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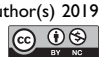
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The Core Deficit of Classical Schizophrenia: Implications for Predicting the Functional Outcome of Psychotic Illness and Developing Effective Treatments

Le déficit de base de la schizophrénie classique : implications pour prédire le résultat fonctionnel de la maladie psychotique et développer des traitements efficaces

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Abstract

Many people suffering from psychotic illnesses experience persisting impairment of occupational and social function. Evidence assembled since the classical description of schizophrenia over a century ago indicates that both disorganization and impoverishment of mental activity are associated with persisting impairment. Longitudinal studies of young people at risk of schizophrenia reveal that both mental impoverishment and disorganization predict poor long-term outcome. These clinical features are related to cognitive impairments. Evidence from brain imaging indicates overlap in the brain abnormalities implicated in these phenomena, including impaired function of long-range connections between sensory cortex and the salience network, a network engaged in recruiting cerebral systems for processing of information salient to current circumstances.

The evidence suggests that the common features underlying these two groups of symptoms might reflect a core pathological process distinguishing nonaffective from affective psychosis. This pathological process might therefore justifiably be designated the "core deficit" of classical schizophrenia. To develop more effective treatments to prevent persisting disability, we require the ability to identify individuals at risk at an early stage. Recent studies provide pointers toward effective strategies for identifying cases at risk of poor outcome. Accumulating evidence confirms that appreciable potential for neuroplastic change in the brain persists into adult life. Furthermore, brain function can be enhanced by targeted neuromodulation treatments. We now have promising tools not only for investigating the psychological and neural mechanisms that underlie persisting functional impairment but also for identifying individuals at risk and for harnessing brain plasticity to improve treatment.

Abrégé

De nombreuses personnes souffrant de maladies psychotiques éprouvent une déficience persistante de la fonction professionnelle et sociale. Les données probantes assemblées depuis la description classique de la schizophrénie il y a plus d'un siècle indiquent que la désorganisation et l'appauvrissement de l'activité mentale sont associés à une déficience persistante. Les études longitudinales de jeunes personnes à risque de schizophrénie révèlent que tant l'appauvrissement que la désorganisation mentale prédisent de mauvais résultats à long terme. Ces traits cliniques sont liés aux déficiences cognitives. Les données probantes de l'imagerie cérébrale indiquent un chevauchement dans les anomalies du cerveau impliquées dans ces phénomènes, notamment la fonction déficiente des connexions longue portée entre le cortex sensoriel et le réseau de

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saillance, qui s'occupe de recruter les systèmes cérébraux pour traiter l'information digne d'attention dans les circonstances actuelles.

Les données probantes suggèrent que les traits communs sous-jacents de ces deux groupes de symptômes pourraient refléter un processus pathologique de base distinguant la psychose non affective de la psychose affective. Ce processus pathologique pourrait donc être désigné de façon justifiable « déficit de base » de la schizophrénie classique. Afin de développer des traitements plus efficaces et prévenir la déficience persistante, nous réclamons la capacité d'identifier les personnes à risque à un stade précoce. Des études récentes offrent des pistes de stratégies efficaces pour identifier les cas à risque de mauvais résultats. L'accumulation de données probantes confirme que le potentiel appréciable de changement neuroplastique dans le cerveau persiste dans la vie adulte. En outre, la fonction cérébrale peut être améliorée par des traitements de neuromodulation ciblés. Nous avons dorénavant des outils prometteurs non seulement pour rechercher les mécanismes psychologiques et neuronaux qui sous-tendent la déficience fonctionnelle persistante, mais également pour identifier les personnes à risque et exploiter la plasticité du cerveau afin d'améliorer le traitement.

Keywords
schizophrenia, psychosis, outcome, disorganization, psychomotor poverty, negative symptoms, core deficit, salience network, neuroplasticity, treatment

Background

A substantial number of people suffering from psychotic illnesses continue to experience persisting disability with impaired occupational and social function despite treatment with antipsychotic medication. Developing a better understanding of the processes that lead to persisting disability is therefore a high priority. The seeds for understanding these processes were sown in the classical descriptions of schizophrenia by Kraepelin[1] and Bleuler.[2] Subsequent investigations have delineated the mental symptoms that are associated with persisting disability, and brain imaging techniques have shed light on the neural features associated with persisting disability.

