What does semantic dementia reveal about the functional role of the perirhinal cortex?

In their recent review, Murray and Bussey discuss in detail the findings from studies of perirhinal cortex function in non-human primates, and propose a model suggesting involvement of the perirhinal cortex in recognition memory and in visual perception[1]. It is interesting to consider how this evidence accords with studies of perirhinal cortex function in humans, and the authors proceed to discuss the emergent literature on this issue. They note that amnesic patients with damage including the perirhinal cortex tend to show recognition memory deficits but that those with damage confined to the hippocampus or fornix perform relatively normally on tests of recognition memory.

One outstanding question that was raised by Murray and Bussey's article relates to whether findings in patients with the disorder of semantic dementia concur with their model of perirhinal function. Semantic dementia results in a progressive, yet selective deterioration of semantic memory affecting both verbal and non-verbal aspects of conceptual knowledge. Other cognitive domains, such as the phonological and syntactic aspects of language, non-verbal problem solving, working memory and visuospatial and perceptual abilities, are relatively unaffected[2,3]. Of note is the fact that, pathologically, such individuals invariably show non-Alzheimer forms of neurodegeneration like that found in other forms of focal lobar atrophy[4]. Murray and Bussey suggest that it is damage to 'the ventromedial temporal cortex, including the perirhinal cortex, [that] results in semantic dementia' (p. 148), and that the perirhinal cortex might, therefore, be associated with the processing of semantic memory. The aim of this letter is to document recent data from semantic dementia which seem potentially problematic for Murray and Bussey's theoretical position.

Recent neuroradiological investigations of semantic dementia have revealed that the disorder is associated with focal atrophy of the anterolateral aspects of one or both temporal lobes, especially the pole and inferior and middle temporal gyri (Brodmann areas 38/20), with sparing (at least at early stages of the disease) of the hippocampal complex (hippocampus proper, parahippocampal gyri and subiculum)[5]. The status of the perirhinal cortex is clearly of vital importance but presents difficult methodological problems: the exact location in humans is controversial. It is currently considered to occupy the banks of the collateral sulcus and extend rostrally onto the medial surface of the temporal pole[6]. This complex morphology without well-defined boundaries (unlike the hippocampus, for example) presents considerable difficulty for current volumetric MRI techniques based upon planimetry or stereology. To overcome these problems we used an automated voxel-by-voxel morphometric technique to identify changes in grey matter volume in six patients with semantic dementia[7]. Although the caudal portion of the perirhinal cortex appeared normal, the status of the rostral section was less certain. Of more importance was the very strong correlation between the degree of anterolateral temporal lobe atrophy and semantic memory impairment, suggesting that this region, rather than the perirhinal cortex, may be the critical area for the processing of semantic knowledge.

Further evidence which seems contradictory to Murray and Bussey's view comes from recent neuropsychological studies that have investigated the integrity of episodic memory in semantic dementia. In contrast to the profound loss of semantic memory that is the hallmark of the disorder, episodic memory is often relatively preserved (see Ref. 8 for a review). Most patients show better recall of recent autobiographical memories compared to those from the more distant past[5], and it has been demonstrated that patients can temporarily relearn 'forgotten' vocabulary through frequent practice, although the benefit of this rote learning is quickly lost once practice ceases[9].

The evidence most pertinent to the debate about the perirhinal cortex in semantic dementia is the robust finding of preserved non-verbal recognition memory in the disorder, using tests akin to the delayed-matching-to-sample tasks employed in animal studies. We have consistently found normal forced-choice recognition memory for both monochrome[10] and colour[11] pictures of objects and animals, despite the patients showing profound impairment on tests of semantic knowledge comprising the same stimuli. A recently conducted series of single-case studies compared yes/no recognition memory for familiar items categorized as still 'known' or now 'unknown' on the basis of prior assessments of comprehension and naming. These experiments demonstrated that patients with semantic dementia typically show normal recognition memory for familiar objects[11] and famous faces[12], irrespective of whether their semantic knowledge about the test items is intact or severely degraded.

The interpretation of some of these results must be treated with a certain degree of caution because of the pervasive problem in recognition memory research of control participants performing close to ceiling. This makes it difficult to establish definitively that recognition memory – although far better than would be expected given the patients' profound loss of semantic knowledge – is truly normal. To address this issue, we recently carried out a study using a demanding recognition memory test designed in order that control participants would not perform at ceiling (Simons *et al.*, unpublished data). We found that the controls did indeed score below ceiling, averaging 55.8 out of 60 (SD = 3.2), and that a group of five patients with semantic dementia were not significantly impaired according to comparisons of d′ sensitivity measures [controls: d′ = 3.47, var (d′) = 0.19, semantic dementia: d′ = 2.69, var (d′) = 0.1, difference not significant]. The evidence suggests, therefore, that patients with semantic dementia do possess intact non-verbal recognition memory even when their semantic knowledge about the test stimuli is severely degraded. This recognition memory capability is supported, we have proposed, by perceptual information about the studied target items[11].

