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Neurocognitive Allied Phenotypes for Schizophrenia and Bipolar Disorder

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Psychiatric disorders are genetically complex and represent the end product of multiple biological and social factors. Links between genes and disorder-related abnormalities can be effectively captured via assessment of phenotypes that are both associated with genetic effects and potentially contributory to behavioral abnormalities. Identifying intermediate or allied phenotypes as a strategy for clarifying genetic contributions to disorders has been successful in other areas of medicine and is a promising strategy for identifying susceptibility genes in complex psychiatric disorders. There is growing evidence that schizophrenia and bipolar disorder, rather than being wholly distinct disorders, share genetic risk at several loci. Further, there is growing evidence of similarity in the pattern of cognitive and neurobiological deficits in these groups, which may be the result of the effects of these common genetic factors. This review was undertaken to identify patterns of performance on neurocognitive and affective tasks across probands with schizophrenia and bipolar disorder as well as unaffected family members, which warrant further investigation as potential intermediate trait markers. Available evidence indicates that measures of attention regulation, working memory, episodic memory, and emotion processing offer potential for identifying shared and illness-specific allied neurocognitive phenotypes for schizophrenia and bipolar disorder. However, very few studies have evaluated neurocognitive dimensions in bipolar probands or their unaffected relatives, and much work in this area is needed.

Key words: neurocognition/schizophrenia/endophenotype/bipolar disorder

Introduction

Revisiting the classification of schizophrenia and bipolar disorder as separate clinical entities with distinct etiology and pathophysiologies has gained momentum recently. Infusion of a growing literature has drawn attention to shared aspects of psychopathology, neurobiology, and treatment efficacy across the 2 disorders. Linkage findings offer a substantial challenge to the traditional Kraepelinian model of the 2 disorders as having fully discrete underlying disease processes. Empirical support for similar pathoetiology in these disorders comes from genetic studies demonstrating shared genetic susceptibility. Yields from linkage studies indicate several loci that may represent risk genes for schizophrenia and bipolar disorder including 18p11.2, 13q32, 22q11–13, and 10p14.[1–4] Candidate association studies have specified several genes (eg, *G72/G30, BDNF, DISC1, COMT, neuregulin 1*, and *dysbindin*) that appear to confer risk for both disorders. Importantly, these shared genetic factors appear to be more common in psychotic bipolar patients and their family members, suggesting that there may be common causes for psychosis across bipolar disorder and schizophrenia.[5–8]

Although differences between the disorders are established, especially the relatively specific familial aggregation of the disorders,[9] shared deficits in neuropsychology,[10–13] neurophysiology,[14–16] gross brain anatomy,[17] and responsivity of both disorders to antipsychotic medications are consistent with the view that these disorders may share aspects of pathophysiology. Genetic models considering both common and unique genetic features of the disorders are of interest, for they bear on fundamental questions about the causes and interrelationship of the 2 most common, serious mental illnesses in adult psychiatry.

Unraveling the role of numerous contributing genetic factors to disease risk, including commonalities and differences across clinical syndromes, requires novel linkage strategies. The allied phenotype approach attempts to break down complex genetic disorders into their component parts by isolating intermediate expression/effects of individual genes. This approach is based on the premise that genetic determination of neurobiological alterations linked to illnesses may be more readily tracked than the genetic causes of overt expression of disorders. Relative to the clinical expression of psychiatric syndromes, this

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might be due to either an enhanced ability to resolve illness heterogeneity or a more direct genetic determination of specific biological traits. As in other medical disorders, this strategy in psychiatric genetics is based on the hope that improved understanding of the genetic causes of variation in allied phenotype expression will accelerate progress in understanding the genetics of complex psychiatric disorders. Given the possibility that schizophrenia and bipolar disorder share overlapping etiologic determinants, the endophenotypic approach may be helpful for delineating shared and unique causal pathways from genetic variation, to altered neural systems and neurobehavioral function, to the overt clinical expression of both disorders.

Useful allied phenotypes help to resolve questions about etiology in part by helping track down illness-related gene variants and also by filling gaps in the causal chain between gene expression and clinical expression. Consistent with suggested criteria for identification of endophenotypic markers,[18–20] allied phenotypes should be: (1) heritable, (2) associated with the illness, (3) stable traits that can be reliably assessed, (4) cosegregated within families, and (5) higher in prevalence for unaffected relatives compared with the general population.

Based on current knowledge of both schizophrenia and bipolar disorder, genetic influence is likely to impact both structural and functional aspects of brain systems in ways that increase risk for the disorder. Atypical patterns in the organization of brain anatomy can be neurodevelopmental in origin,[21–23] resulting in a cascade of events that manifest across a wide range of neurocognitive and affective abilities such as attention, executive function, working memory, affect regulation, affect-cognition integration, declarative memory, spatial processing, and psychomotor function. Consequently, neuropsychological measures are promising allied phenotypes, as are neurophysiological assessments of brain systems that subserve specific neurocognitive processes. The established heritability of cognitive abilities[24,25] and the availability of highly reliable procedures for assessment of most cognitive skills highlight the potential of neurocognitive performance measures as candidate allied phenotypes for schizophrenia and bipolar disorder. To date, the allied phenotype approach has been used much more widely in studies of schizophrenia than bipolar disorder. Yet, patient studies with schizophrenia and bipolar patients have begun to show interesting patterns of separate and overlapping abnormalities in putative allied phenotypes.

