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Item-location binding in working memory: Is it hippocampus-dependent?

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Abstract

A general consensus is emerging that the hippocampus has an important and active role in the creation of new long-term memory representations of associations or bindings between elements. However, it is less clear whether this contribution can be extended to the creation of temporary bound representations in working memory, involving the retention of small numbers of items over short delays. We examined this by administering a series of recognition and recall tests of working memory for color-location binding and object-location binding to a patient with highly selective hippocampal damage (Jon), and groups of control participants. Jon achieved high levels of accuracy in all working memory tests of recognition and recall binding across retention intervals of up to 10s. In contrast, Jon performed at chance on an unexpected delayed test of the same object-location binding information. These findings indicate a clear dissociation between working memory and long-term memory, with no evidence for a critical hippocampal contribution to item-location binding in working memory.

Keywords: working memory, binding, hippocampus, long-term memory

Item-location binding in working memory: Is it hippocampus-dependent?

The hippocampus has been consistently identified as having a key role in associative or relational memory, that is, memory for how different elements within episodes are bound together (e.g. Cohen & Eichenbaum, 1993; Cohen et al., 1999; Horner et al., 2012; Mayes, Montaldi, & Migo, 2007; Moses & Ryan, 2006; O'Reilly, Busby, & Soto, 2003). While there is still debate concerning the precise forms of associative processing in which the hippocampus is involved, these claims typically refer to long-term memory formation, often requiring encoding of numerous associated features and retention over substantial delays. For example, Moses and Ryan (2006) argue for a hippocampal role in the formation of long-term relational associations between distinct elements, as opposed to the rapid creation of unitary representations over the short-term. These approaches typically assume that binding within working memory is independent of the hippocampus and wider medial temporal lobes (MTL), reflecting a commonly held distinction drawn between short-term memory and long-term memory (e.g. Squire, Stark, & Clark, 2004).

This view has been challenged more recently, however (see Jonides et al., 2008; Kumaran, 2008; Ranganath & Blumenfeld, 2005; for reviews). Studies have suggested that patients with MTL damage show impairments on tests of visual working memory (Ezzyat & Olson, 2008; Olson, Moore, Stark, & Chatterjee, 2006). More specifically, it has been claimed that the hippocampus might have a key role in binding in working memory. For example, Henke (2010) suggested that the hippocampus is important in the rapid formation of associations, for short-term retention as well as long-term memory. In line with this, Hannula, Tranel, and Cohen (2006) observed that hippocampal amnesic patients showed deficits on memory for object-location associations within complex 3D scenes (see also Hannula & Ranganath, 2008; Yee, Hannula, Tranel, & Cohen, 2014). Similarly, Olson, Page, Moore, Chatterjee, and Verfaellie (2006) examined MTL patients' recognition memory for sequences

of three objects, locations, and object-location conjunctions within a simple 3x3 grid. Their patient group showed particular impairments on the object-location binding trials, relative to controls (though this decrement was somewhat more consistent for 8s than 1s retention intervals).

Imaging studies have complemented the apparent patterns of impairment on binding tasks in hippocampal patients. For example, Mitchell, Johnson, Raye, and D'Esposito (2000; see also Giovanello & Schacter, 2011) proposed a prefrontal-hippocampal circuit to be involved in the binding of object to location in working memory, and to be responsible for deficits they observed in healthy aging on this task. Piekema, Kessels, Mars, Petersson, and Fernández (2006) examined maintenance of three letter-color or letter-location associations over variable delays of 9-20s, and found right-lateralized hippocampal activation in the letter-location recognition task, but not for letter-color binding. However, Piekema et al. (2006) noted the possibility that the hippocampal activation they observed in object-location binding may actually represent active formation of long-term memory traces, rather than a working memory contribution per se. In line with this, Schon et al. (2004; see also Axmacher, Schmitz, Weinreich, Elger, & Fell, 2008) demonstrated that MTL involvement in working memory predicts later long-term memory formation. More recently, Piekema and colleagues failed to observe increased MTL activation in face-location binding (Piekema, Rijpkema, Fernández, & Kessels, 2010), instead identifying parietal and prefrontal areas as being critical (though see Luck et al., 2010). Jeneson and Squire (2012) have recently developed further the argument that evidence for a hippocampal contribution to binding in working memory may actually reflect LTM involvement. They claim that imaging and patient studies previously suggesting a working memory-based involvement have implemented experimental techniques that increase LTM contributions, through a combination of the type of material, memory load, complexity, and retention duration used. In support of this, Shrager, Levy, Hopkins, and

Squire (2008) found recognition memory deficits on object-location binding tasks in MTL patients only at the highest memory load (six items, rather than 3 items), thus exceeding working memory capacity (e.g. Cowan, 2001). Similarly, Jeneson, Maudlin, and Squire (2010) examined MTL patients' ability to relocate objects to their locations in a real-world task, and found that impairments emerged once again only with higher memory loads (though see Watson et al., 2013).

It is therefore possible that hippocampal involvement in tasks that ostensibly measure binding in working memory may be more likely to emerge when these tasks have a substantial LTM component. Given the conflicting evidence that exists, however (e.g. Watson et al., 2013; Yee et al., 2014), it is important to explore further whether evidence can be found to indicate that item-location binding within working memory is hippocampus-dependent. The current study attempts to address this, examining the ability of a patient with selective hippocampal damage on tasks that require binding of item to location in working memory while minimizing potential LTM involvement. We have previously examined this patient (Jon) on tasks measuring binding between shape and color (and also chunking within sentences), and found him to be intact on these measures (Baddeley, Allen, & Vargha-Khadem, 2010). While this supports the notion that the hippocampus is not crucial for certain forms of working memory binding, the tasks used in that study were not primarily spatial in nature, and did not directly assess binding to location. As the hippocampus is widely accepted to have an important role in processing spatial information (e.g. Burgess, Maguire, & O'Keefe, 2002; O'Keefe & Nadel, 1978), it is possible that binding explicitly involving such information loads on this area (e.g. Postma, Kessels, & van Asselen, 2008). We examined this question using a range of tests (recognition, reconstruction, cued recall) measuring working memory for color-location binding (Studies 1 and 2) and object-location binding (Study 3). As our primary focus in the current work was to establish whether hippocampal damage

impinges on item-location binding within working memory, each study used memory loads typically considered to be within working memory capacity of 3-4 items (e.g. Cowan, 2001). In addition, Study 3 directly contrasted accuracy in working memory with performance on a later long-term memory test for the same binding information.

Case description

Jon was aged 34 years at time of Study 1, and 35 years during Studies 2 and 3. He was born prematurely at 26 weeks of gestation, weighing less than 1kg, and suffered repeated breathing problems during the first 6 weeks of life (requiring intubation and positive pressure ventilation for severe apnoea), leading to hypoxic-ischaemic injury (Gadian et al., 2000). His memory problems were first noted at five years of age and continue to be prominent, alongside steady improvement and normal development in other domains.

Jon shows frequent prospective memory problems, for both regular and novel events, and is typically unable to recount the details of events earlier in the day. He also has spatial awareness problems and shows difficulty in reliably finding his way, consistent with his hippocampal deficit. In line with this, he demonstrates impairment in empirical investigations measuring recall of spatial layouts of an explored virtual reality town (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001), and on forced choice recognition tasks concerning relational configurations within complex three-dimensional scenes when viewpoint is shifted, even at short delays (Hartley et al., 2007; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe. 2002), though these deficits generally only emerge with larger memory loads. Jon also performs poorly on a range of standardized memory tests. Thus, whereas his immediate memory supraspan on the California Verbal Learning Test: II (Delis, Kramer, Kaplan, & Ober, 1987) was at the 73rd percentile, his LTM recall (as reflected in list learning, immediate and delayed recall) was at the 1st percentile on all measures. In terms of visual memory, Jon's immediate Rey Figure copy score was normal at 24/36 but he was

severely impaired after a delay, with no scoreable reproduction (Baddeley et al., 2001; see also Fig 1D in Vargha-Khadem et al, 1997). His profile score on the Rivermead Behavioural Memory Test (Wilson et al., 1999) was 3, in the severely impaired range.

