PCN Frontier Review

Differences in cognitive impairment between schizophrenia and bipolar disorder: Considering the role of heterogeneity

Running title: Cognitive subgroups in bipolar disorder

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Abstract

Schizophrenia is associated with significant cognitive impairment. Bipolar disorder (BP) also presents *with cognitive* deficits that are similar to, *albeit less severe* than those reported in schizophrenia. There has been controversy over whether selective deficits in social cognition or developmental trajectory of cognitive deficits can distinguish schizophrenia from BP. Also, available studies have not generally considered the potential effect of cognitive heterogeneity within both disorders on between-group differences. Current review examines the evidence on the specificity of social cognitive deficits and early neurocognitive impairment to schizophrenia and explores the overall outcome of studies investigating within and cross-diagnosis cognitive heterogeneity in schizophrenia and BP. Current evidence does not support the specificity of social cognitive impairment to schizophrenia. Available studies also suggest that cognitive impairment in premorbid and early stages is evident not only in schizophrenia but also many patients in BP. Both schizophrenia and BP have a number of cognitive subgroups including severe impairment, good functioning and one or more selective or modest impairment clusters. While both disorders are represented in each cognitive subgroup, there are significant cross-diagnostic differences regarding prevalences of individuals belonging to the severe impairment and good functioning subgroups. The individuals with schizophrenia are much more likely to exhibit severe cognitive impairment than individuals with BP and opposite true for having good cognitive functioning. Further identification of neurobiological and genetic characteristics of cognitive subgroups in major psychoses can improve the validity of diagnostic systems and can advance the development of personalized management approaches including cognitive remediation.

Key words: Cognition, schizophrenia, bipolar disorder, heterogeneity, psychosis

Cognitive impairment is a well-established and persistent feature of schizophrenia.[1-3] Cognitive deficits in schizophrenia have been recognized since the delineation of *dementia praecox* by Kraepelin. The range of cognitive deficits in schizophrenia is broad. Multiple cognitive domains including verbal and visual memory, working memory, processing speed, attention, executive functions and social cognition are impaired in schizophrenia.[2-4] Cognitive impairment in schizophrenia is clinically relevant one of the most important determinants of functional impairment observed in this disorder.[5-6] Persisting cognitive deficits and functional impairment had been traditionally considered as specific features of schizophrenia in comparison to manic-depressive psychoses. However, neither cognitive impairment nor functional deficits are specific to schizophrenia. Recent work within last two decades has clearly showed that bipolar disorder (BP) is also associated with cognitive deficits and functional impairment which are also evident in euthymic patients.[7-10] While severity of cognitive deficits is less severe in BP than schizophrenia, evidence suggests that profile of cognitive deficits are similar in both disorders.[3] Importantly, these findings contradict with other observations including evidence for relationship between BP and creativity and premorbid scholastic achivement.[11-13]

However, it can be argued that methodological issues such as the use of cross-sectional assessment, recruitment of patients with chronic illness and lack of information about premorbid cognitive development in most studies can limit our ability to show potential cognitive differences between schizophrenia and BP. One argument is specificity of early cognitive deficits to schizophrenia.[14-15] It has been argued that cognitive impairment is evident in prodromal stage and first-episode of schizophrenia but not in BP. Another notion is the specificity of cognitive deficits which are critical for communication and social functioning (social cognition) to schizophrenia. Theory of mind and other social