The present review was organized to illustrate promising neuropsychological and neurocognitive candidate allied phenotypes with an eye toward guiding future work by identifying potential confounds and other critical factors that highlight areas where more work is needed. To this end, we review neurodevelopmental accounts of schizophrenia and bipolar disorder and the implications for allied phenotype research. Next, we examine the pediatric bipolar disorder and early-onset schizophrenia literatures for indicators of neurodevelopmental disruption, which may represent core allied phenotypic deficits. Finally, we review promising approaches from clinical cognitive and affective neuroscience research that have been used in studies of probands with schizophrenia and bipolar disorder and to a much more limited degree with their family members.

Neurodevelopment

Both schizophrenia and bipolar disorder are associated with neurodevelopmental abnormalities that often manifest themselves early in life. Available evidence suggests that neurodevelopmental disturbances are generally more severe and disabling in schizophrenia. Indeed, relative to bipolar disorder, schizophrenia has been associated with higher rates of pre- and perinatal complications; more frequent developmental cognitive, motor, and language problems; and greater maturational abnormalities in brain regions such as the hippocampus.[26–28]

One neurodevelopmental model has proposed that the greater neuroanatomical and neuropsychological abnormalities in schizophrenia, relative to bipolar disorder, stem from a core set of related genetic risks but that additional susceptibility genes and/or environmental pre- or perinatal insults lay the foundation for a more severe illness expression in schizophrenia.[29] The mechanisms through which neurodevelopmental disturbances might contribute to increased risk for later illness expression, in either schizophrenia or bipolar disorder, are not yet clear. However, various manifestations of neurodevelopmental disturbances may provide promising allied phenotypes for both disorders. Many genetic causes of brain dysmaturation are being identified in basic developmental neurobiological research, and illness expression in the form of cognitive, motor, and social function is often evident well before illness onset during childhood and adolescence.

The time course of the emergence of neurocognitive deficits in schizophrenia and bipolar disorder is variable and not fully understood. However, retrospective studies of schizophrenia patients before illness onset,[30,31] and studies of unaffected family members,[32–34] indicate that at least some cognitive deficits are present before illness onset and thus may represent intermediate cognitive phenotypes. Neurodevelopmental models of schizophrenia have been considered for some time and have been investigated in animal models.[35,36] While less developed for bipolar disorder, the growing recognition of pediatric bipolar disorder as a common clinical condition highlights the need for parallel modeling of brain dysmaturation associated with bipolar disorder.[37]

Proband Studies

Early-Onset Schizophrenia. Similar to adult schizophrenia studies, neuropsychological studies of childhood-onset schizophrenia have revealed impairments across

a broad array of cognitive functions.[38] Generalized cognitive deficits include areas of learning and abstraction as well as attention, which are commonly impaired in adult patients with schizophrenia. Neuropsychological deficits in childhood-onset schizophrenia appear to be greater than those associated with adult-onset patients, particularly in the areas of working memory, perceptual-motor skills, and overall intellectual abilities.[39]

Pediatric Bipolar Disorder. Impairments in attentional set-shifting, visuospatial memory, verbal memory, working memory, and executive functions have been documented in pediatric bipolar disorder, regardless of medication status or illness state.[37,40,41] Affective modulation of cognition has been investigated more extensively in pediatric bipolar disorder than in early-onset schizophrenia. Children with pediatric bipolar disorder misinterpret affective expression of sad, happy, and fearful child faces.[42] Further, children with bipolar disorder display impairments in the identification of emotionally intense happy and sad facial expressions, tending to misjudge extreme facial expressions as being moderate to mildly intense.[43] Whereas cognitive problems are more severe in early-onset schizophrenia, pediatric-onset bipolar disorder is associated with greater impairments in emotion processing. The pattern of more severe neurocognitive deficits in cases with early-onset highlights the potential importance of brain maturational factors in both disorders.

