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From research of mental disorders to clinical application — lessons from diabetes

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Learning from other disorders — analogy to diabetes

We are facing a crisis of translation of research into clinical application in psychiatry. Most diagnoses are thus still observer-based in clinical practice (rather than being based on objective neuronal and/or psychological markers). Moreover, therapy is often based on trial and error, hence the look toward research that may yield biomarkers for both objective diagnosis and therapeutic monitoring and guidance beyond trial and error.

However, most research, including brain imaging and molecular, genetic and biochemical research, has not yet led to biomarkers for clinical diagnosis and therapy. We seem to miss some key ingredient that links basic pathophysiological mechanisms to the various symptoms in a symptom- or disease-specific way. I here propose that the missing link is what the early psychiatrist Eugène Minkowski described as basic or generative disturbance¹: rather than being the main cause, the basic or generative disturbance operates at an intermediate level, which is key in generating those pathophysiological mechanisms that drive and lead to the various psychopathological symptoms. Let me first draw an analogy and comparison of mental disorders with another disorder, diabetes mellitus (DM).

Complexity of symptoms — co-occurrence and comorbidity

How can we understand the symptoms of DM? We know the basic generative disturbance, namely the decreased production of insulin by the pancreas, which in turn leads to increased glucose. Note that insulin decrease may be just 1 intermediate cause on the pathway from the molecular level to the symptom level in DM, where a variety of different causes can modulate insulin (e.g., primary v. secondary diabetes reflecting the heterogeneous nature of DM on the causal level). As insulin decrease can be traced to molecular and even genetic changes, we consider decreased insulin

(or increased resistance to insulin, which I include herein under the concept of decreased insulin) as the basic or generative disturbance of DM. Insulin modulates the level of glucose, including its distribution in the whole body, which in turn generates the various symptoms throughout the whole body from the feet (e.g., gangrene) to the eyes (e.g., retinopathy) and even the brain (e.g., loss of consciousness in hypo- and hyperglycemic states).

Imagine now if we did not know that the various bodily symptoms in DM are all related to glucose and its modulation by insulin. We would probably assume that, as the symptoms are located in dissimilar body parts, they must be related to different underlying disturbances and disorders. Only their clinically often observed co-occurrence would make us think that they may be related in some as yet unclear way. Even the classification of DM as a single disease category would then be debated, raising several questions: Do the different symptoms belong to a single disorder? Are they symptoms of a syndrome that can be traced to different underlying disorders? Or do we need a more sophisticated network approach to understand them?

Does this situation sound familiar? This exactly describes the current situation in psychiatry. We know the symptoms and we know that different symptoms may co-occur (e.g., symptom coupling).² For instance, major depressive disorder (MDD) is characterized not only by mood changes, but also by major cognitive, sensory, motor and somatic symptoms. Analogously so in anxiety disorder (AD). Here the affective symptoms are accompanied, again, by major somatic and cognitive changes. The same holds for schizophrenia and basically almost all other major psychiatric disorders.

One can thus speak of what I describe as “co-occurrence of symptoms” just as we can observe various bodily symptoms in DM: in the same way the whole body is affected in DM, so analogously the whole brain with all its functions is altered in mental disorders. To make matters worse, there is no single symptom that is specific to a particular disorder; they can all occur in several disorders. This co-occurrence can be described as the “comorbidity of symptoms.” Accordingly,

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as in DM, mental disorders confront us with a symptom complexity including both co-occurrence and comorbidity.

Co-occurrence of symptoms

Where and how does such co-occurrence of symptoms come from? In the case of DM, the answer is easy: it comes from elevated glucose levels as the manifestation of decreased down-modulation by insulin. In contrast, we do not yet know the answer to this question as it pertains to mental disorders. We may have explanatory models for single symptoms like auditory hallucination and delusions, but their co-occurrence across the different domains (e.g., affective, cognitive, sensory, motor, somatic-vegetative) remains elusive. So far, we have no pathophysiological or psychopathological models to explain such co-occurrence of symptoms.

This leads us back to the notion of the basic generative disturbance. The basic disturbance in DM is the decreased insulin production by the pancreas, which leads to the elevated glucose level. That, in turn, is distributed all over the body, inducing co-occurrence among the different symptoms all over the body. This pathophysiological chain of events is exactly what we do not know in the case of mental disorders.

Global topographic reorganization of the brain

What do we currently know? We know, for instance, that different neural networks in the brain such as the salience network, default mode network (DMN) and sensory networks are affected in various psychiatric disorders like MDD.³ We also know that these different networks are related to different functions, including affective, cognitive, sensory, motor and somatic functions. Changes in these networks thus lead to changes in their respective functions, which manifest in the respective psychopathological symptoms. But why do the different symptoms co-occur?