cognitive deficits (compared to non-social cognitive deficits) has been suggested to be more specific to schizophrenia.[16] Other authors argued that difficulties in premorbid intellectual development can separate schizophrenia from BP.[17-18] Finally, it is important to note that all of these three arguments about potential differences between schizophrenia and BP are based on the comparison between two distinct disorders. There is a substantial heterogeneity in both disorders. Neurobiological and clinical evidence also suggest considerable overlap between schizophrenia and BP.[19] Familial and molecular genetic studies suggested that there are susceptibility genes common to both disorders. However, it is important to note that familial and genetic studies also suggest that there is also evidence for schizophrenia and BP specific genetic susceptibility factors.[20-21] Available studies have also provided evidence suggesting that shared susceptibility genes can impair neurodevelopment and cognition.[22-23] Therefore, it is expected that there should be considerable heterogeneity of cognitive performances within both disorders which can also affect the extent of differences between both diagnostic categories. The majority of available neurocognitive studies has not considered the relationship between cognitive impairment and heterogeneity within both disorders. In the first part of the current article, studies in schizophrenia and BP were reviewed to discuss the evidence regarding arguments about the specificity of early neurocognitive impairment, social cognitive impairment, and premorbid deficits in the development of intellectual abilities to schizophrenia. In the second part of the article, evidence for cognitive heterogeneity within schizophrenia and BP and the role of heterogeneity in explaining contradictory findings in previous studies were explored.

1- Evidence for specific differences between schizophrenia and BP

Specificity of social cognitive deficits to schizophrenia in comparison to BP

Social cognitive impairment in schizophrenia might be particularly important contributor of functional impairment.[24-26] Deficits in emotion recognition and theory of mind (ToM) are well-established findings in schizophrenia.[27-29] It was suggested that social cognitive impairment might be more specific than non-social cognitive impairment to schizophrenia. In a recent study, Lee et al[16] found that BP patients showed less impairment on social relative to non-social cognitive performance, whereas schizophrenia patients showed more impairment on social relative to non-social cognitive performance. It might be argued that specificity of social cognitive impairment to schizophrenia can explain relatively severe functional impairment observed in schizophrenia compared to BP. However, there is also emerging evidence for social cognitive deficits in BP.[30] Similar to findings of neurocognitive studies, deficits with medium effect sizes in social cognition were observed in BP.[31-32] Evidence also suggests that social cognitive deficits are evident not only during mood episodes but also during remission.

A number of recent studies investigating emotion recognition and ToM have directly compared performances of schizophrenia and BP.[16,33-34] A recent meta-analysis of social cognition explored differences between schizophrenia and BP patients (Bora and Pantelis, under review). This meta-analysis found that schizophrenia patients significantly but modestly underperformed patients with BP in both facial emotion recognition (d=0.43) and ToM (d=0.60). Effects sizes for differences between schizophrenia and BP were similar for social and non-social cognitive abilities. Previous meta-analyses of neurocognitive studies comparing schizophrenia and BP have also found similar effect sizes for differences between these two disorders.[35-36] These findings suggest that differences between schizophrenia and BP on social cognitive deficits are

quantitative only and there is a significant overlap of performances of schizophrenia and BP patients both in social and non-social cognitive domains.

Cognitive impairment in early years of BP and schizophrenia

Most of the available studies that compared schizophrenia and BP included chronic patients. However, it has been suggested that cognitive impairment in BP and schizophrenia might have very different trajectories. In schizophrenia, it is well-accepted that cognitive deficits are evident in first-episode and in young adults who have a high clinical and genetic risk to schizophrenia.[37-38] It was also hypothesized that patients with BP only develop cognitive deficits during the course of illness as a result of neurodegenerative changes and cognitive deficits would be absent or very modest in first-episode BP and premorbid stages of the illness.[15,17] It has been argued that early onset cognitive impairment might be a specific feature of schizophrenia.

First-episode

Recently, a number of studies investigating cognitive impairment in BP has been conducted in first-episode BP and the most of these studies have not supported the preserved cognition argument in first-episode BP. Two recent meta-analyses of neuropsychological studies in first-episode BP have provided strong evidence for cognitive impairment in first-episode BP.[39-40] Meta-analysis of Bora and Pantelis suggested that deficits with medium to large effect sizes (d=0.36–0.83) are evident in verbal and visual memory, processing speed, sustained attention, executive functions, working memory and verbal fluency in first-episode BP.[39] Severity and pattern of such deficits in first-episode BP were similar to findings in chronic BP patients.[7-8] Same meta-analyses also found that cognitive impairment is significantly more severe in FE schizophrenia than first-episode BP but the severity of between-group differences were modest (d=0.25–0.67). This finding is similar to what is established for chronic schizophrenia and BP and suggests that there is a significant overlap between cognitive performances of FE schizophrenia and BP.