Family Studies

Early-Onset Schizophrenia. Psychomotor speed, working memory, and executive function difficulties are seen in unaffected parents of children with schizophrenia.[44] Offspring of schizophrenia, followed from birth to adolescence, showed motor and sensory dysfunction by 1 year of life, perceptual and motor difficulties by school age, and additional attention difficulties and social cognitive difficulties by adolescence.[45] Studies that examined offspring in the high-risk period for illness onset (16–25 years of age) have shown impaired development of intellectual abilities, executive function, perceptual-motor speed, verbal learning, and memory.[46] Other studies of genetically high-risk samples revealed impairments across a wide range of cognitive areas including executive function, information processing speed, motor speed, working memory, sustained attention, verbal fluency, and verbal memory across.[47–51]

Pediatric Bipolar Disorder. The few studies examining cognitive function in children at familial risk for bipolar disorder have reported decreased academic achievement and lower verbal intellectual abilities.[52,53]

Based on existing studies of early-onset schizophrenia and bipolar disorder, commonly affected cognitive domains across both disorders include attention, working memory, verbal memory, and executive function in probands and their families, while motor problems may be more specifically associated with schizophrenia. There is a strong tradition of cognitive research in schizophrenia and affective research in bipolar disorder, with limited overlap. This is a major limitation as affective problems in schizophrenia and cognitive problems in bipolar disorder are now both well established. To address issues of overlap and maximize the utility of the allied phenotypic approach, it will be important to assess cognitive and affective allied phenotypes in both disorders.

More importantly, adopting methods that map cognitive deficits to specific neural systems will be a critical step in tracing neurocognitive changes back to regional neural dysfunction and from there back to genetic variation. Paradigms from cognitive and affective neuroscience that are used in both human and animal models often can be more directly linked to neuroanatomy, neurotransmitter systems, and gene expression than standard clinical neuropsychological tests. Neurodevelopmental models need to specify growth trajectories and the relationships between genotype and neurocognitive development to further clarify how brain dysmaturation impacts cognitive development and potential illness expression.

Neuropsychological Impairments in Adulthood

Proband Studies

Neuropsychological deficits, typically ranging from moderate to marked, have been established in schizophrenia across a wide range of cognitive abilities and are recognized as a "generalized deficit."[54,55] Impairments are present during the first episode of psychosis and endure with minimal change in the early years after clinical stabilization with pharmacological treatment. Cognitive performance often does not change dramatically, even during acute episodes of psychosis.[54–57] Heretofore, a wide array of cognitive abnormalities have been associated with bipolar disorder,[14,58] yet meta-analytic studies have indicated less pronounced impairments compared with schizophrenia samples.[10]

Over time, neuropsychological performance appears to be more stable in schizophrenia relative to bipolar disorder.[59] Level of acute psychopathology may be linked to cognitive performance and long-term deficits in bipolar disorder.[60] Additional reports of improved performance following clinical stabilization for bipolar patients (in the areas of nonverbal memory, executive function, and sustained attention) support this hypothesis.[61–63] Symptomatology in schizophrenia, on the other hand, appears to be relatively independent of cognitive performance as deficits persist after clinical stabilization in first-episode patients.[64] However, the presence of psychotic symptoms may play a key role in the severity and stability of cognitive deficits in bipolar and other affective disorders.[56]

The most commonly observed cognitive deficits in bipolar disorder have been in the areas of attention, executive function, and to a lesser extent verbal memory and spatial working memory.[65] Meta-analysis revealed worse performance for schizophrenia than bipolar patients in 9 of 11 cognitive domains.[10] However, a subsample of bipolar patients with psychotic symptoms displayed a neuropsychological profile that was qualitatively more similar to the profile of schizophrenia patients.[66] Indeed, several recent investigations have reported that psychosis in affective disorders is associated with more severe neuropsychological dysfunction compared with patients with no history of psychosis. For example, psychotic bipolar groups show more severe executive function impairments[67] and differentially impaired spatial working memory[68] when compared with nonpsychotic bipolar samples. Findings of more severe dysfunction have also been associated with psychosis in the context of unipolar depression.[56,69] Overall, a lifetime presence of psychosis appears to be a key contributor to cognitive dysfunction, independent of affective symptoms, and some have suggested that psychotic disorders should be conceptualized as being on a continuum rather than as a group of categorically distinct illnesses.[70,71] This pattern of results is consistent with data indicating a stronger genetic similarity between bipolar disorder with psychosis and schizophrenia.[5–8] The degree to which risk for psychosis accounts for greater genetic similarity and overlapping patterns of neuropsychological dysfunction across these disorders needs to be addressed in future research.

Family Studies

Efforts to uncover the patterns of neuropsychological dysfunction shared among adults with schizophrenia and their unaffected relatives are plentiful.[32–34,72–76] Although cognitive deficits are now well established in bipolar patients, there have been few studies using neuropsychological tasks in family studies of bipolar disorder. Many existing studies are an extension of the schizophrenia literature inasmuch as cognitive performance in bipolar probands and their family members have been collected for comparison with schizophrenia probands and their family members.[66]

