

Neuroimaging Intermediate Phenotypes of Executive Control Dysfunction in Schizophrenia

Grant Sutcliffe, Anais Harneit, Heike Tost, and Andreas Meyer-Lindenberg

ABSTRACT

Genetic risk for schizophrenia is associated with impairments in the initiation and performance of executive control of cognition and action. The nature of these impairments and of the neural dysfunction that underlies them has been extensively investigated using experimental psychology and neuroimaging methods. In this article, we review schizophrenia-associated functional connectivity and activation abnormalities found in subjects performing experimental tasks that engage different aspects of executive function, such as working memory, cognitive control, and response inhibition. We focus on heritable traits associated with schizophrenia risk (intermediate phenotypes or endophenotypes) that have been revealed using imaging genetics approaches. These data suggest that genetic risk for schizophrenia is associated with dysfunction in systems supporting the initiation and application of executive control in neural circuits involving the anterior cingulate and dorsolateral prefrontal cortex. This article discusses current findings and limitations and their potential relevance to symptoms and disease pathogenesis.

Keywords: Cognitive control, Endophenotypes, Executive function, fMRI, *n*-back, Review

<http://dx.doi.org/10.1016/j.bpsc.2016.03.002>

Schizophrenia is a severe mental illness whose pathophysiology involves systems-level dysfunction, likely as a consequence of brain maturational abnormalities. Schizophrenia is associated with reduced cognitive ability in a wide range of domains, and marked impairment is found in a cluster of abilities that can be grouped together under the umbrella term executive function, such as working memory (WM), response inhibition, and the organized production of extended sequences of behavior. Below-normal performance in tasks that involve these abilities has been repeatedly found in schizophrenia patients, an effect that is detectable from the time of the first psychotic episode but is usually more pronounced in chronic patients (1). Milder impairments also exist before the onset of psychotic symptoms and are also found in close relatives and subjects carrying risk alleles, indicating a genetic basis (1–3). As executive function involves the ability to appropriately engage and manage multiple cognitive abilities, executive control dysfunction has been proposed as a parsimonious and plausible impairment contributing to the wide range of cognitive dysfunction found in schizophrenia (4–6). The hypothesis of a central role for executive dysfunction is further supported by findings that schizophrenia patients display gray matter reductions (7) and metabolic abnormalities (8) in prefrontal cortical areas that support executive control, in addition to a clustering of abnormalities in temporal brain regions. Clinically, executive functions are of central interest since they are important for independent living and social function (9) and are correlated with patient functional outcomes (1,10).

The application of modern imaging and genetics techniques has begun to uncover a range of functional abnormalities that accompany genetic risk for schizophrenia (11). A brief summary of findings will be presented here, with a focus on disease-related heritable traits (intermediate phenotypes) based on neuroimaging tests of executive function.

NEURAL ANATOMY OF EXECUTIVE FUNCTION

The term executive function can have different meanings depending on author and research context, so it is helpful to provide a working definition for the purposes of this review. Executive function is related to similar terms such as executive control or cognitive control, and while the terms are sometimes considered to be synonymous (9), in practice cognitive control most often refers specifically to the context-dependent shifting of attention or behavioral set and the inhibition of prepotent responses, while executive function refers to a broader set of abilities including forms of creativity and problem solving (9). We use executive function and executive control interchangeably to mean the ability to engage top-down control of perception and action to optimize behavior in the service of achieving goals, using a process analogous to multidomain attention to send bias signals to perceptual and motor systems to maintain task representations, enhance or maintain perceptions of relevant stimuli, activate context-appropriate stimulus-response correspondences, and inhibit inappropriate prepotent responses (12,13). This includes those functions commonly engaged by tests of cognitive control and

also WM and attention control functions. These abilities activate and require a highly overlapping group of cortical regions, centered around the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and posterior parietal cortex (14,15), and engage a set of overlapping and interdependent cognitive functions (9).

Executive function is heavily dependent on the PFC and, broadly stated, involves a division of labor between the ACC and lateral PFC, which, respectively, serve implementation and initiation functions. During cognitive control tasks, the ACC selectively activates in response to the appearance of conflicting behavioral cues and is believed to be integral to the function of detecting sources of potential conflict and error (16) and engaging additional control to avoid error.

