Figure 1. Final stimuli used in the visual discrimination studies.

A+	C	
A+		B
C	B+	
	B+	A
	A	C+
B		C+

Figure 2. The 6 possible permeations of stimuli using three stimuli (A, B and C) presented in 2 of 3 locations within a PAL task. '+' indicates the correct response to gain an appetitive reward.

for certain images, but that performance was matched when 'lines' and 'circle' were used (see Figure 1). These findings were confirmed within two additional laboratories and selected as the stimuli to be used.

We will also profile the three transgenic lines selected for use within PharmaCog using the harmonised VD protocol. Preliminary data has shown that aged male TASTPM (15 – 18m) were unimpaired in the VD acquisition. Indeed the mice showed enhanced learning compared to age-matched wild type c57/bl6 mice, and were comparable in their performance to young (6m) male c57/bl6 mice. Using a different amyloid transgenic line, tg2576, aged female mice (13m) were again shown to have enhanced performance relative to wild type control animals. This study also examined the pretraining regimen used to train animals to respond to the screen. The results suggested that lengthy pretraining protocols introduced variance into the subsequent VD acquisition data.

Paired Associates Learning

The second task that the team is exploring is paired associates learning (PAL). Poor PAL performance in MCI patients has been shown to be predictive of AD pathology [5]. In this task, a subject must remember not only the visual stimulus that he has been presented with, but also where it was located ('what' and 'where'). A rodent version of the task has been developed using touchscreens in both in rats [3] and mice [4]. In this paradigm an animal is presented with, typically, 2 stimuli in 2 of 3 apertures within a touchscreen mask. An animal learns that it must respond to. stimulus A, e.g., when it is in location 1 but not when it appears in locations 2 or 3 (Figure 2). Hence the animal must learn to associate a visual stimulus with a specific location ('what' and 'where'). It is also possible to increase or decrease the possible combinations of stimuli and location by increasing the number of apertures (i.e. possible locations) and / or changing the number of stimuli that are presented animal is presented with. Studies are ongoing to optimise the number of stimuli and locations to detect deficits in AD transgenic models. PDAPP mice show acquisition deficits in a simple version of the task in which 2 stimuli are presented within 4 locations (4 permutations) compared to age-matched wild type littermate control animals.

Discussion

Touchscreens are a relatively new technology that confers significant advantages over traditional lever-equipped operant chambers due to the range of stimuli that can be presented to the animal. Furthermore, there is translational potential to have analogous paradigms across species including humans. This large collaboration demonstrates the clear advantages inherent in the consortium approach. This multisite series of experiments will allow for novel protocols to be further developed, harmonized and validated rapidly with the aim of identifying translatable paradigms that are sensitive to AD pathology in transgenic mice and hence can be used in drug development and research into MCI and AD.

VD is simple task and we did not anticipate a learning deficit in these mice. If the selective deficit in PAL in the amyloid transgenic animals is found to be robust, this would provide strong validation for the use of this paradigm in AD research. It would demonstrate that amyloid pathology can produce a selective deficit in PAL acquisition rather than a non-specific deficit in touchscreen-based learning *per se* which could potentially reflect a non-cognitive phenotype such as visual deficit. The final stage of this project will be to assess drugs currently used for the symptomatic treatment of AD (donepezil and memantine) and amyloid lowering compounds against performance deficits in mouse models of Alzheimer's disease in touchscreen tasks.

References

1. Bussey, T.J., Holmes A., Lyon L., Mar A.C., McAllister K.A.L., Nithianantharajah J., Oomen C.A., Saksida L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. *Neuropharmacology* **62**, 1191-1203.

2. Talpos J.C., Fletcher, A.C., Circelli C., Tricklebank, M.D., Dix S. L. (2012). The pharmacological sensitivity of a touchscreen-based visual discrimination task in the rat using simple and perceptually challenging stimuli. *Psychophrmacology*, DOI 10.1007/s00213-011-2590-z.

3. Talpos J.C., Winters B.D., Dias R., Saksida L.M., Bussey T.J. (2009). A novel touchscreen-automated paired-associate learning task sensitive to pharmacological manipulation of the hippocampus: a translational rodent model of cognitive impairments in neurodegenerative disease. *Psychopharmacology (Berl)* **205**, 157-168.

4. Bartko, S.J., Vendrell I., Saksida L. M., Bussey T.J., (2011). A computer-automated touchscreen paired-associates learning (PAL) task for mice: impairments following administration of scopolamine or dicyclomine and improvements following donepezil. *Psychopharmacology (Berl)* **214**, 537-548.

5. Swainson R., Hodges J.R., Galton C.J., Semple J., Michael A., Dunn B.D., Iddon J.L., Robbins T.W., Sahakian B.KJ. (2001) Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Demnt. Deriatr. Cogn. Disord.* **12**, 265-280.