Table 1 was designed to illustrate allied phenotype studies in psychotic probands and their unaffected relatives. The sparse citations for family and proband studies in bipolar disorder highlight the strong bias for work in this area focused on schizophrenia. To identify studies reporting significant neuropsychological findings in bipolar probands and their relatives as well as relatives of schizophrenia patients, the title, abstract, and key word fields of Medline were searched using the terms "bipolar" or "schizophrenia"; "neuropscyh*," "neurocognit*," or "cognit*"; and "famil*," "relative," or "twin." The search was limited to English language articles available between 1980 and January 2008. Abstracts and titles were used to determine whether the references might be relevant to this review, and full texts of potentially relevant articles were retrieved to assess for inclusion in the table. Finally, reference lists of relevant articles were also checked for additional citations not identified during the database search. Cited articles were nonreview papers reporting significant heritability estimates or performance deficits, in bipolar probands or schizophrenia/bipolar familial samples ($n > 10$), on one or more neuropsychological tests. Reports of neuropsychological dysfunction in schizophrenia probands were excluded from the table given the large number of relevant studies and the generally accepted profile of diffuse neuropsychological deficits in schizophrenia.

Schizophrenia. Episodic memory impairment may be an indicator of disrupted temporal lobe/hippocampal function. Studies of both high-risk adolescents and unaffected family members of schizophrenia patients have reported episodic memory dysfunction.[46,77] A meta-analysis of family studies in schizophrenia also indicated moderate verbal memory deficits in unaffected relatives.[78] Neuroanatomical findings of decreased temporal lobe and hippocampal volume in unaffected relatives[77,79–81] support these neuropsychological findings and suggest a genetic/neurodevelopmental component.

There is also strong support for a familial pattern of deficits in prefrontally mediated cognitive processes such as working memory, attention, abstraction, reasoning, and planning in unaffected relatives of schizophrenia patients.[82] Working memory, the ability to hold information "online" for planning future behavior, is a critical component of many higher order cognitive skills, and deficits in this area may thus have widespread effects on other cognitive processes. Working memory deficits have been well documented in schizophrenia probands[83–85] and in offspring, monozygotic and dizygotic twins, and other unaffected relatives.[32,86–88] Spatial working memory deficits appear to increase in family members as genetic similarity to schizophrenia probands increases.[33] Using a unique approach to identifying phenotypically homogeneous groups, a cluster analysis of several common neuropsychological tests resulted in 3 groups, comprised of both probands and family members, separated primarily by level of overall dysfunction.[89] The authors proposed that multiple allied phenotypic measures may be helpful in characterizing genetic homogeneity among mixed samples of probands and unaffected family members.

Bipolar Disorder. Unaffected monozygotic co-twins of bipolar patients display impaired face memory, verbal learning and memory, and working memory.[90] Findings have been mixed among the few studies directly

Table 1. Studies Reporting Significant Impairment or Heritability on Neuropsychological Tests in Bipolar Probands and Relatives of both Schizophrenia and Bipolar Probands

Neuropsychological Domain	Cognitive Task	Schizophrenia Relatives	Bipolar Probands	Bipolar Relatives
Intelligence/general cognition				
	WAIS-R/III	46,72,164–166		
	WISC	167		
	WASI	12	12	
	WISC-R/WAIS-R/III: Vocabulary	51,168–170		171
	PPVT-R	164		
	WAIS-III: block design	72,170		
	NART/WRAT	12,51,172,173	174	
	CAMCOG			175
Information processing/ processing speed		176[a]		
	Trail making test	34,44,67,72,158,160,172,177–189	190	175,190,191
	Verbal fluency	46,51,67,157,165,166,178,179, 182,186,187,192		
	Digit symbol/symbol digit	12,34,67,160,180,181,185,187	12,34	171
	Stroop	46,92,184,193,194	92	92,171
	Finger tapping	181		
	Purdue pegboard	192		
	Stop reaction time	195		
Reasoning/flexibility/ abstraction/executive function		75[b],78[b],196[c]		
	Wisconsin Card Sorting	34,72,123,158,172,178,183,184, 187,189,197–201	190,202	190,203
	Tower of London/Hanoi	187,194,204		
	Penn Conditional Exclusion Test	205,206		
	Object sorting test	207		
	CANTAB: ID/ED shift			208
	LNNB: relational concepts	72		
	BRIEF		209	
General memory		75[b],176[a],196[c],210[b]		
	WMS-R/III		90,211	90
	E-RBMT	12	12	12
Verbal memory		78[b],212[a]		
	List learning (eg, CVLT, RAVLT)	34,46,67,170,173,178,188,192, 194,205,206,213,214	90,191,215–217	90,217
	WMS-R/III: logical memory	169,197,200,218–222	217	
	WMS-R/III: associative learning	181,220		
	WMS-R: verbal paired associates	186		
	Word list recall	32		
	Auditory delayed recognition	221		
	Word pairs	188,224		
Visual memory				
	WMS-R/III: visual reproduction	46,169,181,218–221	217	203
	Rey-Osterieth Complex Figure	34		
	Penn Face Memory Test	205,206	217	
	WMS-III: faces	225		
	Penn spatial memory	205,206		
	Visuospatial delayed recognition	223		
	Abstract paired associates	220,221		90
	Brown-Peterson memory test		90	
	CANTAB: spatial recognition			226
Working memory		176[a],196[c]		
	Letter-number sequencing	165,205,227		
	Digit span	86,170,186,187,227–229		226
	Spatial span	165,170,229		226
	Spatial delayed response task	13,32,33,67,88,91,230,231		
	Counting span/sentence span	168,195		

