Impairment in Functional Capacity as an Endophenotype Candidate in Severe Mental Illness

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Impairment in everyday functioning (also referred to as "disability") is a central feature of schizophrenia (SZ) and bipolar disorder, as well as other neuropsychiatric conditions. There is a genetic contribution to both SZ and bipolar illness (BPI), and the primary putative determinant of impairments in everyday functioning across these 2 conditions, cognitive impairments, also show substantial heritability and in fact have been proposed to be endophenotypes for these disorders. In this article, we review data and make our case that impairments in functional capacity, the functional abilities that result in functional disability, may also be a heritable trait that is common across neuropsychiatric illnesses such BPI and SZ. While there has been little previous research on the heritability of these abilities, it is an area receiving substantial research attention. We consider advances in the measurement of cognitive functioning in SZ that may facilitate the discovery of genetic influences on functional capacity. Functional capacity measures are proximal to real-world impairments, measured with suitable psychometric precision to be used in heritability analyses, and appear to be minimally influenced by environmental factors that may cause disability such as environmental factors, symptoms, and disability compensation. Our conclusion is that these functional capacity measures have potential to be the target of genetic analyses and that these measures should be considered across neuropsychiatric conditions where impairments in everyday functioning are present.

Key words: schizophrenia/disability/endophenotypes

Introduction

Individuals with severe mental illnesses (SMIs), such as schizophrenia (SZ) and bipolar illness (BPI), experience impairment across a number of domains of everyday functioning in real-world settings, including social and occupational functioning, residential maintenance, medication management, and basic self-care.[1] These impairments occur even following successful treatment of clinical symptoms and begin early in the course of the illness. In fact, impairment in everyday functioning sets in immediately after illness onset. For example, 50% of SZ patients receive disability compensation within 6 months of diagnosis,[2] only 40% of first-episode BPI patients return to premorbid levels of functioning,[3] and less than 20% of first-episode patients with SZ manifest functional recovery.[4] As a result, the majority of patients with SMI experience some form of impaired real-world functioning, whether in employment, independent living, or social functioning.

In addition to being extremely common, disability in SMI may be heritable. Two separate studies, reviewed below, have indicated that impairment in everyday functioning in SMI, defined with different but equally valid methods, is strongly familial in nature. Thus, despite the multiple nonheritable influences on disability, such as disability compensation and local environmental opportunities, there is a signal that the disability phenotype may be heritable even in the face of strong environmental influence.

Several recent arguments have been made that the study of the genetics of complex diseases such as SZ can be advanced through the identification of intermediate endophenotypes. These are defined[5] as traits that are simpler than the end state disease, more directly influenced by genetics, present in relatives, and are directly treatable.[6] For instance, cognitive and neurophysiological features of SZ have been suggested to be potential endophenotypes and have been studied recently

for their heritability within families[7] and their direct association with genetic variation.[8] Importantly, these same cognitive impairments have been shown to be potential determinants of real-world disability in SMI.[9] Thus, the heritable nature of real-world disability as a complex phenotype may result from its being partially determined by heritable cognitive deficits.

In this article, we propose that there are other potential endophenotypes relevant to the complex disability construct such as impairments in functional capacity, which is the ability to perform critical everyday living skills in controlled settings similar to the environment where neuropsychological (NP) performance is examined. We present the characteristics of functional capacity and examine the evidence for potential heritability of these measures in comparison to cognitive functioning. Functional capacity deficits are a less complex phenotype then real-world disability, while having similar influences on real-world disability across different neuropsychiatric conditions. While real-world disability is a complex and multiply determined phenotype, functional capacity deficits may have the potential to be endophenotypes. In support of our argument of the primacy of functional capacity deficits, we review the evidence suggests that the impairments in functional capacity that underlie real-world outcomes are measurable with suitable psychometric characteristics, separable from other endophenotypes such as cognitive impairments in their influence on real-world outcomes, and minimally influenced by the other factors that may contribute to the real-world phenotype of disability. We argue that these performance-based measures of functional capacity may have equivalent potential for detection of genetic influence as cognitive deficits and thus merit similar investigation and potential consideration as endophenotypes. Other potentially heritable factors, such as social cognition, may also impact disability but will not be considered in detail here.

