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Time or place? Dissociation between object-in-place and relative recency in young APPswe/PS1dE9 mice

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Abstract

This study tests the predictions of a novel analysis of recognition memory based on a theory of associative learning, according to which recognition comprises two independent underlying processes, one relying on the to-be-recognised item having been experienced recently (*self-generated priming*), and the other on it being predicted by some other stimulus (*retrieval-generated priming*). A single experiment examined recognition performance in the APPswe/PS1dE9 (APP/PS1) mouse, a double-transgenic model of Alzheimer's disease, and wild-type (WT) littermates. Performance on two variants of the spontaneous object recognition (SOR) was compared in 5-month-old APPswe/PS1dE9 (APP/PS1) mice, a double-transgenic model of Alzheimer's disease, and their wild-type (WT) littermates, using junk objects. In the relative recency task animals were exposed to object *A*, and then object *B*, followed by a test with both *A* and *B*. In the object-in-place task the mice were exposed to both *A* and *B*, and then tested with two copies of *A*, occupying the same positions as the preeexposed objects. The WT mice showed a preference for exploring the first-presented object *A* in the relative recency task, and the copy of *A* in the 'wrong' position (i.e. the one placed where *B* had been during the pre-exposure phase) in the object-in-place task. The APP/PS1 mice performed like the WT mice in the relative recency task, but showed a selective impairment in the object-in-place task. We interpret these findings in terms of Wagner's (1981) theory of associative learning, SOP, as a selective deficit in retrieval-generated priming.

Keywords: Recognition, associative, Alzheimer's, mouse, episodic memory

Recognition memory plays an integral role in human cognitive activity and is a fundamental part of episodic memory. Although recognition has always been a significant focus of psychological research, this has probably intensified in recent years because recognition memory declines with age (Koen & Yonelinas, 2014), and the proportion of the global population that is elderly is increasing rapidly. Recognition memory is also notably impaired in dementias such as Alzheimer's, a condition from which an increasing proportion of the population suffers. For all these reasons, a substantial amount of research is now conducted on the topic, in both humans and animal subjects; for example, in 2015 Grayson and colleagues noted that in the previous ten years no fewer than 34 reviews had been published on object recognition in rodents alone (Grayson et al., 2015). Yet the mechanisms underlying recognition memory are far from uncontroversial. Probably the main issue is that there is a longstanding debate over whether recognition results from one process or two. The dual process view is that recognition comprises both the sense of *familiarity* elicited by an item and the retrieval of details associated with it – *recollection*. The typical example is the '*butcher on the bus*'; you know he is familiar, but cannot place why until related details are retrieved (cf., Mandler, 1980). These two processes are mirrored by distinct underlying cognitive mechanisms, whose existence is supported by dissociations in sensitivity to procedural variables, and reliance on different neural substrates (e.g. Brown & Aggleton, 2001; Eichenbaum,Otto & Cohen, 1994; Yonelinas & Jacoby, 2014; see also Cowell, Bussey & Saksida, 2006). The alternative, single process view is that recollection and familiarity are not mediated by separate physiological systems (Squire, Stark & Clark, 2004), but are actually different aspects of the same underlying process, and apparent dissociations between the two reflect differences in memory strength relative to a specific decision

criterion (Berry et al., 2012; Wixted, 2007). The fact that familiarity judgements are typically faster than recollection is because it can be achieved with a weaker version of the same underlying memory trace.

A further complication relates to the fact that much of this research is translational: identifying the neural bases of these phenomena, and testing pharmacological treatments for recognition impairments, all require work on animals. This usually employs the spontaneous object recognition task (SOR), which relies on rodents' proclivity for novelty (Ennaceur & Delacour, 1988). In a typical version of the task animals are placed into an arena and allowed to explore two copies of a junk object; then after a delay they are re-placed in the arena and allowed to explore a copy of the previously explored item and another, novel object. Preferential exploration of the novel item is taken as evidence for recognition of the pre-exposed object. This task is very widely used in the neuroscience literature - probably because it is quick, doesn't require complicated apparatus, and has ethological validity – requiring neither special training nor any kind of deprivation (cf. Grayson et al., 2014). However, use of this task highlights the difficulty of mapping recognition memory as conceptualised in the human literature onto rodents: in humans the distinction between recollection and familiarity is frequently captured by the distinction between '*remember*' and '*know*' judgements, that cannot be reproduced in animals in this, or indeed any type of task. Perhaps for this reason there is a prevailing tendency in the animal literature to define the familiarity and recollection components of recognition memory in terms of their underlying neural mechanism, and the effect of damage to structures such as hippocampus and perirhinal cortex on performance in memory tasks. Thus recollection is seen as a hippocampus-dependent process, whereas familiarity is identified by its association with perirhinal

and parahippocampal function (e.g. Brown & Aggleton, 2001). However, this too is controversial, with not all authors agreeing that the existing evidence supports such functional dissociations (e.g. Squire, Stark & Clark, 2004).

One means of circumventing these controversies is to adopt an alternative approach to studying recognition memory that is based more on the behavioural measures used in animal work. A number of authors (Honey & Good, 2000; Robinson & Bonardi, 2015; Sanderson & Bannerman, 2011) have attempted to explain recognition memory in terms of a theory proposed by Wagner—SOP (Wagner, 1981; Wagner & Brandon, 1989). This is actually an account of associative learning, but as the conceptual framework in which it is couched also describes stimulus processing, it can also provide an account of recognition-type processes. This approach offers a number of advantages. First, rather than relying on a phenomenological definition of recognition, it defines it instead as a change in behaviour towards an item as a result of it having been experienced previously. By using such behavioural measures of recognition memory that can be applied to humans and animals alike, there is no need to commit to any underlying neural mechanism. Second, since the SOP account of recognition memory is one part of a broader model of learning, it is parsimonious. Third, by offering a new framework for thinking about recognition, it offers a new perspective on the traditional theoretical position and the controversies that it brings, and suggests novel hypotheses and experimental tests.