Kraepelin[1] provided the foundation for the classification of psychotic illness by distinguishing dementia praecox from manic-depressive insanity. His choice of the title "dementia praecox" implied a persisting disruption of mental activity with onset in young adult life. In contrast, manic-depressive illness is characterized by transient episodes of mood disturbance, with near-normal function between episodes. Kraepelin[3] proposed that the core psychological processes of dementia praecox were disjointed and weakened volition. Bleuler's[2] conception was similar. He saw the core process as "fragmentation of mind" and therefore renamed dementia praecox as "schizophrenia." He described the fundamental symptoms that he considered were present in all cases and at all phases of illness. Prominent among these were looseness of associations and affective blunting. By looseness of associations, he meant the disruption of the threads that bind together the various aspects of thinking. He claimed that looseness of associations was not only fundamental but primary, insofar as other symptoms arose from it.

Multiple Pathological Processes

Following the introduction of dopamine-blocking antipsychotic medication, it became clear that antipsychotics were effective in treating delusions and hallucinations[4] yet less effective in treating negative symptoms that reflect a diminished amount of mental activity. Meanwhile, the introduction of X-ray computed tomography revealed that some patients with schizophrenia had enlarged cerebral ventricles.[5] This led Crow[6] to propose two distinct pathological processes in schizophrenia: dopamine overactivity generating positive symptoms such as delusions and hallucinations and structural brain damage causing negative symptoms.

The concept of loosening of associations, which Bleuler considered was both fundamental and primary, did not fit neatly into Crow's dichotomy. Crow[6] regarded disorder of thought form as a positive symptom on account of its moderate response to antipsychotic medication. However, subtle formal thought disorder, manifest as vague and wandering speech, is poorly responsive to antipsychotic medication.[7] A potential resolution to the status of loose associations was provided by studies employing factor analysis of the symptoms of chronic schizophrenia.[8-10] These studies segregated the symptoms into three syndromes: reality distortion (delusions and hallucinations), disorganization (positive formal thought disorder, inappropriate affect, bizarre behavior), and core negative features (blunted affect, poverty of speech, decreased spontaneous movement). In light of the fact that the term negative symptoms is sometimes used to describe a range of clinical features including attentional impairment[11] that might reflect either disorganized or diminished mental activity, Liddle[9] introduced the term psychomotor poverty to describe the core negative features that reflect a diminished amount of mental activity. Liddle found that both psychomotor poverty and disorganization were associated with impaired role function. Subsequent studies[12] have reported similar findings.

Liddle and colleagues found that in cases with persistent stable symptoms, each of the syndromes was associated with a specific pattern of cognitive impairment, especially executive functions,[13] and a specific aberrant pattern of regional brain activity.[14] Subsequently, numerous brain imaging

studies have investigated the relationship between clusters of symptoms, cognitive function, and brain structure and function in schizophrenia. Diverse cognitive impairments have been reported. The effect size for impaired performance on the Digit Symbol Substitution Test, which assesses speed of processing, attention, associative memory, working memory, and executive functioning,[15] has been shown to be large in schizophrenia.[16] Imaging studies have revealed widespread abnormalities as illustrated in the study of brain structure in a large sample of cases by Nenadic et al.[17] That study confirmed an association between psychomotor poverty and abnormality of left lateral prefrontal cortex, and between disorganization and abnormality of right inferolateral prefrontal cortex. Other brain regions were also implicated. Notably, Nenadic found that both psychomotor poverty and disorganization were associated with reduced gray matter in insula cortex and nearby lateral frontal cortex, bilaterally.

Studies using diffusion tensor imaging to investigate white matter integrity and magnetization transfer ratio to examine myelination demonstrate abnormalities in long tracts including the inferior occipito-frontal fasiculus.[18] In particular, abnormal myelination in posterior parts of that fasiculus is prominent in patients with impaired Digit Symbol Substitution performance. Consistent with the abnormalities in gray and white matter structure extending from occipital to frontal cortex, there is evidence that reduced effective functional connectivity from visual cortex to insula and insula onward to lateral frontal cortex is associated with persisting symptoms and disability.[19]

Using magnetoencephalography, Robson et al.[20] demonstrated that persisting symptoms, cognitive impairment, and poor role function are associated with attenuated post-movement beta rebound (PMBR) in sensorimotor cortex. PMBR is an electrophysiological feature associated with reestablishment of communication between motor cortex and diverse cerebral regions after a movement and has been proposed to reflect the process of maintaining or adapting the brain's internal model that guides movements based on a prediction of the consequences of those movements.[21]

Factor Analyses of Symptoms in Early Phase Psychotic Illness

The results of factor analysis depend on the range of symptoms entered into the analysis and on the composition of the patient sample. McGorry et al.[22] reported a factor analysis of a large sample of early phase cases of psychosis, including both affective and nonaffective psychosis. They found four factors reflecting depression, excitation, reality distortion (delusions and hallucinations), and "Bleulerian" symptoms. The Bleulerian factor included symptoms reflecting both disorganized and impoverished mental activity. While depression and excitation are characteristic of affective psychosis and reality distortion is common to both affective and nonaffective psychosis, it is plausible that the Bleulerian symptoms reflect a process that is more specific to nonaffective psychoses. While mental impoverishment and disorganization load on single factor in the early phase of illness, impoverishment of mental activity becomes more prominent as the illness proceeds,[23] and the distinction between impoverishment and disorganization becomes more accentuated.

