case analyses were also conducted for which the results are presented in Supplementary material Table S5(Singlims, Crawford, Garthwaite, & Porter, 2010).

4.1.4. Results

 A 3 by 2 ANOVA (expectedness x distractor x group) revealed there was a main effect of expectedness of rhymes [F (1, 7) = 21.643, p < .001], but not distractor strength [F (1, 7) = 1.749, p = .190]. There was an interaction between group and expectedness [F (1, 7) = 8.064, p = .006] with patients exhibiting a sharper decline in accuracy in the unexpected condition compared to controls, such that five of ten patients were below the mean control score for both the expected and unexpected condition (Figure 2; controls: F (1, 3) = 13.018, p = .001, patients: F (1, 3) = 16.621, p < .001). Neither patients nor controls showed a significant difference between distractor conditions (F > 16.621, p > .244) and there were no other two or three-way interactions (p> .397; Table 2). These results indicate that pre-existing memories led to inaccurate performance when SA patients were required to learn unexpected episodes.

*Figure 2.* Average accuracy of controls versus patients in expected and unexpected conditions (averaging across distractor conditions) in Experiment 1.

|  |
| --- |
| Table 2: Results of Omnibus ANOVA for Accuracy  |
|  | Accuracy |
|  | *F* |
| Expectedness | 21.643\*\*\* |
| Distractor | .190 |
| Expectedness \* group | 8.064 \* |
| Distractor \* group | .727 |
| Expectedness \* distractor  | .365 |
| Expectedness \* distractor \* group | .000 |
| *\** p < .05 \*\* p < .01 \*\*\* p < .001 |

4.2. Experiment 2: Verbal Mixed

 4.2.1. Rationale

Previous research has suggested a hallmark of SA is highly inconsistent performance, relying on task difficulty rather than the item itself (Jefferies & Lambon Ralph, 2006). Moreover, it has been suggested that SA patients may be impaired at the strategic use of task information to respond appropriately to the task and that this might be associated with lesions to the LIFG (Badre & Wagner, 2007). To explore whether inconsistent performance is seen in episodic memory, we presented the same items as in Experiment 1, but mixed conditions within each block, so that the presentation of the condition could not be predicted. This makes the task harder, as patients can no longer use a strategy to recall items. We predicted (a) that effects found in Experiment 1 would be accentuated, and (b) that item-by-item responses across the two experiments would be highly inconsistent.

 4.2.2. Method

 Experiment 2 follow the same design as Experiment 1 with two exceptions. Firstly, each block was mixed to contain a randomised sample of five expected and five unexpected rhymes, with four blocks in total results in 20 presentations of expected and 20 presentations of unexpected nursery rhymes. Secondly, distractor strength was not manipulated (it was strong in all trials).

 4.2.3. Data analysis

 Data analysis remained consistent across the two experiments, with the addition of a logistic regression analysis to assess whether accuracy of the expected condition predicts the accuracy of the new condition, however patients that were at ceiling (> 95%) or floor (< 5%) were excluded from this analysis.

 4.2.4. Results

 Overall, a 2 by 2 (expectedness x group) ANOVA revealed a main effect of expectedness of rhyme [F (1, 8) = 10.397, p = .005], and a main effect of group, with patients performing consistently worse in both expected and unexpected conditions compared to controls [F (1, 8) = 9.126, p = .008]. Figure 3 shows that six of nine patients were worse than the overall mean control score in the expected condition, and this was true for all patients in the unexpected condition. The effect of expectedness was significant for patients but not controls (controls: F (1, 8) = 2.000, p = .195, patients: F (1, 8) = 9.802, p = .014).

4.2.5. Block versus mixed performance

An additional ANOVA (group x expectedness x experiment) was run looking at the six patients and nine controls who completed both experiments. There was a significant interaction between group (patient versus controls) and expectedness (expected versus unexpected) [F (1, 7) = 20.680, p < .001] with a stronger effect for patients compared to controls, although both showed a significant effect (Patients: p < .001; Controls: p = .006). There was no significant interaction between group and experiment, although this approached significance (p = .065) nor experiment and expectedness (p = .395) or a three way interaction (p = .092).

Additionally, a logistic regression was run on patients who took part in both experiments. The model included Experiment (block versus mixed), expectedness (expected versus unexpected), individual rhyme and patient ID. Experiment, condition and patient ID all contributed to accuracy, however the individual rhyme was not a significant predictor, indicating a lack of item consistency between the conditions or experiments. Participants were significantly better at the expected compared to the unexpected condition (Wald = 14.842, p < .001), and significantly better at the block compared to the mixed Experiment (Wald = 9.376, p < .001). Figure 4 shows performance across conditions and clearly shows a decline in patient scores between block and mixed tasks in the expected conditions, and a further decline between these in the unexpected conditions.

*Figure 4.* Accuracy of patient versus controls across experiments in Expected and Unexpected conditions. .