In comparison to his performance on recall measures, however, his recognition performance is relatively well preserved. Baddeley, Vargha-Khadem, and Mishkin (2001) found that Jon achieved a set of recall scores at the 5th percentile on the Doors and People visual and verbal tests (Baddeley, Emslie, & Nimmo-Smith, 1994), alongside recognition scores in the 50th-75th percentile range. Similarly discrepant performance levels on recall and recognition tests were also found in empirical investigations using verbal material and news videos. More recently, a slightly lower level of performance on other empirical tests of delayed recognition (for encyclopedic facts) has been observed (Gardiner, Brandt, Vargha-Khadem, Baddeley, & Mishkin, 2006). This general pattern of severely impaired delayed recall alongside relatively intact recognition is consistent with the assumption that recognition draws on two separate processes - episodic recollection and familiarity judgments (Yonelinas, 1999) - with Jon being more adept at the latter (Brandt, Gardiner, Vargha-Khadem, Baddeley, & Mishkin, 2009; Düzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Maguire, Vargha-Khadem, & Mishkin, 2001)

These deficits prevail despite Jon's full scale IQ of 118 (high average) as measured at age 33, and his consistently normal performance on standardized tests of reading, syntax, semantics and vocabulary (see Baddeley et al. 2001; Vargha-Khadem et al, 1997). His performance on working memory tasks is at the level of normal-to-high functioning control participants. This has been as observed on standard neuropsychological tests such as forwards and backwards digit and Corsi block recall (Vargha-Khadem et al., 1997). Convergent findings have also emerged in empirical investigations using immediate recognition memory for colored shapes and recall of short sentences (Baddeley et al., 2010) and simple and

complex span tasks measuring verbal, visuospatial, and relational memory (Baddeley, Jarrold, & Vargha-Khadem, 2011).

Direct measurement of Jon's MRI scans indicated a reduction of about 50% in the volume of both left and right hippocampus, with no evident pathology in the rest of the medial temporal lobe (Gadian et al. 2000; Vargha-Khadem et al., 1997).

Study 1: Recognition and reconstruction memory for location, color, and location-color binding

As discussed, apparent evidence exists from patient and imaging studies of a role for the hippocampus in binding objects to locations in working memory (e.g. Hannula et al., 2006; King et al., 2002; Mitchell et al., 2000; Olson et al., 2006; Piekema et al., 2006), although these findings may reflect LTM involvement (e.g. Piekema et al., 2010; Jeneson & Squire, 2012; Shrager et al., 2008). These studies typically used variants of the recognition procedure, either change detection (re-presentation of the entire array with a change inserted on half the trials) or single probe recognition (presentation of a single test item, with participants required to judge whether it had been present in the array). Consistent with a range of previous work (e.g. Baddeley et al., 2010; Mitchell et al., 2000; Olson et al., 2006; Shrager et al., 2008), the first set of tasks in the current study implemented single probe recognition.

In addition, a reconstruction task was also implemented, in order to examine the reliability of any findings from recognition, and explore whether they generalize to other methods of measurement. Previous work with Jon has demonstrated that he shows discrepant performance levels on tasks using recognition and recall, with impairment particularly emerging on the latter task type (e.g. Baddeley et al., 2001; Gardiner et al., 2006), possibly reflecting relatively intact familiarity-based judgments alongside impaired recollection. While these measures typically used LTM-based tasks, it is possible that the high accuracy levels

achieved by Jon on the recognition tasks in the current study are part of this wider pattern. Therefore, we administered the same conditions in a non-verbal reconstruction paradigm. Jeneson et al. (2010) used a reconstruction task that bore some similarities with our measure, though theirs was a real-world paradigm in which MTL patients and controls were required to replace objects in their original locations on a table. They found that the patient group generally performed as accurately as control participants on smaller arrays (often up to 4 items in size), but demonstrated sudden declines in accuracy beyond this, in line with Jeneson and Squire's (2012) claims that the hippocampus and MTL are crucial for LTM binding but not WM. Our aim was to examine whether Jon would show similar intact performance levels as was demonstrated in the recognition measure, on a computerized reconstruction task.

If a deficit emerges in a task measuring binding of item to location, it is important to ensure that this is not the result of problems in processing item or location information itself, or a more general impairment in visuospatial working memory. Therefore, in addition to assessing memory for color-location conjunctions, we also administered conditions measuring memory for colors and locations themselves. Our basic overall prediction was that if the hippocampus has a particular role in binding item to location, Jon should show a specific impairment in this condition relative to control participants, alongside intact performance in tests of feature memory.

Method

Control participants

Seven control participants (2 male, 5 female; age range 26-34 years) performed the visual memory tasks, in the same order as Jon. Jon was tested at the Institute of Child Health, University College London, while the control participants were recruited and tested at the

University of Leeds. Both institutions concerned gave ethical approval, and all participants gave informed consent.

Materials

Experimentation proceeded on a Macintosh laptop with 15" screen. All stimuli and probe items were colored squares of 2.2cm^2. The location condition used black squares throughout, while the color and binding conditions drew from a pool of eight colors (blue, green, grey, orange, purple, red, turquoise, yellow). Presentation and testing proceeded within a black 3x3 grid of 9.3cm^2 (each grid location being 3.1cm^2 in size) centred at the middle of the screen (see Figure 1), on a white background.

Procedure

Participants performed two tasks, described in turn below, during a single half-day experimental session. The presentation and testing procedures (particularly the spatial configurations and timing parameters) were partly based on the short-delay trials implemented by Olson et al. (2006), with some adjustments (use of colored squares instead of colored familiar objects; addition of articulatory suppression). All single probe recognition tasks were administered first, followed by the reconstructive recall tasks.

Single-probe recognition

Location, color, and binding conditions were implemented in separate blocks, with these conditions administered in this order for all participants. In each condition, we first administered a block of 3-item sequences, containing 4 practice trials and 18 test trials. A block of 4-item sequences then followed, containing 4 practice trials and 24 test trials. This produced 8 practice trials and 42 test trials in each of the location, color, and binding conditions.

Each trial commenced with a 1500ms blank screen delay, then a fixation cross was presented at screen centre for 500ms, followed by a 250ms blank screen delay. The to-be-remembered sequence was then presented for 1000ms per item (with 15ms inter-stimulus intervals). A blank-screen 1000ms retention interval followed offset of the final item in the sequence, and then the test phase commenced. Participants repeatedly articulated the digits "1-2" from presentation of fixation cross through to the test phase, in order to disrupt verbal recoding of stimuli.

In the location condition, a sequence of 3 or 4 black squares (depending on memory load) was presented in different grid locations (not including the central location, which was never occupied during presentation in any condition). At the test phase, the probe was presented either in one of the originally occupied locations, or one of the remaining locations that had not been occupied, with participants required to judge whether the location has been occupied on that trial. In the color condition, a sequence of 3 or 4 different colored squares was presented in different locations, with participants informed to only focus on color and disregard location. The test probe consisted either of a target color from the 3- or 4-item sequence or a lure color drawn from the remaining experimental pool (of 5 or 4 colors, depending on memory load), and was always presented at the neutral central grid location. For the binding condition, presentation procedure was identical to the color-only condition, though participants were asked to focus on both the colors and their location. The test probe always consisted of a color and location from the original sequence, either in their correct combination or recombined (i.e. a color presented in one of the other locations that had been occupied). For each condition, participants produced one of two key press responses to indicate whether this location, color, or color-location conjunction was present in the original sequence. Half the trials in each block featured probes drawn from the original sequence (with

an equal number drawn from each serial position across the condition), while half involved new features or conjunctions.

Non-verbal reconstruction

As with recognition, location, color, and color-location binding conditions were implemented in separate blocks. Within these blocks, load-3 trials were implemented first, followed by the load-4 trials. For each memory load block, there were 2 practice trials followed by 10 test trials (thus, 4 practice and 20 test trials in each of the location, color, and binding conditions).

The same stimulus presentation procedure from the recognition tasks was implemented for the reconstruction task (see Figure 1). In the test phase of the location condition, the 3x3 grid was re-presented, with participants using the mouse to select the locations that had been occupied. Clicking each location caused that grid square to momentarily turn black (to signal successful selection) before returning to white when participants released the mouse button. The test display in the color condition involved presenting all eight possible colors at the right side of the screen, with participants required to select the three (or four) that had been presented. On selection, each color was momentarily surrounded by a black outline. Finally, for the binding condition, both the 3x3 location grid and the full set of colors were displayed at test, with participants attempting to select each pair of color and location in turn. A correct response in this condition required appropriate color-location pairings; selecting the features themselves (either in isolation or as part of other pairings) was not enough to be scored as correct.

Participants were encouraged to select the locations, colors, or color-location pairs in their original presentation order, but were also informed that this was not necessary to achieve a correct score. Unlike the single probe recognition task, non-verbal reconstruction potentially provides a measure of memory for every item in each of the sequences. Once all responses

were made, a separate button marked ‘Next’ on the right side of the screen was clicked to continue.