Nonclinical and At-Risk Populations

A potentially fruitful approach is investigation of relationships between schizotypal personality characteristics in nonclinical populations and in young people at risk of developing psychosis, using questionnaires such as the Schizotypal Personality Questionnaire (SPQ).[24] Meta-analysis and subsequent confirmatory factor analysis[25] reveal three dimensions in nonclinical populations: interpersonal ("negative" features), disorganization, and cognitive/perceptual. These map plausibly on the three syndromes characteristic of established schizophrenia. In a 10-year follow-up study of adolescents assessed using the SPQ, Dominguez et al.[26] found that interpersonal deficits (negative features) and disorganization predict subsequent conversion to overt psychosis and secondary functional impairment. This finding not only reveals interpersonal deficits and disorganization as risk factors for poor functional outcome but also implies that impoverishment and/or disorganization are associated with a predisposition to the reality distortion typical of overt psychosis.

A comparable association between Bleulerian symptoms observed prior to overt psychosis and poor long-term outcome is also demonstrated by studies of individuals considered to be at ultra-high risk (UHR) for psychosis. A 6-year follow-up of 41 UHR adolescents by Ziermans et al.[27] revealed that disorganized symptoms, scored according to the Scale of Prodromal Symptoms, were highly predictive of poor functional outcome.

In a longitudinal study of young people identified as exhibiting the "at risk mental state," Koutsouleris et al.[28] examined the relationship between brain structure quantified using voxel-based morphometry and functional outcome at 12 months. They found that in comparison with individuals exhibiting good functional outcome, those with poor functional outcome had relatively lower gray matter density in anterior cingulate cortex, insula, and temporo-parieto-occipital regions and relatively increased gray matter density in cerebellum and dorsolateral prefrontal cortex.

With regard to electrophysiological features, schizotypal features reported by nonclinical individuals are also associated with attenuated PMBR.[29] Furthermore, consistent with the findings in established illness,[20] this association is specifically accounted for by schizotypal features reflecting disorganization and impoverishment of mental activity. Thus, across a spectrum ranging from nonclinical individuals to established schizophrenia, similar neural features are associated with impoverishment and disorganization of mental activity.

The Core Deficit of Schizophrenia

In summary, impoverishment and/or disorganization are not only associated with poor functional outcome in established illness but also predict subsequent functional impairment in both UHR cases and in nonclinical individuals with schizotypal features. In early phase illness, these two groups of Bleulerian symptoms tend to coexist but nonetheless segregate from affective symptoms and from delusions and hallucinations,[22] suggesting that the common features underlying these two groups of symptoms might reflect a cardinal pathological process distinguishing nonaffective from affective psychosis. Furthermore, despite some differences in their association with brain activity, these two groups of symptoms share many features of brain structure and function. The degree to which the shared variance between impoverishment and disorganization predicts persisting disability is an issue requiring further investigation.

This evidence suggests that mental impoverishment and disorganization are manifestations of a core deficit that distinguishes nonaffective from affective psychosis and are associated with impaired cognitive function and persisting impairment of role function. This putative core deficit includes the features that were at the heart of the classical concept of schizophrenia described by Kraepelin and Bleuler.

Both Kraepelin and Bleuler implicitly recognized that the core problem in schizophrenia transcends deficits in specialized domains of mental activity and consists of impaired ability to initiate and/or coordinate mental activity. Effective function of the brain, and therefore of the mind, requires integration between specialized modules, mediated by a network of neural connections. Disruption to the integration of mental activity that is facilitated by this network of connections between brain regions is a plausible candidate for the defining feature of classical schizophrenia.

Some specific brain regions are likely to play particularly important roles. A key role is facilitating the orderly recruitment of appropriate brain circuits (and mental processes) to deal effectively with the current demands. The brain network often termed the salience network, comprising insula and anterior cingulate cortex, plays a key role in the required orderly recruitment.[30] It is therefore noteworthy that Nenadic et al.[17] demonstrated that diminished gray matter in insula cortex is associated with both impoverished and disorganized mental activity in schizophrenia. Nonetheless, as indicated in the evidence reviewed above, both the brain abnormalities associated with persisting disability and impaired role function are much more extensive, embracing circuits extending from occipital to frontal lobes.

