How modern neurophysiology can help to understand schizophrenia

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Summary

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Modern clinical neurophysiology with the new techniques of functional brain imaging has enormously contributed to the understanding of normal and pathological brain functions in the last decade. In our opinion, one of the most important insights is the fact that even the most complex brain functions such as emotions and language are related to the activity of different and definable specialised regions. To explain these intricate psychic functions, however, higher order processes must be assumed which rely on the dynamically concerted activity of several specialised regions. In psychiatry this systemic level of brain function is particularly interesting for schizophrenia with its complex and manifold symptoms which occur in the most characteristically human domains of experience and behaviour. We are convinced that the progress in understanding the biological fundaments of this psychosis will help to improve treatment, social support and empathy for the affected individuals. Based on the simple assumption that variation of behaviour and experience are associated with different patterns of brain activation and, on the other hand, that complex psychic functions cannot be simply and statically localised in single sites of the brain, we deduce that relevant research must be guided by psychopathological concepts and symptom definitions which are closely related to the natural neurophysiological mechanisms of the human brain. This approach is believed to be a necessary condition to find more homogenous patient groups in terms of the related brain dysfunctions. Even if these symptoms are state dependent, transient and dynamically changing, this strategy is necessary to target functional brain research to specialised functional brain circuits efficiently, i.e. with reasonable numbers of patients and simple paradigms. We argue that current symptom definitions were not empirically developed but are based on and through their definitions essentially still bond to historical theories of schizophrenia and therefore may well be questioned for their validity in modern neurophysiological research and also be challenged by competitive and testable alternatives. Relying on the current knowledge of brain structure and functions, we propose to reformulate psychopathology in terms of neurophysiologically meaningful patterns of behaviour and subjective experience. The goal is possibly less difficult to achieve than commonly expected if one applies simple descriptive terms such as excitation or inhibition and follows human abilities, which depend on well-known specialised brain circuits such as language or emotions. We provide concrete examples of possible meaningful symptom definitions including the description of their potential neurophysiological background. In the last part of the article, the successful example of auditory hallucinations is described where the targeted investigation of a neurophysiologically meaningful symptom allowed to reveal specific functional and structural anomalies in those brain circuits which are involved in the generation and understanding of language. Further, we present a scientifically testable model of language-related dysfunctions in schizophrenia which summarises the current findings on verbal hallucinations and additional findings which involve language-related symptoms and structures of the brain.

Keywords: schizophrenia; neurophysiology; language; hallucinations

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Introduction

Symptomatology in psychiatry has the explicit practical goal to allow a diagnosis with its pre-

dictive power for course and treatment. There are, however, more or less implicit objectives which often are perceived as mutually competing: on the one hand, symptom definitions and descriptions should allow comprehensive understanding of the individual patient and so providing empathy of care givers and society. On the other hand, they are expected to allow the translation of observable subjective and objective phenomena to brain dysfunctions and thus improve the understanding of the natural space where consciousness and perceptions occur, and behaviour is generated.

We are convinced that an improvement of the understanding of the basic mechanisms behind schizophrenic symptoms will automatically advance psychiatry towards both aims: a better understanding of the individual human being in its social environment and an advanced knowledge of the related biological events. This conviction derives from the fact that activity of the brain is a necessary condition for any "metaphysical" phenomenon such as consciousness and human will, and from increasing evidence that our general options of thought and behaviour (thinking in pictures or words, or in imagined movements as has been shown for example in musicians [1, 2]) are organised following the genetically predisposed structure of the brain. Experience and education on the other hand are supposed to add contents, control, enrichments and variations but no principally new modalities of thought to our inner world. The experiments of mental imagery [3, 4] have convincingly shown that the biological options of the brain together with life experience shape the mental representations in a way that consciousness can reliably simulate the outer world without the need of a particular, distinct function of judgement. The brain is therefore a powerful instrument to predict future events and the consequences of our possible actions.

