Neurobiology of Schizophrenia: Electrophysiological Indices

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Abstract

The objective of the WPA section on Psychoneurobiology is the promotion of the integration of findings from research fields such as neurophysiology, psychology, neuropsychology and psychiatry. This chapter focuses on the importance of electroencephalographic (EEG) studies for the section's objectives and especially for (a) the study of functional brain abnormalities related to liability to psychosis and schizophrenia pathophysiology and (b) characterization of schizophrenia psychopathological dimensions. The introduction will highlight the

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importance of EEG investigations in psychiatry, outlining a model of brain function, based on the notion of state-dependent information processing, and providing examples relevant to schizophrenia research. The second paragraph will summarize the current state of knowledge about resting state EEG connectivity in subjects with schizophrenia (SCZ) and draw some tentative conclusions about the possible links to the range of cognitive and behavioural abnormalities observed in these patients. The third paragraph will illustrate findings from event-related potential (ERP) studies of subjects at risk for psychosis who later develop schizophrenia-spectrum disorders. Some of the ERP parameters are proposed as biomarkers of the transition to psychosis and, if further validated, can be used to identify subjects for early interventions. The final paragraph of the chapter will summarize findings relevant to the characterization of the psychopathological dimensions of schizophrenia.

27.1 Introduction: The Importance of EEG Studies for the WPA Section on Psychoneurobiology

Martha Koukkou

27.1.1 Why Use the EEG?

In neurophysiological studies, the EEG was used in order to investigate intra-individual variance in the brain's functional state in relationship with the characteristics of the momentary subjective experiences (thoughts, emotions) or behaviours in different populations and experimental settings.

The findings suggested that the brain electrical activity (as manifested in the scalp EEG):

- Is an observable property of large populations of neurons that are engaged in cortical information processing
- Enables functional neuroimaging that attains the high time resolution of human information processing
- Provides information of the level of excitability of the cortical networks

Research in psychoneurobiology showed that there are well established correlations between manifested behavioural development and systematic changes of cortical functioning as manifested in the developmental changes of the awake EEG. In particular, the EEG amplitude and mean frequency, as well as the coordinated patterns of functional connectivity, expressed in the brain electrical microstates, undergo significant developmental changes. Further, EEG coherence between

regions increases with age, differing between hemispheres, and between anterior and posterior areas [1, 2] as well as the "chaotic dynamics" of EEG, i.e. its complexity increases systematically from newborns to adults [3, 4]. Systematic changes of cortical neuroanatomy during development are manifested in the increase of the cortico-cortical connectivity between hemispheres and cortical regions. These changes are the product of the experience-dependent plasticity, with changes related to individual experiences inducing cortico-cortical synaptic complexity.

During Human Development:

- Experience-dependent synaptogenesis results in increased quantity and complexity of the cortical neuronal networks.
- These neuroanatomical developmental changes are accompanied by changes of the scalp EEG and by changes of higher cognitive-emotional functions which characterize the ontogenetic course from childhood to adolescence and adulthood.

The organization and dynamics of neuronal networks represent the product of the development, regulated by multiple factors (genetic and environmental variance) and including the impact of the individual experiences, and lead to the creation of well- or maladapted coping and reality-controlling strategies (the contents of autobiographical memory). For an extended review, see Koukkou and Lehmann [5]. The brain's functional state (which is multifactorially defined), during resting, represents the level of attained complexity of the neural networks during the ontogenetic development, while during information processing, it is a function of memory-driven, dynamic interplay and state-dependent momentary excitability of the same networks.

27.1.2 An Integrative, Complex Living Systems-Oriented Model of the Brain Functions that Create Autobiography

A given degree of coherent coordination among the determinants of the brain's functional state (age, metabolic-hormonal equilibrium, neurotransmitter state) is the prerequisite for a state-adequate level of excitability of the neural network and corresponds to the EEG states. State-dependent, memory-driven processes form the individual's momentary thoughts, emotions and behaviours as well as their conscious perceptions.

In schizophrenia, cognitive-emotional and behavioural changes are caused by the altered excitability of the neuronal networks and disconnection among their main nodes, with altered accessibility of memory contents and "forced" use of state- and/or age-inadequate knowledge in order to cope with usual or excessive stress.

EEG methods are appropriate to investigate the neurophysiology of both normal and psychotic experience and behaviour, based on an integrative, complex living systems-oriented model of brain function outlined above [5, 6].