Do the network alterations co-occur in an intrinsically and systematically organized topographic way? This seems to be the case in both MDD³ and depressive bipolar disorder (BD)⁴: hyperactivity in the DMN co-occurs here with decreased activity in the sensorimotor network (SMN), which, symptomatically, leads to the co-occurrence of increased self-focus with ruminations and psychomotor retardation.^{3,4} One may even be more radical and propose a global topographic reorganization or remapping of the whole brain in mental disorders like MDD.

Global topographic reorganization of brain and mind in MDD

A global topographic view is supported by recent observations of an abnormal whole brain spatial distribution or representation (e.g., topography of global brain activity in MDD).^{3,5} There is strong evidence that primary sensory regions like the visual cortex exhibit decreased representation of global neural activity, leading to impairment in

visual perception.^{6,7} That goes along with corresponding increases in the representation of the global activity in higher-order transmodal regions like the DMN, leading to increased self-focus and rumination.^{3,5} Together, these findings support the assumption of topographic reorganization (or remapping) of the whole brain in MDD.

Such topographic reorganization of the whole brain corresponds well to the reorganization of the mind or psyche in MDD. This is, for instance, manifest in an extreme shift toward higher-order cognitive functions like increased self focus, rumination and emotional attention^{5,8} at the expense of lower-order sensorimotor function like psychomotor retardation and impaired visual perception.⁶ Accordingly, the global topographic reorganization of the brain may translate into a somewhat corresponding global reorganization of the psyche or mind; that is, a re-mapping of the relationships between the various functions of the brain (e.g., social, cognitive, motor, sensory, affective, somatic).

Importantly, these observations enable us to advance in our comparison with DM. The brain's global topographic reorganization may take on the role of glucose in the case of mental disorders. In the same way that changing levels in glucose affect the whole body, the topographic reorganization affects all regions/networks throughout the brain, including all its various functions (e.g., sensory, affective, cognitive, motor, social, self, somatic-interoceptive).

In sum, we are tentatively able to associate the "glucose of mental disorders" with the brain's global topographic reorganization across its different regions/networks. Like glucose exerts its effects all over the body, the topographic reorganization operates throughout the whole brain changing the balances between its different regions/networks — this is manifest in the co-occurrence of symptoms. Topographic reorganization may thus provide the link or connection of brain and mind (i.e., their "common currency").⁹⁻¹¹

Basic generative disturbance

But where does such global topographic reorganization come from, and how? This leads us back to the question pertaining to the "insulin of mental disorders," the basic generative disturbance: what generates the changes in the networks distributed throughout the whole brain? Rather than a single specific region or network, the basic generative disturbance must operate on a deeper level than the regions/networks themselves, just as insulin operates on a more basic and deeper level than glucose.

Various molecular, genetic, biochemical and cellular changes have been observed in mental disorders. However, this targets more the causes of mental disorders, analogous to the causes of the insulin decrease in DM. As distinguished from its underlying causes, the decrease in insulin takes on an intermediate role between the molecular, genetic and cellular causes of DM on the one hand and the glucose-based symptoms on the other hand. Similarly, we assume that the basic generative disturbance of mental disorders is "sandwiched" between the various genetic, molecular, biochemical

