Loss of pattern separation performance in schizophrenia suggests dentate gyrus dysfunction

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ABSTRACT

Motivated by evidence that the dentate gyrus differentially mediates the pattern separation (PS) component of declarative memory function and that dentate gyrus harbors molecular and cellular pathologies in schizophrenia, we examined whether PS performance is altered in volunteers with schizophrenia (SZV) relative to healthy volunteers (HV). In groups of well-characterized SZV (n = 14) and HV (n = 15), we contrasted performance on the Behavioral Pattern Separation (BPS) Task, acquiring two outcome measures, a PS parameter and a Recognition Memory (RM) parameter, as well as specific recognition data by stimulus type. The SZVs showed a significant decrement in PS performance relative to HV (mean ± SEM, SZV: 3.1 ± 2.7%; HV: 17.1 ± 5.8%; p = 0.039, $d' = 0.86$); whereas SZV and HV did not significantly differ in RM performance (SZV: 50.1 ± 8.1%; HV: 59.3 ± 5.5%; p = 0.350, $d' = 0.36$). Moreover, the SZVs showed a selective defect in correctly identifying similar lure items (SZV: 24.0 ± 3.7%; HV: 41.2 ± 4.6%; p < 0.05), but demonstrated no impairment in identifying targets and novel foils. These data suggest that the dentate gyrus is dysfunctional in schizophrenia, a feature that could contribute to declarative memory impairment in the disorder and possibly to psychosis, a conclusion consistent with the considerable molecular pathology in the dentate gyrus in schizophrenia.

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1. Introduction

Human studies have consistently supported an involvement of hippocampal dysfunction in schizophrenia (SZ) based on functional (Heckers et al., 1998; Medoff et al., 2001; Schobel et al., 2013), molecular (Gao et al., 2000; Harrison, 2004) and cellular (Wang et al., 2011) outcomes. These hippocampal alterations could underlie declarative memory dysfunction in the syndrome and mediate some manifestations of psychosis (Tamminga et al., 2010). We have begun to examine the role of subfield-specific hippocampal alterations in SZ, persuaded by evidence of distinct subfield functions in declarative memory formation that is emerging from basic investigations (Leutgeb et al., 2007; Deng et al., 2013; Rangel and Eichenbaum, 2013; Schobel et al., 2013). The dentate gyrus (DG) appears to be differentially affected in SZ compared to other hippocampal subfields, based on the distinctive molecular and cellular changes in DG tissue from SZ cases (Gao et al., 2000; Knable et al., 2004). Reductions in GluN1 protein have been observed in SZ in the hippocampus; moreover, this GluN1 change is expressed selectively in DG (Stan et al., in press). Because GluN1 is the critical subunit in NMDA receptor signaling, it raises the possibility that excitatory signaling in DG is reduced in SZ. Together these findings support the model that pathologically reduced DG signaling onto CA3 pyramidal neurons can alter plasticity dynamics in CA3, potentially increasing neuronal activity there, generating hyper-associations and mistakes in *conjunctive encoding* which could create false memories with psychotic content (Fig. 1) (Tamminga et al., 2010). It is important to establish the presence of meaningful alterations in DG function in living individuals with SZ, to corroborate this hippocampal model of psychosis.

A computational component of declarative memory thought to differentially reflect DG function is *pattern separation* (Yassa and Stark, 2011). *Pattern separation* is the process of establishing independent non-overlapping representations, often thought to be critical for rapidly forming new memories (O'Reilly and McClelland, 1994; LaRocque et al., 2013). This function is essential for sound memory formation in that it establishes whether or not a particular stimulus is new and needs to be held in memory or already exists as a memory trace and merely needs to be recalled. *Pattern separation* processes rely critically on DG function (Marr, 1971; Leutgeb et al., 2007; Bakker et al., 2008; Kumaran and McClelland, 2012; Kesner, 2013; Rolls, 2013). Stark et al. have developed the Behavioral Pattern Separation (BPS) Task (Stark et al., 2013), which aims to indirectly evaluate DG-mediated function

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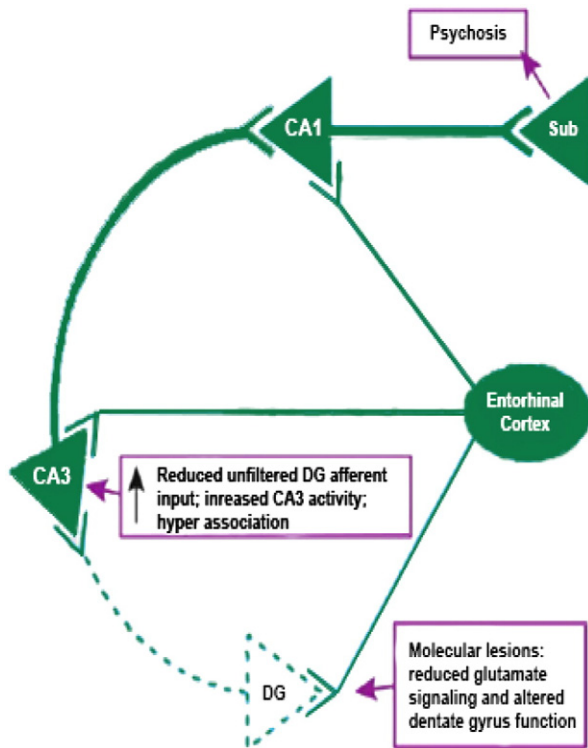
Fig. 1. Model of hippocampal dysfunction in schizophrenia. This illustration is a theoretical model of psychosis in schizophrenia developed from human in vivo imaging and postmortem molecular observations. The model includes a defect in dentate gyrus function which starts with reduced GluN1-containing NMDA receptors in DG and reduced mossy fiber afferent stimulation in CA3. While reduced GluN1 protein and mRNA have been reported, dentate gyrus pathology associated with reduced NMDA signaling would not have to be limited to this single pathology, but could include (for example) decreased neurogenesis (Reif et al., 2006). The outcome of reduced Mossy Fiber tract glutamatergic signaling in CA3 is to sensitize the pyramidal neuron to excitatory stimulation, a situation that (unless it can naturally reverse itself) may lead to hyper-excitability, hyper-associations and the creation of false memories with psychotic content.

