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Clarifying the role of pattern separation in schizophrenia: The role of recognition and visual discrimination deficits

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ABSTRACT

Patients with schizophrenia show marked memory deficits which have a negative impact on their functioning and life quality. Recent models suggest that such deficits might be attributable to defective pattern separation (PS), a hippocampal-based computation involved in the differentiation of overlapping stimuli and their mnemonic representations. One previous study on the topic concluded in favour of pattern separation impairments in the illness. However, this study did not clarify whether more elementary recognition and/or visual discrimination deficits could explain observed group differences. To address this limitation we investigated pattern separation in 22 schizophrenic patients and 24 healthy controls with the use of a task requiring individuals to classify stimuli as repetitions, novel or similar compared to a previous familiarisation phase. In addition, we employed a visual discrimination task involving perceptual similarity judgments on the same images. Results revealed impaired performance in the patient group; both on baseline measure of pattern separation as well as an index of pattern separation rigidity. However, further analyses demonstrated that such differences could be fully explained by recognition and visual discrimination deficits. Our findings suggest that pattern separation in schizophrenia is predicated on earlier recognition and visual discrimination problems. Furthermore, we demonstrate that future studies on pattern separation should include appropriate measures of recognition and visual discrimination performance for the correct interpretation of their findings.

1. Introduction

Memory deficits have a detrimental impact on the quality of life and functioning of schizophrenic patients. In line with this, memory performance has been identified as one of the strongest predictors of illness outcome (Green et al., 2000; Milev et al., 2005) while being poorly responsive to available medication (Goldberg et al., 2007). Most deficits in the disorder lie within the declarative memory system (Ranganath et al., 2008), resulting in impaired encoding and retrieval in associative (Lapage et al., 2006) and inferential memory (Titone et al., 2004), source and contextual recollection and recognition (Aleman et al., 1999), and often leading to interference and confabulation (Elvevag and Goldberg, 2000). However, which precise mechanisms underlie memory deficits in the disorder remains unclear.

Of particular interest is the hypothesis that memory impairments in schizophrenia might be attributable to defective *pattern separation* (PS), a hippocampal-based computation enabling the orthogonalisation of partially overlapping representations within the memory system (Norman and O'Reilly, 2003). Thanks to pattern separation, similar representations can be stored separately, thus leading to more efficient retrieval, reduced interference and improved learning (Yassa and Stark, 2011). A process complementary to pattern separation is *pattern completion* which allows representations to be retrieved (completed) from partial input, thus facilitating generalisation, associative recognition and inferential reasoning (Norman and O'Reilly, 2003). In schizophrenia, aberrant pattern separation could account for reduced new learning, increased interference and inappropriate association and recollection.

At the neurobiological level, human and animal studies indicate that pattern separation is primarily computed within the dentate gyrus (DG) and then enforced onto the CA3 hippocampal subfield via the mossy fibre pathway (Yassa and Stark, 2011); while the CA3 is thought to be mainly involved in pattern completion, and to a lesser extent in pattern separation (Gold and Kesner, 2005). In schizophrenia, reduced DG neurogenesis (Reif et al., 2006) and DG to CA3 projections (Kolomeets et al., 2007), potentially increasing CA3 plasticity, suggest a role for pattern separation in the disorder (Tamminga et al., 2010). In addition, aberrant pattern separation might be involved in the development of loose associations and false memories with psychotic content (Tamminga, 2013). However, the role of pattern separation in the disorder remains largely untested. One recent study concluded in favour of pattern separation impairments in the illness (Das et al., 2014). However, this study failed to clarify whether more basic factors such as recognition and visual discrimination deficits could explain observed group differences. Clarifying the role of such potential confounds is fundamental to

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ascertain the involvement of a specific pattern separation deficit in memory impairments in schizophrenia.

To address this, we used the Behavioural Pattern Separation (BPS) task which has been successfully applied to the investigation of memory decline in ageing adults and in subjects with mild cognitive impairment (Stark et al., 2013). This task was used to estimate the degree of pattern separation ability together with an index of recognition ability. Also, another task was performed to assess the ability of integrating different sources of information during visual discrimination. Altogether this procedure allowed us to explore whether patients exhibit pattern separation dysfunctions and whether such putative dysfunctions are independent of recognition and visual discrimination deficits.

2. Materials and methods

2.1. Participants

Volunteers were 22 schizophrenia patients, stable and treated with atypical antipsychotic medication, and 24 controls without a personal or family history of mental illness. The study was approved by the London Chelsea Research Ethics Committee. The inclusion criteria were: 1) capacity to consent; 2) age between 18 and 60 years; 3) sufficient command of the English language and 4) having an IQ above 80. Participants were excluded if they had: 1) current drug or alcohol dependence; 2) brain disease or damage or if they 3) used psychotropic medication (except patients). All participants underwent cognitive assessment through the National Adult Reading Test (NART; Nelson, 1982), an index of premorbid intelligence, and the California Verbal Learning Test (CAVLT-II; Delis et al., 2007), assessing declarative memory. The diagnosis of schizophrenia was based on the Structured Clinical Interview for DSM-IV-TR (American Psychiatric Association, 2000) and further confirmed by health records, whereas symptoms severity was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

2.2. Behavioural Pattern Separation (BPS) task

The BPS task involved two phases: encoding and memory test. During encoding participants had to judge via button press the indoor/outdoor nature of images of everyday objects. This facilitated and standardised semantic encoding but the actual judgments were not relevant to the study. During the memory test, participants identified presented images as 'OLD', 'SIMILAR' or 'NEW'. A total of 192 images were presented of which a third were exact repetitions of images presented at encoding (TARGET), a third were similar images but not identical to those presented at encoding (LURE), and a third were new images (FOIL). Crucially, LURE images had been selected to reflect 5 degrees of similarity with images at encoding (Lacy et al., 2011; Yassa et al., 2011) and were thus divided into 5 bins (from 1 being the most similar to 5 being the least similar). All participants demonstrated good understanding of task instructions prior to both phases.