Table 1. Continued

Neuropsychological Domain	Cognitive Task	Schizophrenia Relatives	Bipolar Probands	Bipolar Relatives
Visual-spatial or auditory processing				
	Span of apprehension	159,199,232		
	Visual backward masking	91		233
	Penn Spatial processing test	205,206		
	Choice reaction time	32,194		
	Self-face recognition	234		
	Feature uncertainty	183		
	Source monitoring	235		
Language				
	Sentence completion	46,213	202	202
	Grammatical reasoning	188,224		
Attention		212[a]		
	CPT (eg, degraded stimulus, AX, IP, DPX, auditory versions)	32,34,165,173,177,184,192,197, 199,200,205,206,213,236–245		203
	d2	87		
	Dichotic listening	194,197,200,218		
	Divided attention	246		
	Selective attention	224,188		
	n-back	73		

Note: WAIS-R/III, Wechsler Adult Intelligence Test—revised/third edition; WISC, Wechsler Intelligence Scale for Children; WASI, Wechsler Abbreviated Scale of Intelligence; NART, National Adult Reading Test; WRAT, Wide Range Achievement Test; CAMCOG, Cambridge Cognitive Examination; CANTAB, Cambridge Neuropsychological Test Automated Battery; BRIEF, Behavior Rating Inventory of Executive Function; WMS-R/III, Wechsler Memory Scale—revised/third edition; E-RBMT, Extended Rivermead Behavioural Memory Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; CPT, Continuous Performance Test; PPVT-R, Peabody Picture Vocabulary Test—Revised; ID/ED, intra extra-dimensional set shift; LNNB, Luria-Nebraska Neuropsychological Battery; IP, identical pairs; DPX, dot pattern expectancy.
[a]Factor analysis composite.
[b]Meta-analysis.
[c]A priori defined composite.

comparing schizophrenia and bipolar disorder probands and their unaffected relatives, but some deficits for verbally mediated tasks seem to be shared across the disorders. For example, delayed verbal memory deficits were observed in unaffected siblings of both bipolar and schizophrenia patients, whereas unaffected siblings of bipolar patients did not show impairments in general intelligence, working memory, verbal fluency, reasoning, or abstraction.[91] Bipolar patients and their unaffected relatives were comparable to healthy controls on several executive function tests with the exception of response inhibition, as measured by the Stroop test, which was impaired in the relatives of both schizophrenia and bipolar patients.[92] The latter finding suggests that susceptibility to interference and reduced inhibitory processing could be intermediate cognitive markers for similar or related familial vulnerability. McIntosh et al[12] reported memory impairments in schizophrenia and bipolar probands as well as their unaffected relatives. In a Finnish twin study, bipolar probands and their unaffected co-twins did not differ from controls on measures of working memory; however, schizophrenia probands showed impaired verbal and spatial working memory while their unaffected twins displayed poor spatial working memory.[13] Finally, meta-analysis in first-degree relatives of bipolar patients indicated small but significant effect sizes for a familial pattern of impairment for executive function and verbal memory.[93]

In summary, the schizophrenia literature offers more data suggesting that cognitive deficits may provide allied phenotypic markers indicative of liability to illness, and findings generally point to a familial pattern of neurocognitive dysfunction involving working memory, episodic memory, attention, and executive function. In contrast, there are relatively few family studies of neurocognitive function in the bipolar literature. This may reflect that until recently, systems neuroscience frameworks have not had the same level of impact in mood disorder research as in schizophrenia research. The few existing studies of bipolar disorder typically have small sample sizes, and findings are not yet consistent across studies. This is further complicated because factors such as clinical state and presence/history of psychosis in probands may be related to neuropsychological performance and result in greater heterogeneity in family studies of bipolar disorder. Despite the limitations of the bipolar literature,

some cognitive domains (eg, working memory, verbal memory) appear to be affected in individuals with schizophrenia and bipolar disorder and in some of their relatives, thereby pointing to several potential allied neuropsychological phenotypes for future family genetic research.

Cognitive Oculomotor Paradigms

Cognitive abilities have traditionally been assessed using neuropsychological tests. However, performance on neuropsychological measures is not often strongly linked to specific functional brain systems affected by neuropsychiatric disorders and their treatment. Oculomotor paradigms have the advantages of being based on well-developed animal models that have characterized the neural systems supporting performance on different tasks in nonhuman primates,[94] focal brain lesion studies,[95] and functional brain imaging studies of healthy individuals.[96]

Two commonly used cognitive oculomotor tasks are the antisaccade task[97] and the oculomotor delayed response task.[98] During the antisaccade task, subjects are instructed to inhibit the natural tendency to look toward the appearance of a peripheral target but rather to immediately look to the opposite, mirror location. Prefrontal systems are known to support performance on such response suppression tasks. The oculomotor delayed response task requires subjects to remember the location of a briefly presented peripheral target and then to look to the remembered target location after a delay period. Accurate performance on this task reflects the ability to maintain information in spatial working memory, an ability that is also believed to reflect executive function.

