transcriptional co-expression (BrainSpan: Atlas of the Developing Human Brain, 2013) in the dorsolateral and ventrolateral prefrontal cortex during fetal development. Interactions among these genes were not significantly enriched in other brain regions or during other developmental periods, nor were interactions enriched among genes harboring benign *de novo* events. Of the 54 genes disrupted by damaging *de novo* mutations in patients, 50 mapped to this network. These genes are active in pathways critical to neurogenesis, including neuronal migration, synaptic transmission, signaling, transcriptional regulation, and transport. Many network genes share a pattern of high expression in prefrontal cortex during the early fetal development, with transcription levels declining in the late fetal development and childhood only to rise again during young adulthood (Figure 1), coinciding with the typical age of onset of the illness.

The results suggest that aberrant prefrontal cortical development is critical to the pathogenesis of schizophrenia. The prefrontal cortex is highly interconnected with other brain regions, and organizes information to coordinate executive skills, including working memory, attention span, problem solving, and self-regulation (Catts *et al*, 2013). Given the clearinghouse role of prefrontal cortex in brain function, disruptions in this region during early development likely result in the overall loss of neocortical integrity and connectivity. Impairments in executive functions are characteristic of schizophrenia, suggesting that higher-order cognitive deficits are early manifestations of the syndrome, with psychosis emerging as critical brain regions mature.

Some genes with *de novo* mutations in patients function in neurotransmitter pathways that suggest possible avenues for treatment, including GLS (glutamate synthesis), ADCY9 (glutamate and GABA signaling), and SLC18A2 (serotonin, dopamine, norepinephrine, epinephrine, and histamine transport). *CACNA1I*, a brain-specific, T-type calcium channel that regulates neuronal firing in the thalamus, striatum, nucleus accumbens, and prefrontal cortex, was the only gene disrupted in two unrelated probands, each harboring a different *de novo* event. Some antipsychotic medications, including clozapine, inhibit T-type calcium channels (Choi and Rhim, 2010).

Key mechanisms underlying complex psychiatric disorders can be identified by characterizing brain pathways disrupted by mutant genes in affected persons. By integrating genomic analyses with brain mapping strategies, we were able to define possible disease-related processes and to identify potential targets for treatment. Applying the same approach in large-scale sequencing studies will help elucidate basic neurobiological mechanisms underlying normal brain circuitry and neuropsychiatric disease.

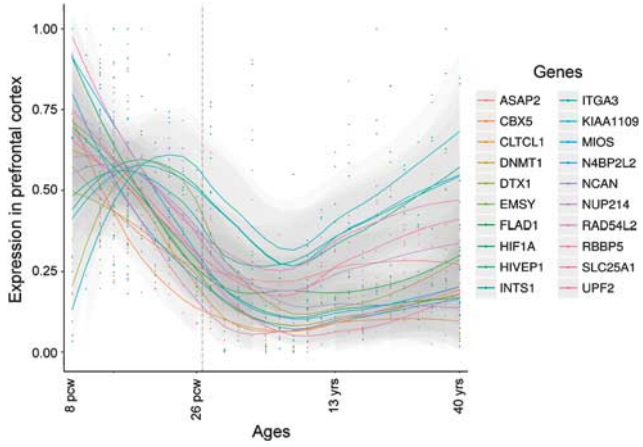

Figure 1. Expression levels of selected genes with damaging *de novo* mutations in dorsolateral prefrontal cortex throughout development (8 post-conception weeks to 40 years). Many network genes were highly expressed during early fetal prefrontal cortical development, with expression declining in late fetal development and childhood, and rising again during adulthood, coinciding with the typical age of onset of schizophrenia. Data were obtained from BrainSpan: Atlas of the Developing Human Brain (2013). RPKM values were max-min normalized and Loess smoothed across time points.

ACKNOWLEDGEMENTS

This work was supported by NIMH grants R01MH083989, R01MH083849, R01MH083756, R01MH084071, and R03TW008696.

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FUNDING AND DISCLOSURE
The authors declare no conflict of interest.