Results and discussion

Relative performance levels demonstrated by Jon and the control participants in each task were analyzed using the method described by Crawford and Howell (1998). Memory load was manipulated (using sequence lengths of 3 and 4 items) primarily in order to allow for individual variability in performance and thus obtain sensitive data. It should be noted that there were no particular differences in patterns between memory loads; analysis indicated the same relative performance levels for Jon and control participants overall and at the different loads, in this study and Studies 2-3. Therefore, for each of the tasks, data are collapsed across memory loads 3 and 4 for the sake of concision.

Accuracy in the recognition task is reported as Hits-False alarms, and is displayed in Figure 2 (upper panel). It is evident that Jon performed very well on all stimulus conditions, responding with near-perfect accuracy in tests of location, color, and binding. Control participants, in comparison, produced variable levels of performance accuracy. Focusing on the binding condition, Jon performed as accurately as the highest scoring control. Thus, there was no evidence of any item-location binding impairment. This fits with the strong profile of performance displayed by Jon across a range of working memory tasks (e.g. Baddeley et al., 2010, 2011). Though accuracy was emphasized as the primary measure of performance, we also analyzed decision latency. Jon produced reaction times within the normal range in each condition, averaging 1251ms in the location condition (controls: 1217, *SD* = 344), 881ms for color (controls: 1084, *SD* = 378), and 1480ms for binding (controls: 1360ms, *SD* = 444). He was neither the slowest nor the quickest participant on any stimulus condition.

For the non-verbal reconstruction task, accuracy is reported as the proportion of the total number of items in each condition that were correctly selected (in any order). Location and color conditions required selection of their respective feature dimensions while binding required correct pairing of color and location selections. The data, displayed in Figure 2 (lower panel), reveal that Jon achieved a high level of accuracy in each of the stimulus conditions, thus mirroring the patterns found in single probe recognition. Focusing on the binding condition, only one of the seven control participants achieved a reconstruction score that was superior to Jon's, again revealing his ability on item-location binding tasks to be at the level of a high-functioning healthy participant. Although item accuracy was emphasized over order for this task, proportional order errors were also examined, as memory for temporal sequences may be compromised following hippocampal damage (Konkel, Warren, Duff, Tranel, & Cohen, 2008). In this Study, and also on the reconstruction task in Studies 2 and 3, order error rates produced by Jon were always within 1 SD of those reported by control participants, and there were always at least two control participants who produced higher error rates than Jon. Analysis indicated there was no evidence of any impairment (at $p < .05$). Nevertheless, as the focus of the present experimental series was on item accuracy rather than ordering, we do not make any strong claims regarding this issue.

Overall, there was no evidence of any binding impairment in single probe recognition or sequence reconstruction, with Jon performing very accurately in all conditions. This was confirmed through analysis of relative performance levels, with no significant impairment in accuracy or reaction time (at $p < .05$) in any task. These findings contrast with those of Olson et al. (2006) among other studies, and instead fit with the claims of Jeneson and Squire (2012) that working memory performance on any task, be it feature or binding memory (see also Baddeley et al., 2010, 2011) is not hippocampus-dependent.

Study 2: Reconstruction and cued recall memory for location, color, and location-color binding over short delays

A second set of tasks was administered in order to replicate and extend the outcomes of Study 1. In particular, we examined whether the high accuracy levels displayed by Jon in feature and binding memory would still be observed a) over short filled retention intervals of up to 10 seconds, and b) on a new cued recall task. Testing by recall is important, given that Jon's LTM deficit is found using recall but not recognition.

There is mixed evidence for hippocampal involvement in item-location binding over brief delays. Olson et al. (2006) only consistently observed location binding deficits in their patient group using retention intervals of 8s (rather than 1s), suggesting that the hippocampus might be engaged when retaining over these slightly longer delays. In contrast, Piekema et al. (2010) did not find increased MTL activation for item-location over delays of 10s in their fMRI study. Therefore, we wanted to establish whether Jon would show deficits when information had to be retained over similar brief delays. The 1s delay trials from Study 1 were implemented again to maintain parity with that study and find whether the outcomes replicated using reconstruction and cued recall (see below). In comparison, a simple verbal filler task (verbal odd/even judgments to visually presented digits) was introduced during 5s and 10s delay trials. This was designed as a concurrent load to disrupt the engagement of active verbal or spatial rehearsal processes during these delays. If Jon is only able to maintain information very briefly in working memory through the use of intact focused attention, deficits relative to control participants should emerge after filled 5s and 10s delays.

In order to further extend the current findings, performance was examined using both non-verbal reconstruction and verbal cued recall. The latter task provides a direct measure of binding performance by cueing each location and requiring participants to verbally recall the

item that was present. An adapted version of this task has been successfully used to probe memory for shape-color binding (Ueno, Mate, Allen, Hitch, & Baddeley, 2011).

Method

Control participants

Six control participants (4 male, 2 female; age range 32-39 years) performed the visual memory tasks, in the same order as Jon. Testing with Jon took place at the Wolfson Centre, University College London, with ethical approval from the Research Ethics Committee of University College London Hospital. Control participants were recruited and tested at the University of Leeds, with accompanying ethical approval from the Institute of Psychological Sciences ethics committee.

Procedure

Testing was implemented in a single half-day session, with participants performing all variants of the reconstruction task first, followed by the cued recall task.

Non-verbal reconstruction

We assessed memory for location, color, and color-location binding (administered as separate blocks in that order for all participants). Each of these conditions used separate blocks of 3- and 4-item memory loads; within each load block, we administered 1 practice trial and 6 test trials at each of the three (1s, 5s, 10s) retention intervals, implemented in this set order for all participants. Collapsing across length and retention interval, this produced 6 practice trials and 36 test trials in each of the stimulus conditions for reconstruction.

The presentation and testing procedures were identical to those used in the reconstruction task from Study 1, the only difference being the varied nature of the retention

interval. For 1s delay trials, the procedure was identical to that in Study 1, with the participant continuing to perform the articulatory suppression (repeatedly articulating "1-2") until start of the test phase. This task was also performed during stimulus presentation on 5s and 10s delay trials. A simple verbal filler task was then introduced in the delay period for these longer retention intervals. This involved presentation of a single digit (Arial font, size 24) every 1s at upper screen centre, with participants required to make an odd/even judgment out loud (recorded by the experimenter). There were 4 digit judgments required during the 5s delays, and 8 judgments during the 10s delays. In order to make these speeded judgments, participants ceased performing the articulatory suppression task on presentation of the first digit (thus, for the 5s and 10s delay trials, participants performed suppression during presentation of the visual memory stimuli, followed by odd/even judgments during the retention interval).

Cued recall

The verbal cued recall task was necessarily focused only on color-location binding. This task used the same presentation and retention interval procedures as the reconstruction paradigm. At test, each occupied location was cued in turn by its outline appearing in bold lines (weight 7), for 2.5s (Figure 3). Participants were required to verbally recall the color that had occupied each location as it was cued, and were encouraged to make a guess response (or say 'blank') if they were not sure of the answer. Locations were cued in a randomized serial order on every trial to minimize possible use of serial ordering strategies.

Separate blocks of 3- and 4-item memory loads were administered, with 1 practice trial and 6 test trials at each of the three (1s, 5s, 10s) retention intervals within each load block, implemented in this set order for all participants. Collapsing across memory load and retention interval, this produced 6 practice trials and 36 test trials for the cued recall task.

Trials proceeded automatically, with a rest screen before each new block of retention interval trials began. As with reconstruction, cued verbal recall provides a measure of memory for every item in each sequence.

Final color recall task

An unexpected delayed test of color memory was administered one minute after the end of the final testing block (with this delay filled with conversation), to measure knowledge of the experimental set. Participants were asked to verbally recall as many of the eight colors as they could, within a period of 60s.

Results and discussion

Starting with the reconstruction task, both Jon and the control participants performed at ceiling in the location condition (Jon achieved a perfect score, while controls averaged .99 proportion correct). Jon also performed very well in the color condition, achieving a mean proportional accuracy score (collapsed across retention durations) of .96 (compared to controls, who averaged .81, SD = .09). Accuracy rates in the binding conditions are displayed in Figure 4 (upper panel). Jon again responded very accurately across the 1s, 5s, and 10s delay trials, performing at or above the level of all control participants. Analysis indicated that there was no evidence of impairment on any measure (at $p < .05$).

Accuracy in the verbal cued recall measure of color-location binding is reported as mean proportion correct (Figure 4, lower panel), with participants required to recall the corresponding color associated with each location. As with reconstruction, Jon's accuracy levels were above the mean score produced by controls, though 2/6 participants achieved slightly higher accuracy scores than Jon at the 5s and 10s delays. It is therefore clear that Jon demonstrates no working memory deficits in color-location binding across brief filled delays,

in either of these different tasks. This was confirmed through analysis of relative performance levels, with no impairment (at $p < .05$) in any task or retention duration.

