Tests of pattern separation and pattern completion in humans – a systematic review

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ABSTRACT

Objective: To systematically review the characteristics, validity and outcome measures of tasks that have been described in the literature as assessing pattern separation and pattern completion in humans.

Methods: Electronic databases were searched for articles. Parameters for task validity were obtained from two reviews that described optimal task design factors to evaluate pattern separation and pattern completion processes. These were that pattern separation should be tested during an encoding task using abstract, never-before-seen visual stimuli, and pattern completion during a retrieval task using partial cues; parametric alteration of the degree of interference of stimuli or degradation of cues should be used to generate a corresponding gradient in behavioral output; studies should explicitly identify the specific memory domain under investigation (sensory/perceptual, temporal, spatial, affect, response, or language) and account for the contribution of other potential attributes involved in performance of the task. A systematic, qualitative assessment of validity in relation to these parameters was performed, along with a review of general validity and task outcome measures.

Results: Sixty-two studies were included. The majority of studies investigated pattern separation and most tasks were performed on young, healthy adults. Pattern separation and pattern completion were most frequently tested during a retrieval task using familiar or recognizable visual stimuli and cues. Not all studies parametrically altered the degree of stimulus interference or cue degradation, or controlled for potential confounding factors.

Conclusion: This review found evidence that some of the parameters for task validity have been followed in some human studies of pattern separation and pattern completion, but no study was judged to have adequately met all the parameters for task validity. The

contribution of these parameters and other task design factors towards an optimal behavioral paradigm is discussed and recommendations for future research are made.

INTRODUCTION

Pattern separation and pattern completion are specific computational processes thought to underlie the storage and retrieval of information by the hippocampus (Treves and Rolls, 1992; O'Reilly and McClelland, 1994). During encoding, overlap between potentially similar incoming activity patterns is minimized (pattern separation) and these representations can be subsequently retrieved, even when only partial or degraded versions of the original input pattern are presented (pattern completion).

The functional neuroanatomy of the hippocampus reflects a representation of cortical activity at a cell-population level (Marr, 1971).Theoretical models of the function of hippocampal subregions (Treves and Rolls, 1992; O'Reilly and McClelland, 1994; Rolls, 2013; Kesner and Rolls, 2015) propose that the dentate gyrus (DG) operates as a competitive neuronal network to perform pattern separation, delivering relatively orthogonal representations to CA3 via sparse mossy fiber projections. CA3 neurones operate as an autoassociation or attractor network (Rolls, 2007), allowing episodic memories to be formed and stored within the CA3 network. Its recurrent collateral connectivity facilitates pattern completion, as the retrieval of a whole representation can be initiated by the activation of some small part of the representation. Thus CA3 may be involved in the performance of both pattern separation and pattern completion depending upon the particular demands of a task, with small changes in the environment causing a pattern completion function, but as the inputs become increasingly dissimilar this switches to pattern separation (Guzowski et

al., 2004). Converging evidence from animal studies (Lee et al., 2005; Leutgeb et al., 2007;

McHugh et al., 2007) and human functional magnetic resonance imaging (fMRI) studies

(Bakker et al., 2008; Lacy et al., 2011) supports the functional specialization of connected

subregions within the hippocampus. Most human imaging studies are limited in their spatial

resolution and cannot reliably distinguish between the DG and CA3 subregions, although a

few studies report to have achieved this (Bonnici et al., 2012b; Wisse et al., 2012).

Performance of pattern separation in the DG is believed to be enhanced by the presence of

adult neurogenesis, with distinct and complementary roles having been identified for

immature and mature adult-born neurons (Clelland et al., 2009; Aimone et al., 2010).

Inhibition or disturbance of these memory processes has been proposed to contribute

towards many neuropsychiatric conditions in humans, including age-related cognitive

impairment (Holden and Gilbert, 2012), cognitive difficulties associated with depression

(Sahay and Hen, 2007), post-traumatic stress disorder (Kheirbek et al., 2012) and

schizophrenia (Tamminga et al., 2010).

A 'good' test should measure what it is intended to measure (i.e. validity). However, the

way in which pattern separation and pattern completion should be most validly tested in

humans has been subject to debate (Hunsaker and Kesner, 2013), as task performance

cannot be directly related to neuronal activity at the cell population level as in animal

studies. Discrepancies have arisen as a consequence of the sometimes extended uses of the

terms "pattern separation" and "pattern completion" to describe behavioral discrimination

or generalization operations, which are not strictly equivalent to the computational

processes as conventionally defined (Aimone, 2011). Tasks are unlikely to be 'process-pure',

and the conditions under which they are presented can influence which process

predominates during their performance. An assessment of task validity will allow future

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studies to decide which test should be used to assess pattern separation and pattern completion in order to make valid conclusions about the computational processes underlying memory and behavior.

Recently, two influential reviews have explicitly described ways in which the validity of tasks that measure pattern separation and/or completion can be optimized in humans (Hunsaker and Kesner, 2013; Deuker et al., 2014). These are summarized as follows:

1) Ideally, pattern separation should be tested during performance of an encoding task and pattern completion during a retrieval task.

Pattern separation and pattern completion processes are performed by different neuroanatomical structures, using distinct coding mechanisms and occur during different phases of memory processing (pattern separation during encoding and pattern completion during retrieval) (Treves and Rolls, 1992; O'Reilly and McClelland, 1994). Hunsaker and Kesner (2014) define an encoding task as one during which encoding is the more efficient strategy to perform the task correctly, and a retrieval task as one during which retrieval is the more efficient strategy to perform the task correctly. If other parameters (below) are appropriately met then it is assumed that pattern separation predominates during encoding tasks and pattern completion during retrieval tasks.

2) If a task uses visual stimuli, then abstract, never-before-seen objects should be used in tests of pattern separation, as familiar objects will cue retrieval of prior associations that will engage pattern completion.

