apparent negative feedback (that is, social stress) (Montgomery *et al*, 2006).

The next logical step is to test whether stress produces a deregulated DA response in clinical populations, such as those with psychotic disorders, addictions, as well as in those at risk. We tested both drug-free patients with schizophrenia and clinical high risk (CHR) for psychosis (that is, putatively prodromal) diagnosed with the Criteria of Prodromal Syndromes in a two-scan protocol: one while doing a Sensory Motor Control Task and another one while doing the Montreal Imaging Stress Task. Our pilot data suggests an increased stress-induced DA release as compared with matched healthy volunteers (HVs) (Figure 1). This kind of studies has important theoretical and clinical implications regarding the prevention of relapse and efforts to abort or delay conversion to psychosis.

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Imaging and genetics advances in understanding geriatric depression

Over a decade has passed since publication of the vascular depression hypothesis that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes (Alexopoulos *et al*, 1997). This construct has catalyzed much research, largely focused on structural neuroimaging, clinical neuropsychology, and in last few years, genetics and cognitive neuroscience. Recent investigations have combined advanced neuroimaging techniques and genetic analyses to delineate key structural and functional findings in late-life depression (LLD).

Vascular brain changes on imaging studies have long been associated with LLD. Genetic analysis of vascular changes is an emerging field, and recent work in older populations has focused on polymorphisms associated with (1) psychiatric disease in younger adults or (2) vascular risk factors. We have previously reported links between *BDNF* (brain-derived neurotrophic factor) polymorphisms (Taylor *et al*, 2008) and serotonin transporter-linked polymorphic region (*5HTTLPR*) polymorphisms (Steffens *et al*, 2008) and white matter hyperintensity (WMH) volumes, supporting theories that these genes also have a role in LLD. The notion that WMHs are vascular in nature led our group to explore relationships between WMH volume and genes associated with systemic vascular risk. These include renin–angiotensin system genes, such as the angiotensin II receptor, vascular types 1 and 2 (*AGTR1* and *AGTR2*) genes. In addition to reports linking *AGTR1* polymorphisms to LLD outcomes, we have also found gender-specific associations between AGTR polymorphisms and WMH progression (Taylor *et al*, 2009). Similarly, the methylenetetrahydrofolate reductase (*MTHFR*) gene, another vascular risk gene associated with folate and homocysteine metabolism, may be associated with LLD, and we are examining *MTHFR* and other genes related to folate metabolism in the occurrence of white matter lesions in LLD. Our studies continue to examine the role of vascular risk genes in LLD, focusing on their influence on brain structure and cognition.

Consistent with the vascular depression hypothesis is the notion the LLD is associated with disruption in frontal-striatal circuitry. These abnormalities in the prefrontal cortex, striatum, and frontal-striatal white matter tracks are also likely related to genetic differences. A previous study noted a link between the *5HTTLPR* short allele and caudate volume in LLD. We recently reported an interaction between two genes, *COMT* (catechol-O-methyltransferase) and *MTHFR*, and putamen volume reduction in LLD (Pan *et al*, 2009). Identification of genes associated with prefrontal cortical structure and function remains an active area of inquiry.

Beyond the vascular depression hypothesis, another avenue of genetic/neuroimaging LLD research examines the observed link between depression and later dementia. The hippocampus is a key structure related to both LLD pathophysiology and increased dementia risk. The *APOE* gene is associated with both depression and Alzheimer's disease, and *APOE* genotype has been associated with specific shape differences in geriatric depression (Qiu *et al*, 2009). Allelic differences in the *5HTTLPR* gene have also been associated with hippocampal volume in LLD by several groups.

Advances in both neuroimaging technologies and genetic assessment allow us to investigate the pathophysiology of affective disorders. Existing paradigms of vascular depression and depression as dementia risk make LLD ideally suited for future genetic/imaging studies.