High-risk studies

Cognitive impairment is already evident in youth with clinical high risk to psychosis.[38, 41] Clinical high-risk paradigms has been used to investigate cognitive impairment in BP only in few studies. However, emerging evidence suggests that cognitive impairment is also evident in individuals at clinical risk for bipolar disorder. Melzler et al[42] reported cognitive deficits in individuals meeting risk criteria for affective psychosis. Also, the ultra-high-risk to psychosis (UHR) paradigm, which was developed to detect early phases of schizophrenia, suggested that UHR is a nonspecific risk paradigm of psychosis and a subset of UHR subjects develop BP at follow-up. Two recent studies in ultra-high risk to psychosis samples found that pre-onset neurocognitive deficits are evident in at-risk subjects who develop BP at follow-up. In the first study, Olvet et al[43] found that global cognition is significantly impaired in at-risk subjects who developed BP at follow-up. In the second study, Ratheesh et al[44] reported deficits in processing speed, executive functions and general intellectual abilities in at-risk subjects who developed BP during follow-up in comparison to healthy controls.

It is also well-established that youth with familial risk for schizophrenia have cognitive deficits which are comparable to UHR subjects in severity.[38] While number of studies investigating neurocognitive abilities in youth with familial high risk to BP is small, available evidence also suggests that cognitive impairment is evident in young relatives of individuals with BP.[45-49]

As a summary, available evidence does not support the notion of specificity of cognitive impairment in early stages to schizophrenia. Emerging evidence suggests that cognitive deficits are also evident in first-episode and at clinical and genetic risk to BP.

Differences in premorbid intellectual abilities between schizophrenia and BP

Intellectual disabilities in schizophrenia and BP

Childhood onset intellectual disabilities are overrepresented in schizophrenia

compared to healthy controls and in people with intellectual disability, psychosis is more prevalent than the general population.[50-51] Morgan et al[51] estimated the prevalence of intellectual disability in schizophrenia as 4.9%. In the same study, the prevalence of schizophrenia among individuals with intellectual disability was 4.4%.

In BP, there is less evidence for severe childhood onset intellectual deficits. Some studies have not found significantly increased the risk for BP in intellectual disability.[51] However, other evidence suggests that there might be a relationship between intellectual disabilities and risk for BP. In a recent study, intellectual disabilities were more common in children of mothers with schizophrenia and BP.[52] Also, there is some evidence suggesting a significant relationship between intellectual disability and rapid-cycling BP.[53] Some evidence also suggest that history of autism spectrum disorders, ADHD and several other syndromes characterised by intellectual deficits might be associated with not only schizophrenia but also BP.[54-56]

Premorbid cognitive deficits in childhood and adolescence in schizophrenia and BP

The existence of premorbid cognitive deficits in people with schizophrenia is well established.[57-60] In many cases, premorbid intelligence quotient (IQ) deficits and learning difficulties in childhood and adolescence precede adult schizophrenia. Evidence suggests that individuals who develop adult schizophrenia exhibit IQ deficit in their childhood (approximately 0.5 standard deviations, 33% non-overlap with controls).[57-58]

A number of studies investigating premorbid cognitive deficits which precede BP is relatively modest. Several studies have not found any evidence of premorbid cognitive impairment in BP.[61-63] However, these studies have inadequate power to detect modest deficits as the number of subjects who developed BP in most studies was small. Two of three studies which had at least 100 subjects with BP found a relationship between poor scholar achievement/cognitive function and risk for BP.[64-66] In a population-based

large national study including over 700,000 individuals, MacCabe et al[64] investigated the relationship between scholastic achievement at age 15–16 and later hospital admissions for BP (280 individuals). The individuals with the poorest grades had a nearly two-fold increased risk for bipolar disorder. In a large cohort of 200,000 male subjects conscripted into the Finnish defence forces, Tiihonen et al[65] investigated the relationship between cognitive assessment and later hospital admission for BP (100 individuals) and found relationship between cognitive impairment in visuospatial abilities and increase the risk for BP at follow-up.

