

Genes and memory: The neuroanatomical correlates of emotional memory in monozygotic twin discordant for schizophrenia

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Abstract

Background. Brain morphology and physiological measures in schizophrenia have yielded inconsistent results. This may be due in part to difficulties in ascertaining precisely to what degree each measure deviates from its genetically and environmentally determined potential level. We attempted to surmount this problem in a paradigm involving monozygotic twin pair discordant for schizophrenia. In this paradigm, the difference score and reaction time between the unaffected member and affected member of a twin pair should represent the degree of pathologic involvement irrespective of actual level.

Method. We investigated, using fMRI, the neural substrate underlying encoding and retrieval of aversive and neutral IAPS pictures.

Results. An ANOVA on reaction time (RT) between schizophrenia patient (J) and normal sister (D) significant difference, ($F = 5.2, p \leq .02$) for J had less RT than D. Conversely, the ANOVA for the correct pictures retrieved was insignificant ($F = 1.8, p \leq .2$). When the brain activity associated with the encoding and retrieval of the aversive pictures was subtracted (J – D and D – J) from that associated with the neutral ones, significant loci of activation were found. During encoding: for J – D the right fusiform gyrus was significantly activated ($p < .0001$) and for D – J the orbitofrontal cortex was significantly activated ($p < .05$). During retrieval: for J – D the right anterior cingulate ($p < .0001$) was activated and the dorsolateral prefrontal cortex ($p < .002$). For D – J only the cerebellum showed activation ($p < .0001$).

Conclusion. Results indicated subtle attenuations in some aspects of memory, thus providing another evidence for cognitive markers of a genetic component in schizophrenia. New approaches in neuropsychiatry-based on genetic methodologies should further define the cerebral physiology responsible for schizophrenia.

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Keywords: Schizophrenia; Monozygotic twin; Explicit memory; Encoding; Retrieval; fMRI

1. Introduction

Life history study of monozygotic (MZ) twins discordant for schizophrenia led to the 1967 hypothesis that phenotypic schizophrenia is an expression of genotypic vulnerability. In accordance, several studies

(see review in Salloway, Malloy, & Duffy, 2001) have demonstrated familial aggregation (nonschizophrenia first-degree relatives) of schizophrenia with deficits in neuropsychological tests sensitive to prefrontal and temporal lobe damage, including tests of working memory. Weinberger et al. (2001) have suggested that genetic liability to schizophrenia may impact prefrontal cortical systems (PFC) preferentially. This interpretation is also supported by evidence that patients with

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schizophrenia, as well as their siblings, show reduced gray matter in the frontal lobes, but not in posterior cortical regions, compared to controls. Specifically, a study by Goldberg et al. (1995) concluded that a comparison between the unaffected twins from the discordant sample and the normal twins indicated subtle attenuation in some aspects of memory in the unaffected group and thus provided evidence for cognitive markers of a genetic component in schizophrenia. A well established distinction within the domain of memory is that between short-term, or “working” memory, and long-term, or episodic memory, the former depending critically on prefrontal cortical regions and the latter depending on medial temporal lobe (Salloway et al., 2001). Hence, in this report we aimed to investigate prefrontal regions (orbitofrontal OFC, anterior cingulate AC, and dorsolateral prefrontal cortex DLPC) in a MZ twin discordant for schizophrenia using a functional magnetic resonance imaging (fMRI) working memory paradigm (encoding and retrieval). We predicted a priori that memory deficits will be observed in the twin sisters.

Case history. Ms. J and Ms. D are French-Canadian 24-year-old MZ twins who are right-handed and discordant for schizophrenia. Ms. J was admitted to a psychiatric hospital for the first time at the age of 22, when she tried to commit suicide, a few months after giving birth to her first baby boy from an unknown father. During her stay, Ms. J was socially disinhibited, abused drugs, escaped from hospitals several times and was involved in prostitution. With respect to her MZ twin, Ms. D lives a normal life. Interestingly, their maternal grand-mother suffered from a psychiatric illness, the nature of which is not clear, and their paternal grand-mother committed suicide in her sixties. In addition, the twins’ father physically abused his children.

2. Methods

Ms. J and Ms. D gave written informed consent and the study was approved by the ethics committee. Blood oxygen level dependent (BOLD) signal changes were measured during two functional magnetic resonance imaging (fMRI) runs: run 1 (encoding) and run 2 (retrieval). Each fMRI run consisted of two experimental conditions, i.e., an *Aversive condition* (disgust, fear, anger, and surprise) and a *Neutral condition* (a chair, a plate, a cup, etc.). Each run consisted of 44 colored visual pictures. All pictures were selected from the International Affective Picture System, to be similar in complexity and quality. Each picture was presented for a period of 2.88 s. The order of presentation of the functional run was counter-balanced. Each block lasted 31.68 s. Blocks were separated by resting periods of 14.4 s during which the subject viewed a blank cyan

screen. Overall, each functional run lasted 6.144 min: (8 blocks: 4 aversive and 4 neutral; 11 pictures per block; 5 volumes separating each block). Subjects were instructed to encode the pictures in run 1 to be retrieved in run 2. In run 2, subjects responded by tapping either by the index finger “yes I saw this picture in run 1” or by the middle finger “no I did not see this picture in run 1.” Echoplanar images (EPIs) were acquired on a 1.5 T system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 3 s in an inclined axial plane, aligned with the AC–PC axis (the duration required to acquire 28 slices was 2.65 s). These $T2^*$ weighted functional images were acquired using an EPI pulse sequence (TR = 0.8 ms, TE = 44 ms, Flip = 90°, FOV = 215 mm, Matrix = 64 × 64). Following functional scanning, high-resolution data were acquired via a $T1$ -weighted 3D volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 ms, TE = 44 ms, Flip = 12°, FOV = 250 mm, Matrix = 256 × 256). Data were analyzed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London, UK). Images for both subjects were realigned to correct for artifacts due to small head movements and spatially normalized (voxel size: 3 mm × 3 mm × 3 mm) into an MRI stereotactic space. Images were then convolved in space with a 3D isotropic gaussian kernel (12 mm FWHM) to improve the signal-to-noise ratio and to accommodate for residual variations in functional neuroanatomy that usually persist between subjects after spatial normalization. Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis. A “fixed-effects model” was implemented to contrast the brain activity associated with the viewing, encoding, and retrieval of the aversive pictures and those associated with the neutral ones.

3. Results

3.1. Behavioral results

Interestingly, an ANOVA on reaction time (RT) between J and D showed a significant difference ($F = 5.2$, $p \leq .02$). J had less RT than D, conversely, the ANOVA for the correct pictures retrieved was insignificant ($F = 1.8$, $p \leq .2$). There was no significant difference in RT for the neutral condition ($F = 0.1$, $p \leq .7$) between J and D. However, J had less RT than D ($F = 7.6$, $p \leq .01$) for the negative condition. The difference in RT between the neutral versus the negative condition was not significant for J ($F = 0.03$, $p \leq .8$). However, D had a significantly longer RT time for the negative condition ($F = 4.4$, $p \leq .03$) versus the neutral one. Hence, D was slower in responding to the negative pictures.

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