27.1.3 Electrophysiological Indices and Schizophrenia: Dissociated Brain's Functional States in First-Episode, Neuroleptic-Naïve Productive Patients with Schizophrenia

For our EEG studies in schizophrenia, 19-channel EEG was recorded during resting and after the presentation of short sentences in first-episode, neuroleptic-naïve patients. Based on EEG measurements, we tested the following hypotheses:

- The scalp EEG provides indices of state-dependent, memory-driven information processing.
- SCZ is characterized by deviations in all determinants of the brain's functional state and thus by deviant EEG activity and reactivity.

I will present the results of three studies in which two different EEG analysis methods were used in order to test the above hypotheses.

27.1.3.1 EEG Spectral Analysis

A total of 70 subjects participated: 3 groups of adolescents, 11-, 13- and 14-year-olds, SCZ and age-, gender- and education-matched controls (also called "adults"). The final diagnosis at discharge was DSM-IV schizophrenia or schizophreniform disorder. EEG was recorded from 19 leads during resting and after the verbal presentation of four short sentences.

The EEG was spectral analysed. For each of the 19 recording leads, the spectrum was divided in 3 frequency bands, 2–7.5 (theta), 8–13 (alpha) and 13.5–26 Hz (beta). For each frequency band, the centroid frequency was extracted. The centroid assesses the shape of the power distribution within the band by one number, independent of the total power in the band. It is the centre of gravity along the frequency axis of the band. It is lower when slower frequencies predominate within the band; it is higher when higher frequencies prevail. The centroid is a sensitive measure of developmental EEG changes.

Figure 27.1 presents a summary of the results. SCZ had lower theta centroids than all four normal groups, in resting and in the average of the four activation conditions. SCZ showed the highest values of all groups in alpha and beta, in resting as well as activation EEG states.

The majority of the expected normal age-dependent differences were found between adults and 11-year-olds in the alpha and beta centroids.

The comparisons of the SCZ with the adolescents showed:

- SCZ had the lowest theta centroids compared with all three groups of adolescents and this mainly over anterior leads.
- SCZ had higher alpha centroids as compared with 11- and 14-year-olds.
- SCZ had higher beta centroids in comparison with all three groups of adolescents with differences in the number of leads with significant results.

Given that the differences between the adolescents and the controls correspond to the normal age-dependent differences, the results of the comparisons between

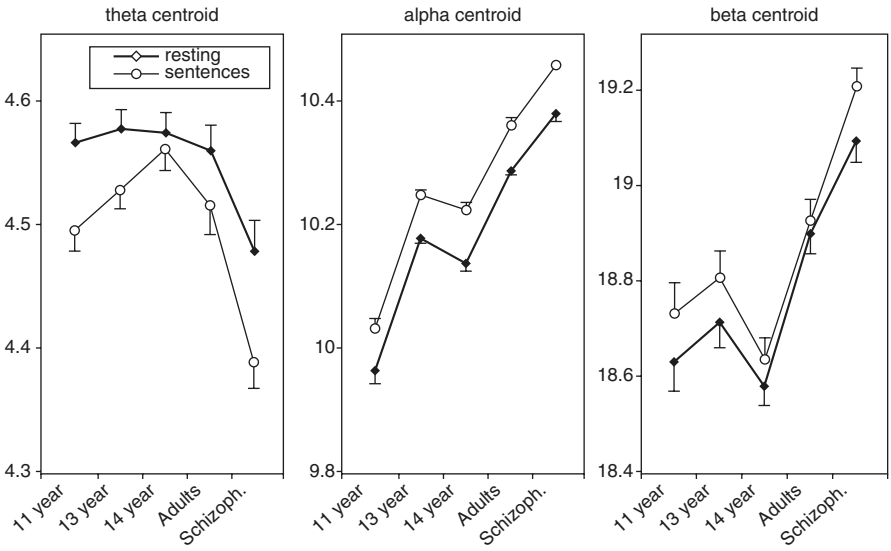

Fig. 27.1 The mean centroids (±1 S.E.) across the 19 leads for resting EEG and for the average of the 4 information-induced states (short sentences) in the theta, alpha and beta frequency bands in the 5 groups (3 adolescent groups, a schizophrenic group and adult normal controls). Reprinted from Journal of Psychiatric Research, Vol 34, M. Koukkou, A. Federspiel, E. Bräker, C. Hug, H. Kleinlogel, M.C.G.Merlo, D. Lehmann. An EEG approach to the neurodevelopmental hypothesis of schizophrenia studying schizophrenics, normal controls and adolescents, 57–73, Copyright (2000), with permission from Elsevier

SCZ and adolescents indicate dissociated, i.e. partially regressed and partially over-activated EEG states. In other words, SCZ show dissociated levels of excitability of neuronal networks, i.e. dissociated levels of the activated and/or inhibited networks [7, 8].