Some evidence also suggests that premorbid cognitive deficits in childhood BP might precede adult BP. Seidman et al[67] showed that children (mean age=7) who will develop BP or schizoaffective, bipolar type in adulthood have cognitive deficits. The effect size of this cognitive deficit was d=0.3 and 23% children had a significant neuropsychological impairment. In the same study, the effect size for cognitive deficits in the schizophrenia group was moderately larger d=0.57 and 42% of children had a significant cognitive impairment.

As a summary, while evidence for the relationship between premorbid cognitive deficits and schizophrenia is stronger compared to BP, emerging evidence suggests that some patients with BP have also premorbid cognitive deficits. While contradictory findings exist, it seems that evidence does not overall support any of the three notions discussed in this section including specificity of social cognition, early and premorbid cognitive impairment to schizophrenia. However, it is important to note that cognitive heterogeneity within and between schizophrenia and BP can have a significant impact on findings of these studies.

2-Heterogeneity of cognitive impairment in BP and schizophrenia

Cognitive subgroups in schizophrenia and BP

Cluster analytical studies in schizophrenia have consistently found several clusters of patients based on their cognitive performances.[68-76] In these studies, a subgroup of

patients with schizophrenia were members of a neurocognitive cluster with very severe and widespread cognitive impairment. A smaller subgroup of patients was characterized with normal neuropsychological performance. The other patients in these studies have been clustered to one or more neurocognitive subgroups characterized by more moderate and selective deficits.

Relatively a small number of studies have investigated neurocognitive subgroups in BP. Several studies have categorised BP patients into cognitively impaired and unimpaired groups based on arbitrary cut-off scores.[77-78]These studies have relatively small number of BP patients included (n=50-110) and used variable cut-off scores such as scoring 1 to 2 SD below controls or scoring at or below the 5th percentile.[77-82] Findings of these studies suggest that around 40 % of patients with BP have no neurocognitive deficits at all and other patients have variable levels of cognitive deficits.[78,82] Studies using strict cut-off scores (such as 2 SD below) found that 25-30 % patients with BP have severe cognitive deficits.[79,83] At the other hand, three other studies have attempted to identify cognitive subgroups of BP with a data-driven approach (rather than arbitrary cut-off scores) using cluster analysis and latent class analysis. Burdick et al[84] have investigated 136 BP patients using hierarchical cluster analysis and found three clusters according to neurocognitive performance. These clusters included a neuropsychologically intact (30 %), selectively impaired (30 %) and globally impaired (40 %) groups. In another cluster analysis study, Lewandowski et al[73] found four clusters including a neuropsychologically normal (40 % of 73 patients with BP), and a global cognitive impairment (15 % of BP) subgroups. In this study, other BP patients were members of two different selective cognitive impairment clusters. It is important to note that there is also cognitive variability in healthy individuals. These cluster analytical studies have not investigated variability in cognitive functioning in healthy controls and cannot tell whether any of the subgroups are more specifically related to BP than controls. In a recent latent class analysis of large sample of euthymic patients with BP (n=556) and healthy controls

(n=416), there were four cognitive subgroups (good performance, severe impairment clusters and 2 groups with modest deficits in executive functions, processing speed and verbal memory) clustered based on performance of patients and healthy individuals on executive functions tests (response inhibition and reasoning/problem solving).[85] In comparison to healthy controls, a larger proportion of BP patients were members of severe impairment cluster (27 % vs 5.3 %). As a conclusion, not only schizophrenia but also, BP has several neurocognitive subgroups including neuropsychologically normal and several clusters with varying levels of cognitive deficits.