Proband Studies

Schizophrenia. Thus far, oculomotor research with neuropsychiatric populations has mostly focused on schizophrenia patients and their family members. Medicated, unmedicated, chronic, and first-episode schizophrenia samples all consistently show higher error rates on antisaccade tasks than do healthy individuals.[99–105] However, some findings with this test have been inconsistent, perhaps due to methodological issues.[106] For example, some studies found prolonged latencies to initiate context appropriate responses in schizophrenia patients,[100,103,107] while others found no impairment.[102,108] Longer antisaccade latencies were observed in treatment-naive but not previously treated first-episode patients, so treatment status may affect response latencies on this task.[101] However, others found no differences between unmedicated and medicated chronic patients,[109] no change in initially neuroleptic naive patients after treatment,[110] and improved but consistently longer latencies compared with healthy participants in first-episode initially medication-naive patients up to 1 year after treatment initiation.[99]

Working memory studies with schizophrenia patients using the oculomotor delayed response task have consistently shown performance deficits compared with healthy individuals.[111] These impairments have been reported in cross-sectional investigations of medicated and untreated patients[109,110,112–116] as well as never-treated first-episode patients.[85,117] These deficits may be greater with longer delay periods during which spatial information needs to be maintained in working memory.[85] Longitudinal studies of treatment-naive first-episode patients also reported impaired working memory performance, but these were restricted to longer delay periods during which spatial information had to be maintained in working memory. After 6 weeks of treatment with atypical antipsychotic medications, patients exhibited an exacerbation of baseline deficits reflected in uniformly inaccurate performance at all delay periods.[85]

Bipolar Disorder. Although few studies have used cognitive saccade tasks with bipolar patients, antisaccade deficits have been reported in both bipolar disorder and schizophrenia.[16,118,119] In a recent comparison of treatment-naive first-episode psychosis patients, antisaccade error rates were elevated in both bipolar and schizophrenia patients.[120]

There have also been few studies investigating working memory performance in bipolar patients using the oculomotor delayed responding task. Findings generally indicated no impairments for chronic, medicated bipolar disorder patients relative to healthy individuals,[84,116,118,121] suggesting that spatial working memory deficits, as assessed by oculomotor delayed responding tasks, may be relatively specific to schizophrenia.

Family Studies

Studies with unaffected first-degree relatives of schizophrenia patients have reported increased rates of antisaccade abnormalities.[102] While some consider this deficit to be a promising phenotype of genetic risk for schizophrenia,[122] large-scale family studies are needed to clarify performance patterns in unaffected relatives and their relation to genotypes. Studies of working memory using oculomotor delayed response paradigms have reported deficits in individuals at high risk for schizophrenia,[123] as have investigations of unaffected family members of schizophrenia probands.[88,124]

In summary, cognitive deficits for response inhibition and working memory are present on oculomotor tasks in both schizophrenia and bipolar patient populations. Available findings indicate a familial pattern in schizophrenia, but little family data are available in bipolar families. Further investigations are needed to assess the usefulness of neurophysiology studies of oculomotor paradigms as allied phenotypes for tracking down

independent and overlapping genetic risks for schizophrenia and bipolar disorder.

Affective/Social Cognition Studies

Proband Studies

Emotion Perception. Facial emotion matching[125] is impaired schizophrenia and perhaps less so in bipolar patients. Individuals with schizophrenia consistently show deficits in the perception of facial affect[126–129] beyond general impairments of face perception. Significant deficits in the interpretation of emotional prosody in individuals with schizophrenia have also been reported.[130,131] The literature in bipolar disorder with regard to perceived facial emotion is mixed, with euthymic patients generally showing no impairments[132] and manic patients showing significant impairments.[133] However, one study found deficits in facial affect matching in a euthymic sample.[134] Direct comparison of emotion perception in schizophrenia and bipolar samples reported no difference in eye movements when visually scanning facial stimuli.[135]

Anhedonia. While anhedonia, or decreased experience of positive emotion, has long been considered a core characteristic of schizophrenia,[136] deficits in this area have not been observed consistently.[137–142] In particular, most studies assessing emotional responses at the moment of exposure to stimuli have found similar emotional responses for schizophrenia patients and healthy controls. The one study comparing anhedonia in schizophrenia and bipolar disorder reported less anhedonia in the bipolar group.[137] Differentiating and measuring affective disturbances in schizophrenia and bipolar disorder, and their utility as endophenotypes, remain largely unexplored.