Finally, for the end of session color recall test, both Jon and all control participants correctly recalled all 8 of the presented colors that were used in this study, indicating comprehensive and intact knowledge of the experimental set. It should be noted that by this point in time, following Studies 1 and 2, Jon had experienced greatly increased exposure to this set, relative to the control participants (none of whom had participated in studies previously). He is therefore likely to have acquired knowledge of the stimulus set over time (cf. Study 3), which may also potentially relate to his particularly strong performance on the working memory measures in this study.

Study 3: Reconstruction and cued recall memory for location-object binding over short and long delays

A final study was administered to examine whether Jon would demonstrate intact location binding performance on reconstruction and recall tasks when using simple images of familiar objects either drawn from a closed (i.e. small and repeated) or open (i.e. large and never repeated) item set. Jon's high levels of accuracy may at least partly relate to his experience of the stimulus set, as indicated by his intact performance in the final test of color knowledge in the previous study. Study 3 therefore examined whether a deficit in binding would emerge using different sets of experimental stimuli.

Previous studies reporting deficits in MTL patients on binding identity to location have often used images of recognizable objects. For example, Olson et al. (2006) presented colored Snodgrass and Vanderwart-like renderings of familiar objects and animals, drawn from Rossion and Pourtois (2004). It is useful to examine whether Jon still shows intact working memory for binding to location when using such stimulus sets. In addition, Olson et

al. (2006) used an 'open' set, with new stimuli presented on every trial. In contrast, Studies 1 and 2 (and also Baddeley et al., 2010) used a 'closed' set of eight colors that frequently repeated between trials (see also Allen, Baddeley, & Hitch, 2006; Allen, Hitch, Mate, & Baddeley, 2012). This closed set was implemented in order to minimize potential long-term memory contributions, instead emphasizing working memory and the need to temporarily bind each set of features anew on every trial. In line with this, Endress and Potter (2013) have recently demonstrated that the use of closed stimulus sets in visual short-term memory tasks leads to increased proactive interference (PI) across trials, which then undermines the use of 'intermediate' and long-term memory to supplement performance. It may be that, unlike control participants, Jon is unable to benefit from LTM support when proactive interference is reduced. We therefore contrasted cued recall performance on sets of closed and open stimuli, to examine whether Jon might show a deficit relative to healthy control participants when tested on materials that are not repeatedly re-used.

In a final LTM recognition test, Endress and Potter (2013, Experiment 4) assessed whether healthy young adult participants were able to pick out the items that had previously been presented during their temporary memory task. They observed near-perfect recognition accuracy for stimuli from the previously presented open (non-repeated) set, indicating that such stimuli had indeed been encoded into LTM during this task. Similarly, van Geldorp et al. (2012) tested controls and patients with Korsakoff's amnesia on memory for pairs of faces and houses (an 'extrinsic' binding task) in a working memory task (over delays of 3s-6s), and then on an unexpected LTM test of the individual elements around 5 minutes afterwards. Healthy control participants were able to perform above chance on the LTM elements test, again suggesting that LTM representations can be formed during encoding for what are ostensibly WM tasks (provided that PI is limited). In contrast, the Korsakoff's group were not significantly above chance on this delayed feature test (and also showed impairments on the

extrinsic WM task). However, we are not aware of any previous studies that have examined patients with selective hippocampal damage in this context, or compared WM and LTM for item-location binding based on the same encoding episodes. Therefore, for the open set, performance on reconstruction and cued recall working memory measures was also compared with a test of long-term item-location binding memory drawn from the same encoding episodes. If Jon has intact working memory binding (as indicated by Studies 1 and 2) but impaired LTM, we would expect to observe a deficit in binding performance only on this final LTM test.

Method

Control participants

Six control participants (5 males, 1 female; age range 27-37 years) performed the visual memory tasks, in the same order as Jon. Jon was tested at the Wolfson Centre, University College London, while the control participants were recruited and tested at the University of Leeds. Both institutions concerned gave ethical approval, and all participants gave informed consent.

Procedure

Testing was implemented in a single half-day session, with regular breaks interspersed between tasks. The working memory (reconstruction and cued recall) tasks for the closed item set were implemented first, followed by the final object recall task for that stimulus set. In this study, we only included reconstruction tests of object-location memory and omitted equivalent single feature tests (i.e. location or object), as his feature recall was consistently very accurate in the earlier studies. After completion of the closed stimulus set tasks, the cued recall task for the open stimulus set was then administered, followed by the delayed object recall and object-location binding tests. As in Study 2, all conditions used separate blocks of

3- and 4-item memory loads, each containing 21 trials, with 1 practice trial and 6 test trials at each of the three (1s, 5s, 10s) retention intervals within each block. Procedures for the reconstruction, cued recall, and different interval durations were identical to those implemented in Study 2.

Objects in this study consisted of greyscale versions of the Rossion and Pourtois (2004) stimulus set. These are Snodgrass and Vanderwart-like renderings of familiar objects from a range of categories. While Olson et al. (2006) used colorized versions of these stimuli, we used greyscale versions in order to minimize color as an additional feature dimension and focus on object-location binding. The closed set used eight of these stimuli (*banana, church, cycle, horse, kite, scissors, shoe, squirrel*), repeatedly sampling from this set in the same way as Studies 1 and 2. For the open set, 147 additional objects were selected on the basis of being recognizable and representing a cross-section of item categories. Unlike the closed set, objects in the open set were only presented once for each participant. In addition, while all previous tasks using closed set items involved the random sampling of items on every trial, each trial in the open set cued recall task was pre-designed to ensure an effective distribution of objects from different categories across the blocks. Thus, each participant encountered exactly the same trials, in the same order, during open set cued recall.

Final object recall tests

As in Study 2, final recall tests of the object sets were again implemented for both the closed and open stimulus sets. Thus, the final block of trials for each of the stimulus sets was followed by a one minute delay (filled with conversation), before requesting that the participant try to recall as many of the objects as possible from that set, within a period of 60s. For the closed set, this meant recalling from the set of eight objects, while for the closed set, participants tried to recall as many of the 147 objects as they could within the 60s limit.

Final object-location binding test

Finally, an unexpected delayed test of object-location binding for the open stimulus set was administered in this study, in order to measure the extent to which participants retain longer-term representations of the item-location bindings that were encountered in the earlier cued recall working memory measure. This was performed after the final object recall test, and involved re-presenting a subset of the objects from across the open set (cued recall) blocks and, for each item, requiring participants to select the location in which it had previously been presented. A single set of 21 objects was used in this test, with all participants being assessed on this same item set. These were pre-selected so that one object was probed from each serial position for each of the two memory loads and three delays, resulting in 9 trials being re-probed from the load-3 trials and 12 from the load-4 trials. Specifically, for each of the blocks of 6 trials within each retention duration (1s, 5s, 10s), objects from trials 2, 4, and 6 were probed for the load-3 blocks, and trials 2, 4, 5, and 6 for the load-4 blocks. These trials were probed in the order in which they were originally implemented (thus, trials from load-3 were probed first).

For each trial, the probe object was presented on the left side of the screen, next to the original 3x3 grid. Participants used the mouse to select the location in which they thought it had appeared during the earlier working memory cued recall task, before clicking a button marked ‘Next’ to proceed to the subsequent item. The programme automatically moved on if no response was logged within 10 seconds of presentation. Participants were encouraged to guess when they were not sure of the answer. Given the short duration of this final test, the final object recall test and subsequent 1-minute delay, and the probing of a subset of trials from across the two sequence-length blocks that had been previously performed, the interval between initial presentation and test ranged from approximately 3-10 minutes.

Results and discussion

Mean accuracy for the closed (repeatedly sampled) stimulus set is displayed in Figure 5, for reconstruction (upper panel) and cued recall (lower panel), while cued recall using the open (non-repeated) set is displayed in Figure 6. Examination of the data indicates that Jon is clearly within or above the normal range of performance as produced by the control participants on each of these tasks and stimulus sets, with analysis indicating no significant impairment (at $p < .05$). It is worth noting that his mean performance levels on the object sets are closer to the level of control participants than was demonstrated in Study 2. Comparing across experiments indicates that while Jon performed somewhat equivalently across the two studies, the control participants (a different group) were generally more accurate in Study 3. While this might be taken to indicate a relative inability on Jon's part in utilizing potential additional cues (including richer semantic information) provided by the familiar object set, Rose and colleagues (Rose, Olsen, Craik, & Rosenbaum, 2012) have argued that this is independent of the MTL, based on work with a different developmental amnesic patient (HC). Therefore, it may instead simply reflect random variation between different groups of control participants. In any case, even in Study 3, Jon showed no evidence of an identity-location binding deficit in working memory tasks overall.