Genetic Influences on Severe Mental Illness

Among the SMIs, SZ and BPI appear etiologically and syndromally heterogeneous, although clearly related to each other and notably influenced by genetic factors. Data from twin, adoption, and family studies suggest that genetic factors are paramount in the etiology of SZ, with a heritability of 70%–85% after accounting for common environment.[10,11] Meta-analyses of 12 published SZ twin studies point to high heritability (81%, 95% C.I. 73%–90%) with a common environmental effect on liability[12] (11%; 95% C.I. 3%–19%). BPI shows evidence of equivalent or greater heritability influences. For instance, Kieseppä et al[13] reported higher monozygotic/dizygotic (MZ/DZ) concordance rates in BPI than those typically reported in SZ (93%, 95% C.I. 69%–100%). Furthermore, Lichtenstein et al[14] found evidence of high heritability for both SZ (64.3%, 95% C.I.

61.7%–67.5%) and BPI (58.6%, 95% C.I. 56.4%–61.8%), with a common environmental effect of 4.5% (95% C.I. 4.4%–7.4%) for SZ and 3.4% (95% C.I. 2.3%–6.2%) for BPI. In addition, classical segregation analysis has been unable to identify a single mode of inheritance to explain the familiarity of SZ. Analyses by Risch[15] shows that SZ liability is best explained by segregation at 3–4 loci with likely epistatic interactions. For BPI, several chromosomal regions have been implicated, although these findings have been difficult to replicate.[16]

Although psychiatric genetic research has placed an understandable emphasis on trying to identify those genes specifically associated with diagnostic entity(ies), until recently less emphasis has been placed on the investigation of individual genetic differences which may not affect the risk for mental illness, but which may have a profound impact on the final manifestation of the disease. These disease-modifying genes, acting in concert with an underlying disease-specific diathesis, may have important moderating, protective, or potentiating effects on final psychosocial outcomes.[17,18] Such disease-modifying genes themselves may also act in an environmentally dependent manner or have very different kinds of impacts depending on the stage of the illness.[19] Identifying genetic factors could offer important insights for the management of patients suffering from these chronic and debilitating disorders. For example, understanding the genetic factors that predispose an individual for SZ or BPI could lead to earlier identification, and therefore earlier intervention. In addition, a better understanding of the complex genetic factors that impact both the development of the disorder and its manifestation, including features such as clinical treatment response or vulnerability to disability, could potentially lead to treatments that would be more personalized, and therefore more likely to be effective.

Cognitive Abnormalities in Severe Mental Illness

One domain of functional ability of particular relevance to real-world outcomes of individuals with SMI is cognitive functioning, including attention, executive functioning, and working memory.[20–23] A large body of evidence supports the notion that deficits in cognitive functioning in people with SMI play a role in determining real-world functional deficits. Several studies following SZ patients post-stabilization[4,23] have demonstrated that patients with better cognitive functioning are more likely to manifest evidence of functional recovery across multiple domains, including social, vocational, and residential outcomes. Evidence does suggest that bipolar patients manifest NP deficits in the same domains as people with SZ, specifically in attention, executive, and memory functions.[24,25] These impairments are also present at the time of recovery from the first episode.[26] Symptomatic BPI patients have been shown to have widespread cognitive abnormalities,[27] while evidence from multiple studies[28] supports the hypothesis

that there are persistent residual NP impairments in patients in nonsyndromal phases. NP studies directly comparing patients with SZ and BPI showed qualitatively similar dysfunction but with an attenuated severity in BPI on tests ranging from higher order executive functioning (the Wisconsin Card Sorting Test[29]) to early visual processing (visual backward masking[30,31]) and on multiple tests from a comprehensive NP assessment.[32]

Disability in BPI

As noted above, the evidence for widespread disability in SZ is widely documented. However, despite the greater focus to date on SZ than BPI and other SMI, there is emerging evidence that disability in people with bipolar disorder is common and often severe. Although many bipolar subjects can have periods of syndromal remission (and a reduced prevalence of disability compared with SZ[33]), these periods are not accompanied by normalization of social, familial, and occupational role function for a substantial proportion of cases.[34] A meta-analysis of 17 studies examining psychosocial outcome in patients with BPI found that 30%–60% of them fail to regain full functioning in social and occupational domains.[35] As noted by Huxley and Baldessarini,[33] the rate of substantial disability in BPI is surprising in terms of the relatively reduced attention paid to disability and its treatment in bipolar disorder.