The SOP account assumes that each stimulus is represented as a set of component elements which may be in various different states of activation. When a novel stimulus is first presented, a probabilistically determined set of its elements

enters a primary state of activation termed *A1*. This may be regarded as being equivalent to the focus of attention, and when in this state they can elicit a vigorous response. However, the capacity of this *A1* state is limited, and so these stimulus elements decay rapidly into a second activation state, *A2*. The *A2* state may be seen as equivalent to the periphery of attention, and so has a larger capacity than *A1*, such that stimulus elements in *A2* decay rather more slowly to the inactive state, *I*. (Figure 1). Critically, elements in *A2* elicit a weaker response than those in *A1*. One critical feature of this model is that a stimulus element must complete this cycle before it can again enter *A1* – such that a stimulus presented twice in quick succession will only be able to elicit a weak response on its second presentation; because many of its elements will still be in the refractory *A2* state when it is re-presented, its elements cannot be reactivated into *A1*, so the response to it is curtailed. This process, whereby stimulus presentation weakens subsequent response to that same stimulus, is termed *self-generated priming*. The model explains associative learning by asserting that, for example, when two novel stimuli are paired this will result in both having elements in A1, which allows an excitatory association to form between them; this means that when one of the stimuli is next presented it can activate elements of the other directly into A2; this process is called *retrieval-generated priming*.

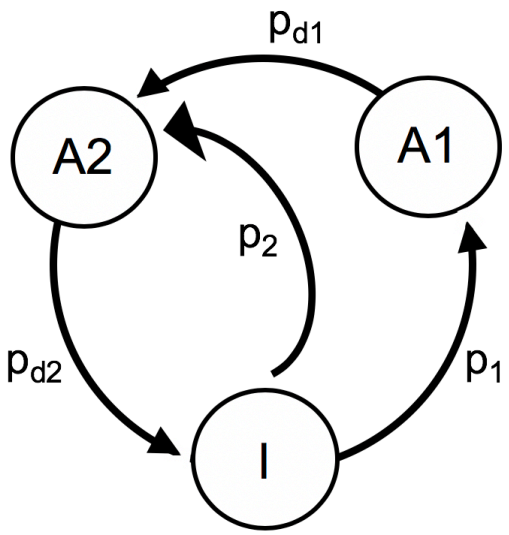

Figure 1: Schematic of activity states proposed by SOP. On presentation of a novel stimulus, its elements pass from the inactive state I to primary activity state A1 with probability p_1. From there they decay rapidly into a secondary state of activation A2 with probability p_{d1}, and thence more slowly back to I with probability p_{d2}. A predictor of the stimulus will send elements directly into A2 with probability p_2 (after Wagner, 1981).

This analysis suggests at least two potential mechanisms for accurate performance on the SOR task. If the retention interval between the sample and test presentations is not too long, some of the sample's elements are likely to remain in *A2* at test, reducing responding to the pre-exposed item at test via the self-generated priming process. Moreover, during sample presentations, associations will form between elements of the object and the contextual stimuli that surround it - so at test the context will prime elements of the pre-exposed object directly into *A2*, reducing responding to it even further via retrieval-generated priming. Both these mechanisms thus reduce responding to the pre-exposed object relative to the novel item, whose elements can enter *A1* freely at test.

As noted above, recognition is often studied in a bid to understand the symptoms of dementia, and we have been using this analysis to analyse the processes underlying recognition memory in a mouse model of Alzheimer's disease (AD; Bonardi et al., 2016; Armstrong et al., 2020). The clinical motivation for this work is relates to the difficulty of diagnosis – it is difficult to distinguish Alzheimer's disease from normal aging or Mild Cognitive Impairment (MCI) in its early stages. This makes it very difficult for any drug treatments to be effective, as a diagnosis of Alzheimer's is usually only confirmed when the condition is advanced (Fiandaca et al., 2014). Increasing importance is thus being placed on gaining a better understanding of the cognitive changes characterising the preclinical stage (Sperling et al., 2011), to facilitate early detection and treatment. In particular, there is mounting recent evidence that recognition impairments are a cognitive marker for prodromal Alzheimer's disease, based not only on clinical diagnosis (e.g. Clark et al., 2012; Crutcher et al., 2009; Hudon et al., 2009; Pitarque et al., 2016; Serra et al., 2010; Westerberg et al., 2013; Wolk et al., 2008, 2013; Zola et al., 2013) but also biomarker evidence (e.g. Goldstein et al., 2019). We have been using the double-transgenic APPswe/PS1dE9 (APP/PS1) mouse to explore this issue. This strain co-expresses the mutated Swedish APP gene, and also the exon-9 deleted variant of the PS1 gene (Lee et al., 1997), and develops the amyloid plaques characteristic of Alzheimer's disease at 4-6 months of age (Garcia-Alloza et al., 2006), paralleled by progressive degeneration of monaminergic (Szapacs et al., 2004, Liu et al., 2008) and striatal (Richner et al., 2009) neurons, and neuroinflammatory reactions (Holcomb et al., 1998) which mirror human Alzheimer's pathology. It also recapitulates the characteristic age-related cognitive decline (Arendash et al., 2001), thought to depend on these neuropathological changes. As it has been suggested

that visual recognition deficits might be a diagnostic marker of early Alzheimer's (Didic et al., 2010; Zola et al., 2012), and levels of oligomeric Aβ in cortex and hippocampus begin to elevate at 3.5-months in this strain (Hu et al., 2010; Shemer et al., 2006) we would expect to see a recognition memory deficit in these animals at this age – but this is not in fact the case. Although SOR impairments are routinely observed in older APPswe/PS1dE9 mice (Donkin et al., 2010; Jardankhazi-Kurutz et al., 2010; Li et al., 2014; Yan et al., 2009; Yoshiike et al., 2009; but see Frye & Walf, 2008), they are only occasionally seen in mice of 6-7 months (Cheng et al., 2014; Pedros et al., 2014; but see Barbero-Camps et al., 2014; Jardankhazi-Kurutz et al., 2010), and never in younger animals (Pedros et al., 2014; Bonardi et al., 2011).

Our proposal is that the SOP account of recognition memory can not only explain this paradoxical pattern of results, but also allow us reveal the dissociation between self- and retrieval-generated priming proposed by this account. As the theory assumes that both these types of priming contribute to SOR performance, it is possible that one of these components *is* impaired at an early stage, but that the other is able to compensate to the point that performance appears normal. This predicts that if it were possible to examine these components separately, a deficit in the young animals would be observed, and so in this way we can use the transgenic animals as a tool to understand the processes comprising recognition memory performance.

