be accepted into the Army, it is important to consider the best course of action when it is discovered, after enlistment, that a soldier who entered service has had (or still has) a psychiatric disorder.

3. Externalizing disorders (probably including the externalizing PTSD phenotype) appear to be a bigger cause for concern than internalizing disorders with regard to suicidal behavior.
4. We need a better understanding of the environmental factors that are associated with suicidal behavior, especially among those at greatest risk. Given the high suicide rate among never-deployed soldiers, there is reason to hope that such factors, once identified, can be modified.
5. Fortifying the mental health and coping capacity of military families is an important goal, given the higher suicide risk among married vs never married soldiers.
6. Future studies need to include National Guard and Army Reservists who may be more vulnerable than Regular Army and who may have unique predictors of suicide risk.

These are only the first articles to come from the groundbreaking Army STARRS initiative.[1-3] Future articles will hopefully provide finer-grained measurements and more in-depth analyses of the variables already mentioned, as well as new information on psychological, neurocognitive, social, biological, and genetic factors. They will also investigate the impact of intervention. It can be expected that our predictive algorithms will become more specific and sophisticated as such information is acquired. The current articles have already provided a very rich context and raise some important issues that were less apparent previously. Even without further data, we know enough to begin to consider better assessment, monitoring, and intervention strategies.

ARTICLE INFORMATION

Author Affiliations: National Center for PTSD, US Department of Veterans Affairs, Washington, DC; Departments of Psychiatry and of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire.

Corresponding Author: Matthew J. Friedman, MD, PhD, Departments of Psychiatry and Pharmacology and of Toxicology, Geisel School of Medicine at Dartmouth, US National Center for PTSD, VA Medical Center, 215 N Main St, White River Junction, VT 05009 (matthew.j.friedman@dartmouth.edu).

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The Striatum and Dopamine
A Crossroad of Risk for Schizophrenia

Guillermo Horga, MD; Anissa Abi-Dargham, MD

Neurobiological phenotypes of schizophrenia can be strategically studied in unaffected relatives to parse out susceptibility phenotypes involved in core pathophysiological mechanisms from phenotypes reflecting consequences of the illness or its treatments. A prime example of this strategy is the work by Grimm et al[1] in the current issue of *JAMA Psychiatry*. The authors showed that unaffected relatives, like their affected counterparts, show a robust deficit in activation of the ventral striatum to anticipation of monetary outcome compared with healthy individuals. This finding strongly suggests that deficient anticipatory activation in the striatum represents a functional phenotype of genetic susceptibility to schizophrenia. Supporting further the use of this phenotype for genetic research, Grimm et al went on to show that, within the healthy comparison group, carriers of a risk allele of the *NRG1* candidate gene for schizophrenia have relatively reduced activation of the ventral striatum to anticipation of monetary outcome compared with carriers of a protective allele.

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This study presents important methodological highlights: (1) The use of a multisite design with careful coordination of methods across 3 sites, and the assessment of potential site effects is a nice example of how imaging studies should

be conducted in an age of limited research funding to achieve adequate power. (2) The assessment of potential confounds is also exemplary. The comparison group was carefully matched to the unaffected relatives on task performance and head motion in addition to neuropsychological and sociodemographic variables. Groups were further comparable on striatal volume based on 2 morphometric methods. This observation importantly rules out the possibility that local volume differences were responsible for the observed functional differences between groups, a legitimate concern given the normal relationship between local volume and functional activations, and suggests that, unlike the functional phenotype, volumetric abnormalities previously detected in this region in schizophrenia may not relate to genetic susceptibility. (3) The evaluation of test-retest reliability of the observed phenotype is a major highlight. The estimated intraclass correlation coefficients of 0.6 or greater, although not perfect, indicate considerably better reliability than other functional magnetic resonance imaging (fMRI) measurements used widely. Similar evaluations of reproducibility and reliability have been surprisingly overlooked in fMRI research until very recently despite their relevance, in particular to longitudinal designs such as those involved in high-risk studies of conversion to illness and clinical trials. Thus, the current demonstration of a reliable endophenotype provides the field with a much-needed potential biomarker that may further facilitate future research into the progression of illness in high-risk samples and development of therapeutic or preventive strategies.

Now let us examine the meaning of the anticipatory activation to monetary outcome in the ventral striatum and its deficit in unaffected relatives. First, given that the blood oxygen level–dependent signals reflect more closely presynaptic activity than postsynaptic spiking[2] and the evidence implicating firing patterns of dopamine neurons in signaling motivational value and salience, the blood oxygen level–dependent signal in the ventral striatum may arise from the input signal from dopaminergic neurons located in the midbrain rather than from striatal neurons. The authors cited evidence that dopamine release during the monetary incentive delay task indeed relates to anticipatory activation in the ventral striatum, although evidence in this respect is mixed.[3] Second, whether value or salience signals drive the anticipatory activations captured by Grimm et al remains an open question. *Value* (or *valence*) is broadly defined as a wanting signal that promotes reward-seeking behavior by representing potential rewards and punishments differentially; conversely, *salience* can be defined as an alerting signal that encodes motivational importance of a stimulus or situation regardless of its associated reward or punishment. In their study, increased activations in the ventral striatum to anticipation of both +€2 rewards and −€2 punishments compared with anticipation of neutral outcomes of zero euros could be consistent with an unsigned salience signal, in line with other evidence cited by the authors. However, early work with the monetary incentive delay task showed that the ventral striatum signals the anticipation of rewards and punishments in opposite manners, consistent with a signed value signal, and subsequent work with this task suggested that the fMRI activations in question conflate value and salience.[4] This mixed evidence about the type of functional signals driving anticipatory fMRI activations in the ventral striatum, essential to the interpretation of the observations made in this article, may be settled in part by direct neuronal recordings in nonhuman primates demonstrating that single dopamine neurons encode multiple, distinct anticipatory signals at different points. Anticipatory signals include an early, phasic salience signal with similar encoding of rewards and punishments linked to orienting responses and a late, tonic value-related signal with differential encoding of rewards and punishments.[5] Such temporal dissociation, which is unattainable with the current monetary incentive delay task, is thus compatible with distinct signals that possibly originate from separate pathways converging into the dopamine system, a possibility that may have significant implications for the pathophysiology and treatment of schizophrenia.