During the application of control, the ACC selectively couples with the anatomically adjacent DLPFC (17). The DLPFC appears to be particularly important for the direction of modulation to sensory and motor circuits, due to its structural connectivity with sensory and motor regions and consistent activation in tasks involving the internal and external direction of attention (12). In the context of cognitive control, the right ventrolateral PFC has a particular importance in response inhibition, the withholding of a frequently performed prepotent response due to additional contextual information (18).

Functional connectivity analyses indicate that both ACC and DLPFC are parts of larger functional networks with related functions. The ACC appears to be part of a network including the ventrolateral PFC, which is involved in the selection and maintenance of behavioral sets, while the DLPFC-associated frontoparietal network supports the direction of top-down modulation (19). Cortical executive control networks are also connected with and dependent on subcortical structures, particularly the dorsomedial striatum and the mediodorsal nucleus of the thalamus (20,21).

Abnormalities in these neural systems will be the focus of the following discussion of the neurogenetic imaging phenotypes related to schizophrenia.

GENETIC PREDISPOSITION AND INTERMEDIATE PHENOTYPES

Schizophrenia is highly heritable, with genetic factors being estimated to account for up to 80% of the disease risk (22). In most cases, genetic risk is believed to result from alterations in an extended developmental cascade due to interacting downstream molecular, cellular, and system level consequences of multiple common risk variants, each of which confers only small increments in risk.

As a method of discovering the proximal biological effects of genetic risk factors, the identification of intermediate phenotypes is a popular strategy for investigating the pathophysiology of psychiatric conditions. Intermediate phenotypes are heritable biological traits that confer risk for a disease and are believed to be causally closer to risk gene effects than the disease itself (23,24). These have been well established for common nonpsychiatric illnesses and have in several cases been demonstrated to have relatively strong associations with specific genes (24). One example is the use of high plasma lipid levels as an intermediate phenotype of coronary heart

disease, which has led to the identification of the protease PCSK9 as a novel therapeutic target in the treatment for hypercholesterolemia (25,26).

Although the terms are essentially interchangeable in practice, many neuroimaging genetics researchers prefer the term intermediate phenotype over endophenotype, as endophenotype was originally meant to imply an unobservable internal feature, which may not necessarily be the case, for example, in the case of a neuropsychological trait. The use of intermediate also emphasizes the concept of biological intermediacy in pathogenesis (23).

Previous analysis has concluded that a neuroimaging intermediate phenotype should fulfill several requirements to be useful for the dissection of the genetic risk architecture of mental illness (23,27,28). Accordingly, an intermediate phenotype should be 1) quantitative in nature; 2) heritable; 3) reliably measurable; 4) associated with the illness in the general population; 5) linked to genetic risk for the illness; and 6) state independent (i.e., traceable in carriers of genetic risk variants whether or not the illness is manifest). However, finding an intermediate phenotype that satisfies all of the criteria is very demanding in practice and rarely accomplished for measures derived from functional neuroimaging (29).

Imaging genetics is the application of the intermediate phenotype approach with structural or functional outcome measures derived from in vivo neuroimaging techniques. In addition to earlier measures of functional activation magnitude, the comparatively recent popularization of functional connectivity analysis techniques has further enhanced the usefulness of the neuroimaging approach (11,28). Functional connectivity analysis is in theory particularly advantageous in the investigation of multimodal higher association areas, such as those involved in executive control, which are involved in multiple cognitive processes and may plausibly change their connectivity profile depending on the specifics of the task at hand (13), which functional connectivity analysis can help uncover (19).

The neuroimaging investigation of unaffected first-degree relatives of patients, ideally twins or siblings, has been a particularly important search strategy for intermediate phenotypes. Unaffected relatives share an enriched set of genetic risk variants but do not manifest clinical symptoms, which attenuates the effects of confounding factors, such as medication, that interfere with functional neuroimaging readouts and complicate the interpretation of patient data. Imaging genetics has been used to explore functional effects of risk genes, such as *ZNF804A* (30) and *CACNA1C* (31), which have been discovered with genome-wide association analysis (32), as well as to test biologically driven hypotheses regarding genes that have a known function, such as *COMT*, which is involved in dopamine metabolism and therefore influences cortical dopamine levels (33).

NEURAL DYSFUNCTION OF EXECUTIVE CONTROL SYSTEMS

Review Method

Candidate studies were identified using PubMed and the bibliographies of relevant reviews and meta-analyses. Studies

Download English Version:

<https://daneshyari.com/en/article/4181403>

Download Persian Version:

<https://daneshyari.com/article/4181403>

[Daneshyari.com](https://daneshyari.com)