Title of Challenge

Wireless recording of the electrophysiology of cognition in psychiatric disease models

Background

Many brain disorders including schizophrenia and Alzheimer's disease are characterised by severe impairments in cognition that are still both poorly understood and treated. There is mounting evidence that some deficits in cognitive function arise through a break down in the coordinated activity of neuronal networks responsible for memory, learning and decision-making. The hippocampus and medial prefrontal cortex are two regions of the brain thought to be central to cognitive processes. The coordinated activity of hippocampal-prefrontal networks is specifically engaged in mice learning to navigate a maze to find food; a paradigm that measures hippocampus-dependent spatial working memory (1,2). It is possible to record both the individual activity of the hippocampal neurons involved as well as the rhythmic activity that arises within networks of neurons using multi-site *in vivo* electrophysiology. By implanting electrodes in multiple brain regions and then recording brain activity while mice run on a T-maze, the rhythms and oscillations that are essential for synchronisation can be identified. Such recordings, in conjunction with behavioural outcome (e.g. how long it takes to find the food, the acquisition of the task and the error rate), will provide for greater validity of the cognitive tasks and disease models employed in drug discovery and consequently, much greater certainty of clinical impact.

An automated, computer controlled, modular maze has recently been developed (3). In this apparatus, mice perform multiple trials with reduced variability and at a much greater rate. The scientific and welfare advantages of this apparatus can only be fully realised if the animals are freely moving. Therefore there is a need to monitor neuronal activity in the hippocampal-prefrontal networks without requiring the animals to be tethered in any way. Some progress in this respect has been made with the introduction of a wireless multi-channel system for mice and rats by Triangle BioSytems (4). However the performance characteristics of this system (weight, size and battery life) are not adequate to exploit fully the advantages of the automated T-maze. Furthermore, software needs to be developed linking electrophysiology with behaviour, not only for this challenge, but ideally in a manner that is readily adapted to the wider use of wireless electrophysiology in other behavioural paradigms e.g. those using operant lever pressing or touchscreen techniques.

3Rs benefits

Traditional T-maze rewarded alternation tasks require intense handling which may alter the affective state of the mouse and so alter cognitive performance. This has been confirmed in a recent study which showed that handling history modified stress levels and subsequent behavioural responses (5). In the automated maze both handling and tethering are avoided. The mouse is able to enter the maze at will at pre-programmed times during the light/dark cycle without any human intervention. This allows the mice to perform when they are naturally more active (i.e. in the dark period). Furthermore, the mouse remains in visual, auditory and olfactory contact with cage mates during the inter-trial interval, giving additional welfare benefits. Automation greatly increases the number of trials an animal can complete in a 24 hour period allowing greater statistical power from fewer animals. For long term recording, lighter and smaller devices with greatly increased battery life will minimise stressful handling. Finally, the potential reduction and refinement benefits of such a device could also be realised in other behavioural experiments if the software is sufficiently adaptable.

Need for collaboration

This project will require a multidisciplinary approach with experts in rodent behaviour and electrophysiology helping mechanical and electrical engineering teams to reach a workable and successful prototype. Software development for data handling and statistical analysis also forms part of the proposal. Winning applications would typically have contributions from both the public and SME sectors with complementary expertise in the needed areas.

Overall objectives

To develop a prototype of a wireless 16-32 channel recoding system that can acquire and transmit data for a minimum of 24 h but ideally for more than 10 days, that can be replaced or recharged with minimal discomfort for the animal and is small enough to be carried by a mouse without affecting its behaviour or welfare.

Key deliverables

A wireless recording device that has the following specifications:

- Capability equivalent to recording 16 channels at 32 kHz;
- Battery life of at least 24 hours and ideally more than 10 days to allow mice to learn multiple tasks within the T-maze uninterrupted and without stressful insults;
- Event tracking to allow the behavioural data to be linked to the electrophysiological data;
- Any part of the system carried by the mouse must not weigh more than 3g;
- Software for the collection, analysis, storage and interrogation of data, with flexibility for adaption to other behavioural paradigms;
- Performance in pre-agreed tasks in the automated T maze for validation of the technology e.g. demonstration of the relationship between hippocampal-frontal synchrony of theta oscillations as the mice make correct or incorrect choices in the maze (1).

Industry sponsor

Eli Lilly

In-kind contributions

Lilly will have 8 of the mazes in operation by early 2012. Lilly will make these mazes available for the project either by hosting visitors to its Erl Wood research laboratory, or by providing them for use by one or more of the applicants in their own laboratories. In addition Lilly has extensive expertise in *in vivo* electrophysiology and amperometry in rats performing complex cognitive tasks in operant chambers and is developing the approach for use in mice. Lilly will make available such experience as needed for the project. Within the company, software for data analysis is continuously evolving with input from internal experts and if the winning applications propose bringing in external software experts Lilly will offer opportunities for collaboration. In the validation phase, Lilly will provide appropriate materials for testing.

Industry sponsor access to foreground Intellectual Property

There will be no restriction on IP exploitation. Applicants will be free to publish or commercialise where appropriate and no preferential access will be required by Lilly.

Duration

Up to three years

Budget

Up to £500,000 in total, inclusive of VAT where applicable

Funding model

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise, and applications are therefore welcomed from consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors). More than one such consortium could be funded, particularly if the proposed technologies take substantially different routes.

References

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Keywords

Cognition, spatial navigation learning, telemetry, wireless, EEG, oscillations, psychiatric disease, animal behaviour, central nervous system.