Experiment 1

Bonardi Pardon & Armstrong (2016) examined this possibility using two variants of the SOR task, which they argued tap the self-generated and retrieval-

generated priming processes relatively independently. Self-generated priming can be examined using the *relative recency* task (Mitchell & Laiacoma, 1998), in which mice are exposed to two objects in sequence. In a subsequent test with both objects, animals tend to preferentially explore the first-presented object. This can be explained easily in terms of the self-generated priming process. During pre-exposure, elements of both objects will have entered A1 and then started decaying through A2 to the inactive state. However, as the elements of the first-presented object will have had more time before the test to decay back to the inactive state than those of the second-presented object, more elements of this less recent object will be available to enter the A1 state, and hence the response elicited by this object will be more vigorous. Moreover, as both objects will have been presented in the experimental context, both will have had the same opportunity to become associated with it, and so retrieval-generated priming of the two objects at test should be equivalent*[1].

In contrast, retrieval-generated priming can be examined using the object-in-place task (Dix & Aggleton, 1999). In one variant of this task, animals are exposed to four objects in an array, before being tested with the same objects, but rearranged such that two retain their original positions while the position of the second two is reversed. Animals typically explore the items which have exchanged position more than the static objects, an effect which can be explained in terms of retrieval-generated priming. During pre-exposure, associations form between each object and the surrounding environmental cues, which develop the ability to prime elements of

[1] * this logic assumes that extinction of associations between the context and the first-presented object do not extinguish substantially during presentation of the second. This is based on the common assumption that inhibitory learning is considerably slower than excitatory learning, and indeed the original formulation of SOP assumes that inhibitory learning takes place at one fifth of the speed of excitatory learning.

their respective objects directly into the *A2* state. At test, therefore, elements of the static object are primed into *A2*, reducing the strength of the response they can elicit. In contrast, the objects whose positions have been switched are less susceptible to this process, because they are not immediately surrounded by the contextual cues that predicted them during pre-exposure. Moreover, as all four objects have been experienced equally recently, it is not possible to explain this differential performance at test in terms of the self-generated priming process.

Bonardi Pardon & Armstrong (2016) applied this logic, conducting a series of studies with 5-month old APPswe/PS1dE9 mice and their wild-type littermates. In the first of two studies they compared performance on a standard spontaneous object recognition task with that on a relative recency task in which mice were exposed to *B*, and 24 hours later to *A*, before being tested with *A* and *B*. No sign of a deficit in the APP/PS1 mice was observed on either task. In the second study they tested a new group of animals on the object-in-place task, in which the mice were exposed to four objects in an array, and then five minutes later tested with the same objects, but in an array in which two of them had exchanged position, just as described above. These same mice were also tested on the spontaneous object recognition task. Once again they showed no deficit in the SOR task – but at the same time displayed a significant impairment in the object-in-place task. This pattern of findings supports the conclusion that, at this relatively young age, these animals show a selective deficit in the retrieval priming process, while self-generated priming is relatively intact.

However – as these authors noted at the time – there were a number of reasons to be cautious about these conclusions. As these were opportunistic experiments, the recency and object-in-place tasks were conducted in different

animals; in addition, the recency task differed in a number of ways from the recency experiments, such as the duration of the pre-exposure phase and the number of objects present at test. Moreover, although it was not statistically significant, the APP/PS1 mice performed numerically worse on the recency task than the wild types, raising the possibility that a more sensitive test might have revealed a deficit in this task too. Accordingly, the aim of the present study was to replicate these results under more controlled conditions. All animals experienced both the recency and the object-in-place tasks, with order of testing and identity of objects employed counterbalanced across the two tasks. In addition, the two tasks were matched for duration of the pre-exposure phase and number of objects present at test. To this end, a different version of the object-in-place was used, in which the mice were pre-exposed to objects *A* and *B*, and then tested with two copies of *A* in the pre-exposed object locations (Ameen-Ali et al., 2012; Eacott & Norman, 2004). Retrieval priming should ensure greater exploration of the copy of *A* occupying the position in which *B* had been placed during pre-exposure.

Methods

Subjects

All experimental animals were bred in the University of Nottingham's transgenic animal facility from breeding stock of APPswe/PS1dE9 (APP/PS1) purchased from the Jackson laboratory (stock # 34832-JAX). This double transgenic APP/PS1 mouse line expresses the chimeric mouse/human APP (Mo/HuAPP695swe) and Presenilin (PS1-dE9) mutations crossed onto a C57BL/6 background. The experiments employed 46 experimentally naïve male mice, 21

APP/PS1 transgenic mice and 25 wild-type (WT) littermates. The experiments were run in four replications, of 7/8, 5/4, 3/5 and 6/8 APP/PS1 / WT mice respectively. Testing began when they were between 15 and 21 weeks old, and lasted about three weeks. All mice were housed in the same room, which was maintained on a 12/12 hour light cycle, with lights on at 07:00 hours; the room temperature, relative humidity and air exchange were automatically controlled. Animals were group-housed with *ad libitum* access to food and water, and provided with nesting material, chew sticks and a play tube for environmental enrichment.

Apparatus and Stimuli

The experiments were conducted in two identical rectangular arenas with walls and floors of white translucent plastic (length × width × height: 60 cm × 40 cm × 45 cm), located in a quiet, brightly lit room. A camera was suspended from a frame 90.0 cm above the centre of each arena, flanked by two LED spotlights 22 cm apart, producing a floor-level illumination of 50 lux. The camera view (~ 45° arc) included the entire floor and the lower part of the four walls. The trajectory of the animals' heads was tracked by Any-maze software (Version 4.5; Stoelting, Wood Dale, Illinois). Multiple copies of ten assorted junk objects served as stimuli (see *Objects* in Supplementary materials). Square zones of uniform size (with sides of approximately 9.5cm) were defined in the relevant positions of the arena (see below), and the object placed in the zone centre. In this way the time for which the mouse's head was within this active zone could be computed. For the object-in-place tasks the same apparatus was employed, but with the addition of wall inserts to increase the distinctiveness of the local features of the context. These inserts were made from medium density fibreboard lined with linoleum, and each one covered the whole of one of the shorter walls, and half of both longer walls, of the arena; thus two inserts

covered the entire arena wall. They were 45.0 cm high, and when inside the arena reduced the floor space to 42.0 cm x 32.0 cm. Two different patterns were used, one on each side of the arena: *Mb,* a mosaic of 2.3 cm^2 blue squares whose edges were 45° from horizontal, and *Dw,* a mosaic of white 272-cm^2 squares whose edges were 90° from horizontal, with a black, 16-cm^2 square superimposed at each point where four white squares met (see *Apparatus with Inserts* in supplementary materials).

