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Towards a Neurophysiologic Support for Diagnosis and Therapeutic Control in Psychiatry

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Abstract

The stages of construction of Auditory Brain-stem Evoked Response bio-markers are described. Earlier research is summarized regarding brain stem dysfunctions and psychiatric states. Preliminary studies show promising results and validating studies by other researchers are referred to. In a final comprehensive remark the logic of constructing operationally defined diagnostic support is presented.

Keywords: Auditory brain-stem response; Bio-markers; Schizophrenia; ADHD; Neurophysiology

Introduction

When diagnosing psychiatric disorders several difficulties are encountered. A thorough anamnesis has to be worked through, a process which is often hampered by patients' decreased ability or lack of will to communicate. As psychiatric diagnoses substantially rely on subjective evaluation, a great clinical experience is demanded from the physician/psychiatrist. If he/she has to comply with any diagnostic system (as e.g. DSM or ICD) further delimitation is introduced in the process [1,2]. Some symptoms may be more or less patognomonous, but the complete picture may not justify a diagnosis. This may have serious consequences for a failing therapy, which otherwise could stop future episodes of overt psychosis. Illnesses of this kind are life-long and symptoms vary over time. At a given time of observation they will be extremely difficult to identify. It almost always takes a very long time, often several years, to establish a diagnosis, especially psychotic and neuropsychiatric ones. This is due to many circumstances. Patients mostly try to cover symptoms and dissimulate, consciously or unconsciously. Doctors are reluctant to set the diagnosis because this means dooming the patient to a life long suffering or bad prognosis.

It regrettably also happens that there are conflicting views among staff members which may delay the final decision and introduction of therapy. There is thus a great need for objective measures to support the process of diagnosing in psychiatry. Early and safer diagnosis may mean adequate treatment, which delays, and even may prevent the outbreak of psychotic episodes. There is an aggravation of degenerative processes related to every such outbreak, which underlines the importance of early medical intervention [3]. This review will advocate the importance of introducing neurophysiologic markers for diagnoses in psychiatry and introduce the present method as a possible way to achieve that goal.

Some current diagnostic support in psychiatry

It has been seen that brain imaging methods are not conclusive in depicting a consistent pattern e.g. for schizophrenia. Instead different studies show varying topographic lesions, mainly in fronto-temporal, limbic and calcarine areas. This reflects a characteristic aspect of the disease, namely its patchy distribution of symptoms, dysfunctions, and associations with afferent and efferent nervous systems. There is still a debate whether the anomalies are developmental or degenerative, as Kraepelin presupposed ("dementia praecox"). Many studies support the former explanation [4]. Ithas e.g. led Mirsky and Duncan to suggest a more profound role of other structures-notably the brainstem-in diseases comprising attentional deficits such as schizophrenia and ADHD [5].

Experimental physiological and electrophysiological indices have been extensively sought for to provide clinically useful markers for psychiatric disorders. Smooth pursuit eye movements, blink reflex, startle response, and perceptual and cognitive tasks have been studied in combination with electrophysiological registration. The visual, hearing, somato-sensory and olfactory systems have been investigated as well as motor systems.

In schizophrenia cortical and other aberrances in electrical responses have been documented such as "mismatch negativity of the cortical response", aberrant responses after 300 ms, decreased inhibition of the normally positive deflection after 50 ms in the auditory pathway, etc. [6,7].

By linking the responses to a specific stimulus one has a way to average the response of many identical stimuli and thus produce a so called evoked electrical response of the stimulus. This technique has contributed to better sensitivity and specificity. However, electrophysiological methods do not reach more than around 70 percent sensitivity for e.g. the schizophrenic diagnosis [8].

Psychological tests are frequently used to support diagnosing. These usually measure cognitive functions, but there are others measuring diverse perceptual, attentional and psychophysical functions. The speed with which one sorts cards or handles spatial problems is changed in states of altered attention. Difficulties to recognize facial expression may be mentioned as an example of a fairly specific test for schizophrenia. An improvement of the accuracy of testing technique may be achieved if the experimental stimulation is expanded into series of repeated events. In that way the adaptation or habituation comes into play, a reaction that is clearly and consistently weakened in attentional disorders. An overflow from, and overreaction to stimuli, sometimes denoted “overinclusion” may be related to habituation problems [8]. Neurophysiological correlates of such disturbances have been studied and successfully demonstrated [7].