in living humans by assaying behavioral expressions that putatively reflect *pattern separation* function. The task has been normed in healthy humans; and, until now, it has been applied mostly in age-related hippocampal decline, where it signals memory impairment (Stark et al., 2010). The BPS task further distinguishes 'pattern separation' from 'recognition memory' function, potentially offering a means to determine whether *pattern separation* is differentially impaired relative to other aspects of declarative memory function.

To test whether the apparent DG tissue changes previously documented in SZ have a functional fingerprint, we examined performance on the BPS task in SZ volunteers. We hypothesized that DG-dependent performance is reduced in SZ due to molecular deficiencies in DG, and as such, we a priori predicted that the ability of persons with schizophrenia to distinguish subtle target differences would be reduced and that the 'pattern separation' parameter calculated from the BPS task (as explained below) would be reduced in individuals with SZ compared to healthy volunteers.

2. Methods

2.1. Participants

Fourteen SZ volunteers (SZV) and 15 healthy volunteers (HV) were recruited for the study through advertising and referrals from community out-patient centers. Individuals with a history of major neurological or decompensated medical illness, mental retardation, traumatic brain injury, substance abuse within the last month, or substance dependence within the last three months were excluded from the study. The study

was approved by the UT Southwestern Medical Center IRB and all volunteers provided written informed consent before participating.

The SZV psychiatric diagnoses were based on the Structured Clinical Interview for DSM-IV-TR Diagnosis (SCID-I/P) (First et al., 1996). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to evaluate active symptoms and their severity. All volunteers completed the Brief Assessment of Cognition in Schizophrenia (BACS) scale (Keefe et al., 2004); subscale and total z-scores were calculated. *The Behavioral Pattern Separation (BPS) Task* was done with all volunteers.

The BPS task consists of two phases, initially, an incidental 'encoding' phase (runs 1–2) and subsequently, a 'test' phase (runs 3–4). In runs 1–2, volunteers were exposed to 128 pictures of everyday objects in each run, with each object shown for 2 s followed by a 0.5 s inter-stimulus interval (ISI); volunteers identified each object as either belonging "indoors" or "outdoors". Total run time for the encoding phase was 320 s. In the test phase, runs 3–4, volunteers were exposed to 192 pictures in each run, with a picture exposure time, as before, of 2 s and an ISI of 0.5 s. Sixty-four of these pictures were exact repetitions of objects from runs 1–2; 64 pictures were completely new objects, and 64 were similar objects (lures) to pictures shown in runs 1–2. Each test run lasted 480 s. Volunteers were instructed to identify each object as a repeated picture ("old"), as a new picture ("new"), or as a similar picture ("similar").

2.2. Analysis

Outcomes from test phase/runs 3–4 were calculated as percent response on each of the three stimuli types, 'target (old)', 'foil (new)', and 'lure (similar)'. These data were used to calculate the 'Pattern Separation' (PS) parameter ['*similar*' responses to *lures* minus '*similar*' responses to *new*] and the 'Recognition Memory' (RM) parameter ['*old*' responses to *targets* minus '*old*' responses to *new* (Stark et al., 2013)]. To test the a priori hypothesis postulating a reduction in the PS parameter in the SZV group with no change in RM, the primary analysis was a two-tailed t test directly contrasting SZV vs NV on the two key task parameters, PS and RM. In the exploratory analysis, to examine between-group differences in response accuracy to each of the task conditions underlying the PS and RM parameters, we conducted a three-way repeated measure ANOVA with two within-subject factors [stimulus type ('target', 'lure' and 'new') and response ('old', 'similar', and 'new')] and group as the between-subject factor, followed by nine post hoc pair-wise comparisons using adjusted ANOVA mean square error terms and using the Bonferroni correction for multiple comparisons (Bailey, 1977; Winer et al., 1991). Finally, Pearson correlations between the PS and RM parameters and the PANSS total and positive subscale scores, as well as BACS total and verbal memory subscale scores were carried out. Two-tailed t test and chi-square test were used, as appropriate, for demographic and cognitive variables. Alpha was set at 0.05 for all analyses. The analyses were carried out using the NCSS-8 (Hintze, 2012).

3. Results

Both HV and SZV were evaluated with the diagnostic, cognition and symptom data, as described; these outcomes are shown in Table 1. No between-group differences were found in any demographic characteristics, including age, sex, race, and handedness. SZV showed a trend toward lower total BACS scores compared to HV (p = 0.093). The majority of SZV were treated with antipsychotic plus other medications. Only one SZV was off any medications while active in the study; 11/15 SZV (73%) were taking more than one medication. All were clinically stable and optimally medicated.

Based on the assessed accuracies of volunteer responses on the BPS task, two primary constructs were calculated, the PS parameter and the RM parameter. Pairwise comparisons directly contrasting SZV with HV on each of the BPS task parameters (PS and RM) revealed a