Understanding the psyche in this way, the dichotomy mind–brain makes no more sense. Consciousness can thus be understood as a completely new phenomenon which is not merely the sum of the constituting biological events. It may be metaphorically compared to a rainbow based on a particular constellation of necessary physical conditions, but in itself is a completely new and unique phenomenon, which is not contained neither in the number or the arrangement of raindrops, nor in the intensity and angle of the sunlight. Vice versa, however, the complex conditions needed to generate a rainbow cannot be understood if the lower order conditions are simply neglected by referring to the fundamental difference between the basic constituting and the emerging high order phenomena.

A brief historical glance on schizophrenia diagnosis

In the current diagnostic manuals, schizophrenia is defined on the basis of a series of symptoms which were not developed empirically, but are derived from historical clinical descriptions of the disorder. The major influences to our today's concept of schizophrenia can approximately be summarised as follows: Emil Kraepelin's comprehensive view of psychosis introduced the view of two major psychotic disorders rather than a collection of different psychotic disorders which were previously distinguished by various inconsistent and largely non-explicit criteria. The contribution of Eugen Bleuler was then the definition of a set of symptoms based on the psychology of associations derived from the Freudian psychoanalytical theory. In contrast to Kraepelin's mainly longitudinal definition of dementia praecox, the Bleulerian symptoms were aimed to allow a cross-sectional diagnosis of schizophrenia. Furthermore, they extended the diagnosis of schizophrenia including "many impure melancholias and manias of other schools" [5], thus improving the overall prognosis with respect to Kraepelin's dementia praecox.

A subsequent important contribution was the reduction of schizophrenic symptomatology to a limited number of well-defined criteria (first- and second rank symptoms) by Kurt Schneider. His definitions had the ambition to create pathognomonic symptoms and were in some sense a breakthrough in the diagnosis of schizophrenia, because for the first time diagnostic criteria were provided which fulfilled the prerequisites of what was later called "operational" (i.e. unique, explicitly defined and reliable). In fact, the modern classification systems which went through the process of operationalisation initiated by the APA after the intervention of the empirical philosopher Hempel [6] and were first applied comprehensively in the Diagnostic and statistical manual of the American Psychiatric Association in 1980 [7] still largely rely on Schneiderian symptom definitions.

Approaching a neurophysiological psychopathology

Current symptom descriptions of schizophrenia are time honoured, widely accepted, have been demonstrated to be suitable for reliable diagnosis and valid for successful treatment. However, there are serious doubts of whether they are equally valid to guide research to the basic disturbances of emotion, cognition and behaviour which link to the

respective events in the human brain. The present single symptom descriptions are characterised by rather complex combinations of and interactions between thoughts, emotions and behaviour. They are probably far from reflecting basic components of psychopathology but rather represent an unclear mixture between primary dysfunctions and psychological reactions. A paranoid delusion, e.g., usually involves intensive feelings of threat along with a relevant distortion of the normal mechanisms of logical and social control of one's beliefs. At last, to be able to detect the symptom, there must also be the urge or at least the compliance of the subject to communicate about his or her beliefs.

The complex symptom "paranoid delusion" can be simplified by modelling it as the output of a feedback loop involving anxiety, misperceptions and false explanations. It can be assumed that a disturbance in any of the nodes of such a loop can lead to similar behavioural results: pathological anxious excitation can result in false perceptions due to information overflow. Consequently, the patient unconsciously tries to keep control of the situation by applying a logically distorted explanation (as every medical doctor well knows, even in normal human psychology, a false explanation is much more anxiolytic than no explanation at all). On the other hand, deficits in the conceptual boundaries or oddities in the associative aura of perceived words can reasonably lead to anxiety and false convictions. Similar feedbacks must be assumed for psychomotor disturbances of catatonia, which render the intentions of the affected subject, apparently expressed by her or his psychomotor behaviour, unpredictable; the consequent misunderstandings then can generate heavily anxiogenic social situations.