Stress Reactivity. Individuals with schizophrenia can show intense responses to stressful situations, including family interactions with high levels of critical comments. High levels of criticism from relatives predict relapse of illness[143] and increasing speech disorganization,[144] while frequent contact with positively perceived relatives has been associated with longer periods without psychotic exacerbation.[145] Similarly, individuals with bipolar disorder demonstrate higher levels of relapse when home environments include a highly critical relative[146,147] and more disordered speech in response to negative situations.[147] Thus, heightened social stress reactivity appears to be a common feature of both disorders, but its prevalence in family members has not been systematically explored.

Social Competence. Individuals with schizophrenia and bipolar disorder often have significant difficulty in effectively managing interpersonal situations. In schizophrenia, this social impairment is known to be present prior to onset of psychotic illness and is characterized by fewer and less satisfactory social relationships.[148] Although both disorders are associated with poor premorbid social functioning in adolescence, premorbid adjustment difficulties typically appear earlier and are more debilitating in schizophrenia.[149] However, recent findings suggest minimal differences between the 2 disorders for participation in social activities or frequency of social relations[150] after illness onset. This observation highlights the growing recognition of significant functional disturbances in bipolar disorder, even during euthymic periods.

Social Cognition. Although few studies have compared social cognitive abilities in schizophrenia and bipolar disorders, available findings indicate that both disorders show similar impairments in social knowledge[151] and social problem solving.[152]

Family Studies

There are few studies of emotion perception in family members of individuals with schizophrenia and fewer in family members of bipolar patients. Findings have been mixed with regard to deficits in affect perception in relatives of schizophrenia probands. Whereas one study reported no differences among probands, family members, and healthy controls in recognition of basic emotions,[145] 2 recent studies showed impaired emotion recognition among unaffected siblings.[153,154] Similarly, inconsistent findings have been reported for social judgment. One study reported a mixed pattern of no deficits for facial affect recognition or social judgment but impaired nonverbal behavior sensitivity in unaffected family members.[155] In contrast, recent reports have indicated impaired social judgment in unaffected first-degree relatives, albeit less severe than in schizophrenia probands.[156] Disturbances in affect perception were reported for facial, vocal, and combined modalities in unaffected siblings.[157]

Studies assessing emotional experience, to our knowledge, have been limited to relatives of schizophrenia probands. Two studies[158,159] found significantly more self-reported physical anhedonia, and a third study[160] found more social anhedonia in unaffected relatives of schizophrenia patients. However, observational studies of emotion-modulated startle have not found differences among schizophrenia probands, their unaffected relatives, and healthy controls.[138]

Although social competence is rarely assessed in relatives of patients, studies using measures of schizotypy have reported social dysfunction and social-interpersonal deficits in unaffected relatives of schizophrenia probands.[161] Direct comparison of relatives of both schizophrenia and bipolar probands using schizotypy ratings indicated not only very minimal group differences but

also a significant intrafamilial resemblance for social behavior (lack of close friends, constricted affect, excessive social anxiety) in both groups.[162]

Overall, schizophrenia probands display greater levels of dysfunction than their bipolar counterparts in the expression of anhedonia as well as when decoding facial expression or emotional cues in the prosody of speech. However, similar levels of dysfunction have been reported for response to interpersonal stressors, social activity, and social cognition. Oddly, given the cardinal clinical characteristics of the disorders, there has been much more laboratory research on emotional deficits in schizophrenia than in bipolar probands. Moreover, the discrepancy is even greater for studies of family members where there has been little quantitative laboratory assessment of emotional characteristics in the unaffected relatives of bipolar probands. Studies of affective processes, and their neural substrate, may provide important endophenotypes for studies of both bipolar disorder and schizophrenia. With the emergence of affective neuroscience as a field, and the parallel emergence of neurophysiological and neuroimaging tools to study emotional brain systems, significant progress in this area is likely in coming years, especially in family studies of bipolar disorder.

Limitations

The allied phenotype approach has garnered much enthusiasm owing, in part, to the assumption of a more direct association between related genetic characteristics and both neurophysiological measures and narrowly parsed psychological processes, compared with the overt expression of clinical disorders. Support for this approach remains indirect, based on its success in other medical disorders rather than a compelling track record in psychiatric genetics. For psychiatric disorders, it remains unclear whether more detailed phenotyping or gathering much larger samples will ultimately prove the best strategy for unraveling the genetic contributions of complex psychiatric disorders. Experience in unraveling the genetics of neurological disorders such as epilepsy and dementias may prove useful in this regard. There, phenotypic delineation of subtypes of syndromes has been crucial to unraveling their genetic basis. The value of extensive laboratory phenotyping for psychiatric genetics may also depend on the utility of allied phenotypes for resolving the heterogeneity of the broadly defined syndromes of schizophrenia and bipolar disorder into subgroups of patients with more homogeneous etiopathology.