Use of images of everyday objects in pattern separation tasks might lead to the retrieval of existing memory representations during experimental encoding, thus increasing the difficulty of dissociating pattern separation and pattern completion. A similar issue arises if a task requires participants to learn a list of words, as the meaning of the words will be automatically retrieved when read during the encoding phase (Hunsaker and Kesner, 2013). This problem may be mitigated by using abstract, never-before- seen objects during encoding for which no prior associations have been formed (Deuker et al., 2014).

3) Retrieval tests utilising partial cues will bias towards pattern completion compared to presentation of similar but not identical ('noisy') cues, through minimization of encoding of novel features that will engage pattern separation.

A partial cue is defined as a subset of the original activity pattern, whereas a noisy cue is a subset of the original activity pattern with the addition of novel features. The latter would tend to preferentially engage pattern separation (O'Reilly and McClelland, 1994), whereas the former would be more likely to engage the pattern completion process in a manner directly proportional to the degree of cue similarity (Treves and Rolls, 1992).

4) Parametric alteration of the degree of interference of stimuli or degradation of cues should be used to generate a corresponding gradient in behavioral output.

A graded behavioral response that scales with the degree of interference allows stronger conclusions to be made about the memory processes involved, than if results were solely a binary same-different response. Incremental changes in the environment may influence the

balance between pattern separation and pattern completion processes in the hippocampus (Guzowski et al., 2004; Leutgeb et al, 2007; Lacy et al, 2011).

5) Studies should explicitly identify the specific memory domain under investigation (sensory/perceptual, temporal, spatial, affect, response, or language) and make attempts to control or account for the contribution of other potential memory attributes involved in performance of the task.

The attribute model of memory (Kesner, 2013) describes memory attributes as the component processes of a memory system that can interact with each other and map onto specific anatomical regions. Pattern separation and pattern completion can occur across any attribute (Hunsaker and Kesner, 2013). The sensory/perceptual attribute involves memory representations of sensory/perceptual stimuli in any modality, i.e. visual, odor, sound, taste, somatosensory. The temporal attribute involves memory representations of the duration, temporal sequence, and associations between sensory/perceptual stimuli. The spatial attribute involves memory representations of egocentric (location of object relative to self) and allocentric (location of object relative to another object/part of object) spatial locations. The affect attribute involves memory representations of (positive and negative) reward value and emotional experiences. The response attribute involves memory representations of motor responses to stimuli, learned stimulus-response and action-outcome associations. The language attribute, presumed to be unique to humans, involves memory representations of phonological, lexical, syntactical, and semantic information. Application of the attribute model to task design will allow a researcher to emphasize the attribute being tested and explicitly account for confounds or the contribution of other attributes.

Although a range of tasks has been used to test pattern separation and/or pattern completion in humans, no previously published review has systematically assessed these tests in relation to the above strategies for optimizing validity. The valid use of task performance as a putative correlate for pattern separation or pattern completion has the potential to improve the understanding, diagnosis and treatment of memory disorders and other neuropsychiatric conditions. The aims of this study were to systematically review the characteristics, validity and outcome measures of tasks that had been described in the literature as assessing pattern separation and pattern completion in humans.

METHODS

Literature search

Online literature databases (PubMed, PsycINFO, Embase and Web of Science) were searched up to 14th September 2015 using the search terms "pattern separation" OR "pattern completion" OR "memory resolution". The term memory resolution was proposed in a recent review (Aimone et al., 2011) to describe the unique pattern separation function of the DG secondary to two neuronal populations that arise from neurogenesis. The combined properties of immature and mature adult-born DG granule cells are proposed to enhance memory resolution and improve behavioral discrimination.

Inclusion/exclusion criteria and screening

Studies were included if they were published, peer-reviewed papers in human subjects aged at least 18 years old with any or no mental or physical health condition. Pattern separation was defined as the computational process for encoding representations of similar input

patterns as more distinct from each other, by reducing the overlap between similar input patterns before they are stored. Pattern completion was defined as the computational process for retrieving stored output patterns when presented with partial or degraded input patterns. To ensure that the outcome measure was specific as possible to pattern separation or pattern completion, the presence of a stated a priori hypothesis including these terms was required, or a statement saying that the behavioral task had aimed to assess these processes.

Studies were excluded if mention of pattern separation or pattern completion was only made in post-hoc discussions of data findings, or if the study failed to describe the behavioral task in any detail. Pattern separation and pattern completion refers specifically to memory processes and consequently, studies that did not use an encoding or retrieval test were excluded. An encoding task was defined as any study having a learning or sample phase, or an incidental encoding task. A retrieval task was defined as any study that included a test or choice phase.

Studies were independently screened and selected for inclusion based on study titles and abstracts by two authors RG and KL. Discrepancies were resolved through discussion to reach a consensus.

Data extraction

Four authors (KL, MC, RG and EW) independently extracted data on study characteristics, behavioral task design and task validity using a structured form, and each study was rated by two authors. Discrepancies were resolved through discussion.

Qualitative assessment of validity

In order to assess the validity of pattern separation and pattern completion tests, relevant factors in task design (detailed in the Introduction) were identified from reviews retrieved from the literature search and used as the parameters for validity. A study that met more of these parameters was assessed to have better task validity. Studies were also rated for general validity factors (use of a comparison group or task, correlation with additional investigations, use of practical training and generalizability). The outcome measures of pattern separation and pattern completion tasks were also recorded and compared in order to assess the validity of the scoring methods used.

Studies were judged to have used novel, abstract stimuli if these were shapes, silhouettes or lines and were not easily identifiable as everyday objects, faces, animals or scenes. A partial cue was defined as any cue that was a subset of the original stimulus, as opposed to a 'noisy' cue, which was a subset of the original stimulus with the addition of novel features. A study was judged to have parametrically altered the degree of interference of stimuli or degradation of cues if it employed two or more degrees of change for the stimulus or cue, e.g. low/high similarity, or use of a rating scale scoring from 1-5, etc. Continuous recognition paradigms were regarded as involving both encoding and retrieval elements and were classed separately to those with distinct encoding and retrieval phases.