These considerations convince us that the attempt to link brain physiology and typical behavioural phenomena in psychiatric diseases is legitimate and indispensable to cut the Gordian knot of schizophrenia research. Further, that the current psychopathology at the symptom and syndrome level is not a god-given constant to be categorically protected, but must be challenged by novel, competitive and dynamic concepts and by symptoms that preferably are an immediate expression of brain functions, which in part can be studied with neuroimaging techniques today.

How can we approach this latter goal? In human history the idea of understanding the link between brain and thought is as old as the insight that thought without the brain is not conceivable. Freud, Wernicke, Bleuler, Kraepelin and many others who dedicated their lives to the suffering of the mentally ill were convinced that psychosis is a brain disease, though they admitted that it was not possible for them to demonstrate the fact with the available methods. We are now in the fortunate situation of having the possibility to see aspects of the working brain that would have elated Freud and Kraepelin, but, at the same time, we impede ourselves from liberating us from their self-recognised conceptual limitations. What prevents us objectively to take the freedom to look over the border into the fascinating new results showing that our brain is organised neuroanatomically and – physiologically into feedback loops that are closed, but mutually interacting. Some of these loops have already largely been described: among the best known in the frontal brain are the motor loop, steering the psychomotor functions; the executive loop involved in planning, i.e. the anticipatory sequencing of actions; and the limbic loop, which is involved in the generation of emotions. Minor, subordinated and more specialised loops are undoubtedly present but less comprehensively described. Eye movements and language certainly dispose of distinct neuronal engines, acting as feedback circuits, though more circumscribed for the former and phylogenetically more recent and unilaterally dominant for the latter.

This outline is thought to stimulate the reader to consider a reordered psychopathology based on the available systems of the brain functions. These appear to be stratified at least into the (1) simple input functions of the primary cortex at a lower level, (2) the associative functions which provide the templates or "Gestalten" in the available sensory modalities in an intermediate level, and (3) in a higher order, combinations of the modality specific, sensory and motor templates; these combinations result in concepts or "Begriffe" as Wernicke called them [8]. Further, at the output or executive side of the brain, which is situated in prefrontal areas, the following systems may be recognised: (1) the simple output functions at the lowest level, (2) the higher order motor templates such as eye movements or the extrapyramidal movement patterns at an intermediate level, and (3) the executive functions of the dorsolateral frontal loop that may coordinate at the highest organisation level the combination and sequence of behavioural patterns and templates.

A useful translation from these brain functions into the observable psychopathology might be less difficult than one may expect. As aforementioned, the executive part is localised in the prefrontal brain (i.e. anterior to the central sulcus) and basically disposes of the motor and the autonomic output. In humans, these outputs are grouped into important specialised higher order behavioural

systems: psychomotor behaviour, which finds its probable anatomo-functional correlate in the motor loop; language, relying on a specialised fronto-temporal loop with variable, most frequently left hemispheric dominance; and emotion with specialised motor templates (emotional gestual and mimic expression such as the smile) and the concomitant characteristic vegetative phenomena, which are related to the limbic loop (see e.g. [9]).

The sensory part of the brain, which is essentially localised in post-central regions, is in principle based on the sensory input organs and disposes of different levels of higher order association areas which are at our current knowledge the site of the Gestalten: decoding, mental images and memories [10] of complex objects (visual, acoustic, tactile, proprioceptive, etc.). The association areas of the temporal and parietal cortex on their part are connected with prefrontal, motor regions by the long cortico-cortical fibre bundles. On this highest organisation level, distant higher order brain regions in the sensory association areas and in the executive brain can thus be coupled with electrophysiological binding to feedback loops and instantaneous global brain states that possibly are a sufficient condition for the phenomenon of consciousness ("the rainbow") to emerge. Possible electrophysiological equivalents of these global brain states have been identified and referred to as "atoms of thought" [11, 12].

Based on this outline, the observable psychopathology can easily be allocated to the major behavioural domains: psychomotor, language and emotion, and in the same way to the subjective experiences including the subjective part of emotions (feelings). The example of a paranoid delusion can then be analysed trying to understand whether the basis is primarily emotional or linguistic. Within the domains, the type of the disturbance can further be described in physiologically meaningful terms, e.g. whether an emotion is elated (physiologically relaxed) or anxious (excited), or whether the speech disturbance consists of violations of the rules for sequencing the words (logical or grammatical disorder) or in the attribution of meaning and whether speech production is rich (uninhibited) or poor (inhibited). In a similar way, anomalies in the psychomotor domain can be described in the physiological terms of excitation, inhibition and whether abnormal motor patterns occur.