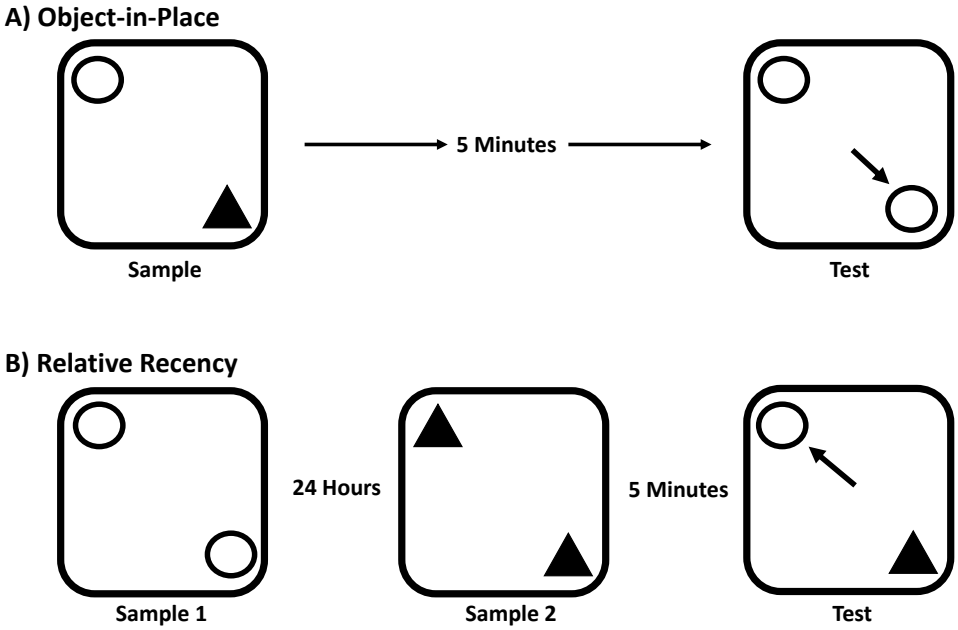

Figure 2. Schematics of the two object recognition tasks: Object-in-place (A), relative recency (B). The arrows signify the object that is less recent, or in a displaced location. See text for details of the behavioural procedure.

In all replications, the two genotypes were (as far as possible) counterbalanced across the two arenas. The objects were positioned in zones at the top left and bottom right of the arena for the first repetition of the recency task, and in the top right and bottom left for the second. Likewise, for the object-in-place task the first repetition used zones on the left and right of the arena, and the second zones at the top and bottom.

Procedure

Pre-exposure. Before the start of training each mouse was habituated to the empty arena. In each of six sessions the mouse was placed in the centre of the apparatus and allowed to explore for 5 min. The floor and walls of the apparatus were cleaned with diluted alcohol before each mouse was placed in the arena. Before the start of training proper all animals experienced a pretraining task (see *Pretraining Task* in Supplementary materials).

Training: Immediately after the pretraining task animals were tested on two repetitions of the relative recency task, and two of the object-in-place task, in a counterbalanced order (see Table 1). All sample phases were of 10-minutes duration, and all test phases 5 minutes; the test phases always followed the preceding sample phase by five minutes. At the start of each phase of all the tasks, the mouse was placed in the arena centre facing the gap between the two objects; on its removal the objects, walls, floor and objects were cleaned with diluted alcohol. The objects were divided into four sets which were counterbalanced across the different tasks (see *Stimulus Sets* in Supplementary materials) :

Task Pair / Replication	*1*	*2*
1	*Recency 1&2*	*Place 1&2*

2	*Recency 1&2*	*Place 1&2*
3	*Place 1&2*	*Recency 1&2*
4	*Place 1&2*	*Recency 1&2*

*Table 1: Order of relative **recency** and object-in-**place** tasks in each of the four replications. Object sets were counterbalanced across the four tasks. For more information see text and Table 1a in Supplementary materials.*

Relative Recency: In the first sample phase mice were exposed to two copies of object *A* and 24 hours later, in the second sample phase, two copies of object *B*; during the test which followed they were exposed to objects *A* and *B*.

Object-in-place: In the sample phase mice were exposed to objects *A* and *B*, and in the test which followed to two copies of object *A*. (See Figure 2).

Within each repetition of both tasks, stimulus identity and object position were counterbalanced (see *Table 1a* in Supplementary materials): thus, for example, for a recency task half the mice in each genotype might have object *x* as *A* and *y* as *B*, and the remainder the reverse; then all would be tested with *x* at top left and *y* at bottom right. As all animals should approach the less recent object A, this means that half the mice in each genotype should approach object *x* in the top left position, and the remainder *y* in the bottom right position.

Data Treatment

During the habituation phase the group mean distance travelled per minute is reported, averaged across each 10-minute session. In subsequent phases the key measure was exploration time – the amount of time the mouse's nose was inside each active zone. This was computed in 1-minute bins for each of the object types in each phase for each mouse. Visual inspection suggested that effects had dissipated by the second repetition for both types of task; thus data from the two repetitions were analysed separately. Data from the sample phases were summed across all ten minutes, separated by object type: for each repetition of the recency task, group mean exploration time in the first and second sample phases was compared, whereas for each repetition of the object-in-place task the comparison was of group mean exploration between the to-be-switched objects and the objects that remained static at test. Data from the test phases were computed separately in three 1-minute bins for each repetition of each of the two tasks; in the recency task this was a comparison between the first-presented and second-presented objects, while in the object-in-place task exploration during the switched and static objects was compared. Finally, in the test phases, bins where exploration times were disproportionately high (for example, when mice were sitting on the objects and appeared reluctant or unable to step down) were dealt with as follows. For each type of test, the mean and standard deviation of all 20 scores (from five, 1-minute bins for each of the two types of object for both repetitions) for each animal were computed. Then each one-minute bin in which the exploration time was more than three standard deviations greater than the mean for that mouse was identified. If this bin occurred in the first three minutes of the test (and would therefore be included in the test analysis) the subject was excluded. This led to the exclusion of three (WT) and