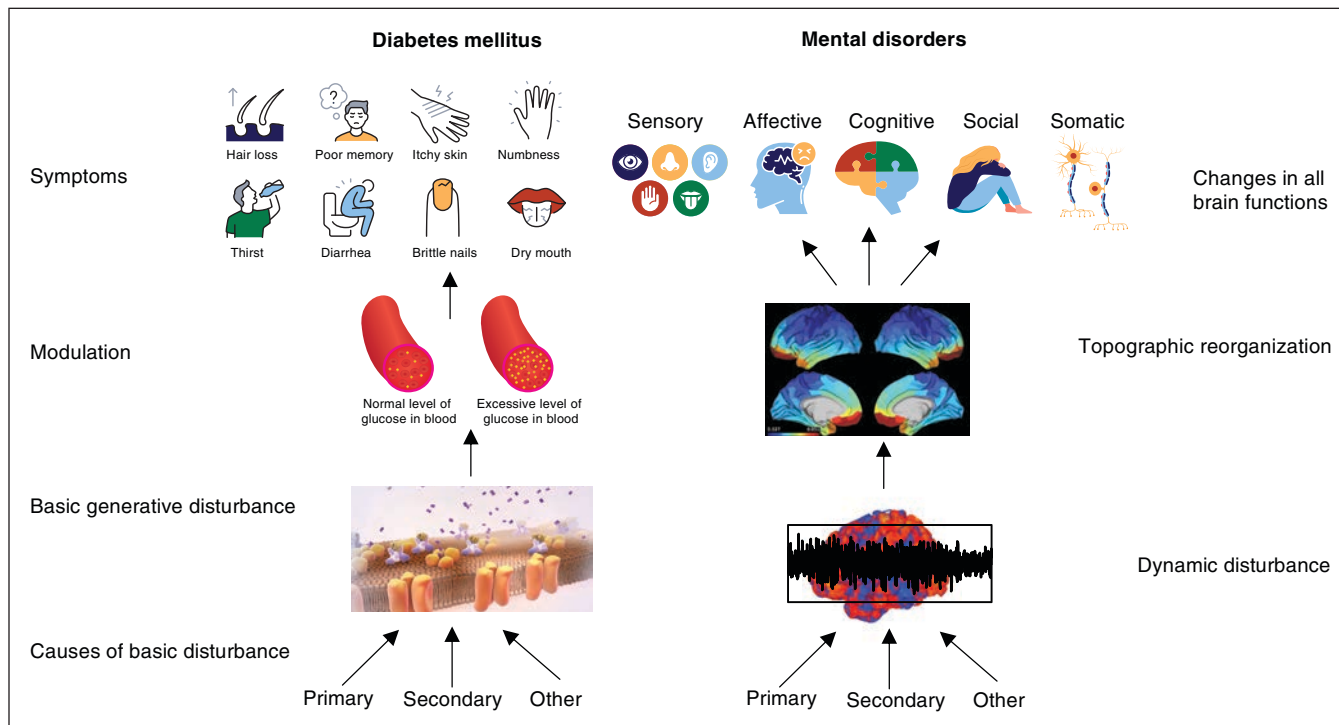


Figure 1: Comparison of diabetes mellitus and mental disorders.

and cellular causes on the one hand and the topography-based symptoms on the other hand (Figure 1).

What is the basic generative disturbance in mental disorders that, on the one hand generates the symptoms and on the other hand provides the link to their underlying cellular, molecular, biochemical and genetic causes? We currently do not know. This leads us to the temporal domain, the dynamics that refer to the pattern of change over time.

Albeit tentatively, we suppose that changes in the brain's dynamics constitute the basic disturbance in mental disorders. Just like changes in insulin modulate glucose and thereby generate the various DM symptoms, changes in the brain's dynamics modulate its topographic reorganization, which in turn generates the co-occurrence of psychopathological symptoms. To make this more specific, let us return to our example of MDD. We suppose that the basic disturbance in MDD consists of a speed disturbance featured by decreased speed, with abnormal slowness in information processing throughout both the whole brain and its various psychological functions.

Is depression a basic speed disturbance?

The hypothesis that MDD is indeed a speed disturbance is supported by various findings. Thoughts in MDD, which can be measured through their degree of change over time, are too slow (e.g., thought dynamic resulting in rumination).⁸ Visual perception and their underlying visual cortical regions are also too slow,^{6,7} and the same holds for movements and the motor cortex leading to psychomotor retardation and, in extreme cases, to catatonia.^{2,10} Even affect and mood are too slow, showing decreased changes over time.¹² Additional support also

comes from the perception of time: patients with MDD report increased slowness, decreased changes and abnormally long durations in their inner time consciousness, which neurally is related to decreased change (e.g., neural variability in the motor cortex that mediates inner time speed perception).^{13–16}

Does the brain also show abnormal slowness in its neural activity in MDD? Recent studies do indeed support such a hypothesis. The visual and motor cortex remain insensitive to especially fast stimuli, as manifest in decreased response without any differentiation from slow stimuli.^{6,7,17} Increased slowness of neural activity can already be observed during the resting state of MDD, where it, modulating topographic reorganization toward the DMN, leads to increased self-focus and ruminations.^{3,5,8,15,18}

Together, these findings strongly support the assumption of a basic dynamic disturbance in MDD, namely decreased speed with abnormal slowness in information processing. Just as insulin modulates glucose, the basic dynamic disturbance modulates the brain's topographic reorganization and thereby its mental topography, resulting in the co-occurrence of symptoms. However, that is only half of the puzzle.

While decreased speed generates the brain's topographic reorganization and thereby the co-occurrence of symptoms, as in the case of insulin, it may also provide the link to the underlying biochemical, molecular, cellular and genetic causes. For instance, initial findings show that decreased speed in MDD may indeed be related to biochemical features like the disbalance of dopaminergic and serotonergic subcortical–cortical modulation, which, through dynamic and topographic reorganization, modulates the co-occurrence of symptoms.^{9,19,20} Future studies are warranted.