RESULTS

Identification and characteristics of included studies

Literature searches identified 2164 potential studies, 62 of which met inclusion criteria for data extraction (Figure 1, PRISMA flow diagram).

Supplementary Table S1 summarizes the characteristics of 62 studies that assessed pattern separation, pattern completion or both. Within these studies, 43 assessed pattern separation, seven assessed pattern completion and 12 looked at both. Most (57) studies employed a cross-sectional design, five were longitudinal and 31 included a comparison group. The majority (49) of studies were done in healthy, non-clinical populations and 12 studies were in a defined neuropsychiatric clinical population. If an independent variable was investigated, this was most frequently age (18 studies), followed by mood or general arousal (nine studies) and cognitive impairment (four studies). Other factors investigated included the effects of fear or reward, drug or diet, hippocampal damage, exercise, schizophrenia and autistic spectrum disorder. Most (37) studies tested younger adults (mean age 24 years), five studies tested older adults (mean age 71 years) and 19 studies looked at both age groups. 59% of all study participants were female. The number of years of education was included in 17 studies (mean = 15.5 years).

Qualitative validity of pattern separation and pattern completion tests

Validity and outcome measure data for studies that aimed to assess pattern separation are presented in Table 1, for pattern completion in Table 2, and for both in Table 3.

Assessment of studies in relation to the parameters for task validity

Only 11 out of 55 studies that tested pattern separation did so during a distinct encoding task, and this was stated to be incidental encoding in seven studies. The majority (15 out of 19 studies) of studies that tested pattern completion did so during a distinct retrieval task. A continuous recognition paradigm (and hence involved both encoding and retrieval elements)

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was used in nine pattern separation studies and four studies that assessed both pattern separation and pattern completion.

All of the studies reviewed used visual stimuli. Out of the 55 studies that tested pattern separation, 11 used novel, abstract stimuli. One study used English words (Ly et al., 2013) and the remainder employed familiar and easily identifiable everyday objects, faces, animals or scenes.

Out of the 18 studies that tested pattern completion, three used non-verbal partial cues. Two studies used typed English words (Horner and Burgess, 2014; Horner et al., 2015); in the later study a partial cue was represented by the word or 'element' presented to cue retrieval of other elements from the encoded 'event'. The remainder of the pattern completion studies employed 'noisy' cues (a subset of the original stimulus with the addition of novel features).

All three studies that tested pattern completion with non-verbal partial cues parametrically altered the degree of degradation to generate a corresponding gradient in behavioral output, either by changing the number of wall cues in a 3D navigation task (Paleja et al., 2011; Paleja and Spaniol, 2013) or the degree of completeness of stimuli (Vieweg et al., 2015). Twenty six out of 55 studies that tested pattern separation parametrically altered the degree of interference to generate a corresponding gradient in behavioral output, either by using subjective ratings of similarity between pairs of stimuli, or by employing objective degrees of change, such as size, location, rotation and appearance using computer software. Several studies used mnemonic ratings for each lure obtained from false alarm rates on a separate behavioral test, where a higher probability of a lure item being called "Old" corresponded to greater mnemonic similarity (Lacy et al., 2011; Yassa et al., 2011a; 2011b; Kim et al., 2013; Bennett et al., 2015).

The primary memory attribute under investigation could be identified from the description of all the studies, but the degree to which this was stated explicitly varied as no study described using the memory attribute model for task design. As all of the studies used visual presentation of objects or images it was judged that the sensory/perceptual domain was always involved, however only seven studies reported to have controlled for perceptual processing or visual discrimination differences by using a comparison task. Other potential memory attributes overlooked by almost all studies was the response and language domain, which could have been operating during button-presses, reading and use of language tags. Four studies clearly controlled for motor responses by using a baseline task (Paleja and Spaniol, 2013; Staresina et al., 2013) or by employing multi-voxel pattern analysis to functional imaging data (Bonnici et al., 2012a; 2012b).

Although no study explicitly used the memory attribute model for task design, five studies were judged to have adequately fulfilled the other parameters for task validity and attempted to account for at least one confounding factor. Two of these assessed pattern separation (Bonnici et al., 2012a; Fujii et al., 2014), two assessed pattern completion (Paleja and Spaniol, 2013; Vieweg et al, 2015) and one assessed both (Paleja et al., 2011).

General validity factors

A comparison group or task was used in 36 studies, and 31 studies explicitly accounted for the effects of specific confounding factors such as the sex of participants, reaction time, level of confidence in response accuracy, stimulus class, cognitive differences and attention. Practical training was given in a total of 13 studies, mostly in tasks that assessed pattern completion (10). Additional investigations were used in 38 studies, and behavioral

performance was most frequently correlated with hippocampal fMRI activity (23 studies).

Performance on the Rey Auditory Verbal Learning Test (RAVLT) and Hopkins Verbal Learning Test-Revised (HVLT-R) was correlated with decreased pattern separation scores in older adults, but was less sensitive than the discrimination task in revealing variability within a healthy older adult group (Roberts et al., 2013, Holden et al., 2012; 2013; Sheppard et al., 2015). Generalizability of results was limited as 30 out of 62 studies were performed in young, healthy adults, and only two studies gave details on ethnicity of participants (Das et al., 2014; Martinelli and Shergill, 2015).

Outcome measures for pattern separation and pattern completion

The most commonly adopted outcome measure for pattern separation was the discrimination of similar but not identical 'lures' to a target object, or a measure of the fMRI response to lures. Thirty-three of the 55 studies that tested pattern separation calculated a corrected pattern separation score, but different methods were used to estimate this. For example, 26 studies subtracted a "similar" bias rate (misidentification of novel foils as similar), whilst 4 studies corrected for a 'false alarm' rate, sometimes referred to as a pattern completion bias (misidentification of lures as "old"). One study (Shelton and Kirwan, 2013) did both, (p("similar" | lure) −p("similar" | foil)) − (p("old" | lure) − p("old" | foil)).