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Neuronal signaling pathways: genetic insights into the pathophysiology of major mental illness

Psychiatric genetics has turned a corner—increasingly robust findings can be placed in a neurobiological context, with practical implications for understanding disease pathogenesis and developing of therapeutics. A milestone in this effort was the discovery of the *DISC1* (disrupted in Schizophrenia 1) gene, found via analysis of a large Scottish family with a high rate of schizophrenia and psychotic affective disorder. All affected members of the family carry a (1;11)(q42.1; q14.3) translocation; the chromosome 1 translocation break point falls between exon 8 and 9 of *DISC1*, presumably resulting in loss of *DISC1* expression. This finding has launched an entire subfield of schizophrenia genetics and neurobiology, with an emphasis on the role of the *DISC1* gene product and its protein interaction partners in neurodevelopment and synaptic function (Chubb *et al*, 2008).

In the past year, DISC1 has been put into the context of key signal transduction pathways and other genetic findings. In one critical study (Mao *et al*, 2009), DISC1 was shown to modulate the 'canonical' Wnt-signaling pathway. This pathway (Komiya and Habas, 2008) is activated when a member of the *Wnt* family of secreted glycoproteins binds a member of the Frizzled receptor family along with coreceptors. Pathway activation reduces GSK3β kinase activity, resulting in diminished phosphorylation of β-catenin. Unphosphorylated β-catenin accumulates in the cytoplasm and is translocated into the nucleus, where it functions as a transcriptional coactivator. Among other effects, this transcriptional activity can drive neuronal neurogenesis. DISC1 directly interacts with GSK3β, inhibiting GSK3β phosphorylation of β-catenin and thus increasing β-catenin-induced transcriptional activity. The effect is to mimic Wnt pathway activation. Loss of DISC1 inhibits β-catenin-induced transcription, providing a potential mechanism by which *DISC1* loss of function mutations might exert their effect.

DISC1 has also been linked to pathways involving Neuregulin-1 (*NRG1*), one of the most robust candidate genes for schizophrenia (Mei and Xiong 2008). Extracellular NRG1, cleaved from Pro-NRG1, interacts with and activates the ErbB family of receptor protein kinases (ErbB2, 3, 4, and EGFR), starting a cascade that activates a number of partially overlapping pathways, including Raf—MEK–ERK and PI3K–Akt. NRG1 signaling has been implicated in neuronal migration, axon guidance, synapse formation, myelination, and oligodendrocyte development. NRG-1 activated Akt inhibits GSK3β, tying NRG1 signaling to Wnt and DISC1 activity. The related effects of DISC1 and NRG1 have been highlighted in a zebrafish model, in which DISC1 loss produced developmental deficits very similar to loss of NRG1 signaling, including failure of normal oligodendrocyte development and near total failure of olig2-positive cerebellar neuron development (Wood *et al*, 2009). The effect of psychotropic agents on these pathways provides an additional link to major mental illness. For instance, lithium activates Akt and inhibits GSK3β, whereas antipsychotic agents, by antagonism of D2 receptors, block the stimulatory effect of dopamine on Akt.

Overall, the convergence of genetic, pharmacological, and neurobiological data have opened the door to multiple novel potential therapeutic targets in the DISC1–Wnt–NRG1 systems, and this neurogenetic approach holds considerable promise for future research. For instance, the recent association of the MHC locus on chromosome 6p with schizophrenia (e.g., Stefansson *et al*, 2009) supports the long standing concept that environmental factors such as infection may have a role in schizophrenia, and provides a rationale for models of disease that encompass both genetic and environmental factors. Associations of neurogranin on 11q24.2 and transcription factor 4 (*TCF4*) on 18q21.2 with schizophrenia (Stefansson *et al*, 2009) may lead to new pathways with additional therapeutic targets. Psychiatric research has entered an era in which genetic findings implicate specific signaling pathways, leading to new insights into disease pathogenesis and the development of new approaches to therapeutics.

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