Cross-diagnostic investigation of cognitive subgroups

Cross-diagnostic data-driven approaches, such as latent class analysis and cluster analysis, can provide an opportunity to group individuals without considering their diagnoses. These methods can potentially define cognitive subgroups including the ones that are common to both disorders or unique to one of them. To date, a vast majority of available data-driven studies investigating cognitive subgroups have investigated within diagnosis rather than cross-diagnostic heterogeneity.

Only two studies have investigated cognitive subgroups using cluster analysis or latent class analysis in a cross-diagnostic sample (Lewandowski et al[73]; Bora et al[86]). Using K-means cluster analysis, Lewandowski et al[73] supported a four-cluster solution including a 'neuropsychologically normal' cluster, a globally and substantially impaired cluster, and two clusters of mixed neurocognitive profiles. Schizophrenia and BP were distributed amongst all clusters, although patients with schizophrenia were more likely to be members of global impairment than 'neuropsychologically normal' cluster (opposite for BP). In another study, Bora et al[86] has investigated heterogeneity of non-social and social cognitive functions (reasoning and decoding aspects of theory of mind) using latent class analysis. The findings of this study supported four clusters including neuropsychologically normal, severe impairment clusters, and two subgroups of mixed

neurocognitive profiles (selective impairment in social cognition (20 %) and executive dysfunction with modest deficits in social cognition (% 40)). In this study, compared to BP, a significantly larger proportion (27.8 % vs 9.3 %) of schizophrenia patients were members of severe impairment and smaller percentage (9.3 % vs 25.6 %) of schizophrenia patients were included in cognitively normal subgroup. Importantly, an equal proportion of patients with schizophrenia and BP were members of mixed neurocognition clusters (approximately 60 % from each of the two groups).

Good cognitive functioning and premorbid and post-onset characteristics in BP and schizophrenia

Many patients with BP and a small minority of patients with schizophrenia members have normal or supranormal cognitive abilities. The fact that relatively large proportion of patients with BP have good cognitive skills is important for explaining observations suggesting a relationship between BP and creativity and premorbid scholastic achivement.[11-13] It is likely that a neurobiologically distinct subtype of BP might be characterized by normal neurodevelopment and cognitive functioning and it can be hypothesised that individuals in this subgroup of BP would outperform many healthy controls in scholar achievement thanks to the advantage of some temperamental characteristics related to BP (i.e. goal-directed, positive, approach).[13] Also, the combination of bipolar disorder-related temperamental characteristics and the absence of developmental cognitive impairment can explain the association between artistic/scientific achievement and creativity and bipolar diathesis.[12,87] It is important to note that there have been some conflicting results in studies investigating the relationship between above average scholar achievement/intellectual abilities and risk for BP.[63,66,88-92] However, two large conscript studies provided strong evidence for the relationship between risk for BP and above average scholastic achievement and good

premorbid cognitive functioning. Tiihonen et al[65] clearly showed that increased risk for BP was significantly associated with good performance in arithmetic abilities. MacCabe et al[64] reported the students with the best grades had a nearly four-fold increased risk for BP. There is limited evidence for clinical differences between BP patients with good cognitive function and others cognitive subtypes. Occupational functioning has been found to be significantly better in cognitively normal subgroup in Burdick et al.[84] Smaller proportion of patients with schizophrenia has normal or near-normal cognitive functions.[93-94] Schizophrenia patients in this group might have better premorbid functioning.[95] However, unlike BP, the evidence does not suggest a relationship between risk for schizophrenia and scholastic achievement. This is an apparent striking difference with schizophrenia and BP.