In tasks that measured fMRI activity in the DG/CA3 region, a pattern separation signal was indexed by higher activity in DG/CA3 to lure correct rejections compared to exact repetitions but similar to first presentations in some studies (Bakker et al., 2008; Lacy et al., 2011; Azab et al., 2014) or higher activity in DG/CA3 during lure correct rejections compared to false alarms in one study (Leal et al., 2014). In studies that used fMRI to study pattern separation processes during the encoding phase of a task, pattern separation was indexed by increased

activity in the hippocampus (Kirwan and Stark, 2007) or DG/CA3 region (Fujii et al., 2011) that predicted subsequent memory, or by increased neural pattern distinctiveness in the hippocampus compared to the medial temporal lobe cortex (MTLC) (Bonnici et al., 2012; LaRocque et al, 2013; Huffman and Stark, 2014).

Outcome measures for pattern completion were more heterogeneous. As for pattern separation studies, response to lures was a common outcome measure. Five out of 19 studies that tested pattern completion measured the lure 'false alarm' rate (misidentifying lures as "old"), and three of these corrected lure false alarm scores for baseline false alarm rate (misidentification of novel foils as "old"). Seven studies measured the fMRI activity accompanying lure presentation, either looking for distinct memory traces or neural activation patterns during retrieval (Kuhl et al., 2010; Bonnici et al., 2012b), or the difference in fMRI activity between similar and old or novel cues (Lacy et al., 2011; Motley and Kirwan, 2012) and between conditioned and unconditioned stimuli (Lissek et al., 2014). Most pattern completion studies that used fMRI signal as an outcome implicated the hippocampus as a whole; one study (Lacy et al., 2011) associated CA1 activity with pattern completion. Correctly matching previously learned direct or indirect associations was also used as a measure of pattern completion in several studies (Dudukovic et al., 2011; Horner and Burgess, 2014; Staresina et al., 2013; Horner et al., 2015), as was correct navigation to a learned spatial location (Paleja et al., 2011; Paleja and Spaniol, 2013).

DISCUSSION

Aspects of good task validity were variably addressed by the reviewed studies. Testing pattern completion during a retrieval task was a validity parameter that was most

adequately met, and the explicit attempt to account for other memory attributes that potentially contributed to performance was a parameter that was least adequately addressed by the reviewed studies. For studies that tested pattern separation, only 20% did this during an encoding task, the same proportion used abstract, novel stimuli and 47% parametrically altered the stimuli to generate a corresponding gradient in behavioral output. Only 17% of studies that tested pattern completion used parametrically altered partial cues.

Encoding and retrieval tasks

Assessment of pattern separation during a distinct encoding phase has required concurrent measurement of neural activity within specific anatomical regions using functional imaging as an outcome measure. The main criticism of assessments of pattern separation that have used behavioral discrimination of lures as an outcome measure (and thus have employed an explicit retrieval task or continuous recognition paradigm) is the potential use by subjects of a 'recall to reject' strategy. Incidental encoding is thought to reduce this (Lacy et al., 2011; Yassa et al., 2011b), and many studies have used an incidental encoding task prior to presentation of an unexpected or surprise memory test. The effectiveness of these designs in reducing the use of a 'recall to reject' strategy relative to intentional encoding is, however, not established (Huffman and Stark, 2014; Motley and Kirwan, 2012). A recent study (Stark et al., 2015) showed that the age-related lure discrimination impairment in healthy older adults remained despite changing the task format from an incidental study phase to an intentional design. The same study also showed that changing from a study/test design to a continuous recognition paradigm did not rescue the age-related lure discrimination impairment. However, continuous recognition led to improved overall

performance, possibly due to the reduced time lag between first presentation and lure in continuous designs compared to a study/test format.

Several studies associated performance on a discrimination task with both pattern separation and pattern completion, and corrected pattern separation scores for a pattern completion bias. However it is unclear how much pattern completion contributes to discrimination behavior if similar rather than partial or degraded cues are used, and the false alarm rate could be due to poor initial encoding rather than a bias towards pattern completion (Molitor et al., 2014).

Any measure of pattern completion will be contaminated with some degree of encoding, and the behavioral outcome will also depend on the quality of initial encoding. To overcome poor initial encoding, some pattern completion studies delivered practical training to ensure subjects reached a minimum performance standard before the retrieval test (Bonnici et al., 2012b; Vieweg et al., 2015), or employed self-paced encoding (Shelton and Kirwan, 2013). Practical training partially addresses the issue of poor initial encoding by familiarising participants with the environment and equipment using different visual stimuli prior to testing may reduce potential novelty and practice effects. However, the quality of encoding on any given trial can be subject to many other sources of variability, such as attention, previously stored information, and cognitive differences.

Stimuli and cues

Although the use of novel abstract images is favored over familiar everyday objects in the valid assessment of pattern separation, studies that employed the latter still showed activation of hippocampal regions (DG/CA3). Whilst this finding does not dispute the validity of these tasks in taxing pattern separation, it is not proof that pattern separation is occurring

in these regions (Poldrack, 2006) and does not exclude other plausible explanations for the findings, such as a match-mismatch signal (Kumaran and Maguire 2009). In the design of a valid pattern separation task, it may be more important to assess the ability to discriminate similar items whilst controlling for stimulus category (e.g. faces, objects, scenes), as these may each be processed differently by the hippocampus. Pattern separation tasks that compared face and object categories differed in hippocampal fMRI activation patterns and behavioral accuracy (Kirwan and Stark, 2007; Kirwan et al, 2012). Although it was proposed that this could be due to the higher degree of similarity between faces, it is also known that faces are processed differently to objects by the visual system (Kanwisher et al., 1997; Haxby et al., 2000) and this may influence output. In contrast, another study (Huffman and Stark, 2014) showed lack of category discrimination in the hippocampus during tasks that used faces and scenes or faces and objects, supporting a 'representationally agnostic' role in pattern separation, but the authors acknowledge that this conclusion was constrained by the fMRI resolution available.

