

Dr Sophie Dix

Eli Lilly and Company, Lilly Research Centre, Erl Wood Manor, Sunninghill Road,
Windlesham, Surrey, GU20 6PH, United Kingdom

Dix_Sophie@lilly.com

Challenges of Translating Preclinical Cognitive Assays to the Clinic

Cognitive impairment is a key feature of many neurodegenerative and psychiatric disorders including Alzheimer's disease, Parkinson's disease, schizophrenia and depression. At present, there are few effective therapies for the treatment of cognitive impairment in these diseases. Indeed, despite great advances in *in vitro* screening technologies in the past decade, the discovery of true nootropic compounds remains as elusive as ever. The attrition rate of such compounds is high and at present occurs quite frequently at the later stages of the drug discovery process, e.g. Phase II or III clinical trials. Such expensive failure has brought the predictive validity of animal tests of cognition into question.

While animal models make it possible to investigate brain-behaviour relationships and are essential for the discovery of novel therapeutic approaches, there has been an over reliance on behavioural paradigms that have strong face validity with little regard to the full characterisation of the assay. Put simply, an assumption is often made that if a test looks like it is measuring effects on cognitive processes, then it must be doing so. The reality is that behaviours measured in a test of cognition are affected by many other processes than memory. When using these tests, effects on motor function, sensory processes, anxiety and arousal must all be accounted for before any conclusions can be made concerning cognitive function. Three of the most widely used preclinical tasks of learning and memory (passive avoidance, object recognition and Morris water maze) can be easily misinterpreted.

The use of normal animals in the search for cognitive enhancers may also be hindering progress. It is possible that if a normal rat is sufficiently motivated during testing, then its cognitive performance may already be optimal in this context. This implies that there may be no window in which effects of cognitive enhancers could be measured in the first place. It may therefore be necessary to develop appropriate models of cognitive disruption in order that there is sufficient dynamic range to detect cognitive enhancement. A variety of experimental manipulations have been assessed for their utility as cognitive deficit models, including behavioural, pharmacological, and environmental approaches. Modern techniques in neuroscience have also allowed exploration of genetic and lesion approaches to this problem. Each type of cognitive deficit model has different

levels of face, predictive and construct validity and is associated with a different set of potential confounding factors.

In conclusion, the discovery of novel cognitive therapies will require the development and appropriate use of a battery of valid, refined behavioural tests combined with the development of rodent models of cognitive disruption with good predictive and construct validity.