Cognition, Disability, and Genetic Susceptibility Factors

Quite interesting in the context of overlap in real-world disability and cognition on the part of people with SZ and bipolar disorder is the notion of overlap in genetic susceptibility factors for the overall syndromes. Meta-analyses of genome-wide linkage studies in both disorders have documented overlap in susceptibility regions (chromosomes 13q and 22q, for example).[36] These same regions have been implicated in a linkage scan of pedigrees with psychotic affective illness.[37] Previous analyses of outbred multiplex SZ pedigrees revealed increased homogeneity of linkage findings when the SZ families cosegregating psychotic affective disorder were analyzed alone.[38] These data have lead in part to a reevaluation of the historical Kraepelinian dichotomy between manic-depressive insanity and dementia praecox.[39]

Increasingly, studies have identified similarities in susceptibility genes related to both illnesses.[39] Striking evidence for overlap between SZ and BP exists within a Scottish pedigree cosegregating psychiatric illness with an apparently predisposing chr1:11 translocation. This pedigree segregates for both SZ and BPI; eg, a bipolar translocation carrier has transmitted the translocation to an offspring, who has SZ.[40] Variation in a gene interrupted by this translocation, *DISC1* on chromosome 1, is associated with both SZ and severe affective disorder, further supporting a potential common etiology.[41] In

addition, a recent genome-wide meta-analysis,[42] using a haplotype strategy identified 5 loci that were associated with both SZ and BPI. While the details are beyond the scope of this review, other candidate genes for SZ, such as *G72/DAOA* and *NRG1*, have also been shown associated with bipolar disorder, again suggesting a common pathology. For example, The International Schizophrenia Consortium[43] found evidence for a substantial polygenetic component to the risk of SZ that also contributed to the risk of BPI but not to several other, nonpsychiatric illnesses. Further, recent studies (eg, Burdick et al[44]) have suggested that genes have similar influences on cognition in SZ and bipolar disorder. Thus, the fact that cognitive impairments and real-world functional deficits are seen in both conditions (and are part of the current diagnostic conceptualization), combined with the suggestion that similar genetic influences may be involved for both the overall syndrome and its phenotypes, suggests that these 2 illnesses should be examined in concert for the association between cognition, functional capacity, disability, and joint genetic influences.

Cognition as an Endophenotype Across Severe Mental Illnesses

Cognition is a candidate as a genetically transmitted endophenotype and appears to meet all necessary criteria described above. Impaired cognitive performance is associated with SMI but has also been demonstrated in probands' nonaffected relatives.[45,46] Patients experience cognitive deficits that do not appear to be the result of other features of the illnesses because they precede the onset of psychotic symptoms.[47,48] They also occur independently of clinical symptoms, persisting even after effective treatment of psychosis.[49] Finally, in line with our comments above, cognitive impairments are present prior to the development of other symptoms in individuals who are destined to develop SMI.

It has been known for years that cognitive impairments tend to have a heritable component and estimates of the heritability of performance on NP tests are quite high, with average heritability over 0.40.[50] Many of the more disability-relevant aspects of cognitive impairment are known to be consistently heritable,[50] including episodic memory (heritability range = 0.3–0.6), attention/vigilance (mean = 0.54), working memory (range = 0.3–0.6), and executive functioning (range = 0.3–0.6). Thus, what are considered central elements of impaired cognition in SZ may be a collection of heritable endophenotypic traits in families of patients with SZ. Similar evidence has recently been presented in bipolar disorder[51,52] and while this evidence is preliminary compared with the more established findings in SZ, it is rapidly developing and consistent. The similarity in the profiles of cognitive impairments, the functional relevance of cognitive impairments, and the association between cognition

deficits and impaired everyday living outcomes provides assurance that the discussion of heritability of cognitive impairments and related traits in SZ and bipolar disorder has congruence.

One large-scale examination of cognitive endophenotypes for SZ is the Consortium on the Genetics of Schizophrenia (COGS).[50] The COGS project is aimed at utilizing the 6 key cognitive abilities in SZ for molecular genetic studies. These abilities were carefully selected based on their fit with previous vulnerability research, as well as their potential to be reliably and validly measured. The 6 cognitive abilities are abstraction/mental flexibility; attention; verbal, face, and spatial memory; spatial processing; sensori-motor processing; and emotion intensity discrimination.[50] Thus, the central premise in the COGS study is that cognitive impairments are simpler than the syndrome of SZ, but themselves potentially genetically complex. Across the 7 sites, COGS recruitment was successful with 164 complete families studied.[53] Analyses of performance data in 219 to 322 family members of a schizophrenic proband indicated strong and significant heritabilities for the antisaccade task ($h^2 = 0.55$, $P < .0001$), working memory (measured by letter number span; $h^2 = 0.46$, $P < .0001$), attention (measured by the continuous performance task; $h^2 = 0.40$, $P < .0001$), spatial processing ($h^2 = 0.37$; $P < .005$), and sensori-motor dexterity ($h^2 = 0.49$, $P < .0001$).