A recent study (Horner et al., 2015) that assessed pattern completion of elements (represented by words of locations, people and objects/animals) from encoded multi-element 'events' showed that each element type activated distinct neocortical regions, and that hippocampal activity during encoding predicted subsequent memory performance. Only four studies tested pattern completion using partial cues and more research is needed to assess the significance of this validity parameter, and whether verbal and non-verbal partial cues are mnemonically equivalent.

Parametric manipulation

Reviewed studies employed several different methods for parametric alteration of a stimulus or cue similarity. It is not yet clear whether changing input objectively on a morphometric scale is equivalent to changing the level of mnemonic difference assessed by subjective ratings (Lacy et al, 2011). The former method may be more suitable for presentation of abstract images and the latter for recognizable objects. Discrimination of everyday objects shown in a continuous recognition paradigm, without any parametric alteration of interference, was still associated with DG/CA3 activity (Yassa et al., 2010; Yassa et al., 2011b; Bakker et al., 2012; Doxey and Kirwan, 2015). It is possible that parametric alteration of interference may not be reflected linearly in memory, especially if the mnemonic computation is not sensitive enough to detect small parametric changes. Thus a non-parametric manipulation of a non-abstract stimulus may produce an equivalent mnemonic representation to detect differences in pattern separation or pattern completion. However, parametric alteration of objective or subjective similarity does appear to increase the sensitivity of the task to detect changes in pattern separation with age in healthy adults (Tolentino et al., 2012; Paleja and Spaniol, 2013; Reagh et al., 2014; Leal and Yassa, 2014; Pidgeon and Morcom, 2014; Roberts et al., 2014).

Memory attribute model

There is evidence that multiple domains of memory can be processed by the hippocampus, and the DG may act as a domain-general, 'universal pattern separator' (Azab et al., 2014; Roberts et al., 2014). Although few studies explicitly accounted for additional memory attributes that may have potentially confounded performance on a task, some of the findings show that these factors can contribute to performance and thus support the use of the memory attribute model.

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Sensory/perceptual memory attribute

The sensory/perceptual domain was divided into conceptual (semantic) and perceptual similarity in two studies in older adults (Ly et al., 2013; Pidgeon and Morcom, 2014). Although these studies differed in their findings, it is probably that the semantic content and perceptual differences of images of meaningful objects (Stark et al., 2010; Yassa et al., 2011a), or nameable shapes (Tolentino et al., 2012) can differentially influence estimates of age-related impairments in spatial, temporal, or perceptual discrimination.

Temporal memory attribute

The duration of encoding and retrieval, the delay between them, as well as the order and number of repetitions within the presented paradigm could significantly affect computational and behavioral performance. Participants were more likely to correctly identify lures if they followed new trials than if they were presented after old trials, and this effect was strongest for a shorter inter-stimulus interval (ISI) (500ms) than a longer ISI duration (2500ms) (Duncan et al., 2012). In addition, repeated exposures (1 or 3) of stimuli improved target recognition but also impaired discrimination of similar lures (Reagh et al., 2014), although the latter finding was subsequently opposed in a recent study that used signal detection theory to measure lure discrimination (Loiotile and Courtney, 2015).

A recent study (Stark et al., 2015) showed that neither reducing the set size (and thus time and number of intervening items between study and test) nor repeated testing on two independent runs had any effect on age-related lure discrimination impairment. The study proposed a minimum number of 20 items per condition (lures, foils, targets) to obtain a

reliable measure of age-related lure discrimination bias, but the full 64-item per condition set would allow lures to be classified based on their similarity.

Affect attribute

The memory of visual stimuli with an emotional component may be better preserved over time compared to neutral stimuli (Leal et al., 2014a), and the internal emotional state of participants may also influence performance, whether that be general arousal level (Segal et al., 2012) or the presence of depressive symptoms (Déry et al., 2013; Shelton and Kirwan, 2013; Fujii et al., 2014; Déry et al., 2015). Incorporation of reward or negative stimuli into a paradigm can also act to condition behavioral discrimination (Bonnici et al., 2012; Lissek et al., 2013).

Response and language attributes

Tasks that used visual object paradigms often required participants to use linguistic tags to mentally name or describe the objects, which could potentially involve the language attribute (Hunsaker and Kesner, 2013). Most of the reviewed studies asked participants to respond with a keyboard press, and several studies controlled for a motor component of task performance by using a baseline task.

As "similar" trials should demand a greater load on pattern separation than "old" trials, many studies used an explicit three-alternative forced choice task where a "similar" response to lures was assumed to be more selective for pattern separation. The main criticism of this design is the inability to characterize the "similar" response to lures; some "similar" responses might represent a low-confidence "old" judgement. To counteract this

issue, a recent study (Loiotile et al., 2015) advocated for an "old" or "new" recognition judgement in a two-alternative forced choice task to measure lure-old discrimination using a signal detection theory model. However, these differences in task design did not change the finding of an age-related deficit in lure discrimination in healthy older adults (Stark et al., 2015).

Directions for future research

A number of observations concerning the most valid potential experimental approaches emerge from our review of the published studies of pattern separation and completion in humans. Here we use the available evidence to refine the existing published parameters of validity and highlight where further original research is required.

The measurement of hippocampal fMRI activity during lure discrimination in an encoding task has been the most valid method of assessing pattern separation. Future studies should aim to replicate or extend current neuroimaging paradigms and analysis techniques to detect this cognitive process. Although behavioural lure discrimination in a continuous recognition paradigm has been consistently associated with fMRI activity in DG/CA3, further investigation of this signal's response to graded levels of novelty will strengthen the validity of utilising behavioural lure discrimination as a measure of pattern separation

The heterogeneous range of outcome measures for pattern completion reflects the different retrieval processes it is believed to underpin. The extent to which pattern completion is involved when studies presented stimuli to prompt retrieval, demanded exact identification or naming, or asked participants to indicate "old, similar, or new" versus "remember or know" requires further research that may also benefit from concurrent functional neuroimaging.