Differential diagnosis of mental disorders

We are now ready to come back to our initial question: What are we missing in our aim to bridge the gap from research to clinic? The discussion thus far seems to be strongly academic. This changes once we put the notion of basic generative disturbance in a wider clinical context. We suppose that different mental disorders (or syndromes, if one opts for a dimensional view) are featured by different basic generative disturbances. For instance, schizophrenia (or schizophrenia spectrum or psychosis) may be characterized by a different basic dynamic disturbance than MDD. Recent findings strongly hint that temporal imprecision in the millisecond range is present in schizophrenia as it can be observed on neural,^{21–23} psychological²⁴ and phenomenological (experience)^{13,25} levels. Such temporal imprecision, in turn, is present throughout the whole brain, by which it modulates and reorganizes both neuronal and mental topography in an abnormal way. This is manifest in the co-occurrence of symptoms like hallucination, delusion, thought disturbances, ego disruption, basic self disturbance, affect blunting and psychomotor changes such as catatonia.

This carries high clinical relevance. We may want to use the various topographic and dynamic measures for the differential diagnosis of MDD and schizophrenia. Moreover, other disorders may also need to be characterized in such topographic and dynamic terms. For instance, there is strong evidence that the basic dynamic disturbance of anxiety disorders may be characterized by temporal uncertainty while its topographic reorganization shows a strong shift toward anterior subcortical–cortical limbic regions (e.g., amygdala) at the expense of cortical midline regions of the DMN.²⁶ Together with the reported findings on MDD and schizophrenia, different topographic and dynamic markers may then allow for differential diagnosis of all 3 disorders. Obviously, this could and needs to be enlarged in the future by including dynamic topographic characterization of other mental disorders such as posttraumatic stress disorder.

Accordingly, it is not the single (unspecific) symptoms that are diagnostically specific, but rather their co-occurrence and, in particular, their underlying basic dynamic disturbance and its related topographic reorganization of the whole brain. Clinical translation may then focus on those topographic and dynamic markers that indicate the respectively assumed basic dynamic disturbance. Moreover, comorbidity of symptoms is then no longer a big problem, as single symptoms are no longer “used” for diagnosis.

Topographic and dynamic measures: biomarkers for diagnosis and therapy?

This opens the door for clinical translation and application. For instance, the various dynamic and topographic measures of abnormal slowness on neural, psychological and phenomenological levels may provide a diagnostic marker for MDD, while those indexing temporal imprecision may rather favour the diagnosis of schizophrenia/

psychosis. Obviously, this needs to be extended to the dynamic and topographic characterization of other mental disorders. In that case, the measures of the basic dynamic generative disturbance (e.g., the insulin) and its modulation of the brain’s global topographic reorganization (e.g., the glucose) may hold the promise of translating into biomarkers for differential diagnosis.

Beyond differential diagnosis, the dynamic and topographic markers may also be useful in enabling individualized precision-based therapy. Based on the observation of decreased global activity representation in the visual cortex, a recent therapy study successfully applied transcranial magnetic stimulation in the visual cortex of individuals with MDD, which, importantly, “normalized” decreased speed in both the visual cortex and anterior midline regions.²⁷

Let us return to the example of DM. Here, the ideal therapeutic approach is already realized. One can install an insulin pump (or other means, depending on the causes of the decreased insulin) that, according to the momentary level of glucose, injects insulin. Analogously, one would ideally like to install a speed pump in MDD that injects individually tailored speed into the brain’s neural activity or its psychological functions (e.g., movements, visual perceptions, thoughts). That would enhance the dynamics/speed and thereby reverse the topographic reorganization of both brain and mind as well as the co-occurrence of the various depressive symptoms.

Spatiotemporal psychopathology is a translational approach

In conclusion, a look toward other disorders may provide us with a template of how to approach research in mental disorders in order to translate it into the clinical realm of diagnosis and therapy. The notion of basic generative disturbance may be key, as it may provide clues to how the symptoms are generated and why there is such symptom complexity with both co-occurrence and comorbidity.

I propose here that what we recently introduced as “spatiotemporal psychopathology”^{10,18} may provide key insights into the basic generative disturbance of mental disorders; that is, their different “neurowaves”.²⁸ This opens the door for the usage of these spatiotemporal (e.g., topographic and dynamic markers) in both clinical diagnosis and therapy. Following up on proof-of-concept studies, large-scale clinical trials (> 1000 participants) probing these and other dynamic topographic or better spatiotemporal markers in clinical diagnosis and therapy are needed to translate basic research into clinical application.

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