A cognitive task sensitive to dentate gyrus activity which has implications for assessing neurogenesis status in various conditions including normal and pathological ageing

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BACKGROUND

- The seminal discovery that the human dentate gyrus (DG) retains its ability to generate neurons throughout life (Eriksson et al., 1998), has raised the possibility that therapies could be developed to protect or promote this neurogenesis as it deteriorates due to ageing, insult and disease.
- The DG plays a crucial role in associative memory, and the degenerative changes which compromise neurogenesis in the DG are believed to contribute to memory disturbances in normal ageing and the early stages of AD (Dohrn, 2007).
- Pattern separation has been demonstrated to be under the control of the DG, and fMRI studies have identified the DG to be highly and selectively active when volunteers perform visual object pattern separation tasks (Kirwan & Stark, 2007).
- The CDR System picture recognition task assesses object pattern separation, and in a cohort of over 3000 healthy volunteers aged 18 to 87 years, a selective, marked and highly significant age-related decline was identified in the ability to discriminate originally presented pictures from different but very similar pictures (Wesnes, 2010). Further, patients with MDD Cognitive Impairment were shown to be selectively inferior on this discrimination compared to age-matched healthy controls.

THE CDR SYSTEM

- The CDR System has been used from Phase I through IV & investigator led research in:
  - > 1200 Clinical Trials
  - > 140 Phase I Units
  - > 300 Sites in patient studies in > 60 countries
  - > 500 Compounds
  - > 60 Patient populations
- The CDR System has:
  - > 50 alternate forms of each test
  - > 65 language versions
  - Scientific Presentations:
  - >300 peer-reviewed publications
  - >500 conference abstracts

METHODS

THE CDR SYSTEM PICTURE RECOGNITION TASK: AN OBJECT PATTERN SEPARATION TASK

Part A: 20 pictures are presented to the subject at the rate of 1 every 3 seconds.

Part B: 15 minutes later, the 20 pictures are represented mixed with 20 very similar ones.

For each picture, the subject is required to press YES as quickly as possible if it was the original picture, or NO if it is a similar but different picture.

RESULTS

Figure 1: Discriminating the similar pictures from the originals is the assessment of dentate gyrus activity. (RMI) shows selectively greater dentate gyrus activity in this condition.

Figure 2: Dentate Gyrus - roles in neurogenesis and pattern separation and consequences of either disruption or therapy.

Figure 3: Ability to correctly reject similar but different pictures

INTERNET TESTING

Replication of previous work showing selective declines (n=3,021; 18-87 years) with task data gathered via the internet (n=147, 731 aged 18-102 years).

PARKINSON’S DISEASE

- Post-mortem evidence indicates that neurogenesis is compromised in the DG of PD patients.
- Data from 348 PD patients are compared to 17/8 healthy age matched controls.
  - A marked and selective decline on identifying the closely similar pictures is identified.
  - This could be the first human cognitive evidence of impaired neurogenesis in PD.

LATE-LIFE DEPRESSION

- Patients aged over 60 years with MDD compared with age matched controls.
  - All CDR System domains were impaired in the patients compared to controls.
  - Ability to correctly identify original pictures was not impaired (94% v 89.4%), whereas there was a significant decline in the ability to correctly reject similar pictures (70.4% v 59% p<0.03).

DISCUSSION & CONCLUSIONS

- This study has replicated and extended our knowledge of this task which provides measures relevant to DG neurogenesis.
- Besides being compromised in ageing and MDD, it is impaired in late-life depression and PD. Other work with the task has also identified deficits in younger depressed patients, oncology patients and those with chronic pain, which will be presented at different meetings.
- The task provides an opportunity to assess DG activity in various clinical populations.
- The task will prove valuable as part of the assessment profile in exploratory or therapeutic trials of compounds aimed at promoting, maintaining or restoring neurogenesis.
- The opportunity to study large populations via the internet has applications to the various long-term patient registries being set up to study preclinical dementia.

REFERENCES

Kirwan SR, Stark WA. Memory and pattern separation: a puzzle for decoding the role of the dentate gyrus in memory decades. Alzheimer’s & Dementia 2010; 6:198-204.