In conclusion, current evidence points toward a pervasive but subtle problem of communication within and between brain networks, which occurs with a spectrum of severity and produces symptoms indicating impoverishment and/or disorganization of mental activity. Evidence indicates that these symptoms are associated with disordered connectivity in distributed brain circuits. This broad dimension of psychopathology might therefore justifiably be designated the "core deficit" of classical schizophrenia.

Assessment of Disorganization and Impoverishment of Language

Reliable and sensitive assessment of mental disorganization is difficult. To address this challenge, Liddle et al.[31] developed the Thought and Language Index (TLI), a sensitive scale for assessing subtle language disorders. An alternative approach is provided by automated speech graph analysis of the connectedness of speech samples.[32] In a sample of individuals with early phase of psychotic illness, comparison of speech graph attributes of the patients' speech with the attributes of graphs generated by randomly reordering the words predicted a diagnosis of schizophrenia 6 months later.[33] Furthermore, in those early phase cases, disorganization of speech derived from speech graph attributes was correlated with severity of negative symptoms. Palaniyappan et al.[34] demonstrated in a sample of cases with established illness that speech graph attributes reflecting disorganization of speech were correlated with TLI scores and also with occupational and social dysfunction and with abnormal brain structure and connectivity.

In a different approach to the automated processing of speech, Bedi et al.[35] applied machine learning to data derived from both latent semantic analysis and tagging parts of speech, to identify a classifier of psychosis in a sample of high-risk cases. The discriminating variables were minimum semantic coherence, shortened sentence length, and a decrease in the use of pronouns to introduce dependent clauses. This classifier outperformed clinical ratings in predicting onset of psychosis.

Thus, several different approaches to assessment of the organization of speech in individual at high risk, or in the early phase of illness, provide measures that predict subsequent overt psychosis and/or impaired role function in the established phase.

Enhancing Outcome

Although Kraepelin's[1] term dementia praecox implied progressive deterioration, that is not the inevitable course. A recent meta-analysis of studies of first episode psychosis found that over a mean follow-up duration of 7.8 years, recovery occurred in 38%.[36]

Despite concern that brain structure might be relatively fixed in adult life, recent evidence reveals that the brain is more plastic that hitherto believed. Repeated practice of a motor skill such as juggling leads to increases in gray matter[37] and enhanced integrity of white matter[38] in brain circuits engaged in the relevant skill. Similar effects can be produced by practicing cognitive tasks.[39]

In schizophrenia, cognitive training produces significant but relatively small enhancement of performance.[40]

Enhancement of relevant brain structure and function might be achieved more effectively by using either pharmacological or electrophysiological modulation to promote an optimum balance of excitatory and inhibitory activity within relevant brain circuits during training. In stroke rehabilitation, use of transcranial Direct Current Simulation (tDCS) during skill training enhances the efficacy of training.[41] With regard to the possibility of enhancing function of the salience network, which the evidence considered above indicates is implicated in the core deficit, it is noteworthy that tDCS applied so as to influence the salience network resulted in improved performance during an inhibitory control task in a nonclinical sample.[42]

If we are to better understand the processes that lead to occupational and social dysfunction in psychotic illness, we should focus attention on identifying the psychological and neuronal mechanisms responsible for the impoverishment and disorganization of mental activity that constitute the putative core deficit. We now have promising tools for investigating these psychological and neural mechanisms, and there is accumulating evidence that it is plausible to harness brain plasticity for therapeutic benefit.

While the first purpose of delineating the clinical features associated with risk of persisting symptoms and disabilities is to contribute to better understanding of pathophysiological mechanisms and to improve management, the proposal that the Bleulerian features constitute the core deficit of classical schizophrenia has implications for diagnostic terminology. Consolidation of the evidence that Bleulerian features have practical prognostic implications would indicate that adding a modifying label to the term schizophrenia (e.g., "classical" schizophrenia) might improve the prognostic value of the diagnostic description. However, it might well be argued that any radical change in diagnostic labeling should be deferred until reliable brain correlates have been firmly established. It is also noteworthy that developments in computational techniques for predicting outcome based on clinical and brain imaging data (e.g., Koutsouleris et al.[28] and Viviano et al.[43]) offer the prospect of combining diverse types of data to enhance estimation of prognosis and to refine diagnosis.

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