Based on the neuroradiological and behavioural evidence, therefore, we believe that Murray and Bussey's assumption that the perirhinal cortex is damaged in semantic dementia[1] is unproven. We also suggest that the data from semantic dementia may be problematic for the position that the perirhinal cortex supports both recognition memory and the processing of semantic knowledge. We have demonstrated that, even when stringent tests are used, most patients with the disorder show normal non-verbal recognition memory based, presumably, on the preservation of the perirhinal cortex. In our studies it is only patients who have reached advanced stages of the disease who show a deficit on tests of recognition memory, presumably because the pathological process has progressed to regions in the medial temporal lobe by this late stage of the disease (J.S. Simons *et al.*, unpublished data). Moreover, if the perirhinal cortex is intact in most patients with semantic dementia, it is difficult to see how their profound impairment of semantic memory can be explained by a model that assumes the perirhinal cortex is responsible for semantic memory processing as well as recognition memory.

To summarize, it is currently unclear whether it is valid to base a putative association between the perirhinal cortex and semantic memory upon

evidence from semantic dementia. Recent findings suggest that at least the caudal portion of the perirhinal cortex may be preserved in semantic dementia, with atrophy confined, in at least the early stages, to polar and inferolateral aspects of the temporal cortex. This claim is supported by behavioural studies showing normal non-verbal recognition memory in the disorder, and the finding that degree of semantic memory impairment correlates highly with the amount of anterolateral temporal lobe atrophy. It seems plausible, therefore, that the integrity of the perirhinal cortex underlies the normal recognition memory demonstrated in semantic dementia, and that it is the inferolateral temporal lobe that is associated with the processing of semantic knowledge.

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Reply

In a recent article[1], we described a model of the function of the perirhinal cortex (PRh) that can account for some of the puzzling effects of PRh lesions in monkeys[2]. We also suggested that the object information thought to be stored and processed in networks including PRh was akin to semantic memory in humans ('the perirhinal cortex is the core of a system specialized for storing knowledge about objects, analogous to a semantic memory system in humans', p. 146). Simons, Graham and Hodges have raised several salient points concerning our model and its relationship to semantic memory and semantic dementia (SD) in humans[3]. Specifically, their main points are as follows: first, they provide preliminary evidence suggesting that caudal regions of PRh may be spared in SD, and that the extent of anterolateral temporal cortex damage is correlated with semantic memory impairments. Second, Simons *et al*. report that in patients with SD there is relatively preserved episodic memory, including recognition memory.

We believe that the finding reported by Simons *et al*., that the severity of SD is related to the extent of damage to the anterolateral temporal cortex, is entirely consistent with our model, regardless of whether the damage includes PRh. This is because our model assumes that the neural circuitry coding a visual representation of an object is widely distributed throughout inferior temporal (IT) cortex. Thus the greater the tissue damage in this region, the more this distributed representation will be compromised. Furthermore, based on anatomical considerations, damage to caudal cortical fields might be expected to have two effects: (1) removing parts of representations stored in that cortical field, and (2) 'disconnecting' downstream fields from their normal pattern of sensory input. If this analysis is correct, then damage to more lateral or caudal portions of IT might be expected to have a somewhat greater effect on semantic memory than would damage to rostral regions alone.

It is the hierarchical organization of this distributed object representation, however, that allows the model to explain the pattern of lesion effects in monkeys. Similarly, the pattern of errors made by SD patients suggests a hierarchical model of semantic knowledge. Specifically, SD patients make errors that are generally category coordinate or superordinate, suggesting that pathology in SD 'prunes back the semantic tree', thus damaging 'finer-grained (subordinate) aspects of these patients' knowledge' but leaving higher-order categorical information intact[4]. Similarly, in our model, a lesion disrupts complex representations of the conjunctions of object features stored in downstream regions of IT, but leaves intact the simple features stored in upstream regions. This property of the model may go some way towards explaining the dissociation between stimulus recognition and semantic memory reported by Simons *et al*. One can imagine that when a subject is asked if a particular item was in the study list, she could respond accurately by recognizing a feature or subset of features of the stimulus (e.g. she could recognize 'red' in a red object that had been presented earlier). Detailed knowledge of the object may not be necessary. On the other hand, in order to answer questions designed to assess specific semantic knowledge pertaining to that object, the subject must know the precise identity of the object. Thus SD patients might, according to our model, be disproportionately impaired on tests of semantic versus recognition memory even if the stimulus material were the same. The model thus makes a prediction that if a stimulus were manipulated between study and test so that it was then difficult to recognize on the basis of component perceptual features alone, then SD patients might evidence a deficit. Remarkably, this is precisely the effect reported by Graham, Patterson and Hodges[5].

Even without this alternative account, however, the finding of spared recognition in SD is entirely consistent with the data from monkeys, and with our model. The apparent discrepancy comes down to differences between what we and Simons *et al*. mean by the term 'recognition'. Recognition memory impairments following PRh lesions in monkeys are observed when items are *novel*. PRh lesions in monkeys do not affect recognition memory when items are *familiar*[6]. In the recognition task reported by Simons *et al*., however, all items are familiar. When items are familiar, recognition tests might be solved by episodic 'recollection' rather than 'familiarity'[7]. It is possible that the latter, and not necessarily the former, involves PRh and other regions in IT. Thus we agree entirely with Simons *et al*.'s conclusion that episodic and semantic memory are dissociable, and we