There were also no substantial differences generally between cued recall accuracy on the closed and open sets; collapsing across retention intervals, Jon achieved a mean score of .72 on the closed set and .80 on the open set, while controls averaged .78 (*SD* = .16) and .80 (*SD* = .11) for closed and open sets respectively. This suggests that any build-up of proactive interference related to item identity as a result of using a closed item set does not particularly impinge on temporary memory for item-location associations, and furthermore that variations in use of closed or open sets between previous studies (e.g. Studies 1 and 2; Baddeley et al.,

2010; Olson et al., 2006) does not account for variation in the presence or absence of hippocampal-related impairment.

In comparison to the general absence of impairment in 'working memory' tasks, clear differences in performance were observed on the unexpected final 'long-term memory' tasks. For the free recall test of closed set items, Jon recalled 2/8 correct, compared to the control average of 7.66/8 (*SD* = .52), a significant difference, t (5) = 10.16, $p < .05$. In the free recall test of the open set, given 60s to recall as many as possible of the 147 items that had been presented during the earlier cued recall task, Jon only managed to produce 3, while controls averaged 21.83 (*SD* = 5.78). This difference was again significant, t (5) = 3.02, $p < .05$. Thus, for both the closed and open item sets, impaired long-term memory for the previously presented materials is apparent. These impairments contrast with Jon's intact delayed recall of colors as observed in Study 2, with this likely to reflect differences in familiarity between the sets.

Finally, performance on the final item-location binding test is illustrated in Figure 7. While control participants averaged a proportional score of .53 correct (or 11.17 out of a maximum score of 21), Jon scored at .14 (3/21) correct. This difference was marginally significant, t (5) = 1.70, $p < .10$. As illustrated in Figure 7, Jon's accuracy represents a level of performance that would be expected by chance (at .125 proportion correct, or 2.63 items out of 21), therefore indicating that he is at floor on this task. In contrast, control participants performed significantly better than chance, t (5) = 4.71, $p < .01$, illustrating that they were indeed able to retain some item-location associative information over the longer term. This pattern therefore indicates dissociation in item-location binding between working memory and long-term memory, based on the same encoding episodes.

General Discussion

We examined the ability of Jon, a patient with selective hippocampal damage, to perform a range of different tests examining identity-location binding in working memory. Across single probe recognition, non-verbal reconstruction, and verbal cued recall, retention intervals up to 10s, and using colors (Studies 1-2) or familiar objects (Study 3), Jon achieved high levels of accuracy, always performing at or above the levels of control participants. These findings complement Jon's highly proficient performance on measures of feature-feature binding and within-sentence chunking (Baddeley et al., 2010) and on a range of tasks measuring verbal and visuospatial working memory (Baddeley et al., 2011), and contrast with his severely impaired delayed recall and recollection (e.g. Baddeley et al., 2001). The present findings, and in particular Study 3, extends this dissociation to item-location binding and memory for the same encoding episodes when tested over a few seconds, or minutes later. Specifically, when assessed after brief delays up to 10s, Jon is as accurate as control participants; when unexpectedly tested again on the same encoding episodes a few minutes later he only performs at chance level. Thus, while it is clear from Studies 1-3 that Jon is able to create and temporarily store identity-location bindings very effectively, the final binding test in Study 3 suggests that, unlike control participants, he is not able to form and retain robust longer-lasting representations of this information over the course of a few minutes.

It is possible that the hippocampus is important in relational memory, including binding item to location (e.g. Postma, Kessels, & van Asselen, 2008), but this may be limited to the formation of long-term representations. The general concept of a hippocampal contribution to long-term binding is well established (Cohen & Eichenbaum, 1993; Cohen et al., 1999; Horner et al., 2012; Mayes et al., 2007; Moses & Ryan, 2006; O'Reilly et al., 2003). For example, Horner et al. (2012) have recently demonstrated that recognition memory for binding between item and context correlates with hippocampal volume in amnesic patients and healthy controls. In convergence with this, MEG recording at retrieval indicated early and

sustained hippocampal-dependent frontotemporal modulation that was associated with contextual recollection in controls but not in patients. The present findings suggest a distinction between temporary coding that can be used to successfully support memory judgments over brief periods, and longer lasting representations that can be utilized at a later point in time. The performance of healthy control participants in Study 3 indicates that both forms of representation can originate from the same encoding phase. In contrast, Jon's selective hippocampal damage means that, while he is able to set up bound representations in working memory that support his performance in tasks using only brief delays (up to 10s), such information does not remain accessible over time.

Jon's consistently accurate performance across a range of working memory tasks fits with some recent evidence indicating intact performance on various item-location binding tasks at lower memory loads/short retention intervals in MTL patients with developmental (Picard et al., 2013) and adult-acquired (e.g. Jeneson et al., 2010; Shrager et al., 2008) deficits. The observation of analogous findings to groups of patients with adult-acquired injury might argue against Jon's intact performance being attributable to abnormal brain development arising from his early-acquired hippocampal damage. However, it remains possible that given the early age at onset of severe bilateral hippocampal damage in the case of Jon, compensatory recruitment of brain regions outside the hippocampal network may be a contributory factor to efficient working memory performance demonstrated on the current tasks. The issue remains to be completely resolved.

A number of neuropsychological studies do argue for a hippocampal and wider MTL role in working memory for spatial and topographical information, and item-location binding (e.g. Burgess et al. 2002; Hartley et al., 2007; King et al., 2002; Olson et al., 2006). In response to this, Jeneson and Squire (2012) argue that evidence apparently indicating a hippocampal involvement in any 'working memory' measure actually reflects a critical role

for long-term memory. The hippocampus and wider MTL may potentially contribute to encoding and storage in any measure of working memory, but not as a direct result of working memory involvement per se. Instead, as stimuli are encountered that require retention, both temporary and more robust, long-term representations are constructed, with the hippocampus crucially contributing only to the latter. Both these forms of representation may contribute to task ostensibly measuring 'working memory', but LTM-based hippocampal activity only becomes critical in circumstances in which working memory capacity becomes overloaded and representations are lost. In the case of the measures used in the current study (and also Baddeley et al., 2010), the task parameters (involving 3-4 items and brief retention delays) focused on working memory storage and minimized the need for long-term retention.

This raises the question of where such processing does take place, if not the hippocampus. One possibility is that binding in working memory requires critical support from prefrontal regions. For example, Prabhakaran, Narayanan, Zhao, and Gabrieli (2000) identified PFC area right BA10 as being particularly active during binding of letters to locations (see also Campo et al., 2005; Mitchell et al., 2000). However, several studies have failed to support this (Campo et al., 2008; Luck et al., 2010; Owen, 2004; Piekema et al., 2006; Todd & Marois, 2004), though these studies may again have emphasized LTM over working memory. Another possibility is that parietal regions are key for binding within working memory (e.g. Kessels, Kappelle, de Haan, & Postma 2002; Campo et al., 2008; Friedman-Hill, Robertson, & Treisman, 1995; Shafritz, Gore, & Marois, 2002; Todd & Marois, 2004).

However, a few recent studies have reported difficulties in spatial tasks involving short retention intervals and small numbers of objects, in contrast to the current work (and that of Jeneson & Squire, 2012). For example, Watson et al. (2013) tested hippocampal amnesic patients and healthy controls on a spatial reconstruction task involving real objects

laid out on a table, and observed increased error rates (particularly minor displacements and swap errors) in the patient group, even on two-item arrays. Increased swap errors (that is, exchanging the location of two objects) might suggest that the hippocampus is important specifically for binding of object to *relative* location. Forms of 'swap' or binding error can also be examined in the current study, in the reconstruction task (through selection of a location or colour that was present, but not in the correct combination) and cued recall task (through recall of a feature that was present in a different location to that which was cued). However, this further analysis did not produce significantly increased error rates in Jon vs. control participants in any comparisons (all p values > .05). It should be noted that the patients reported by Watson et al. (2013) had adult-acquired injury (in contrast to Jon), and in some cases had additional damage beyond the hippocampus. Their task also involved reconstruction of a real-world multi-item array, presented simultaneously for an extended (and unspecified) duration, with which participants interacted and named during encoding on every trial. In the present study, in contrast, simple 2D items were briefly presented sequentially and articulatory suppression was applied to disrupt verbal recoding. Any of these variations in the extent and selectively of the hippocampal pathology in the patient group, or differences in task procedure, may have contributed to the different patterns observed. For example, the use of serial presentation in the current study may have de-emphasized *relative* item-location information (which according to Watson et al., 2013 may be particularly hippocampal-dependent) in favour of memory for absolute item-location combinations.