Many interview schedules and questionnaires are available to help the clinician or the researcher. But to mention one currently popular example, this would be the PANSS (Positive and Negative Symptoms Scale) scale [9]. As mentioned above, the clinical sensitivity and knowledge of the physician is unconditional for any diagnose. Questionnaires should be interpreted with care and not by themselves be allowed to determine a diagnosis.

Planning electrophysiological markers for psychiatry

For the understanding of the elaboration of the new method here to be described, some steps in the developmental process would help to explain the rationale for it.

In the late 20th century our group was occupied with music perception. It was noted that psychiatric clinical groups-like obsessive neurotics, hysterical neurotics, depressives, manic psychotics and those with panic disorder-differed in their evaluation of music structures in a way that it became possible to separate them into their respective diagnostic categories. Individuals with schizophrenia, however, did not report sufficiently characteristic deviations to define their pertinence to a specific category. This was of course remarkable as perceptual misinterpretations are a core part of exactly their disease [10]. By changing the stimuli from excerpts of western symphonic music to electronically generated sound clusters, only a few additional significant differences, in this case between schizophrenic and manic patients, appeared [11].

The measurements until then had been paper and pen ratings of semantic differentials (7-graded scales of opposite meanings of adjectives) and multifactorial statistical analysis had been applied. All results were then expressions of evaluations at the highest mental-cognitive and perceptual-levels.

Because it seemed as if individuals with schizophrenia in principle were able to compensate for perceptual deficiencies when listening to extensively complex music structures, we started to search for simpler sound stimuli in order to target circumscribed perceptual processes. It became reasonable to look into primary processing of perception, which is highly suspected to be disturbed in schizophrenia. Studies were then directed into auditory neurophysiology and its behavioural counterpart, psychoacoustics, a subject with borders to acoustics, psychophysiology and psychophysics.

Psychoacoustic experiments

In 1991, Albert Bregman published his outstanding book "Auditory Scene Analysis" in which he describes psychoacoustic experimental examples and the conditions for them to be heard [12]. The work he presented is i.e. a catalogue of tests targeting integrative processes at a primary, unconscious and automatic level. This "automatic sensory grouping" was the field that we assumed to be useful for revealing perceptual dysfunctions of the schizophrenic disease.

The approach turned out to be fruitful. In a series of studies of automatic grouping in individuals with schizophrenia clear dysfunctions were demonstrated [13]. None of the about 25 test subjects with schizophrenia reported overall compatible results with a corresponding number of subjects without schizophrenia. Interesting was that no general and consistent pattern emerged, but scattered serious deficits of the different psychoacoustic functions were seen.

The psychoacoustic stimuli of automatic grouping regarded e.g. pitch streaming.

In the perceptual process discontinuous sound may become grouped, separated in parts, as when we hear melodies in an orchestral performance. It works automatically, at an unconscious level and is impossible to subjectively influence. The hearing of the pitch streaming test was aberrant from healthy individuals’ in schizophrenics.

Further, the restoration process was dysfunctional in individuals with schizophrenia. The neural processing of fragmented sound samples means that sounds may be "healed" so that in e.g. speech, acoustically non-existent syllables are restored by the auditory system and become distinctly and unequivocally perceived.

A third interesting function was equally dysfunctional, namely, the integration of directional hearing.

Under certain conditions the spectral content dominates over phase or intensity directed binaural interpretation. A reflected sound normally will be heard as coming from its source of origin due to spectral similarity. This prevents us from confusion by echoes in our sounding environment. Individuals with schizophrenia tended to hear separated sources, and integration of the stimulus did not occur to a normally expected extent.

Neurophysiological correlates of stimulation

At this stage psychoacoustic aberrances in schizophrenia were demonstrated with certainty. The question of where the neurophysiological disturbances anatomically were located must be solved if it would be possible to construct objective

measures (markers) of the disorder. An fMRI study was designed to address it. The abovementioned streaming example was used as stimulus and subjects had to report the hearing of it. Among control subject some individuals could give a completely reliable report on the presence of streaming, and their maps of activation were interpreted. It could be seen, that streaming became processed without inclusion of structures farther than the supra-temporal gyrus. Auditory streaming was built up in subcortical structures. It seems to depend on gradual sorting through the many nuclei in the auditory pathway and not on cortical association processes [14].

Now, knowing that schizophrenic aberrances could be related to the mesencephalic level, studies on brain stem neurophysiology and measuring methods, notably ABR (Auditory Brain stem Response) were undertaken. From the literature it could be learned, that standard ABR yields differences between individuals with and without schizophrenia, but not with any validity appropriate for predicting purposes in the diagnosing process. By using many categories of stimuli (targeting grouping of frequency, spectrum, amplitude, phase, and time relations in the hearing), the schizophrenic aberrances would be more precisely differentiated [14].