2.3. Visual Discrimination task

The visual discrimination task was introduced at the end of the testing session to control for the effect of visual discrimination deficits on BPS performance. Here participants judged whether 160 pairs of images were identical to, different from, or similar to each other. The task had no time limit and included all images from the BPS memory test phase.

2.4. Analyses

Statistical analyses were conducted using the SPSS (21.0, 2012) (IBM Corp. Released, 2012) and Matlab (The Mathworks, 2013). A two-tailed significance level of $\alpha = 0.05$ must be assumed for all analyses unless stated otherwise. In line with Stark and colleagues (2013), the Baseline Pattern Separation index was measured as the ratio of SIMILAR responses to LURE items minus the ratio of SIMILAR responses to FOILs (the latter accounted for biases towards responding SIMILAR). To assess recognition, the Corrected Hit Rate index was measured as the ratio of OLD responses to TARGETs minus the ratio of OLD responses to FOILs. Bivariate correlations were performed to assess the relation between task measures and symptoms severity and medication. Appropriate parametric tests were used to assess group differences in pattern separation and basic visual discrimination, and the influence of similarity bins on both BPS and visual discrimination tasks. Mediation analyses were performed using Preacher and Hayes' (2008) bootstrapping methodology, thus estimating the direct (*Path c*) and indirect effect (*Paths ab*) of the hypothesised causal model (see Fig. 2), while generating confidence intervals associated to the indirect effect. Our results are based on 5000 bootstrap samples, bias corrected and with 95% CI.

3. Results

3.1. Baseline Pattern Separation and Corrected Hit Rate indexes

Demographic and clinical characteristics are shown in Table 1. Percentage responses in the BPS task are shown in Table 2. Patients showed reduced performance on both Pattern Separation ($t(44) = 2.10$, $p = 0.04$) and Corrected Hit Rate ($t(44) = 1.98$, $p = 0.05$). Further comparisons revealed that patients gave less SIMILAR responses to both TARGET ($t(44) = 2.25$, $p = 0.04$ adjusted) and LUREs ($t(44) = 3.32$, $p = 0.01$ adjusted), but also more NEW responses to LUREs ($t(44) = -2.48$, $p = 0.03$ adjusted) and TARGETs ($t(44) = -1.85$, $p = 0.02$ adjusted). Crucially, no differences were detected on the amount of OLD responses to LUREs, even without correcting for multiple comparisons ($t(44) = -1.01$, $p = 0.32$). This pattern suggested a potential mediating role of recognition deficits on pattern separation group differences. To test this we ran a mediation analysis with group as the independent variable, Baseline Pattern Separation index as the dependent variable, and Corrected Hit Rate index (a measure associated with recognition abilities) as a putative mediator. This analysis revealed that Group had a significant effect on Corrected Hit Rate (*Path a*: $B = -0.10$, $t(45) = -1.98$, $p = 0.05$), that Corrected Hit Rate had a significant effect on Baseline Pattern Separation (*Path b*: $B = 0.35$, $t(45) = 2.15$, $p = 0.04$) and that Group had a significant effect on Baseline Pattern Separation (*Path c*: $B = -0.13$, $t(45) = -2.1$, $p = 0.04$), but that this was reduced and became non-significant when controlling for Corrected Hit Rate (*Path c'*: $B = -0.09$, $t(45) = -1.48$, $p = 0.15$), thus suggesting full mediation. The mediating role of Corrected Hit Rate on the relation between Group and Baseline Pattern Separation was further confirmed by the 95% confidence intervals of the indirect effect generated by the 5000 bootstrap resamples ($B = 0.04$,

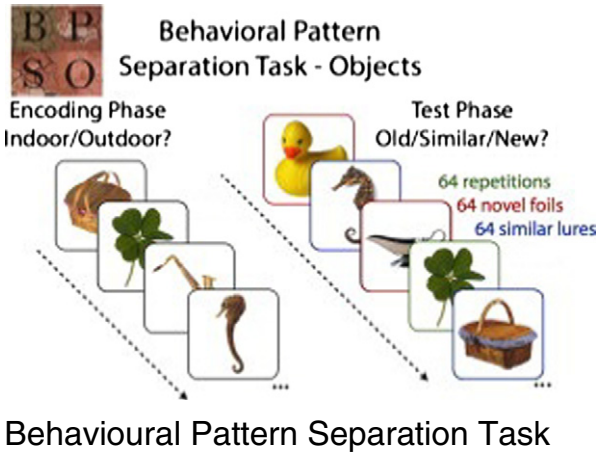

Fig. 1. Behavioural Pattern Separation task.