Further studies that use partial cues to test pattern completion are required. In addition, any task that uses recognizable visual stimuli should ideally select stimuli that originate from the same stimulus class (e.g. faces, objects, or scenes). Although the use of novel, as opposed to never-before-seen objects, or incidental versus intentional encoding theoretically improves task validity, the evidence for this is not fully established.

Wherever possible, interference or degradation should be parametrically altered to increase the sensitivity of the task to detect differences. Future studies should compare the effects of different methods of altering similarity and whether perceptual, semantic or mnemonic similarity changes are equivalent.

Consideration of the attribute model (Hunsaker and Kesner, 2013) is useful in accounting for changes in other memory domains that may contribute to performance. In addition, baseline differences such as age and gender should be accounted for, and a control task or group should be used to control for response bias.

Finally, longitudinal studies are required to investigate potential changes in pattern separation performance with ageing, disease progression or the effects of potential therapeutic interventions.

Limitations of the review

This review excluded studies that did not include the terms "pattern separation" or "pattern completion" in their hypothesis or introduction, but attributed their results to these processes post-hoc. Non-peer reviewed studies including posters and dissertations were also excluded. These excluded studies may have used other tasks for testing pattern separation or pattern completion that were not reviewed, and inclusion of these studies may have

altered the results and conclusions of the review. As the main aim of the paper was to assess how pattern separation and pattern completion have been tested in humans, a quantitative statistical review was not conducted so this review cannot comment on effect sizes.

CONCLUSION

This review found evidence that some of the parameters for task validity in tests of pattern separation and pattern completion have been followed in some human studies, but no study was judged to have fulfilled all the parameters for optimal task validity. Other aspects of general validity were variably addressed, with only half of the studies using a comparison group or task to address additional confounding factors, and the majority of studies were conducted in healthy young adults limiting generalizability to other populations. Future studies that employ and evaluate these parameters are needed in order to make strong conclusions about the computational processes that underlie task performance.

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REFERENCES

Aimone JB, Deng W, Gage FH. 2010. Adult neurogenesis: integrating theories and separating functions. Trends Cogn Sci 14:325-337.

Aimone JB, Deng W, Gage FH. 2011. Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation. Neuron 70:589-596.

Ally BA, Hussey EP, Ko PC, Molitor RJ. Dec 2013. Pattern separation and pattern completion in Alzheimer's disease: Evidence of rapid forgetting in amnestic mild cognitive impairment. Hippocampus 23:1246-1258.

Azab M, Stark SM, Stark CE. 2014. Contributions of human hippocampal subfields to spatial and temporal pattern separation. Hippocampus 24:293-302.

Bakker A, Kirwan CB, Miller M, Stark CE. 2008. Pattern separation in the human hippocampal CA3 and dentate gyrus. Science 319:1640-1642.

Bakker A, Krauss GL, Albert MS, Speck CL, Jones LR, Stark CE, Yassa MA, Bassett SS, Shelton AL, Gallagher M. 2012. Reduction of Hippocampal Hyperactivity Improves Cognition in Amnestic Mild Cognitive Impairment. Neuron 74:467-474.

Bennett IJ, Huffman DJ, Stark CE. 2014. Limbic Tract Integrity Contributes to Pattern Separation Performance Across the Lifespan. Cereb Cortex .

Bennett IJ, Stark CE. 2015. Mnemonic discrimination relates to perforant path integrity: an ultra-high resolution diffusion tensor imaging study. Neurobiol Learn Mem http://dx.doi.org/10.1016/j.nlm.2015.06.014

Bonnici HM, Kumaran D, Chadwick MJ, Weiskopf N, Hassabis D, Maguire EA. May 2012a. Decoding representations of scenes in the medial temporal lobes. Hippocampus 22:1143-1153.

Bonnici HM, Chadwick MJ, Kumaran D, Hassabis D, Weiskopf N, Maguire EA. Oct 2012b. Multi-voxel pattern analysis in human hippocampal subfields. Frontiers in Human Neuroscience 6 Oct:Art 290-13.

Borota D, Murray E, Keceli G, Chang A, Watabe JM, Ly M, Toscano JP, Yassa MA. 2014. Post-study caffeine administration enhances memory consolidation in humans. Nat Neurosci 17:201-203.

Brickman AM, Khan UA, Provenzano FA, Yeung L, Suzuki W, Schroeter H, Wall M, Sloan RP, Small SA. Dec 2014. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. Nat Neurosci 17:1798-1803.

Chadwick MJ, Bonnici HM, Maguire EA. Jul 2014. CA3 size predicts the precision of memory recall. PNAS Proceedings of the National Academy of Sciences of the United States of America 111:10720-10725.

Clelland CD, Choi M, Romberg C, Clemenson GD,Jr, Fragniere A, Tyers P, Jessberger S, Saksida LM, Barker RA, Gage FH, Bussey TJ. 2009. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science 325:210-213.

Das T, Ivleva EI, Wagner AD, Stark CE, Tamminga CA. 2014. Loss of pattern separation performance in schizophrenia suggests dentate gyrus dysfunction. Schizophr Res 159:193-197.

Déry N, Pilgrim M, Gibala M, Gillen J, Wojtowicz JM, MacQueen G, Becker S. 2013. Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. Frontiers in Neuroscience 7:66.

Déry N, Goldstein A, Becker S. 2015. Hippocampal neurogenesis at multiple time scales: a study of recent and remote memory in humans. Behav Neurosci 129: 435-449.

Deuker L, Doeller CF, Fell J, Axmacher N. 2014. Human neuroimaging studies on the hippocampal CA3 region - integrating evidence for pattern separation and completion. Front Cell Neurosci 8:64.

Doxey CR, Kirwan CB. 2015. Structural and functional correlates of behavioral pattern separation in the hippocampus and medial temporal lobe. Hippocampus 25:524-33.