two (one APP/PS1, one WT) mice from the first and second repetition of the recency task respectively, and three and one (all WT) from the first and second repetitions of the object-in-place task respectively. The resulting data were analysed using mixed ANOVAs; significant two-way interactions explored with simple main effects analysis, using the pooled error term for interactions involving group; η_p^2 was reported for significant effects and interactions. In addition group mean discrimination ratios of form $a/(a+b)$ where a is time exploring the first-presented/switched object and b the time exploring the second-presented or static object, were computed for the exploration times pooled over all three minutes of test; a value of 0.5 indicates no preference, anything over 0.5 preference for the first-presented/switched object. These values were compared each other using Mann-Whitney independent samples *t*-tests, and to 0.5 with one-sample *t*-tests. Inspection of the data revealed that results from the second recency and second object-in-place tasks revealed no significant differences. Thus in what follows data from only the first repetition of each type of task are analysed; analysis of data from the second repetition of each task type may be found in the Supplementary materials.

Results

In the habituation phase we recorded the average distance per minute travelled over each of the six habituation sessions. The resulting data are presented in Table 2: activity decreased over successive sessions, and was higher in the APP/PS1 mice. ANOVA with genotype and session as factors revealed significant main effects of genotype, $F(1, 43) = 21.58$, $p < .001$, $MSe = 2.45$, $\eta_p^2 = .33$, and session, $F(5, 215) = 122.13$, $p < .001$, $MSe = 2.76$, $\eta_p^2 = .74$, and a significant interaction between these

two factors, $F(5, 215) = 7.28$, $p < .001$, $MSe = .28$, $\eta_p^2 = .15$; simple main effects revealed significant genotype effects on sessions 1 and 2, $p = .02$ and $p = .007$ respectively, but not thereafter, smallest $p = .173$. Thus the group difference in activity had dissipated by the end of habituation training.

Session	1	2	3	4	5	6
APP/PS1	5.59 (.216)	3.71 (.253)	2.92 (.197)	3.10 (.187)	2.87 (.150)	2.99 (.128)
Wild type	4.06 (.179)	2.38 (.119)	2.27 (.171)	2.45 (.145)	2.28 (.141)	2.40 (.129)

Table 2: Group mean distance (m) travelled per minute each of the six habituation sessions. SEM shown in brackets.

Relative recency Exploration during the sample phases of the two experiments was calculated separately for the first and second samples, in each case pooled over the entire ten-minute session. This was to examine whether there was any difference in exploration of *A* and *B*; for example, if *B* was explored *less* than *A* this could result in more exploration of *B* at test simply because it was less familiar than *A*, rather than because it was less recent. For the first task repetition, the group mean exploration of *B* was, for Groups APP/PS1 and WT respectively, 60.08 and 56.65s; the corresponding means for *A* were 58.45 and 51.83s. These data suggest slightly higher levels of exploration in the transgenic mice, and also slightly lower levels of exploration in the second pre-exposure session, but ANOVA with group (APP/PS1 / WT) and sample (B/A) as factors revealed nothing significant, largest $F(1, 43) = 2.32$, $p = .21$, $MSe = 1.45$ for the main effect of sample. This tendency in both genotypes to explore the first-presented objects more would, however, reduce the size of any

recency effect, as it would render the first-presented and less recent object more familiar at test.

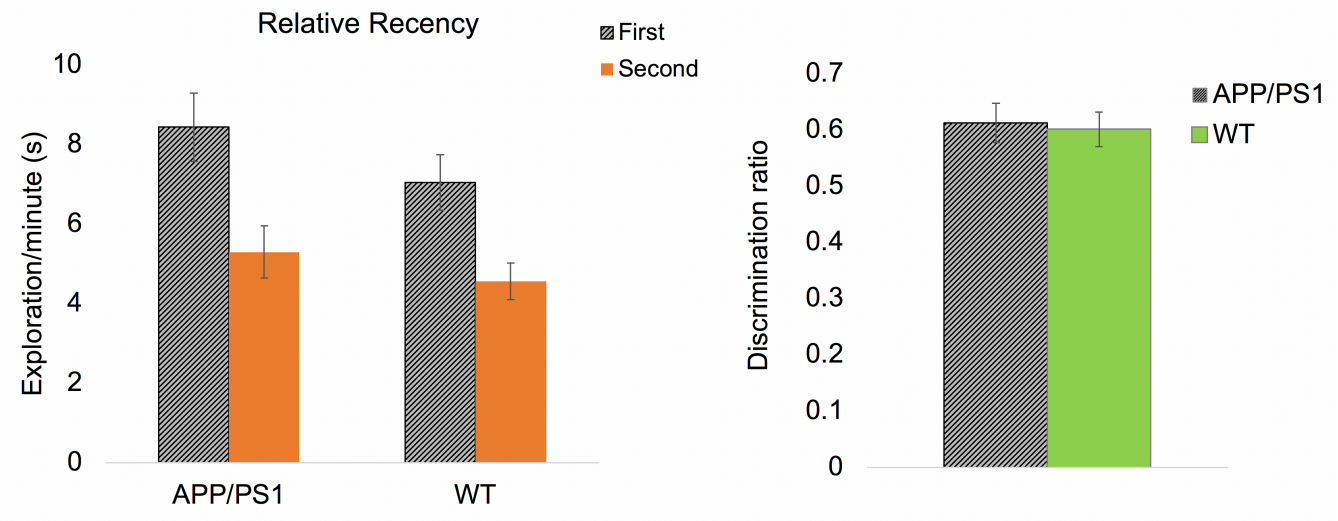

Figure 3: Left panel: Group mean exploration per minute, pooled over all three minutes of test, of the first- and second-presented objects in the first repetition of the Relative Recency test. Both APP/PS1 (n=20) and WT (n=22) mice showed greater exploration of the first-presented object. Right panel: Discrimination ratios. Data expressed as means +/- SEM.