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Neuropsychopharmacology Reviews (2014) **39,** 238–239; doi:10.1038/npp.2013.219

Repetitive Transcranial Magnetic Stimulation as a Treatment for Auditory Hallucinations

With transcranial magnetic stimulation (TMS) a rapidly fluctuating magnetic field is delivered over a specific part of the brain, which can change brain activity in the underlying cortex. When targeting the motor cortex, TMS

can induce movements of the hand; when delivered at the visual cortex it can induce phosphenes. At the UMC Utrecht, we visualized these effects using a novel approach. An MR compatible TMS coil and flexible MR receive coils are applied to allow stimulation of specific brain areas interleaved with fMRI. When stimulating the motor cortex and the temporoparietal cortex, activation was observed close to the stimulated location, but not directly at the stimulated location (Figure 1). In addition, TMS pulse-triggered activation was observed in distal areas connected to the targeted site (de Weijer *et al*, in press). This shows that single-pulse TMS is able to induce both local and distal effects on the cortex in healthy volunteers. When TMS is delivered repetitively, longer-lasting effects are thought to occur, which may be based on synaptic plasticity presumably analogue to long-term potentiation (LTP) or long-term depression (LTD) in single-cell recordings. When LTD can be induced in brain circuits involved in psychiatric symptoms, such as hallucinations, rTMS may lower symptom severity. The exact effect of rTMS on brain activation and connectivity in hallucinating patients is not well understood and we are currently exploring these effects with our MR compatible TMS equipment.

Several studies have tested efficacy of this method to decrease hallucinations in psychotic patients. We recently performed a meta-analysis on 19 studies that used rTMS for auditory hallucinations and found a mean weighted effect size of 0.43, significant at $P<0.0001$ (Slotema *et al*, in press). Heterogeneity was moderate and the failsafe number was >2000. Of these 19 studies, 10 restricted inclusion to patients with medication-resistant hallucinations, which yielded similar efficacy. This indicates that rTMS is effective against hallucinations and may be especially useful for medication-resistant patients. However, some uncertainties remain. We noted that initial reports found rather large effects and the mean effect size has decreased considerably over the past 10 years (Slotema *et al.,* 2012); a trend that can be observed with many new treatments (Munafo and Flint, 2010). Another point of concern is that after 1 month follow-up, the difference between the rTMS and the placebo group is no longer significant (Slotema *et al.,* 2012). The use of individual fMRI scans to determine the location of hubs during hallucinatory activity may improve efficacy, although an RCT of our group failed to show a significant advantage of fMRI guidance (Slotema *et al.,* 2011). We therefore conclude that, although the mechanism behind longer-lasting rTMS effects is not clear yet, it may be a useful treatment option for hallucinations, especially in medication-resistant patients. The additional advantage of fMRI guidance is not yet proven and maintenance treatment with rTMS may be necessary to obtain lasting effects.

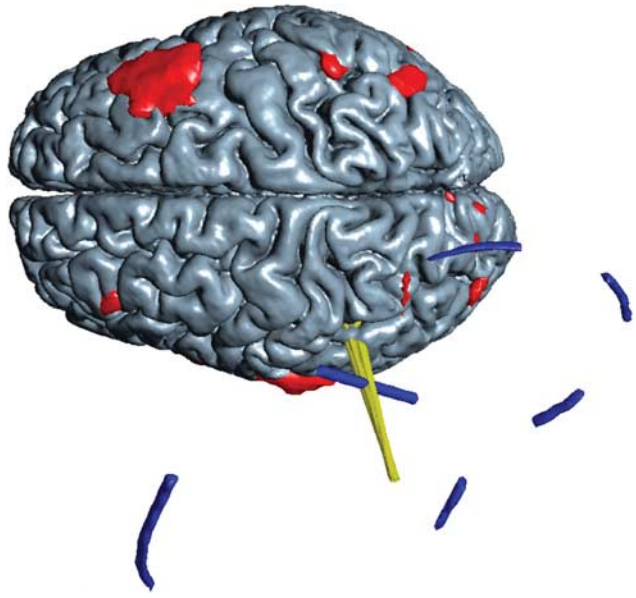

Figure1. 3D renderings of TMS evoked activation (110% vs. 70%MT) superimposed on a rendering of the gray matter surface, for SMG stimulation stimulated in 2 different subjects (S1 and S2). The estimated TMS pulse center line is rendered as yellow rods, their scatter indicates the accuracy at which the TMS pulse location could be reconstructed. The blue rod rendered perpendicular to the yellow rods indicates the direction of the induced current (the line in between both coil windings, pointing into the direction of the coil handle). The blue tube indicates where water filled tube encircling the TMS coil was located, and is based on the T2 weighted scan made for registration purposes. Small parts of the tube are missing due to limited T2 coverage and low contrast in some parts of the tube.

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FUNDING AND DISCLOSURE
The authors declare that over the past 3 years SFW Neggers has received a minor compensation for work performed from Brain Science Tools BV, The Netherlands, the manufacturer of The Neural Navigator for TMS, and that SFW Neggers holds a minority share in this spinoff company of the UMC Utrecht, and that he acts as the managing CEO of this company besides his position at the UMC Utrecht. The compensation received did not have a direct relationship with the present publication.

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Neuropsychopharmacology Reviews (2014) **39,** 239–240; doi:10.1038/npp.2013.225