Pattern Separation Deficits in Man Support Animal & Postmortem Work to Provide Breaking Behavioral Evidence of Impaired Neurogenesis in Schizophrenia

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Methods

INTRODUCTION

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.

BACKGROUND

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

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

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

RESULTS I: Differences to Controls

An Automated Human Object Pattern Separation (OPS) Task

First data using fMRI to show a pattern separation task can reflect CA3 & Dentate Gyrus Activity

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HYPOTHESIS

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

RESULTS II: Disease Severity Comparisons

Within the 91 patients, CGI-S was significantly associated with the Closely Similar Pictures, the DG-sensitive score (p<0.05) but not Original Pictures, the non-DG sensitive score (p=0.91)

The effect size of the difference between CGL-2 and CGI-S 4 for the DG sensitive score was 1.28

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

METHODS

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

The speed scores supported the poorer accuracy scores; DG sensitive responses being 1.81 ms slower in CGL-2 than CGI-S; but <1 ms for the non DG sensitive score

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DISCUSSION & CONCLUSIONS

This is to our knowledge the first cognitive data from an OPS task with established DG sensitivity to show a significant and large effect sizes.

The demonstration by Siahay 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 (Aguis & Nandra, 2012) has identified evidence that atypical antipsychotics such as olanzapine, risperidone, paliperidone, aripiprazole and possibly quetiapine do promote neurogenesis, whereas first generation antipsychotics such as haloperidol or clozapine do not.

Some novel antipsychotics now entering clinical trials also possess such effects

REFERENCES