On the sensory or subjective side of symptomatology, the description can be treated in a similar way. For example, the typical symptom of schizophrenia, the acoustic hallucinations can be allocated to the language system since only complex verbal auditory hallucinations are diagnostic for schizophrenia.

This approach is in our view important for schizophrenia research, since very different clinical pictures exist where psychotic anxiety, incoherence, motor excitation or inhibition dominates the picture in very distinct patterns. We know paranoid schizophrenics who are affectively extremely excited but logically lucid; others are confused with heavy logical disturbances of thought but affectively perfectly intact with regard to any non-verbal communication. Some patients are perplexed and agonize for the meaning of every word; others are verbally disinhibited and joyfully produce an incomprehensible melange of words. Physiologically, it is very unlikely that the brain in these different conditions is active with the same dysfunctional patterns. Furthermore, Kraepelin's and Bleuler's widely accepted assumption that one pathological process can lead to these very different phenomena is obviously not less speculative than our hypothesis that they are caused by distinct pathological processes of the involved brain systems, i.e. of the anatomically prearranged functional loops. This view appears particularly convincing in those patients who psychopathologically remain stable in terms of the most affected domain (e.g. language, emotions or motor behaviour).

The advantages of this approach are obvious: symptomatology can be studied clinically, neuropsychologically and with functional brain imaging. The symptoms allow to sort out patients with neurophysiologically similar patterns and to focus the study on defined brain regions or circuits, such as the limbic, the motor or the language-related loops. In our experience, there is even an immediate clinical benefit for many patients in terms of individualised treatment, since the predominantly impaired domain can be identified and the therapeutical efforts can be focused on the remaining intact domains. This means in practice that an affectively highly irritable paranoid patient with clear cognition is accessible for communication by means of respectful reasoning, but is refractory or even further excited by gestual signs of confidence or attempts of intimidation. On the other hand, a person with severe thought disorders should not be pressed to logically work up his or her condition but can surprisingly well communicate through common activities or gestual interactions.

Obviously, the significance of the described approach has to be proved by empirical research. On the other hand, it should be considered that the current, substantially unsuccessful psychopathology of psychosis cannot be challenged scientifi-

cally if the community is demanding criteria for competing alternatives, which the current system is far from fulfilling itself. In the following, based on the example of language, we intend to demonstrate that the potential gain is worth the risk to make experiments with different and new approaches to the understanding of psychopathology in psychosis.

The example of language and schizophrenia

Many schizophrenic symptoms are language related, but not every schizophrenic patient has disorders of speech, verbal thoughts or verbal perceptions. In our logic, this commits us to study this type of symptoms separately in terms of brain function. Among the language type of symptoms, acoustic hallucinations in the form of speaking voices, formal thought disorders, errors in logical thinking and neuropsychologically detectable deficits in receptive speech are most common.

This view is supported by our neurophysiological findings. In fact, it was possible to distinguish psychotic disorders with signs of left hemispheric deficits from those with signs of a generalised overarousal [13, 14]. The left hemispheric abnormality was present in chronic and subchronic patients and consisted of an abnormal asymmetry of auditory evoked potentials. These changes in brain activation relied on conscious sensory discrimination and silent counting (to distinguish sounds of different pitch and to count the outliers). The particular pattern of the brain electrical field was related to neuropsychological deficits in verbal but not in visual discrimination and memory functions [15]. The other psychotic patients showed signs of a global overexcitation without hemispheric lateralisation. This latter feature, instead, was related to a favourable longitudinal course [16].