Additionally, preliminary results from the COGS study suggest that there are significant associations between several genes thought to be of biological relevance to SZ and the cognitive deficits being examined in the project.[8] COMT, eg, was associated with tasks measuring Pre-Pulse Inhibition, verbal learning, and face memory. In addition, ERBB4 was associated with 10 endophenotypes and NRG1 was associated with 7 endophenotypes. Although the impact of any one genetic polymorphism on cognitive functioning in SZ may be small (eg, by one estimate the COMT genotype accounts for only 3% of observed variance in working memory[54]), twin studies suggest that the total genetic contribution to cognitive performance may ultimately be much higher (closer to 50%).[54–56]

Neurocognitive functioning has also been used as a phenotype to in more recent genetic studies in an attempt to identify susceptibility genes for SZ. For example, Hallmayer et al[57] found that the use of a composite neurocognitive score was beneficial in allowing the selection of families at high genetic risk thereby increasing their power to detect genetic susceptibility.

Familiarity of Real-world Disability

There is surprisingly little work on the concordance for people with SMI and their relatives on indices of functional outcomes in the real-world despite the centrality of such disability in nosological definitions: only 2 studies provide direct information and both study only reported on SZ. One such study is the Roscommon Family Study,[58] performed in a rural area of Ireland in the late 1980s–1990s. In that study, the relative co-occurrence of various features of the between index cases with SZ and their first-degree relatives, including the presence of subclinical "schizotypal" signs, everyday functioning, cognitive impairments, as well as other conditions such as alcoholism, were examined in samples of people with SZ and their families and similar samples of healthy controls. Interestingly, compared with healthy controls, the greatest OR for relative concordance of a behavioral trait, OR = 3.4, was for occupational dysfunction, meaning that first-degree relatives of SZ index cases were 3.4 times as likely as healthy comparison samples to share vocational deficits with their identified index case. This rate is compared with ORs of 1.9 for concordance of positive schizotypal signs and 1.6 for concordance for social avoidance. Thus, in that study, vocational dysfunction was shared between relatives and people with SZ, suggesting a strong familial relationship. Several strong points of the Roscommon study support the validity of these conclusions. Although the influence of factors other than genetics, such as shared environments and familial resources, are likely to contribute to familiarity as well, it is important to note that all of the relatives and cases for both SZ patients and controls in this study lived in the same area and shared the host of environmental factors that could affect employment, such as social supports, educational opportunities, and the availability of employment.

A second study[59] was published very recently and also examined the potentially familial nature of impairments in everyday functioning in SZ. In an aggregate analysis of 1199 cases examined with comprehensive assessments of current real-world functioning and clinical symptoms, 9 different dimensions of functioning were identified using factor analysis and these traits were then examined for their concordance with other mentally ill relatives. The dimension with the highest concordance was impairment in everyday functioning ($h^2 = 0.61$) followed by disorganization ($h^2 = 0.60$), negative symptoms ($h^2 = 0.53$), and scholastic functioning ($h^2 = 0.51$). Sociability as a child, which is often viewed as an indicator of premorbid functioning, was the least concordant trait. Thus, across 2 studies in different countries with quite different subpopulations, the trait with the greatest concordance between SZ and family members was deficits in real-world functioning. Real-world disability, therefore, appears familial and possibly heritable, despite its multiply determined nature, and the fact that there are clear influences on real-world disability of factors that are not genetic (although they co-occur in families), such as receipt of disability compensation.[60]

