

### Dementia and Animal Activities of Daily Living

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## Opinion

One area of psychiatry that remains challenging is dementia. This “Cinderella” disease, in all its many forms, is as yet virtually untreatable, with the notable exception of Parkinson’s disease. For Alzheimer’s Disease (AD) there may be some improvement to be gained by administering one of the licensed acetylcholinesterase inhibitors, or the partial NMDA glutamate receptor antagonist memantine. These compounds are not very effective, however, and then only in the early stages of dementia.

Several new pharmaceuticals are in the pipeline, but their efficacy remains to be seen. But are the pharmaceutical companies screening for the right drug profile? Although one normally thinks of dementia as a disorder of memory, in clinical practice, it is the loss of the ability to perform “Activities of Daily Living” (ADLs) that is the crucial debilitating factor. Poor ADL performance inevitably leads to the need for carers and/or hospitalisation.

However, most pharmaceutical companies looking for cognition-enhancing new drugs, naturally, use preclinical animal tests of learning and memory. But it is now well known that the type of memory so damaged in dementia is episodic memory for events, episodes, that can be temporally ordered and are full of multi-modal sensory detail. For example, you went to the shop and on the way met Mrs T, an old friend. She’d changed her perfume and hairstyle since you last saw her. Anyway, she was complaining about the price of bacon, when a car suddenly blasted its horn – some kiddy had just run into the road. This comprehensive, episodic form of memory is unlikely to be present to any significant extent in the experimental rats and mice that the big Pharma are doing their preclinical screening on. Sure, they can show that their drug improves a rat’s ability to remember where it had a nasty foot shock, or where there is a hidden island refuge in a pool of deep water, but that’s not quite the same as human episodic memory. After all, the amnesic lady patient, of the Swiss

physician Claparede (subconsciously) remembered perfectly well that he had previously painfully pricked her hand with a hidden pin on the previous morning, although she had virtually no conscious recall of that episode.

So, what’s the alternative? Fortunately, there is one, due to recent discoveries in mice. Monitor their ADLs. Or, if you prefer, their natural “species-typical behaviours”, and give them drugs that might improve the latter. Preferably make them demented first, so it’s easier to see an improvement. Complicated and difficult? – No.

Working at Oxford, our group discovered that surgically removing the hippocampus of mice, or disabling it by infection with a prion agent, scrapie, virtually eliminated their propensity to engage in species-typical behaviours. Particularly, their ability to burrow and make nests (Deacon, et al. 2001, 2002) [1,2]; (Figure 1). Dementia generally involves deterioration of the hippocampus, particularly in its most prevalent form, AD.

Building a nest is somewhat similar to making up a bed, so the mouse activity is fairly close to that of a human, giving the nesting test a certain amount of “face validity”. By comparison, finding a submerged “island” in a pool of deep water bears little relationship to memory in humans.

Degus are small rodents, endemic to the plains of central Chile, living a semi-fossorial existence in underground burrows, which they dig themselves. By a great stroke of scientific luck (or, more prosaically, the fact that the precursor protein of degu  $\beta$ -amyloid differs from that of humans by only one amino acid), some spontaneously develop AD-associated brain pathology - the characteristic extra-neuronal  $\beta$ -amyloid plaques and the intraneuronal hyper-phosphorylated tau protein neurofibrillary tangles (Inestrosa, et al., 2005) [3]



**Figure 1: Top:** A control (normal), mouse with a nest it has made the previous night. **Below:** A comparatively poor nest made by a mouse with a hippocampal lesion.

The problem is, that rats and mice do not spontaneously show such AD-associated pathology. Extensive (and expensive) genetic modification is required to produce to produce a mouse or rat with human-like AD histopathology. If, however, degus with incipient or extant AD could be identified, preferably at a young age, then novel putative pharmacological therapies could be tested on them. Fortunately, identifying degus with amyloid deposits in the brain is very easy, thanks to a simple and ultra-sensitive natural test of behaviour (thus obviating the need for invasive bio-sampling) developed for mice at Oxford (Figure 2) and employed on degus in S. America. Degus, like many rodents, are semi-fossorial (underground) burrowing animals. Although the burrowing test was originally developed in mice (Deacon et al.

2001), when Chilean degus were given an opportunity to burrow in the laboratory, some proved to be good burrowers, others poor [4]. Subsequently, post mortem, it was shown that the brains of the poor burrowers (but not those of good burrowers) contained significant amounts of the AD-associated  $\beta$ -amyloid protein (Deacon, et al. 2015) [4].

Thus, poor burrowers could be repeatedly tested in the burrowing paradigm, with a novel chemical entity (potential new drug) occasionally given to them before the test. Fortunately, degus never seem to tire of burrowing. This is hardly surprising, since burrowing is part of their natural lifestyle. Moreover, since they appear to find this activity rewarding, it could be considered as a form of environmental enrichment, to alleviate the boredom of their laboratory lives. Thus, the experiment would reflect the “Refinement” of Russel and Burch’s (1959) “3 Rs” [5] (Figure 2).



**Figure 2:** A mouse in a laboratory “burrow”.

The methodology would be so easy that a child could do it. Simply give the degus an opportunity to burrow three times a week. On two control days, dose them before burrowing with the drug vehicle (say, water) alone. After these two baseline control days, on the third day give them the novel chemical entity (putative new drug). If they burrow more after the drug, then repeat the burrowing test with more animals to check the reliability of the initial test. Because the animals serve as their own controls, a Reduction (Russel and Burch, 1959) in the number of animals used could also be achieved [5].

If the results of this primary screen could be verified by secondary and tertiary animal preclinical tests, human trials could begin. Firstly, healthy young men would be tested, to check for

any untoward effects. Then, in stages, patients with dementia, progressing to international randomised multiple-patient double-blind trials.

If, maybe ten years later, it is finally proved that the drug is active against dementia, all that remains is for the initial discoverers to book their flights to Stockholm (to receive their richly-deserved Nobel Prizes!).

Meanwhile, there is a new compound, J147, that has shown promising results in animal studies. J147 is a trifluoro derivative of curcumin, a biphenolic compound found naturally in the curry spice turmeric. Known as “haldi” in India, where it is said that the incidence of AD is considerably lower than in the USA. As of 2018, clinical trials are now in progress, and more preclinical work in degus and mice is due to start soon.

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