In preliminary studies, it was ascertained that varying psychoacoustic stimuli produce specific changes of the patterns of the evoked response. Then, differences were assessed between the two study groups, schizophrenia and non- schizophrenia. As a start, only wave V, emanating from colliculus inferior, was scrutinized.

Amplitudes of wave V in individuals with schizophrenia were different from those of control subjects, changes both of spectral content (pitch) and SPL (Sound Pressure Level) of the stimulus occurred. Also, latencies of peak V after varying stimuli showed differences between the two groups.

This means that integration and grouping within the auditory pathway are different in schizophrenia, at least at the level of colliculus inferior. Further, side differences (right/left ear registrations) were discovered in the schizophrenia group compared with the no schizophrenia group. This held both for changes in stimulus SPL and spectral content. Right-left differences are not only limited to the hemispheres, as is well known, but evident also in the brain stem [15,16]. The goal of establishing an objective neurophysiological correlate between psychoacoustic stimuli and schizophrenic aberrances had been achieved.

Systematic blindly performed studies and comparisons between groups of individuals with schizophrenia, with ADHD and healthy controls were worked through. The results were as follows (Table 1).

Table 1: Frequency of complex ABR positive results for the respective group of test subjects. The indexes are determined so that no control subject must get an index of disorder. From the clinical groups only 3 ADHD and 2 schizophrenia patients got no index of pathology and 1 patient with ADHD got a pathological index for schizophrenia as well [1].

Clinically diagnosed subjects Complex ABR diagnoses	Control subjects	ADHD subjects when medicated	ADHD subjects when medicated	Subjects with schizophrenia
N=91	35	26	11 (out of the 26)	30
No diagnosis	35	3	0	2
ADHD	0	23	1	1
Normalization by Methyl-phenidate®	0		10	0
Schizophrenia	0	(1)	0	27

Firstly, schizophrenia could be differentiated from no schizophrenia in 27 out of 30 subjects, with the requisite that no healthy person must be appointed a schizophrenic diagnosis. This reflects a very high sensitivity compared to most methods described till now. Secondly, in a sample of 26 clinically diagnosed cases of ADHD, 23 were correctly identified under the same pretext. An effect of methylphenidate could also be assessed (Table 1).

The method has not yet contributed very much to the knowledge of schizophrenia, but it reveals a general polymorphism characterizing the disorder. Pin-pointing detailed connections between specific symptoms and ABR traits will be the charge of future research. The findings in relation to ADHD were a successful test for using the method for disorders of less serious impact. Markers for MDS (Manic-Depressive Syndrome), ADHD and ASD (Autism Spectrum Disorder) have been shown recently [17-22].

Comprehensive and completing remarks

The fundamental idea behind this search for neurophysiological markers in psychiatry was based on the fact that psychiatric diagnoses are multifactorial. To experimentally mimic the clinical process one has to collect a huge amount of data. Stimulation with complex sounds targeting psychoacoustic processes satisfies this request. The analysis of

the ABR data must be able to handle a similar huge quantity. Then one gets a mean to compare patterns of data within and between different clinically well diagnosed samples. In this way indexes for clinical states can be constructed which will present operationally defined diagnoses. The limits of this technique may be very flexible. In a report by two of our psychology students an example was given of separation of extrovert from introvert personalities.

In order to grasp more details of the ABR, a non-standard procedure had to be introduced with regard to analysis. In audiology, analysis of ABRs is confined to the reading of amplitudes and latencies of the troughs and peaks of the curves. A new ABR device was constructed, digitalization of the waveforms was applied and mathematization of overall differences between groups of individuals with and without pertinence to a psychopathological group was brought into practice. The possibility to be able to "objectively" support the diagnosing of organic and other dysfunctions is of great importance in many psychiatric settings. Not only for reasons described in the introduction, but still more when it comes to decisions in connection with forensic psychiatry and to verification of the existence of a disorder before authorities of different kinds. It may also be valuable to be able to exclude the presence of biological markers, which should lead to further explorations. It is however imperative that the final diagnostic judgement always must be made by the responsible doctor. By its flexibility, the method may be made sensitive to culturally more specific diagnostic categories or those temporarily in fashion. It can be adapted to new conditions by additional comparisons between local clinical samples.

The discussions presented in this article point to some promising preliminary results which may nourish the hope to one day see biologically solid markers for diagnoses in psychiatry being established.

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