The Complex Determinants of Real-World Functional Impairments

While the most consistent determinant of impairments in everyday functioning across neuropsychiatric conditions appears to be cognitive impairments,[61] NP deficits account for only a moderate amount of variance in concurrent everyday functional impairments; the correlation is in the range of $r = .3-.5$.[9,62,63] In addition, not all real-world functional outcomes are consistently related to cognition. For example, variation in cognitive functioning was recently found to be a strong predictor of residential functioning in people with SZ,[64] while cognitive impairment in the same sample was unrelated to social and vocational milestones. Directly relevant to this point is the finding by Rosenheck et al[60] indicating that race and disability compensation status had the largest impact on vocational outcomes of all of the predictor variables measured. In fact, the relative importance of disability compensation status on likelihood of employment was markedly larger than the influence of cognition. Similarly, in a recent cross-national study,[65] people with SZ in the United States and Sweden differed minimally on performance on both a clinical NP assessment and an assessment of their everyday living skills and were rated as equally impaired in their ability to live independently by their case managers. Yet, the people with SZ from Sweden were more than twice as likely to be living independently as their American counterparts, probably because of the $2000 per month in disability compensation and housing supports that they received from the local health authority. These findings lead to the conclusions that impairments in everyday functioning are influenced by a host of factors other than ability, making it quite remarkable that heritability of these outcomes can be reliably detected. The convergence of these findings raises the question as to whether there are robust, measureable, and detectable individual-differences influences on real-world functional outcomes, other than cognition, that may be suitable for genetic analysis.

One solution that has been proposed to counteract problems in assessment of real-world outcomes and circumvent environmental influences is the direct assessment of functional capacity (ie, the ability to perform functionally relevant skilled acts). Based on the premise that skills capacity (what one can do) can be separated from skills performance (what one actually does) and that capacity is under reduced environmental influence compared with real-world functioning, direct assessments of functional capacity have been applied to several neuropsychiatric conditions and in healthy aging. Performance-based measures of functional skill are assessments during which participants are asked to actually perform everyday tasks such as managing money, paying bills, or performing adaptive communication tasks. These performance-based measures, unlike other assessments, do not require participants to be accurate with their self-report. Assessing the ability to perform the tasks under optimal conditions, in the laboratory, further reduces the potential for rate-limiting external factors to impact measurement because they might in the real world. Thus, the measurement strategies for these ability measures are similar to those employed in the assessment of cognitive performance. Like cognitive performance measures, these direct assessments of abilities have more potential to be under direct genetic influence than indices of real-world performance, which receive multiple environmental inputs.

Two recent studies conducted by our research group directly bear on the usefulness and predictive value of performance-based assessments of functioning for real-world disability. These results have suggested that the cross-sectional correlations between cognitive functioning, the ability to perform critical everyday living skills, and real-world disability are very similar in people with SZ and BPI, again arguing that environmental influences do not operate in a manner that adversely affects assessment results. The first study, Mausbach et al,[66] compared ambulatory patients with SZ ($n = 116$) to patients with BPI ($n = 89$) on a performance-based measure of everyday living skills, the University of California, San Diego Performance-based skills assessment (UPSA), and a NP assessment. The results of these performance-based assessments were then correlated with the achievement of real-world functional milestones, including independence in residential status and employment as well as informant real-world functioning ratings. Bipolar patients were less impaired than people with SZ on the performance-based disability measures, had better overall real-world outcomes, and were rated as less impaired across functional domains. However, the correlations between performance-based disability measures and informant ratings of everyday functioning were statistically significant and very similar in the 2 samples. Further, performance-based disability measures predicted residential independence in the 2 samples, with diagnosis adding no variance to the prediction after performance-based disability measures were considered.

In the second study,[67] an expanded version of this same sample of subjects was used to develop confirmatory path models predicting real-world outcomes, while considering the relationships between affective and psychotic symptoms, cognitive impairments, performance-based disability measures, and those real-world functional outcomes. In the model predicting real-world community activities, it was found that performance-based measures of the ability to perform the skills required for these everyday outcomes were the single best predictor in both samples. The total variance accounted for was 53% in SZ and 39% in BPI, suggesting that performance-based ability measures and cognitive performance are separately accounting for substantial variance in real-world outcomes in both SZ and bipolar disorder.

Functional Capacity as a Potential Endophenotype

In contrast to rapidly developing findings in cognition as an endophenotype, the state of the research evidence on direct genetic influences on impairments in functional capacity is quite limited. There are several issues that need to be evaluated in terms of the likely ability of research to identify genetic contributions to functional capacity and to the more complex phenotype of real-world functional disability. These include (1) Providing evidence that functional capacity deficits manifest the familial characteristics that are a prerequisite for possible genetic relationships, (2) Determining whether it is possible to separate these abilities from other symptomatic or global influences such as environmental or social factors, (3) Understanding the level of precision possible in the measurement of functional capacity, and (4) Evaluating the psychometric properties of ability measures. Cognitive performance indices have been selected for previous studies because they can be measured with precision and, as noted above, have shown considerable stability across variations in time between assessments and changes in clinical state.