The results of the first test are shown in Figure 3; as there was no interaction of any of the effects of interest with minute, data are shown pooled across all three minutes of test (minute-by-minute data are presented in the supplementary materials). It is evident that the less recent *B* was explored more than the more recent *A*, and there was no sign of a transgenic deficit – indeed the effect appeared slightly larger in the APP/PS1 mice. ANOVA with group (APP/PS1 or WT), object (A/B) and minute as factors revealed a significant effect of object, $F(1, 40) = 16.13$, $p < .001$, $MSe = 30.9$, $\eta_p^2 = .077$; nothing else was significant, largest $F(1, 40) = 2.67$,

p = .11, MSe = 26.71 for the main effect of group; critically, the interaction of object and group did not reach significance, F < 1. The discrimination ratios were .612 and .601 for APP/PS1 and WT mice respectively, and these scores both differed from 0.5, p = .005 and .004 respectively, but not from each other, p = .65. Thus in this first test there was a robust relative recency effect that did not differ between the two groups.

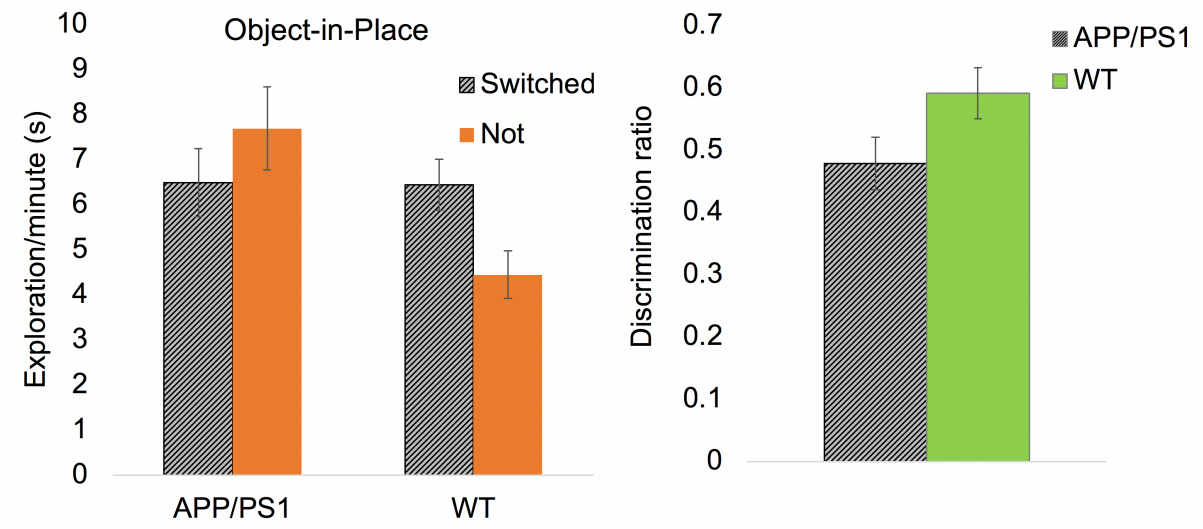

Figure 4: Left panel: Group mean exploration per minute, pooled over all three minutes of test, of the first- and second-presented objects in the first repetition of the Object-in-Place test. WT (n=22) mice showed greater exploration of the switched object but the APP/PS1 (n=20) mice did not. Right panel: Discrimination ratios. Data expressed as means +/- SEM.

Object-in-Place Exploration during the single sample phase was analysed to compare exploration of the objects in the position that was to accommodate the switched object at test with exploration of the object in the position that would house

the static object at test, to see if there was any bias that could compromise interpretation of the test results. In the first repetition the group mean exploration of the switched object position was, for APP/PS1 and WT mice respectively, 6.40 and 6.03s, and the corresponding means for the static object position 5.82 and 5.89s. ANOVA with group and object revealed nothing significant, *Fs* < 1.

The results of the first object-in-place test are shown in Figure 4, which shows that the WT mice appear to explore the switched object more than the static object; however if anything the opposite pattern was evident in the APP/PS1 animals. ANOVA with object, group and minute as factors revealed a significant interaction between object and group, $F(1, 40) = 4.73$, $p = .036$, $MSe = 33.98$, $\eta_p^2 = .029$; there was also a significant main effect of group, $F(1, 40) = 6.16$, $p = .017$, $MSe = 27.57$, $\eta_p^2 = .133$, but nothing else was significant, largest $F(2, 80) = 2.42$, $p = .096$, $MSe = 15.73$ for the effect of minute. Simple main effects analysis performed on the significant interaction revealed a main effect of object in Group WT, $p = .026$, but not in Group APP/PS1, $p = .34$. In addition, the discrimination ratios were .478 for Group APP/PS1 and .591 for Group WT; although the difference between them did not quite attain staistical significance, $p = .057$, the ratio for the WT mice differed from 0.5, $p = .038$, whereas that for the APP/PS1 mice did not, $p = .61$.

Discussion

The results of this experiment support the conclusions drawn by Bonardi Pardon & Armstrong (2016). Just as in that study, the APP/PS1 mice performed like the WT mice in the relative recency task, but showed a significant impairment in the object-in-place task, relative to the WT controls. However, the present findings

improve on those reported by Bonardi et al. (2016) in a number of ways. First, the two tasks were both performed in the same animals, in counterbalanced order and with matched objects. Second, both tasks were matched in the durations of both pre-exposure and test, and in the number of objects employed. Third, in contrast to the findings of Bonardi et al. (2016), there was no sign of any APP/PS1 deficit in the relative recency task – if anything the effect was numerically larger in the APP/PS1 animals.

General Discussion

The results of this study support our contention that aspects of recognition memory are impaired in young transgenic APP/PS1 mice, and that the failure of most previous studies to observe deficits are probably due to the types of test employed (Bonardi et al., 2011; Cheng et al., 2014; Pedros et al., 2014; but see Barbero-Camps et al., 2014; Jardankhazi-Kurutz et al., 2010). According to our theoretical analysis, recognition memory has two components: the effects of having experienced the target item recently, and the extent to which the target item is predicted or retrieved. Performance on a generic SOR task can arise through both mechanisms, and so could survive a deficit in one if the other can sustain performance. By using tests that isolate these component mechanisms independently, we were able to demonstrate a selective deficit in the retrieval-generated priming component. The other, self-generated priming process appeared to be intact. These results might therefore be of use in guiding development of diagnostic tests for the early stages of Alzheimer's disease. As noted above, there is increasing evidence that recognition is impaired in prodromal Alzheimer's disease

(e.g. Clark et al., 2012; Crutcher et al., 2009; Goldstein et al., 2019; Hudon et al., 2009; Pitarque et al., 2016; Serra et al., 2010; Westerberg et al., 2013; Wolk et al., 2008, 2013; Zola et al., 2013) and so understanding how this is manifest in animal models at an early stage is of crucial importance for preclinical testing of potential treatments, that could be administered before the irreversible degeneration produced by this condition sets in (e.g. Caldwell et al., 2015).