Another possibility, set out in a recent framework by Yonelinas (2013), is that while the hippocampus consistently contributes to recollective experience in LTM tasks, a critical factor in whether working memory (or perception) tasks place noticeable demands on the hippocampus concerns the extent to which they require the creation and utilization of complex *high-resolution* bindings. Under this approach, tasks that require only simple or low-

resolution associations are less likely to indicate impairments as a result of hippocampal damage. In the current tasks, following previous key studies (e.g. Mitchell et al., 2000; Olson et al. 2006), location judgments were categorical (with locations clearly marked on a grid). It is possible that accurate performance on these tasks could be achieved without the need for high-resolution binding, potentially explaining why the impact of Jon's hippocampal damage was not observed. Further research will be required to explore possible distinctions between different forms of binding, and the relative reliance they may place on hippocampal function.

Overall, our results provide clear evidence that Jon is capable of temporarily storing and retrieving the basic relationship between an object and its spatial location in visual working memory, but cannot effectively retain this information over the longer term. As noted earlier, it is clear that Jon does indeed have a deficit in a range of spatial processing and memory tasks of a broadly topographical nature (e.g. Hartley et al., 2007; King et al., 2002), raising the question of the nature of this particular deficit. This might be a simple function of capacity (Jeneson & Squire, 2012), or the requirement for relational (Watson et al., 2013) or high-resolution (Yonelinas, 2013) binding. Alternatively, as suggested by Baddeley et al. (2011), the crucial distinction might be between viewer-centred egocentric visual processing and storage on the one hand, on which Jon performs well, and viewer-independent allocentric processing which relies heavily on the hippocampus, and is hence impaired in Jon's case. Testing this will require the development of egocentric and allocentric visual working memory tasks. More generally, it remains productive for future work to explore the boundary conditions under which amnesic patients' performance starts to break down on different tasks; this may require consideration of multiple contributory factors, including configuration complexity and accuracy resolution, as well as time, intervening activity (Dewar, Cowan, & Della Sala, 2007), and materials (Rose et al., 2012).

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Figure Captions

Figure 1. Illustration of presentation method and testing procedures for each stimulus condition in the recognition and reconstruction paradigms.

Figure 2. Mean recognition accuracy (Hits-False alarms) and reconstruction accuracy (proportion correct) for Jon and control participants in the location, color, and binding conditions in Study 1 (with standard deviations as error bars for control participants)

Figure 3. Illustration of cued recall procedure used in Studies 2 and 3.

Figure 4. Mean reconstruction and cued recall accuracy (proportion correct) in the color-location binding conditions in Study 2 as a function of retention interval (1s, 5s, 10s) for Jon and control participants

Figure 5. Mean reconstruction and cued recall accuracy on the object closed set for Jon and control participants in Study 3

Figure 6. Mean cued recall accuracy on the object open set for Jon and control participants in Study 3

Figure 7. Mean accuracy in the final object-location binding test for Jon and control participants in Study 3, with expected chance-level performance indicated

Figure 1

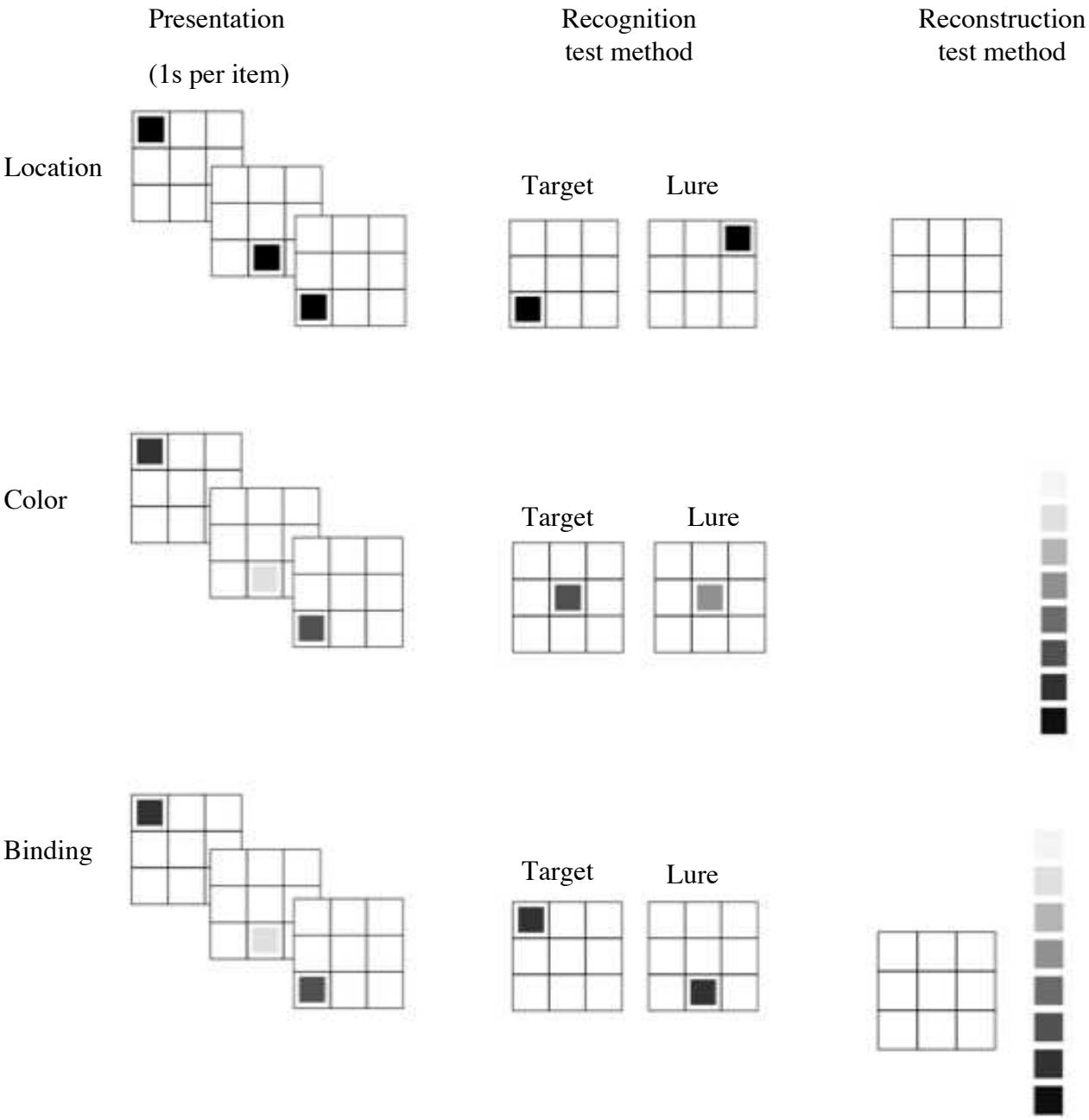

Presentation
(1s per item)
Recognition
test method
Reconstruction
test method
Location
Target
Lure
Color
Target
Lure
Binding
Target
Lure