These results support the view that first, psychosis can be distinguished in neurophysiologically distinct groups, and second, that these groups can be defined by neurophysiologically meaningful symptom patterns, i.e. deficits in hemispherically lateralised, language-related functions in one case, and in a global hyperarousal with the consequent effects on perception and judgement (e.g. information overflow) in the other.

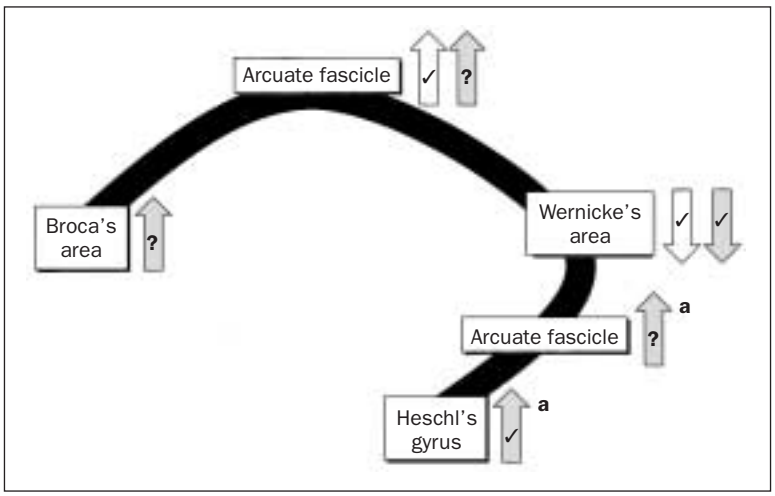
Following the issue of language in schizophrenia, verbal hallucinations are extremely fascinating since they are probably one of the most elementary phenomena of schizophrenia in terms of direct access to brain mechanisms. It therefore challenges a paradigm which is operant in psychiatry since Jaspers blamed Wernicke's early attempts to link mind and brain as "brain mythology" [17] and quasi morally obliges researchers to neglect the possibility of a direct link to the underlying nature of psychological phenomena due to a humble reverence to its intrinsic complexity.

There are some patients who intermittently hear voices. They are able to indicate the moments when they hear voices and the periods when they do not. This is a pattern which scientifically allows the study of this completely subjective phenomenon with the available functional brain imaging methods in a small number of selected subjects. Dierks and coworkers [18] were able to show in these patients that hallucinations were distinctly associated to an activation of the primary acoustical cortex, i.e. Heschl's gyrus along with the motor speech region in Broca's area. This is in contrast to the physiological brain activation pattern during inner speech which is related to activity of Broca's region along with a reduction of activity in Heschl's region [19]. The finding indicates that the conscious experience of acoustic verbal hallucinations in schizophrenia is due to an abnormal coactivation of the region that is usually active only when an external stimulation occurs, and that this coactivation gives the erroneous quality of a real sensory perception to internally generated words and sentences during verbal thought (or inner speech).

The frontal and temporal speech-related and acoustic regions are connected by a large fibre bundle, the fasciculus arcuatus. These fibres can, to our current knowledge, instantaneously connect speech and language perception-related brain regions to a functional circuit by electrophysiological binding; this is supposed to create a momentaneous brain state involving distant brain regions, each contributing its distinctive specialised function to the conscious content of the brain state. The pathologically coactivated primary auditory cortex would then contribute to this state the erroneous quality of "coming from outside".

To explain in this context how this pathological retrograde activation beyond the physiological borders of an internal speech-related circuit occurs, two different mechanisms can be speculated on: either a lack of inhibition of the primary cortex or an increase in its excitatory stimulation. In a recent study, Hubl et al. [20] showed that the shorter fibres of the lateral fasciculus arcuatus, which connect Broca's to Wernicke's area, are increased in terms of directionality in hallucinating schizophrenic patients compared to both healthy controls and never hallucinating schizophrenics. This is consistent with the hypothesis that a fronto-temporal hyperstimulation is at the basis of the coactivation

Figure 1 The language loop in schizophrenia.



white arrow = structural changes
dashed arrow = functional changes
arrow up = increase
arrow down = decrease
a = during hallucinations
✓ = empirical findings
? = hypothesis

of the primary auditory cortex during hallucinations.