Severe cognitive impairment and premorbid and post-onset characteristics in BP and schizophrenia

Many individuals with schizophrenia and a sizeable minority of individuals with BP are included in cognitive subgroups of patients with severe and widespread cognitive impairment. In schizophrenia, patients in cognitive subgroups characterized by severe deficits might have higher negative symptom ratings.[96] Schizophrenia patients in severe impairment cognitive subgroup might have more brain imaging abnormalities compared to schizophrenia patients with near-normal cognition.[97-98] Emerging evidence also suggests that there might be specific genetic risk factors for schizophrenia cognitive subgroup with severe impairment.[96,99]

A sizeable minority of patients with BP have also severe cognitive deficits comparable to schizophrenia. Also, the risk for BP is not only associated with good scholastic achievement but also with low premorbid cognitive functioning and scholastic underachievement. Overall these findings suggest a U-shaped relationship between

premorbid cognitive impairment and risk for BP in which both poor and good premorbid cognitive/scholar functioning predict BP in adulthood and risk for BP. No studies have investigated neurobiological and genetic correlates of membership to BP subgroup with severe cognitive deficits. However, it has been hypothesized that severe cognitive deficits in BP might be evident only in individuals who share common genetic risk factors with schizophrenia.[13] It can be argued that BP associated with genetic risk factors with schizophrenia (BP-S) might have similar trajectory of cognitive development to schizophrenia and cognitive development in other BP (BP-NS) patients might be normal (Figure-1).

----------*Figure 1..... Aproximately here.....*

As a summary, evidence suggests that there are three to four cognitive subgroups within both schizophrenia and BP including cognitively normal and severe impairment clusters. Cognitive heterogeneity might have an important role in explaining contradictory findings for differences between schizophrenia and BP in both disorders. For example, studies who recruited a higher proportion of individuals with schizophrenia from severe cognitive impairment cluster or included a higher proportion of BP patients from good cognitive performance subgroup are likely to find more significant differences for social and non-social cognition between schizophrenia and BP including first-episode, prodromal and premorbid stages.

Conclusion

Neuropsychological studies investigating differences between schizophrenia and BP have reported conflicting findings, however, their findings have not supported the specificity of cognitive or social-cognitive deficits to schizophrenia including premorbid and early stages of both disorders. Neuropsychological studies treating schizophrenia and bipolar disorder as two distinct and cognitively homogenous diagnostic groups are not likely to

show strong evidence for between-group difference. It is important to acknowledge that there are multiple cognitive subgroups and individuals from each diagnostic categories are members of each of these clusters. Differences between schizophrenia and BP are driven by relative proportions of individuals in cognitive clusters. Defining cognitive subgroups within schizophrenia and BP can have implications for management (i.e target groups for cognitive rehabilitation).

It is also important to mention a number of limitations in the available studies investigating cognitive heterogeneity in schizophrenia and BP. Many of the studies, especially in BP have used arbitrary cut-off scores rather than data-driven methods. Also, cluster analysis has been the method of choice in most data-driven studies. However, other methods, including latent class analysis can have advantages over cluster analysis including yielding a smaller misclassification rate, its ability to choose the number of clusters more objectively based on the tests of goodness of fit, being based on a probabilistic model that describes the distribution of original research data instead of finding clusters with chosen distance measures that are theoretical or arbitrary.[100] Another limitation is that cognitive heterogeneity has been investigated mostly in chronic samples with BP and schizophrenia. Therefore, there is a need for further studies investigating cognitive heterogeneity in early and premorbid stages of the disorder. An important limitation is the cross-sectional nature of available studies and there is a need for the stability of neurocognitive clusters in schizophrenia and BP. Also, sample sizes of many of the available studies were small and clinical and functional correlates of cluster membership need to be further investigated. Future studies investigating neurobiological, brain imaging and genetic factors related to specific cognitive subgroups in schizophrenia and BP can be helpful in developing a more valid diagnostic system of major psychoses.

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Dr. Bora has nothing to disclose.

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Figure 1 Trajectory of cognitive development in schizophrenia, BP associated genetic risk factors with schizophrenia and other BP patients