The potential value of the allied phenotype approach has recently been challenged on theoretical grounds.[163] Reflecting on findings from a meta-analysis of the effect of *COMT* on promising allied phenotypes, these investigators caution that allied phenotypes and disease phenotypes may both reflect many genes of small effect.[163] The notion that the allied phenotypes currently being used in proband and family studies are genetically complex has merit, yet the allied phenotype approach may have value if the genetics of allied phenotypes are significantly simpler than that of the disorder.

The genetic complexity of allied phenotypes notwithstanding, this approach also has the advantage of providing more reliable and objective laboratory assessments for large multisite family genetic studies. This can potentially help define homogeneous etiological groups and detect biomarkers of illness susceptibility that can help guide earlier diagnosis and intervention. Also, the intermediate phenotype approach can potentially contribute to enhanced understanding of disease pathophysiology from gene to protein expression to biochemistry to neurophysiology to behavior that will ultimately provide better theoretical models for understanding the neurobiology of serious mental disorders, both those unique and common to currently defined clinical syndromes.

Cognitive Epidemiology

Distinguishing potential genetic effects from normative aging, sex, and education effects is critical for identifying and using allied phenotypes in family genetic research. Often, it is unclear whether the variability in patient performance can be attributed to specific genes or to complex population stratification effects. Normative data provide a means for equitable comparison among test takers relative to well-defined performance expectations. In this respect, the clinical neuropsychological approach to assessing cognition is promising due to its standardized procedures and published normative data. However, the drawback to using neuropsychological measures is the complexity of the tests and therefore the high likelihood that the determination of test performance itself has a high-level genetic complexity. Tests that isolate discrete neurocognitive processes or neurophysiological measures are likely to have less genetic variance and more apt to link with specific genes. Despite all these advantages, it remains fair to say that many of the most intriguing allied phenotype measures have not yet proved their value in associating specific genes with discreet neurocognitive processes in schizophrenia or bipolar disorder research.

Part of this issue may be related to the need for better and more refined allied phenotypes. Outside the ''usual suspects'' (eg, P3, P50, global eye tracking performance, and the Wisconsin Card Sorting Test), there is very little family data with newer neurocognitive tests, newly defined neural systems, or new cognitive neuroscience constructs to guide their selection for use in larger family studies. The fields of experimental cognitive and affective neuroscience are rapidly evolving. Research in this area typically focuses on ever changing tools to investigate the most current theoretical frameworks. The same test is

rarely used in subsequent studies, tests are often developed with difficulty levels suitable for undergraduate populations, and psychometric properties are rarely established or even examined. As these fields mature, a critical step forward will be developing standardized testing procedures for the most useful measures complete with well-developed psychometric exploration. Systematic assessment of normative parameters in diverse samples from various geographical regions across varied age and educational levels will be essential for establishing the utility of newer phenotypes in large-scale family genetic studies.

Concluding Remarks

Can progress in molecular genetics lay the framework for major advances in psychiatric genetics? Advances in the development and utilization of allied phenotypes have generally lagged behind, but developments in cognitive and affective neuroscience provide a framework for substantial progress in this area over the coming decade. Revised and refined paradigms will be needed for clinical studies; base rates of deficits must be established for patient studies and followed by adequately powered family studies to evaluate the prevalence of deficits in family members as well as association with subclinical illness manifestations. Refocusing our efforts systematically will inevitably proceed more slowly than advances in molecular genetic methodologies, yet there is considerable potential for efforts to dissect clinical syndromes into neurobiologically discrete subgroups. In this manner, the field can begin to more effectively define the underlying causes of polygenetic disorders such as schizophrenia and bipolar disorder.

Importantly, this approach may be useful for bipolar disorder as well as schizophrenia. To date, a variety of factors have led to far more investigation of potential allied phenotypes in schizophrenia compared with bipolar disorder. Yet, as the field of affective neuroscience proceeds, and as persistent cognitive deficits and functional deficits even during euthymic states are recognized in bipolar patients, especially those with a history of psychosis, one can expect a significant increase in the use of the allied phenotype approach in investigations of bipolar disorder. This work may have considerable impact in reframing understanding of the boundaries and overlaps between schizophrenia and bipolar disorder in ways that may have considerable impact on clinical practice.

At first glance, neurocognitive dysfunction in bipolar probands and their unaffected relatives appear less severe than the impairments associated with schizophrenia. However, the level of cognitive deficit is more similar for individuals with schizophrenia and bipolar disorder patients with a history of psychotic symptoms. Moreover, differences in the 2 disorders with respect to severity of impairments in specific cognitive domains may vary in ways that are yet to be fully specified. Deficits in affective processes and social cognition are important potential allied phenotypes that require considerably greater research attention as these may be even more useful for defining the boundaries of schizophrenia and bipolar disorder. To advance the use of the allied phenotype approach in family research, data are needed both to establish disorder-specific allied phenotypes and to evaluate the extent to which putative allied phenotypes are linked to shared or specific genetic risk factors.

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