INTRODUCTION

- Eriksson et al’s demonstration in 1998 that neurogenesis occurred in the dentate gyrus (DG) of the adult human brain, reversed in a stroke one of the central dogmas of neuroscience; namely that after early postnatal development no new nerve cells were produced.

- This instigated a still ongoing concerted research effort to develop compounds which may correct compromised hippocampal neurogenesis and thus treat memory disorders in a variety of clinical conditions including pathological ageing.

- Recent evidence indicates that the G-protein coupled receptor, SREB2/GPR85, a known schizophrenia risk factor, negatively regulates hippocampal dentate gyrus neurogenesis-dependent spatial pattern separation in mice (Chen et al., 2012).

- Post-mortem evidence of compromised hippocampal dentate gyrus (DG) neurogenesis in schizophrenia has also just appeared (Walton et al., 2012).

- The CDR System OPS task has already identified deficits consistent with preclinical work of impaired hippocampal neurogenesis in Late-life depression, Chronic pain, Parkinson’s disease & Alzheimer’s disease (Wesnes, 2012).

HYPOTHESIS

- The purpose of this study was to determine if DG-sensitive OPS is selectively compromised in schizophrenia.

METHODS

- The CDR System OPS task was administered to 91 stably mediated schizophrenic patients aged 22 to 63 years and the results contrasted to 2,330 age-matched healthy controls.

- Performance on the OPS task was also assessed according to Clinical Global Impression Severity (CGI-S) scores.

RESULTS I: Differences to Controls

- The difference in % accuracy scores between the populations in the DG-sensitive measure was: 12.8 (95% CI 10 &16; Effect size =1) compared with: 5.3 (95% CI 2 &8; Effect size =0.4) for the non-DG sensitive measure.

- Further, the speed of the DG sensitive responses was significantly (p<0.005) but not for non-DG sensitive ones (p=0.3).

- No such interaction was seen in a comparable forced choice non-DG differentially sensitive verbal recognition task (p=0.57), indicating that the OPS effect was not due to response style on such tasks.

DISCUSSION & CONCLUSIONS

Evidence that improving neurogenesis will improve performance on object pattern separation tasks

- This is to our knowledge the first cognitive data from an OPS task with established DG sensitivity to show a significant and large effect sized selective deficit in schizophrenics compared to normals; further supported by reliable disease severity deficits, again with large effect sizes.

- The demonstration by Sahay et al (2011) that increasing adult hippocampal neurogenesis improves OPS confirmed the suspected two-way relationship between DG activity and hippocampal stem cell production; thus making OPS tasks both non-invasive proofs of mechanism for compounds which target this process, as well as cognitive outcome measures.

- The implications from the present study are that part of the memory deficit in schizophrenia is related to compromised DG neurogenesis, and that this deficit may respond to medications which influence hippocampal neurogenesis.

- A recent review (Agius & Nandra, 2012) has identified evidence that atypical antipsychotics such as clozapine, risperidone, paliperidone, azapirone and possibly quetiapine do promote neurogenesis, perhaps as a class effect, whereas first generation antipsychotics such as haloperidol or clozapine do not.

- Some novel antipsychotics now entering clinical trials also possess such effects.