Figure 2

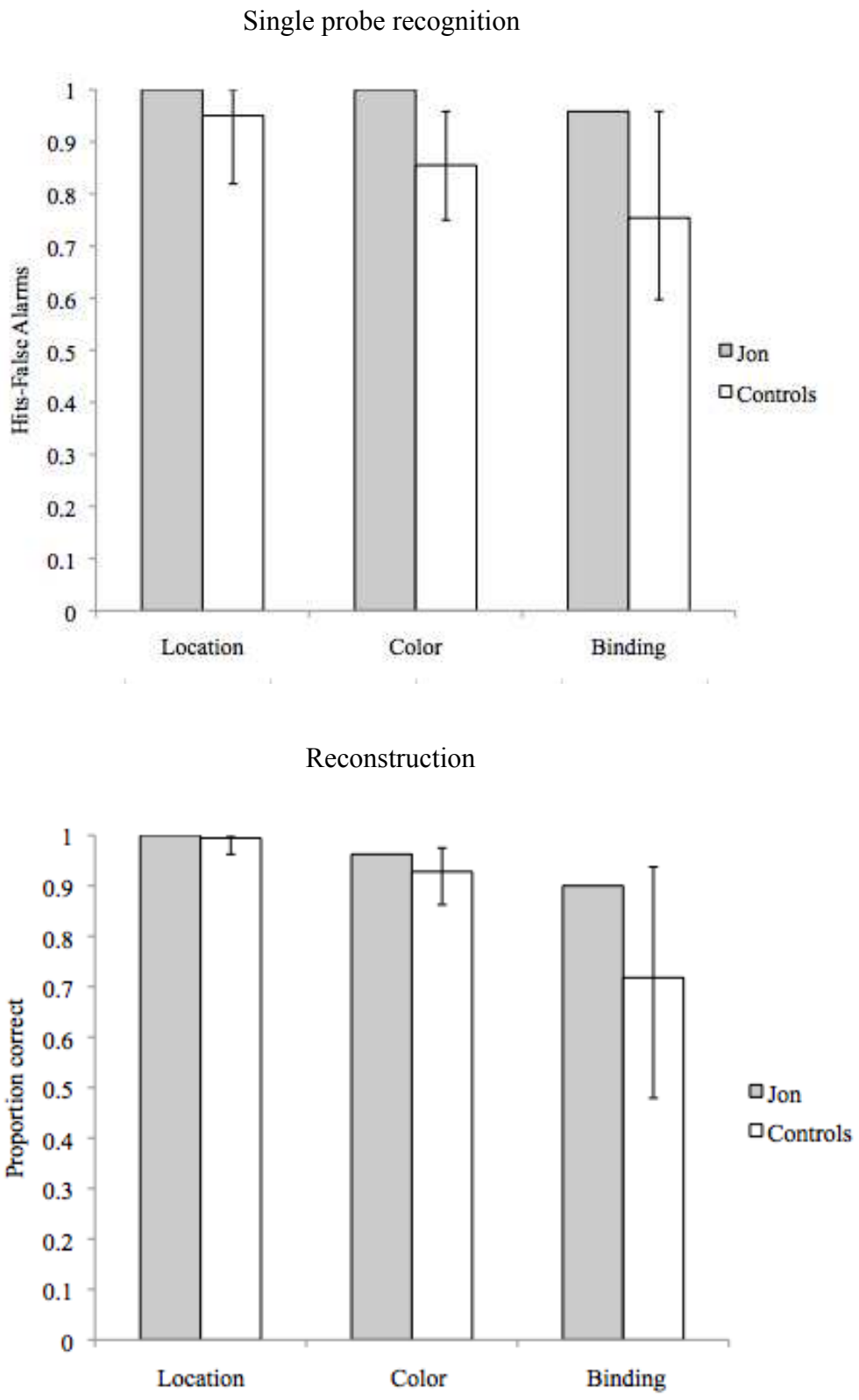

Single probe recognition
Hits-False Alarms
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Location
Color
Binding
Jon
Controls
Reconstruction
Proportion correct
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Location
Color
Binding
Jon
Controls

Figure 3

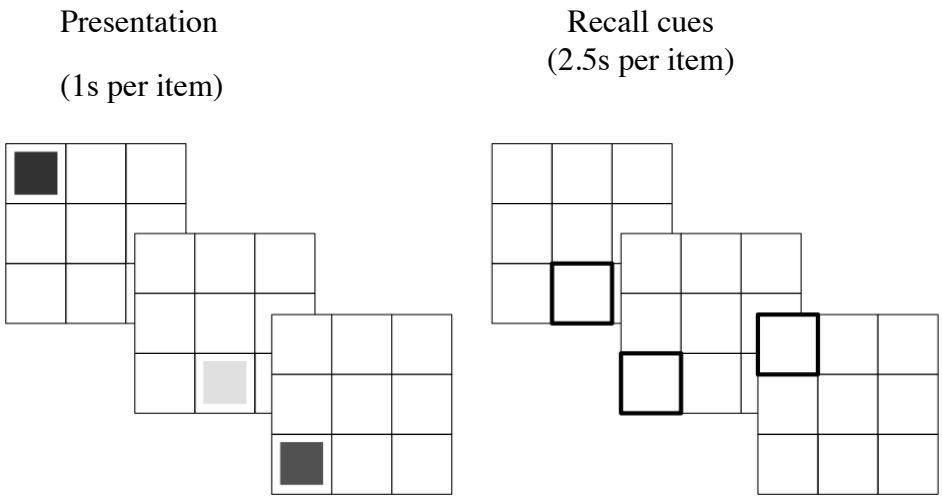
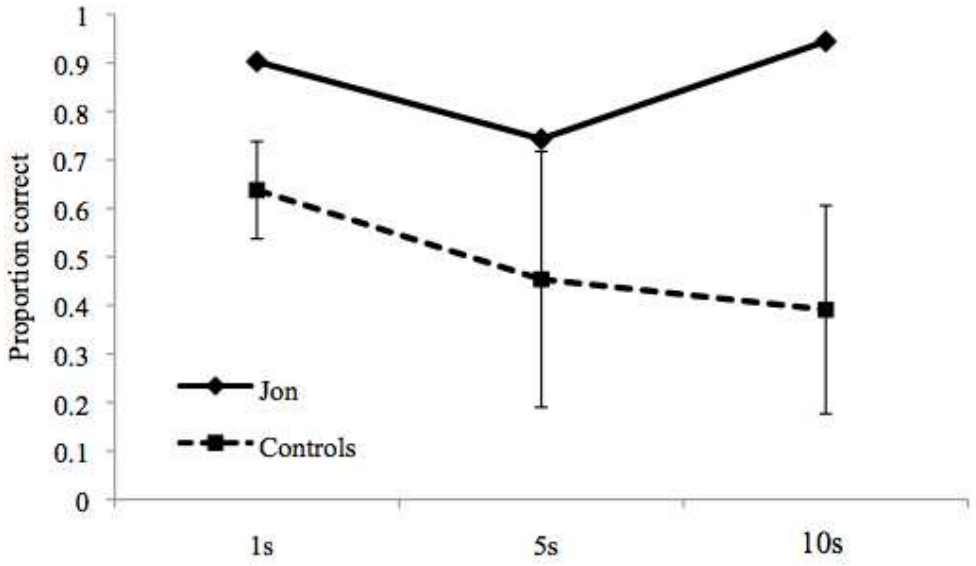


Figure 4

Binding condition - Reconstruction



Binding condition – Cued recall

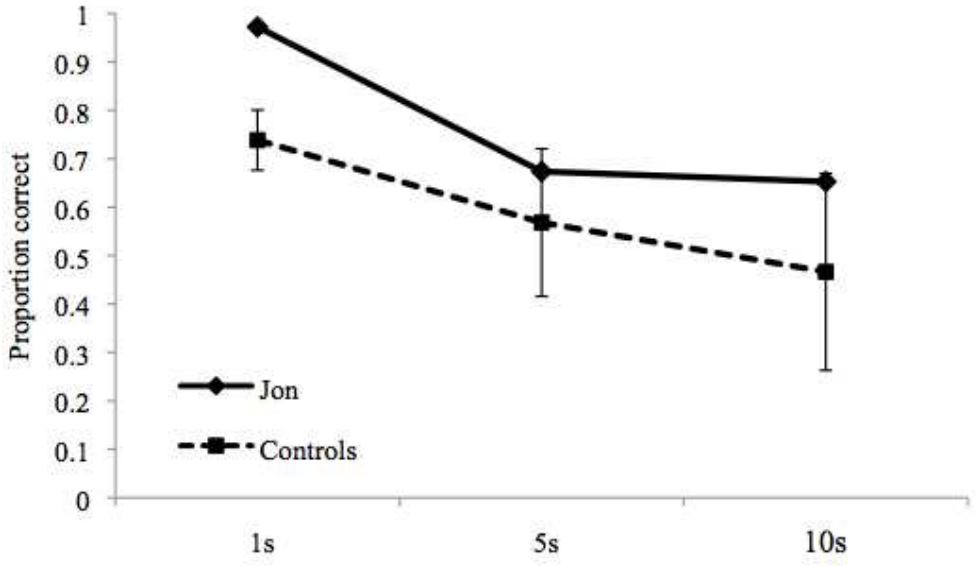
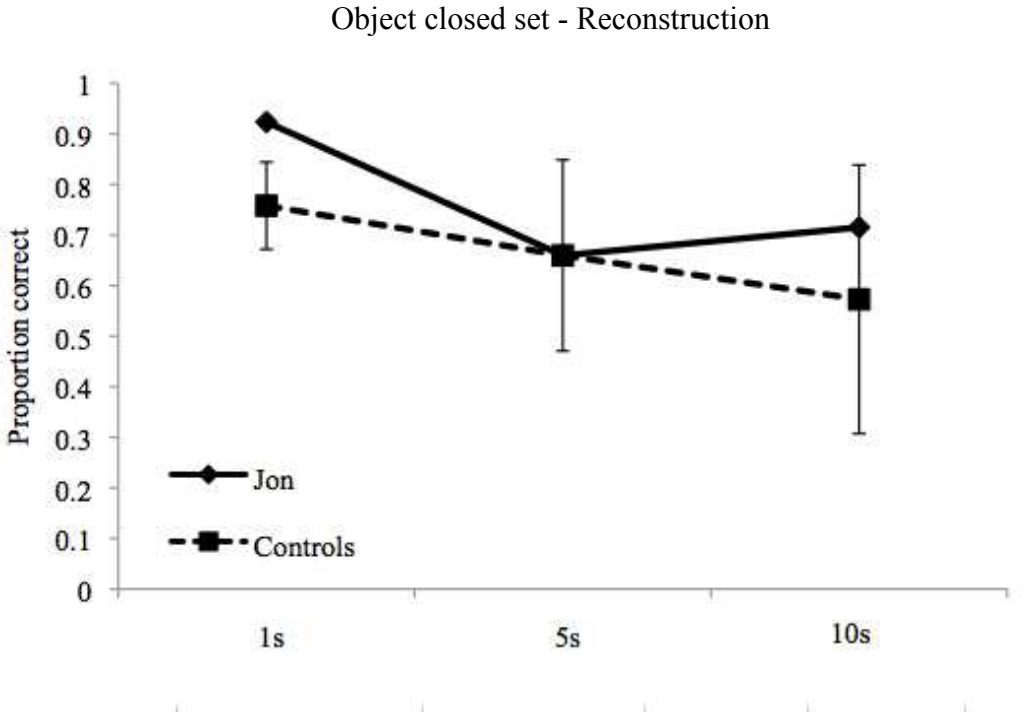