These results appear to be parts of a puzzle that may be the key to the understanding of speech-related symptoms of at least part of our schizophrenic patients. In the following we want to introduce a comprehensive hypothesis of language-related disorders and language-related hallucinations in schizophrenia. One basic assumption is that language decoding, internal speech, verbal thought and active language production rely on the same fronto-temporal circuit involving among others Heschl's gyrus, Wernicke's region, Broca's region and the subordinated motor loops for the generation of spoken language. The different momentaneous contribution of the circuit members to the momentaneous brain state determines the output and the subjective quality of the system: spoken words if the motor loops are coactivated, thoughts if the primary input and output regions are suppressed or listening if the primary auditory cortex is active. In this context, the finding that primary auditory regions are suppressed during inner speech can be interpreted as a protection of the conscious internal verbal imagery ("thoughts"), by an active reduction of the relative contribution of contemporaneous sensory stimuli from outside to the momentaneous conscious brain state.

One of the key regions indicated by schizophrenia research is the left posterior superior temporal lobe and also the planum temporale, where Wernicke's region is located. As mentioned above, the P300 is asymmetrically reduced with focus on left temporal regions and major generators are localised in the superior temporal lobe. This suggests that these areas are functionally deficient but also, as consistently reported, show structural deficits in terms of volume reductions (see e.g. [21, 22]). Additionally, language disturbances in terms of verbal but not figural memory [15] and deficits in receptive speech (e.g. [23]) have been reported. No functional deficits, however, have been described to our knowledge in Broca's or generally in left frontal regions, or in Heschl's gyrus proper.

In summary, the available parts of the puzzle are (1) a structural and functional deficit in left hemispheric Wernicke's area, (2) signs of a functional increase in left Heschl's gyrus and in Broca's area during the hallucinations and (3) an increase of directionality in the fibre bundles which connect the motor with the sensory language-related areas and can be assumed to sustain the left hemispheric language circuit.

Based on the above described model of language-related brain functions, the specific disturbance during hallucinations can be described as follows: the subclinical and usually only neuropsychologically detectable deficit in receptive speech, which is due to a structural weakness of the sensory speech area and may derive from genetical, developmental or ambiental factors, leads to chronic social stress and a compensatory overstimulation driven by activity of Broca's area. This excessive compensatory stimulation can explain three findings in schizophrenia as a consequence: a dysfunctional overexcitation of Wernicke's area resulting in erroneous output (false associations, incoherence, receptive language disturbance); a retrograde excitation and coactivation of the primary auditory cortex during internal speech, resulting in the subjective experience of hearing one's own verbal thoughts as voices; and a plastic reaction with increased organisation of the involved white-fibre bundle, the fasciculus arcuatus. This hypothesis is summarised in figure 1, indicating the empirical evidence and the hypothetical parts of the model.

While the puzzle is still largely incomplete and of course several alternative explanations are possible for each of the single findings, we think that our hypothesis reasonably combines the current evidence. Further, as can be distinguished in figure 1, every question mark allows formulating an empirically testable hypothesis that can challenge the entire model. We are therefore convinced that this speculation is not only scientifically legitimate, but also useful to formulate meaningful questions with regard to this highly interesting, exclusively human and among the most specific group of schizophrenic symptoms.

Conclusion

We discussed a neurophysiological approach to schizophrenia psychoathology showing how symptoms can be redefined to describe physiologically meaningful phenomena. One might argue that a major advance with the current operational classification systems was the atheoretical definition of the diagnosis and that redefining symptoms based on theories of mind is a drawback. We argue instead that our proposal is an advance in this perspective, too; because first, it is not based on theories but just on an attempt to reformulate symptoms in neurophysiological instead of historical or socially relevant terms; and second, it allows to create testable hypotheses on underlying brain dysfunctions which are accessible with independent empirical methods. We think that this approach is apt to escape from the often tautological impasse of optimising the reliability and validity of psychiatric diagnoses by a limited number of measurable clinical effects.

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