Dudukovic NM, Preston AR, Archie JJ, Glover GH, Wagner AD. Mar 2011. High-resolution fMRI reveals match enhancement and attentional modulation in the human medial temporal lobe. J Cogn Neurosci 23:670-682.

Duff MC, Warren DE, Gupta R, Vidal JPB, Tranel D, Cohen NJ. May 2012. Teasing apart tangrams: Testing hippocampal pattern separation with a collaborative referencing paradigm. Hippocampus 22:1087-1091.

Duncan K, Sadanan A, Davachi L. Jul 2012. Memory's penumbra: Episodic memory decision induced lingering mnemonic biases. Science 337:485-487.

Fujii T, Saito DN, Yanaka HT, Kosaka H, Okazawa H. Feb 2014. Depressive mood modulates the anterior lateral CA1 and DG/CA3 during a pattern separation task in cognitively intact individuals: A functional MRI study. Hippocampus 24:214-224.

Guzowski JF, Knierim JJ, Moser EI. 2004. Ensemble dynamics of hippocampal regions CA3 and CA1. Neuron 44:581-584.

Haxby JV, Hoffman EA, Gobbini MI. 2000. The distributed human neural system for face perception. Trends Cogn Sci 4:223-233.

Holden HM, Gilbert PE. May 2012. Less efficient pattern separation may contribute to age-related spatial memory deficits. Front Aging Neurosci 4:9.

Holden HM, Hoebel C, Loftis K, Gilbert PE. Sep 2012. Spatial pattern separation in cognitively normal young and older adults. Hippocampus 22:1826-1832.

Holden HM, Toner C, Pirogovsky E, Kirwan CB, Gilbert PE. Jul 2013. Visual object pattern separation varies in older adults. Learning & Memory 20:358-362.

Horner AJ, Burgess N. 2014. Pattern completion in multielement event engrams. Curr Biol 24:988-992.

Horner AJ, Bisby JA, Bush D, Lin WJ, Burgess N. 2015. Evidence for holistic episodic recollection via hippocampal pattern completion. Nat Commun 6:7462

Huffman DJ, Stark CE. 2014. Multivariate pattern analysis of the human medial temporal lobe revealed representationally categorical cortex and representationally agnostic hippocampus. Hippocampus 24:1394-1403.

Hunsaker MR, Kesner RP. 2013. The operation of pattern separation and pattern completion processes associated with different attributes or domains of memory. Neurosci Biobehav Rev 37:36-58.

Kanwisher N, McDermott J, Chun MM. 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 17:4302-11

Kesner RP, Rolls ET. 2015. A computational theory of hippocampal function, and tests of the theory: New developments. Neurosci Biobehav Rev 48:92-147

Kheirbek MA, Klemenhagen KC, Sahay A, Hen R. Dec 2012. Neurogenesis and generalization: A new approach to stratify and treat anxiety disorders. Nat Neurosci 15:1613-1620.

Kim J, Yassa MA. Apr 2013. Assessing recollection and familiarity of similar lures in a behavioral pattern separation task. Hippocampus 23:287-294.

Kirwan CB, Stark CEL. Sep 2007. Overcoming interference: An fMRI investigation of pattern separation in the medial temporal lobe. Learning & Memory 14:625-633.

Kirwan CB, Hartshorn A, Stark SM, Goodrich-Hunsaker NJ, Hopkins RO, Stark CEL. Jun 2012. Pattern separation deficits following damage to the hippocampus. Neuropsychologia 50:2408-2414.

Kuhl BA, Shah AT, DuBrow S, Wagner AD. Apr 2010. Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. Nat Neurosci 13:501-506.

Kumaran D, Maguire EA. Feb 2009. Novelty signals: a window into hippocampal processing. Trends Cogn Sci. 13:47-54

Lacy JW, Yassa MA, Stark SM, Muftuler LT, Stark CEL. Jan 2011. Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity. Learning & Memory 18:15-18.

LaRocque KF, Smith ME, Carr VA, Witthoft N, GrillSpector K, Wagner AD. Mar 2013. Global similarity and pattern separation in the human medial temporal lobe predict subsequent memory. The Journal of Neuroscience 33:5466-5474.

Leal SL, Tighe SK, Yassa MA. May 2014a. Asymmetric effects of emotion on mnemonic interference. Neurobiol Learn Mem 111:41-48.

Leal SL, Tighe SK, Jones CK, Yassa MA. Sep 2014b. Pattern separation of emotional information in hippocampal dentate and CA3. Hippocampus 24:1146-1155.

Leal SL, Yassa MA. Oct 2014. Effects of aging on mnemonic discrimination of emotional information. Behav Neurosci 128:539-547.

Lee I, Jerman TS, Kesner RP. 2005. Disruption of delayed memory for a sequence of spatial locations following CA1- or CA3-lesions of the dorsal hippocampus. Neurobiol Learn Mem 84:138-147.

Leutgeb JK, Leutgeb S, Moser MB, Moser EI. 2007. Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science 315:961-966.

Lissek S, Bradford DE, Alvarez RP, Burton P, EspensenSturges T, Reynolds RC, Grillon C. Aug 2014. Neural substrates of classically conditioned fear-generalization in humans: A parametric fMRI study. Social Cognitive and Affective Neuroscience 9:1134-1142.

Loiotile RE, Courtney SM. 2015. A signal detection theory analysis of behavioral pattern separation paradigms. Learning & Memory 22:364-369.

Ly M, Murray E, Yassa MA. Jun 2013. Perceptual versus conceptual interference and pattern separation of verbal stimuli in young and older adults. Hippocampus 23:425-430.

Manelis A, Paynter CA, Wheeler ME, Reder LM. Jan 2013. Repetition related changes in activation and functional connectivity in hippocampus predict subsequent memory. Hippocampus 23:53-65.

Marr D. 1971. Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci 262:23-81.

Martinelli C, Shergill S. 2015. Clarifying the role of pattern separation in schizophrenia: the role of recognition and visual discrimination deficits. Schizophr Res 166:328-33.

McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S. Jul 2007. Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. Science 317:94-99.