Figure 5


Object closed set - Reconstruction
Proportion correct
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Jon
Controls
1s
5s
10s

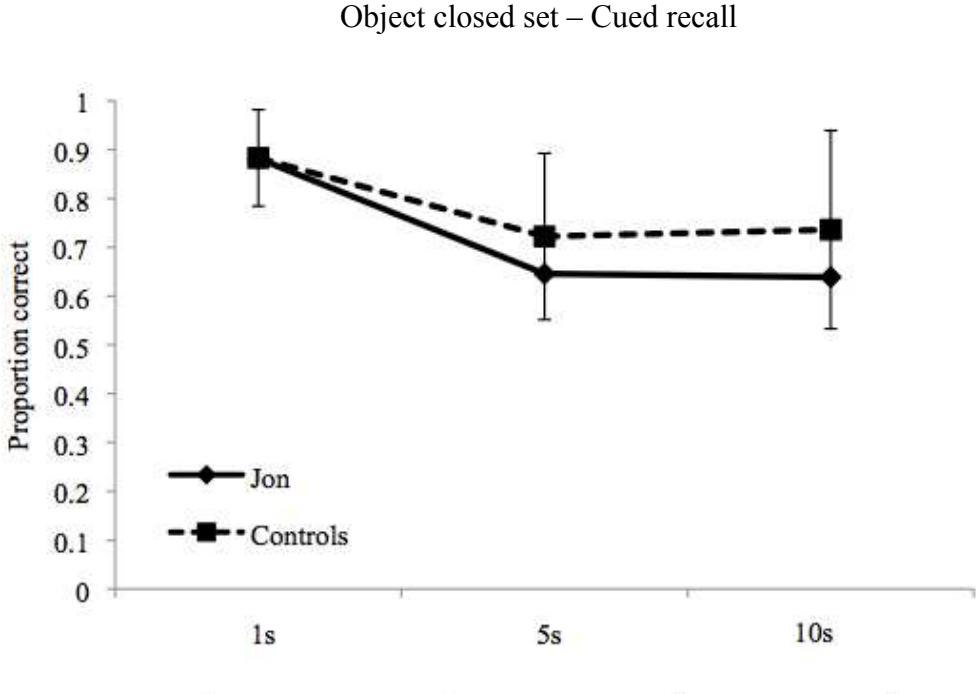

Object closed set – Cued recall
Proportion correct
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Jon
Controls
1s
5s
10s

Figure 6

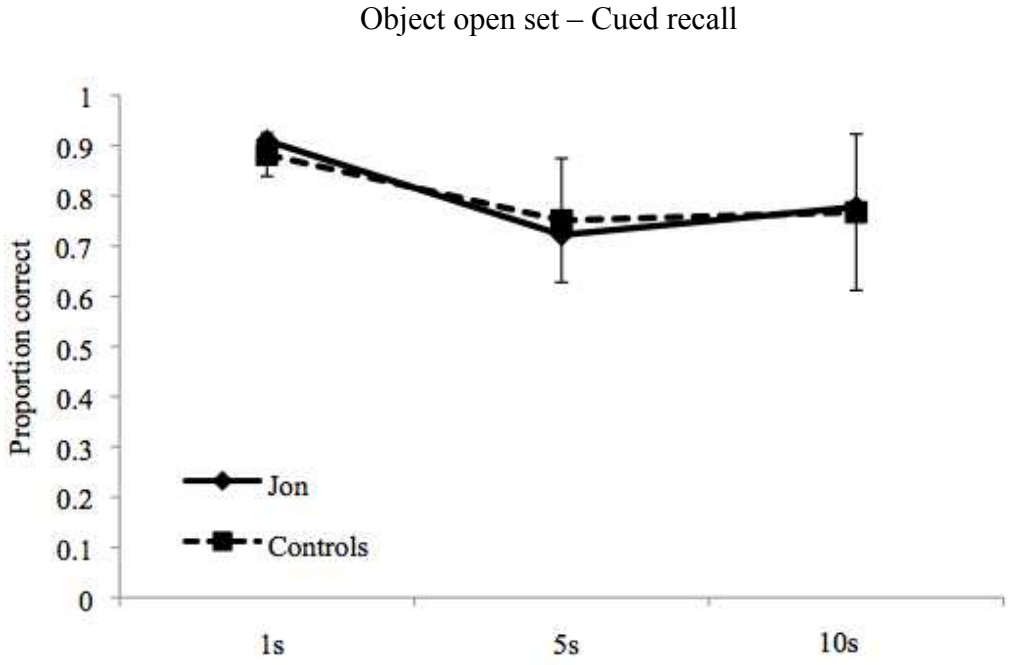
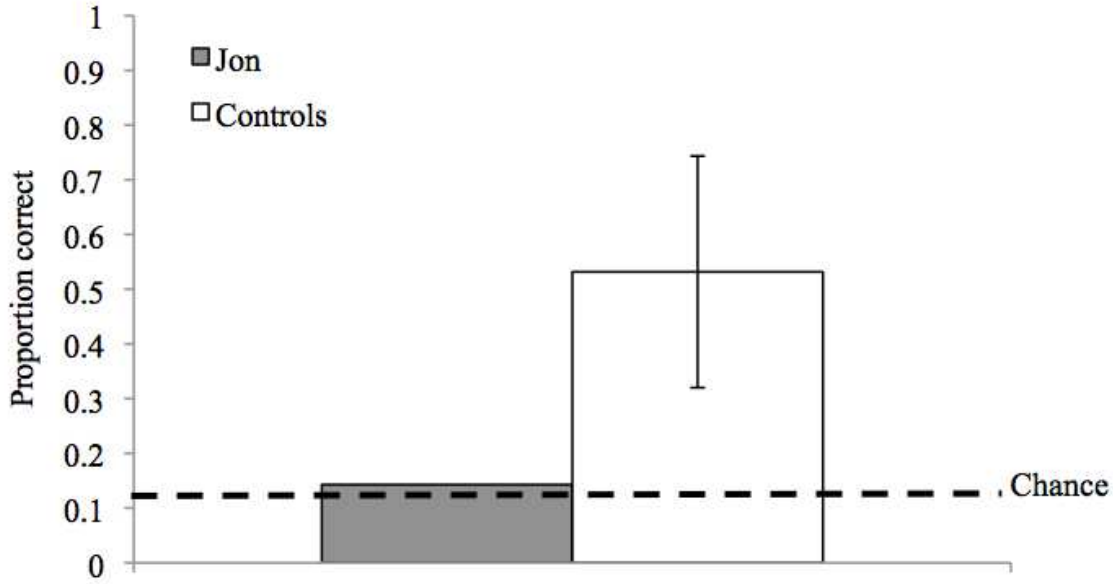

Object open set – Cued recall
Proportion correct
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Jon
Controls
1s
5s
10s

Figure 7


1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Proportion correct
Jon
Controls
Chance