These results accord with our interpretation of recognition memory in terms of Wagner's (1981) SOP model, according to which exploratory behaviour, the primary measure in the SOR task, is only maximal if the stimulus's elements are inactive and free to enter the A1 state. The attenuated exploration that characterises recognition comes about because of two *priming* processes that suppress stimulus processing. Self-generated priming results from recent experience with that same stimulus; if the elements of the stimulus have not had sufficient time to decay from the A2 state to inactive, there will be fewer available to enter A1 when the stimulus is re-presented. A similar effect occurs with retrieval-generated priming, but here it is caused by an associate of the stimulus placing the stimulus elements directly into the A2 state.

However, this interpretation is not without problems. First, we concluded that the young transgenic mice are selectively impaired on the retrieval-generated priming process, and that their intact SOR performance depends on self-generated priming. But self-generated priming is inherently transient: given enough time all the stimulus elements will become inactive again, meaning that SOR at longer delays cannot be due to this process (Bonardi et al., 2016). It follows that these transgenic animals should *only* show normal SOR at relatively short sample-test delays – and this is not the case: Bonardi et al. (2016) demonstrated intact SOR performance with a 24-hour delay between sample and test in these animals. Although it is impossible

to quantify the temporal parameters for decay between the different activity states, it stretches the bounds of plausibility to suggest that decay from A2 to inactive takes more than 24 hours. So how is performance maintained? Bonardi et al. (2016) suggested that our interpretation of the retrieval-priming deficit may need to be refined. When an object is presented in the sample phase, associations may form not only between elements of the stimulus and the surrounding context but also among elements of the stimulus itself, and both of these could in principle contribute to performance. The object-in-place task variants we employed manipulated cues extraneous to the target objects; thus it is possible that the transgenic animals are selectively impaired at forming these associations, rather than those between components of the stimulus itself. There are a number of differences between these two types of association that could mediate this selectivity; for example, different components of the same object are likely to be both spatially and temporally more contiguous than those of the object and the surrounding context; perhaps the transgenic animals are selectively sensitive to this factor (cf. Pistell et al., 2008; Ramirez-Lugo et al., 2009). Moreover, it remains unresolved as to whether their impairment lies in the formation of associations, or their use of the associations for retrieval - either could produce the pattern of deficits observed.

Another issue relates to the nature of the object-in-place task employed in the present study. In order to equate the number of objects used in the two types of task we employed this variant in which the mice are tested with two copies of the same object, only one of which is in the same position as during pre-exposure (Ameen-Ali et al., 2012; cf. Davis et al., 2013a). However, although ostensibly more elegant than the four-object version (Dix & Aggleton, 1999), it introduces further complications. For example, according to SOP, during the pre-exposure phase object *A*, which will

appear at test, becomes associated with the contextual cues surrounding it in one section of the arena. At test, when *A* is encountered in its pre-exposure position its elements should therefore be primed into the A2 state, whereas when it is in the alternative position they will not. The complication is that these are *elements of the same object*: so if, for example, the mouse explores the object in its pre-exposure position, the object's elements will be primed into A2, and remain there while the mouse crosses the arena to look at the second copy of the same object; this means *the object's elements will remain primed in A2 even when it is encountered in the novel position*. Thus, arguably, it is only possible to discriminate between the two objects *before* the primed object has been experienced. Given mice tend to switch between the two objects over the course of the test, it is difficult to see how a discrimination between primed and unprimed object could be sustained, according to this analysis. Moreover, this issue is not confined to SOP. Any account which assumes the cognitive processes accompanying experience of an object are shared by two copies of the same item would encounter the same problems when trying to accommodate these findings. One solution might be to assume that the object is perceived differently depending on where it is encountered; thus the copy of the object experienced in the 'wrong place' might be perceived as different and therefore novel, and explored for that reason. This would mean that, rather than being based on a judgement that the object is in the wrong place, animals are responding to what they experience as a novel item. This is of course a potential problem for all tasks of this type, for which the test is by definition a discrimination, either within or across phases, between the same object in different locations. However, although difficult to rule out, it is not impossible. For example, Whitt and Robinson (2012) trained rats with object *P* in context *x* and object *Q* in context *y*, before testing both *P* and *Q* in

the absence of either context – so that both objects were equally affected by the context change at test. However, interposed between training and test the rats experienced context *x*, so that at test *P* would have been primed, but not *Q*. The fact that the rats tended to explore *P* less than the unprimed *Q* cannot therefore be attributed to their being perceived as novel because they are in an unusual location.

An alternative, and perhaps more interesting, explanation of performance on the object-in-place task is that *A* does indeed suffer a type of generalisation decrement when it is presented in the 'wrong' place, but for associative rather than perceptual reasons. When *A* is encountered in the position normally occupied by *B*, elements of *B* may be retrieved at the same time by the surrounding context, and it is these that alter perception of *A*. In terms of SOP, for example, the elements of *A* would be accompanied by elements of *B* in the A2 state when it is presented in the incorrect position. While elements in A2 command less responding than those in A1, they could boost overall responding; thus even if – as we have seen is likely in this task variant – both instances of *A* do command the same amount of A2 activity, the one in the wrong position will be accompanied by *B*'s A2 activity as well, which could still result in more overall responding.