We argue that functional capacity measures may be promising candidates for understanding the heritability of impairments in the complex phenotype of everyday functioning in SMI. These measures are psychometric tests, so their administration and scoring is quite precise and the distribution of scores can be characterized. There is considerable evidence that they can be reliably assessed in SMIs and they have considerable evidence of validity, including lack of overlap with most symptoms, similar levels of impairment across diverse populations, and construct validity. Because these measures are based on task performance, they can be repeated in order to examine test-retest reliability. In several studies of real-world outcomes and the relationship of these outcomes to functional capacity and NP measures, the functional capacity measures were as strongly related to real-world outcomes as NP performance. Further, they are minimally affected by other confounds such as symptoms and features of the cultural environment, similar to NP performance. For examine, in the study by Bowie et al[68] of 222 patients with SZ, the path coefficients for relationships between depression, positive symptoms, and negative symptoms and the performance-based measure of everyday living skills were all nonsignificant, in spite of these clinical symptoms having various rate-limiting relationships with real-world behavior. Further, in a study conducted in the United States and Sweden, scores on the performance-based measures of everyday living skills were identical in patients from the 2 countries, despite the substantial differences in real-world residential outcomes reviewed above.[65]

There is also developing evidence that performance-based disability measures have psychometric characteristics that are similar to those seen in NP tests. NP tests have been shown to perform suitably in studies of cognitive genomics, as evidenced by the COGS data reviewed above. In a recent article,[69] we examined the psychometric characteristics of performance-based measures of social and everyday living skills at follow-up intervals ranging from 6 to 36 months and compared their test-retest stability, vulnerability to practice effects, and reliable variance to a battery of NP tests. Our results suggested that NP and performance-based functional capacity measures were quite similar in their characteristics. For instance, 6-month test-retest stability was (Pearson) $r = .77$ for both NP and functional capacity measures and 36 month test-retest stability was $r = .73$ for the performance-based capacity measure and $r = .79$ for the NP composite score. Practice effects were also nearly identical, suggesting that these 2 ability domains are persistently impaired in people with SMI and that exposure to the testing situation was not adequate to eliminate these impairments.

Limitations and Future Directions

Although these preliminary results are promising, a considerable amount of work remains. There are no studies to date of the familial nature of functional capacity deficits. Studies of functional capacity in prodromal individuals have been completed but not published. Studies of the genetic correlates of functional capacity performance are underway at several sites, with all of these studies poised to examine the shared or differential genetic influences associated with functional capacity and some of the cognitive performance measures examined in the COGS study.

Conclusions

There is considerable evidence that disability is a complex and potentially heritable phenotype that is present across many SMIs. We have presented information to support our argument that current measurement technology is advanced enough to allow for the detection of genetic influences on functional capacity, similar to neurocognition. There is no research to date on the potential heritability of functional capacity, but these performance-based measures have promise that may be equivalent to indices of other endophenotype variables such as NP tests. While measures of functional capacity have not been studied in the same detail as NP performance measures, they have shown considerable promise and quite consistent results across studies.[70]

It also seems possible that functional capacity measures are more proximal to real-world functional impairments than performance on NP tests. These performance-based measures measure central elements of skills required to function in everyday life and genetic influences on them may underlie the apparently heritability of the complex

phenotype of real-world disability. They also appear to be similarly impaired in populations where sociocultural variables and aspects of the health care system are quite different,[65] suggesting that they capture core features of SMI, similar to NP deficits. As a result, identification of genetic influences on the complex phenotype functional disability might be simplified by identifying potential genetic variation associated with measures of functional capacity, rather than by identification of genetic factors which influence cognitive variables which then in turn influence disability. This is an empirical question and we do not suggest in any way that elements of cognitive impairment are not potentially important endophenotypes. These tests are measures of impaired brain functions in serious mental illness and have features that separate them from functional capacity measures. Rather, it is our position that impairment in functional capacity is a central feature in SMI and has potential to be influenced by genetic factors. Considerable information on the relationship between genetic factors and impairments in functional capacity in SMI is currently being collected, allowing for a detailed assessment of these hypotheses in the near future.

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