4.3. Experiment 3: Non-verbal mixed

4.3.1. Rationale

Experiment 3 replicated the design of Experiment 2, but in a non-verbal domain. SA patients show parallel impairments in semantic memory in verbal and non-verbal domains (e.g., Jefferies & Lambon Ralph, 2006). This may be due to pictures being more likely to bypass the semantic route and gain direct access to the hippocampus via a ventral visual route (Baddeley & Hitch, 2017; Graham et al., 2010). However, Stampacchia et al., (2018) failed to show an effect in their non-verbal task across the episodic domain, which could potentially be explained because the images used did not require a deep level of processing and therefore were more likely to be visually matched. In our task, therefore, we used complex images to elicit a deeper level of processing (logos). We predicted that if picture pairs drew on pre-existing memories, they would require a control mechanism to be retrieved. If control mechanisms between semantic and episodic memory are shared, patients with damage to these mechanism will show impairments on this task. There was no manipulation of blocking (all items were mixed) or distractor strength (all distractors were strong) in this experiment.

4.3.2. Method

In each presentation, a context image was presented, alongside a logo that was expected in the context or unexpected, simulating the previous conditions (see Figure 5 for examples). Items were mixed, with 5 expected and 5 unexpected pairs of images randomised within each block, with a total of four blocks completed during separate sessions. Upon completion of the task, a recognition task was used to establish prior familiarity with the logos for all participants.

|  |  |  |
| --- | --- | --- |
|  | Expected | Unexpected |
| Learning |   |   |
|  | Expected (strong) | Unexpected (strong) |
| Recognition  |  |  |

*Figure 5.* Example of each expected and unexpected learning and recognition block in Experiment 3.

4.3.3. Materials

Logos were chosen according to a pilot test of 10 age matched individuals who did not take part in the final experiment. They were asked to indicate whether they would expect to see the logo in the context of the image it was presented with, and pairs were selected if 75% of participants rated them as expected within the context.

4.3.4. Results

 A 2 by 2 (expectedness x group) ANOVA revealed a main effect of group [F (1, 24) = 19.592, p < .001], with patients performing worse in the unexpected condition compared to the expected condition. Patients were consistently worse at recall of images in both conditions compared to controls [F (1, 24) = 12.240, p = .002] as shown in Figure 6, with three of seven patients scoring worse in the expected condition, and five in the unexpected condition.

A logistic regression was performed to ascertain whether performance in the expected condition, could predict the accuracy of the unexpected condition. The logistic regression model was not significant (Wald= .486, p= .49), with the model explaining 10% (Nagelkerke R2) of the variance. This indicates a lack of consistency between the conditions, as accuracy cannot be predicted by performance in the other condition.

4.3.5. Verbal versus non-verbal

*Figure 6.* Accuracy of controls versus patients in expected and unexpected conditions in Experiment 3.

Figure 7 shows a comparison of the accuracy of the six patients who completed both mixed conditions (Experiments 2 and 3). T-tests revealed there was no significant differences between the expected and unexpected conditions dependent on modality for either patients or controls [Patients (Expected: p = .193, Unexpected: p = .599); Controls (Expected: p = .222, Unexpected: p = 785)], with patients displaying deficits in the unexpected condition irrespective of modality.

*Figure 7.* Accuracy of controls versus patients across verbal and no verbal tasks.

# 5. Discussion

This series of experiments investigated the effect of semantic control deficits on episodic retrieval in SA patients. These novel experiments explore the nature of the episodic impairment found in SA, showing that long-established memories interfere with new ones that require overriding of previously learnt associations, with parallel deficits found in verbal and non-verbal tasks. Our tasks revealed that the way the items were presented mattered, with greater deficits found on conditions where the pattern of presentation could not be predicted. Patients showed highly inconsistent performance on the same items across tasks. These patterns reflects the hallmark inconsistency found in the semantic domain in these patients (Gardner et al., 2012, Corbett et al., 2009, Jefferies & Lambon Ralph, 2006).

 The patient population typically has damage to the areas of the multiple demand cortex, including inferior frontal and TPO regions (See Figure 1). These regions have been implicated in semantic control (Noonan, Jefferies, Visser, & Lambon Ralph, 2013; Davey et al., 2015; Hallam, Whitney, Hymers, Gouws, & Jefferies, 2016) and are influential in episodic control (Hayes, Buchler, Stokes, Kragel, and Cabeza, 2011; Barredo, Öztekin, & Badre, 2013). However, almost no work has been done to explore the relationship between semantic and episodic control, particularly in the causal role of these regions using patient populations. In this series of experiments, SA patients with semantic deficits display parallel deficits to inhibit the interference of automatically activated memories in an episodic task regardless of modality. This adds further weight to the existence of a neural mechanism with overlapping brain regions that drives both episodic and semantic retrieval.

Frontal lesions have been associated with an increased susceptibility to interference, particularly proactive interference, where recall of a target memory is interfered with by a previously formed memory (Henson, Shallice, Josephs, & Dolan, 2002). The LIFG (specifically, BA 45) has been implicated in controlling interference, with proposals that it selects from amongst competing responses in order to perform appropriately for the task demands (Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009). The inability to overcome proactive interference from previously established memories in favour of newly encoded pairs would particularly impact performance when presentation was mixed, as previously learnt associations would act as a distractor, in some cases a relevant cue but in other cases irrelevant.