The distinction between value and salience is particularly relevant to schizophrenia given widespread suggestions that abnormal reward signals related to value underlie negative symptoms, whereas misattribution of salience to irrelevant stimuli underlies positive symptoms of psychosis, although a universal operationalization of the latter remains elusive.[6] Hence, the limitation of the current paradigm in distinguishing value from salience complicates the interpretation of the observed group differences. For instance, if anticipatory activations reflected expected values, the presence of seemingly symmetric deficits for expected rewards and punishments in unaffected relatives—as described by the authors in eTable 2 in their Supplement—could suggest a genetic impairment of both the direct and indirect pathways of the basal ganglia, but this interpretation would be likely incorrect if activations instead reflected salience. Another open question remains whether different subregions of the striatum preferentially encode value vs salience. This is also a fundamental issue in light of the complex dopaminergic dysfunction in the striatum, where excess dopamine relates best to psychosis in the associative striatum and, to some extent, also in the ventral striatum, while lower presynaptic dopaminergic transmission in the ventral striatum relates best to negative symptoms.[7] If the endophenotype described here embodies deficits in value representation, likely associated with deficits in the fine tuning of dopaminergic signaling to expected values, it would suggest that specific dopaminergic deficits in value signaling in the ventral striatum are a primary, possibly genetically influenced, condition, potentially related to the pathophysiology of negative symptoms and fundamental to the risk for schizophrenia.

This work underlines the importance of understanding in cellular and molecular terms the nature of the dopaminergic dysfunction in the striatum because it is not only relevant to the symptoms and the treatment, but also to the risk for the disease. The complexity of the findings in this regard from molecular and functional imaging studies may suggest an overall dysfunction that encompasses both value and salience signaling. This could occur if the dopaminergic signals are altered not only in their amplitude, but also in their dynamics and timing. Translational studies are needed to investigate the common mechanisms that may lead to

dual phenotypes underpinning the abnormal processing of both value and salience.

In sum, we believe that the study by Grimm et al presents an important advance in the schizophrenia literature and symbolizes a new generation of methodologically enhanced studies focused on the identification of robust systems-level phenotypes suitable for large-scale imaging genetics and treatment research. At the same time, it emphasizes the need for mechanistic research using targeted fMRI approaches that, informed by basic and computational neuroscience, are better able to dissociate specific functional signals with presumably distinct origins and pathophysiological roles in neuropsychiatric illness.

ARTICLE INFORMATION

Author Affiliations: Department of Psychiatry, New York State Psychiatric Institute, Columbia University Medical Center, New York (Horga, Abi-Dargham); Department Radiology, New York State Psychiatric Institute, Columbia University Medical Center, New York (Abi-Dargham).

Corresponding Author: Anissa Abi-Dargham, MD, Columbia University, New York State Psychiatric Institute, 1051 Riverside Dr, Unit 31, New York, NY 10032 (aa324@columbia.edu).

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Large-Scale Brain Network Coupling as a Potential Neural Metric for Nicotine Abstinence Effects on Craving and Cognitive Function

Edythe D. London, PhD; Dara G. Ghahremani, PhD

In this issue of the journal, Lerman et al[1] report on a new composite measurement, the resource allocation index (RAI), which represents the relative strength of interactions during the resting state between the 3 major brain networks: the "default mode" network (DMN), the "executive control" network (ECN), and the "salience" network (SN). This work benefits from the recent extension of functional connectivity assessment with functional magnetic resonance imaging to studies of large-scale networks and their interaction to provide systems-based evaluations of the nervous system.[2] As the authors note, separate brain networks are thought to subserve task-relevant vs task-independent (eg, internally focused) cognitive processing. The ECN is implicated in cognitive control and goal-directed attention,[3] and the DMN shows reduced activity during cognitive tasks and reflects self-referential and episodic memory processing.[4] The SN facilitates orientation to external vs internal information.[5] Using the RAI, Lerman et al[1] illustrate a fundamental role of the SN in toggling resource allocation between the ECN and the DMN during the different states of brain function associated with smoking abstinence and smoking satiety in heavy smokers. They also show a negative association of the RAI with abstinence-induced craving for smoking and a positive association of the RAI with DMN activity suppression during subsequent performance of a working memory task.

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The findings point to the importance of the interactions between large-scale brain networks in tobacco dependence and perhaps other psychiatric disorders. They extend prior observations that individual differences in the improvement in cognitive symptoms of nicotine withdrawal are associated with increased inverse coupling between the ECN and the DMN.[6,7] The unique feature of the present study[1] is its linkage of the SN to these phenomena through the use of the RAI. The authors suggest that the RAI should be more sensitive than coupling measured between individually paired networks because the composite index explains smoking behavior whereas individual coupling measures (ie, SN-ECN and SN-DMN couplings) do not. It is not clear from their study,[1] however, whether the RAI has a greater predictive value as a clinical biomarker than an assessment of ECN/DMN coupling alone. Nonetheless, it does have heuristic value as a unifying approach and could serve as a common metric across studies.

It might be argued that sophisticated brain imaging techniques are not needed to provide new knowledge about tobacco use and dependence, and that behavioral measures are adequate to evaluate a smoker's clinical condition or the success of a treatment. However, evidence for a link between sub-