This Week in The Journal

Working-Memory Deficits in Parietal Cortex in Schizophrenia

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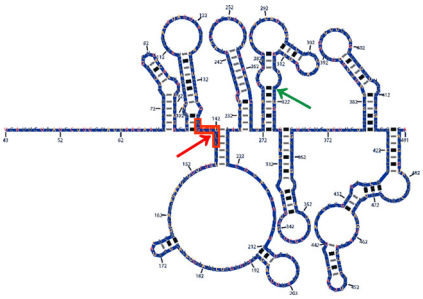
(see pages 8378 – 8387)

Hallucinations and delusions are the most widely recognized symptoms of schizophrenia, but deficits in basic cognitive functions might be more debilitating. Many of these deficits stem from impairments in working memory, the ability to maintain and transform mental representations of stimuli. Manipulation of items in working memory depends on activity in the prefrontal cortex (PFC) and numerous studies have demonstrated that prefrontal circuits are altered in schizophrenia. But other brain areas are also thought to participate in working memory. For example, activity in the posterior parietal cortex (PPC) is thought to help maintain mental representations. Therefore, deficits in PPC function might contribute to working-memory deficits in schizophrenia.

Hahn et al. tested this hypothesis by administering a change-detection task, which requires maintenance, but not manipulation of items in working memory. On each trial, participants viewed an array of 1–7 colored squares, then after a brief delay, they viewed a single one of these squares and reported whether it had changed color. Based on participants' performance, the authors calculated *K* value, a measure of the number of items stored in working memory. This value increases with the number of presented items until it peaks at working-memory capacity, after which it decreases, because participants can no longer maintain representations of all items. Although *K* values were smaller in schizophrenia patients than in controls, the inverted-U relationship between *K* value and set size was apparent in both groups.

The authors next used functional magnetic resonance imaging to identify regions in which activity varied linearly with *K* value. A cluster in PPC including superior and inferior parietal lobules and the intraparietal sulcus showed significant differences in activation patterns between groups. Whereas activation significantly increased with *K* value in control participants, the slope was statistically indistinguishable from zero in schizophrenia patients. Notably, the slope was correlated with scores on a cognitive assessment in both groups, and differences in slope explained >40% of the differences in cognitive scores between groups.

These results suggest that impairment in PPC function contributes to working-memory deficits and, likely as a consequence, other cognitive deficits in schizophrenia patients. Therefore, future studies of cellular- and circuit-level mechanisms of schizophrenia should examine PPC as well as PFC.



Predicted structure of the rs3800373 minor allele mRNA, with miR-320a seed site (red arrow) and SNP (green arrow) indicated. See Linnstaedt et al. for details.

FKBP5 mRNA Structure Linked to Post-Traumatic Pain Risk

Sarah D. Linnstaedt, Kyle D. Riker, Cathleen A. Rueckeis, Katrina M. Kutchko, Lela Lackey, et al.

(see pages 8407– 8420)

Interactions between environmental and genetic factors influence how people are affected by traumatic experiences. Genetic influences include single-nucleotide polymorphisms (SNPs) in genes that regulate stress responses. Many SNPs lie outside protein-coding regions of DNA, yet affect protein function by altering gene expression. For example, SNPs in promoter or enhancer regions can affect the binding of transcription factors or cofactors and thus disrupt transcriptional regulation. Recently, researchers discovered that SNPs in noncoding regions of mRNA can also affect protein expression. These SNPs, called ribosnitches, change mRNA secondary structure and thus alter mRNA splicing, transport, or degradation. Linnstaedt et al. report that this type of SNP influences the development of chronic pain after traumatic injury.

Previous work suggested that SNP rs3800373 in *FKBP5*—a gene that regulates levels of inflammatory mediators and glucocorticoids—influenced the risk of developing chronic pain after motor-vehicle collisions. Linnstaedt et al. now report that rs3800373 genotype interacts with stress to enhance pain risk. Specifically, in people who possessed at least one copy of the minor allele of rs3800373, the amount of distress reported immediately after an accident was correlated with the severity of chronic pain reported 6 weeks later. In addition, *FKBP5* mRNA levels were positively correlated with cortisol and glucocorticoid-receptor mRNA levels in these patients during their initial treatment.

Analysis of *FKBP5* using various bioinformatics tools indicated that rs3800373 likely influences base-pairing in *FKBP5* mRNA. Notably, the minor allele appears to promote formation of a stem-loop structure in a region where microRNA miR-320a binds. Consistent with this, *in vitro* assays showed that miR-320a binding to *FKBP5* mRNA was lower for the minor allele than for the major allele, even though rs3800373 is distant from the miR-320a binding site. Furthermore, whereas *FKBP5* mRNA and miR-320a levels were inversely correlated in people with the major rs3800373 allele, the levels were unrelated in people with minor alleles.

Together with previous work, these results suggest that by changing mRNA secondary structure, the minor allele of rs3800373 impairs binding of miR-320a, which normally represses *FKBP5* expression. This might disrupt regulation of the stress response or increase expression of inflammatory mediators. Future work should further elucidate the molecular mechanisms linking this allele to chronic pain risk.

This Week in The Journal was written by Teresa Esch, Ph.D.