In this work, SA patients displayed similar patterns across modalities. Much work into stroke aphasia has used verbal stimuli, and yet semantic deficits are found in verbal and non-verbal domains (Gardner et al., 2012, Corbett et al., 2009, Jefferies & Lambon Ralph, 2006). Intriguingly, Stampacchia et al. (2018) did not find these parallel control impairments across modalities in their episodic paradigm, with no effect of their manipulations of distractor strength (e.g., sofa for target chair) or the relatedness of the probe and target (E.g., rocking chair-dining chair vs. bulb-lamp). However, pictures of concrete objects are typically easier to remember, bolstering findings in episodic (compared with semantic) tasks. The ventral visual stream provides a direct route for pictures to be retained in hippocampal memory (Baddeley and Hitch, 2017; Graham et al., 2010). Because our task relied on more visually abstract items (logos), deeper processing may have been required to recall one logo from the four presented. The current findings suggest no modality difference in episodic control.

This study did not find an effect of distractors, although in the semantic domain this patient group has shown numerous examples of difficulty suppressing strong distractors (c.f., Noonan et al., 2010, Soni et al., 2009). An unexplored reason for this is a difference of confidence. Patients appeared more confident when incorrectly selecting the expected nursery rhyme, even when wrong (e.g., baa baa black sheep). However, with weak distractors where the expected ending was not present, patients appeared to guess a response. In both cases (strong vs. weak distractors) the patient was incorrect, but for potentially different reasons. Another possibility is that by providing participants with an entire sentence from the rhyme, chosen to make the task more ‘naturalistic’ rather than single stimuli, performance was higher as it allowed them to ‘hook’ the unfamiliar target words into this sentence.

SA patients have previously shown evidence of difficulty in maintaining performance levels when the task goal changes rapidly and repeatedly, such as in refractory task paradigms (Jefferies et al., 2007; Gardner et al., 2012; Thompson et al., 2015). Intriguingly, it is those with prefrontal damage, and not those with damage restricted to temporo-parietal cortex, who show this impairment (Gardner et al., 2012; Thompson et al., 2015). The current experiment had a “mixed” presentation condition, whereby the nursery rhyme had an expected ending in one trial, and an unexpected ending in another, presented in a counterbalanced order. “Top-down” guidance of control relies heavily on prefrontal cortex, damaged in our patient population. Therefore, despite the task remaining the same, the nature of presentation heavily impacted results, a finding which has important clinical implications.

Inconsistent performance on the same items across tasks is a hallmark pattern of SA patient performance (c.f., Jefferies & Lambon Ralph, 2006; Gardner et al., 2012). To a certain extent this was seen here, as performance was not guided by a specific rhyme or logo, but by the task demands, however this inconsistency was not across the same items in similar semantic tasks, but across the same concepts stored in different semantic or episodic stores. SA patients were unable to regulate and reshape the information required to respond appropriately in the task, despite the same concepts being probed. It is important to note however, that consistency across congruent and incongruent conditions is difficult to measure, as the information may be the same, but it is stored in different systems; one already exists and the other is encoded *de novo*. Therefore inconsistencies may be present due to the storage or retrieval aspects, rather than the particular items. This suggests that it is not that the patients are unable to recall particular items because of degraded episodic stores, but that the retrieval mechanisms themselves misfire.

5.1. Limitations

Neuropsychological work is critical to explore the causal role of particular regions for a psychological process. However, it is limited by the large lesions typical of this population of patients. This research suggests a shared mechanism between semantic and episodic control. However, it is possible that these are separable, but lie side-by-side. fMRI research could be used to detangle this further. As Figure 1 shows, the two networks are overlapping but not identical, with areas such as posterior temporal cortex implicated in semantic control alone. It may be that overarching control demands, such as selecting amongst competing items and retrieving weak traces, are common between semantic and episodic memory control, but other control elements are distinct. For example, semantic control is required for correct interpretation over an evolving context, seen in ambiguous sentences such as “the ash and the beach were common in the local forests” (Rudd et al., 2005). Episodic memory does not have a clear equivalent. Conversely, episodic memories involve items as well as a context (or source) which is not necessary for semantic memory (Dobbins et al., 2002). Some of these distinctions may be beneficial to explore in greater detail when mapping semantic and episodic networks.

5.2. Conclusion

 This series of experiments employs a novel paradigm in order to explore the nature of episodic memory impairments in SA. It suggests a pattern of performance parallel to that seen in semantic tasks: highly inconsistent performance on an item-by-item basis, impacted by the task demands not the items themselves. SA patients showed an inability to strategically utilise task knowledge to overcome interference from automatically activated memories across verbal and non-verbal modalities, and this effect was exacerbated when patients were unable to predict condition. This supports the proposal that there are shared neural mechanisms for semantic and episodic control.

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