Molitor RJ, Ko PC, Hussey EP, Ally BA. Jun 2014. Memory-related eye movements challenge behavioral measures of pattern completion and pattern separation. Hippocampus 24:666-672.

Motley SE, Kirwan CB. Sep 2012. A parametric investigation of pattern separation processes in the medial temporal lobe. The Journal of Neuroscience 32:13076-13084.

Paleja M, Girard TA, Christensen BK. Aug 2011. Virtual human analogs to rodent spatial pattern separation and completion memory tasks. Learn Motiv 42:237-244.

Paleja M, Spaniol J. 2013. Spatial pattern completion deficits in older adults. Front Aging Neurosci 5:3.

Paleja M, Girard TA, Herdman KA, Christensen BK. 2014. Two distinct neural networks functionally connected to the human hippocampus during pattern separation tasks. Brain Cogn 92C:101-111.

Pidgeon LM, Morcom AM. 2014. Age-related increases in false recognition: the role of perceptual and conceptual similarity. Front Aging Neurosci 6:283.

Poldrack RA. 2006. Can cognitive processes be inferred from neuroimaging data? Trends Cogn Sci 10:59-63

O'Reilly RC, McClelland JL. 1994. Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. Hippocampus 4:661-682.

Reagh ZM, Roberts JM, Ly M, DiProspero N, Murray E, Yassa MA. Mar 2014a. Spatial discrimination deficits as a function of mnemonic interference in aged adults with and without memory impairment. Hippocampus 24:303-314.

Reagh ZM, Yassa MA. Jul 2014b. Repetition strengthens target recognition but impairs similar lure discrimination: Evidence for trace competition. Learning & Memory 21:342-346.

Reagh ZM, Yassa MA. Oct 2014c. Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans. PNAS Proceedings of the National Academy of Sciences of the United States of America 111:E4264-E4273.

Roberts JM, Ly M, Murray E, Yassa MA. Oct 2014. Temporal discrimination deficits as a function of lag interference in older adults. Hippocampus 24:1189-1196.

Rolls ET. 2007. An attractor network in the hippocampus: Theory and neurophysiology. Learning & Memory 14:714-731.

Rolls ET. 2013. The mechanisms for pattern completion and pattern separation in the hippocampus. Front Syst Neurosci 7:74.

Sahay A, Hen R. Sep 2007. Adult hippocampal neurogenesis in depression. Nat Neurosci 10:1110-1115.

Segal SK, Stark SM, Kattan D, Stark CE, Yassa MA. May 2012. Norepinephrine-mediated emotional arousal facilitates subsequent pattern separation. Neurobiol Learn Mem 97:465-469.

Shelton DJ, Kirwan CB. 2013. A possible negative influence of depression on the ability to overcome memory interference. Behav Brain Res 256:20-26.

Sheppard DP, Graves LV, Holden HM, Delano-Wood L, Bondi MW, Gilbert PE. Spatial pattern separation differences in older adult carriers and non-carriers for the apolipoprotein E epsilon 4 allele. Neurobiol Learn Mem http://dx.doi.org/10.1016/j.nlm.2015.04.011

South M, Stephenson KG, Nielson CA, Maisel M, Top DN, Kirwan CB. 2015. Overactive pattern separation memory associated with negative emotionality in adults diagnosed with autistic spectrum disorder. J Autism Dev Disord DOI 10.1007/s10803-015-2547-x

Staresina BP, Cooper E, Henson RN. Aug 2013. Reversible information flow across the medial temporal lobe: The hippocampus links cortical modules during memory retrieval. The Journal of Neuroscience 33:14184-14192.

Stark SM, Yassa MA, Lacy JW, Stark CEL. Oct 2013. A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. Neuropsychologia 51:2442-2449.

Stark SM, Stevenson R, Wu C, Rutledge S, Stark CEL. Jun 2015. Stability of age-related deficits in the mnemonic similarity task across task variations. Behav Neurosci. 129:257-268

Tamminga CA, Stan AD, Wagner AD. Oct 2010. The hippocampal formation in schizophrenia. Am J Psychiatry 167:1178-1193.

Tolentino JC, Pirogovsky E, Luu T, Toner CK, Gilbert PE. Jun 2012. The effect of interference on temporal order memory for random and fixed sequences in nondemented older adults. Learning & Memory 19:251-255.

Toner CK, Pirogovsky E, Kirwan CB, Gilbert PE. May 2009. Visual object pattern separation deficits in nondemented older adults. Learning & Memory 16:338-342.

Treves A, Rolls ET. 1992. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 2:189-199.

Vieweg P, Stangl M, Howard LR, Wolbers T. 2015. Changes in pattern completion - A key mechanism to explain age-related recognition memory deficits? Cortex 64:343-351.

Wesnes KA, Annas P, Basun H, Edgar C, Blennow K. 2014. Performance on a pattern separation task by Alzheimer's patients shows possible links between disrupted dentate gyrus activity and apolipoprotein E in4 status and cerebrospinal fluid amyloid-beta42 levels. Alzheimers Res Ther 6:20.

Wisse LE, Gerritsen L, Zwanenburg JJ, Kuijf HJ, Luijten PR, Biessels GJ, Geerlings MI. 2012. Subfields of the hippocampal formation at 7 T MRI: in vivo volumetric assessment. Neuroimage 61:1043-1049.

Yassa MA, Stark SM, Bakker A, Albert MS, Gallagher M, Stark CEL. Jul 2010. High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic mild cognitive impairment. Neuroimage 51:1242-1252.

Yassa MA, Mattfeld AT, Stark SM, Stark CEL. May 2011a. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. PNAS Proceedings of the National Academy of Sciences of the United States of America 108:8873-8878.

Yassa MA, Lacy JW, Stark SM, Albert MS, Gallagher M, Stark CEL. Sep 2011b. Pattern Separation Deficits Associated With Increased Hippocampal CA3 and Dentate Gyrus Activity in Nondemented Older Adults. Hippocampus 21:968-979.