We are not aware of any other studies looking at performance in both recency and object-in-place tasks in this transgenic mouse line. However, experiments examining performance on this variant of the object-in-place task have been conducted in other transgenic strains. For example, Davis et al. (2012) conducted a series of such studies in a 6-month-old triple transgenic model of AD.They reported a selective deficit in what they term a *what-where-which* task in which two objects, *P* and *Q*, are exposed twice, in configuration *P/Q* in context *x* and in the reverse configuration *Q/P* in context *y*, before a test with two copies of *P* in

context *x*; the mice should explore *P* more when it is in its context *y* position, an effect which the authors argue relies on episodic-like processes. In contrast they reported no deficit in what they term the *egocentric what-where* task (two objects *P* and *Q* exposed only once, in configuration *P/Q* in context *x*, before the same test with two copies of *P* in context *x*). As this is essentially an analogue of our object-in-place task, Davis's results do not seem to accord with our findings. But in fact both tasks were very similar, both requiring the animal to respond differently to an object in a position it had never been experienced before; they differed only in the number of context-object pairings given during pre-exposure – and in fact there was *numerical* evidence of deficit in the object-in-place analogue as well. This suggests that perhaps performance on both tasks was impaired, but this only reached reliability in the *what-where-which* task because it was more sensitive. There were a number of factors that could have reduced the sensitivity to differences in the object-in-place analogue task task. For example the *what-where-which* task was conducted first for all animals and, like ours, involved explicit contextual cues, whereas the *what-where* task was conducted after some interposed SOR and object location tests, and did not include explicit contexts the animals could use to identify the positions of the objects. In support of this conclusion is a more recent report of a deficit in precisely the same task as we employed, in the TgCRND mouse, another transgenic model of AD, in 2-month old animals – a pre-plaque stage (Hamm et al., 2017), and the fact that similar effects have also been reported in much older mice (e.g. Good, Hale and Staal, 2007a, in 10-12-month old Tg2576 animals, and Evans et al. 2019, in 14-16-month old PDAPP mice).

The suggestion that tasks of this type can reveal very early stages of cognitive decline in these animals, even when more global tests of recognition appear to show

no impairment, has further parallels in the human literature. For example, Liang et al. (2016) reported that asymptomatic carriers of the presenilin 1 or amyloid precursor protein genes implicated in familial Alzheimer's disease were impaired on a touchscreen task in which they had to move a previously experienced image to the location in which it had originally appeared, although they were as good as control participants at remembering the images and locations in isolation. Similar findings have been reported by Sapkota et al. (2017), who found that patients with MCI given a visual short term memory featuring binding task ,in which they were required to identify whether or not an object, a location or a combination of the two had been seen before, showed a selective deficit in the combined object-location condition, but performed normally in the object-only and location-only conditions, All these findings are consistent with the view that a deficit in the object-in-place task might serve as a cognitive marker for the early stages of Alzheimer's disease.

Such a deficit might also contribute to the episodic memory impairments that are so characteristic of Alzheimer's disease, even in its early prodromal stage (Bondi et al., 2008). The content of episodic memory is usually defined as comprising the *what-where-when* aspects of a memory episode, and behavioural tasks that are sensitive to these factors have been used to explore episodic memory in nonhuman participants (although see e.g. Tulving, 2002). There have been a number of approaches to this , several of which involve combining variants of these SOR-type tasks (Binder et al. 2015; Crystal, 2008). One of these is the *what-where-which* task described above (Davis et al., 2012), which combines what and where components, although neglects to incorporate time. Tasks that do include a temporal component include variations on the *what-where-when* task (e.g. Dere et al., 2005; cf. Good et al., 2007a, b). The latter is especially relevant here as it combines components of

both recency and object-in-place tasks. For example, in one variant (Good et al., 2007a, b) animals are exposed to two pairs of two objects in separate sample phases, first *A* and *B,* then *C* and *D,* each in a unique location. In the subsequent test all four are presented, but *A* and *D*, one from each sample phase, exchange locations. In this way one can compare new (recent) static *C*, new switched *D*, old static *B* and old switched *A*. Animals explored stationary A more than all the other objects, which they argued shows integration of *what-where-when* information (although see Kart-Teke et al., 2006, who in a minor variant found a rather different result). Good and colleagues have reported that older Tg2576 mice, a transgenic model of AD, show deficits in this task, as well as in the object-in-place task; the performance of these animals was instead based entirely on recency, with greater exploration of the less recent items. This result is consistent with our findings, albeit in much older animals, and suggests that the early deficit in episodic memory might stem from a more fundamental deficit in the *where* component that is reflected in the object-in-place task. This could in turn reflect involvement of the hippocampus, a brain area that is affected early in the course of the disease (e.g. Braak & Braak, 1995) and is heavily implicated in spatial processing (e.g. O'Keefe, 1976). In fact Good et al. (2007b) showed that rats with excitotoxic hippocampal lesions showed the same pattern of impairments on these tasks as their Tg2576 mice, which is consistent with this view. Yet the hippocampus has also been implicated in temporal processing (cf. Meck, Church & Olton, 1984), and we have also observed an early-emerging timing deficit in these same transgenic animals (Armstrong et al., 2020). It may be that more subtle tests may reveal that the temporal component of episodic memory is also affected in early Alzheimer's cases.

Our SOP analysis is a departure from traditional analyses of recognition in terms of recollection – retrieval of information about the target item – and familiarity, the sense it has been encountered before. Although drawing an analogy between familiarity and self-generated priming on the one hand, and recollection and retrieval-generated priming on the other seems possible, the apparent parallels do not stand up to scrutiny. Familiarity is not usually conceptualised as a transient phenomenon, and recollection refers to the target item's ability to retrieve its associates, which in turn aids recognition, while retrieval-generated priming works in the opposite way, relying on the presence of associates to retrieve memories of the item itself. Moreover, although the mechanisms promoting self- and retrieval generated priming are different, their priming effect of putting elements into their A2 state is essentially identical, such that their effects on recognition are mediated by a common final mechanism. Moreover, at an empirical level this position would predict a selective impairment in recollection, but not familiarity, in the early stages of AD, and the human literature does not support this prediction. Although there is certainly a consensus that recollection is impaired in prodromal Alzheimer's disease (Embree et al., 2012; Hudon et al., 2009; Pitarque et al., 2016; Serra et al., 2010; Westerberg et al., 2006, 2013; Wolk et al., 2008, 2013), quite often familiarity deficits are also observed (Embree et al., 2012; Pitarque et al., 2016; Wolk et al., 2008, 2013; although see Hudon et al., 2009; Serra et al., 2010; Westerberg et al., 2006, 2013 for reports of familiarity being left intact). Nonetheless, we hope that our analysis could offer a novel perspective on the controversy surrounding the study of recognition memory in both animals and human participants.

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