27.1.3.2 EEG Microstate Analysis

In further studies, using new methods for resting EEG analysis, differences were found between neuroleptic-naïve SCZ and age- and gender-matched healthy controls (HC).

In such studies [9] the 19-electrode EEG was recorded in resting, and the momentary electric field configurations were estimated as sequences of momentary maps. The map series were assigned to four microstate classes and tested for differences between SCZ and HC.

One microstate class displayed significantly different field configurations and shorter durations in patients as compared to the matched HC.

In a multicentre study in acute, first-episode, medication-naïve SCZ [8], EEG microstates differed in duration and syntax (i.e. the sequence of transition from one to another microstate class over time) from matched HC.

27.1.4 Discussion

It was the psychiatrist Hans Berger who, in 1929, first provided published evidence of EEG in man [10]. Shagass [11] published in *Biological Psychiatry*, an electrophysiological view of schizophrenia.

What is the relevance of our results for further understanding of the pathogenesis of schizophrenia? We concentrate on what the finding of dissociated EEG states may suggest as to the pathogenesis of the frequent first manifestation of schizophrenia during late adolescence in individuals who earlier had functioned normally.

In adolescence, distinct changes occur (reorganizations) of all determinants of the brain's functional state (the most obvious is the hormonal reorganization), suggesting reorganization in the level of excitability of the neuronal networks. The adolescent is also confronted with expectations and/or demands for social adaptation to the adult ways of life. It has been proposed that adolescence and early adulthood may be experienced as existential and/or environmental stress and that the efficiency to cope with stressful events depends on the quality of the adaptations worked out during development in order to cope with comparable events.

In schizophrenia, heterogeneous and non-specific deviations of all determinants of the brain's functional states have been described to precede the manifestation of the symptoms (including sleep disturbances and behavioural changes indicating stress), as well as to accompany the symptoms, suggesting deviant levels of excitability of the neural networks.

The results suggest that the frequent onset of schizophrenia during late adolescence may be due to imbalances in the coordination of the determinants of the brain's functional states. These imbalances may have multifactorial origins rather than be due to an abnormal function at a single location or due to a fixed brain lesion acquired early or late in life. They lead to the cognitive-emotional and behavioural changes (seen at schizophrenia onset) through an altered excitability of neuronal networks and thus altered accessibility of memory contents which "forces" the individual to use state- and/or age-inadequate knowledge in order to cope with usual or excessive stress.

27.2 EEG Indices of Resting State Connectivity in Schizophrenia

Thomas Koenig, Anja Bänninger, Kathryn Rieger, and Laura Diaz Hernandez

Patients with a diagnosis of schizophrenia respond, in the average, in an often blunted and less accurate and efficient form in a very broad range of tasks. In fact, this range is so heterogeneous that it is difficult to conceive a particular deficit that could commonly explain these observations. One possible solution to this problem may be that we take into account that environmental input does not meet a brain that is essentially inactive but interacts with its momentary baseline activity. Brain and

behavioural responses to a specific stimulus thus vary depending both on the baseline state and on the content of the input. If we assume that there may be systematic alterations of baseline activity in SCZ, the notion of state dependency of brain information processing may explain the broad range of abnormal responses based on a potentially much smaller set of abnormalities of the brain baseline states. In addition, baseline states precede stimulus responses in time and may therefore also causally precede alterations in task response.

Resting state brain activity displays a remarkable amount of organization in space and time that has allowed to characterize in particular the so-called resting state networks. Interestingly, schizophrenia has for a long time been characterized as a disconnection syndrome [12] and has therefore become a domain where the analysis of resting state networks has steadily gained attention. In the study of resting state networks and brain functional connectivity, EEG and magnetoencephalography (MEG) data have a unique place because their excellent time resolution is compatible with the speed of human brain information processing. The aim of the following brief review is to summarize the current state of knowledge about resting state EEG connectivity in SCZ and draw some tentative conclusions about the possible links to the abnormal responses seen in so many domains.

EEG analyses of brain functional connectivity need to take into account the confounding effects of volume conduction [13]. Volume conduction in EEG and MEG refers to the fact that even a single source in the brain produces a field on the scalp that is potentially widely distributed and that the scalp fields of several such sources are additive. A similarity of two signals recorded on the scalp may thus potentially be caused by the same source that simultaneously affects both recording sites. Based on how this problem is addressed, analyses of resting state EEG and MEG connectivity can be divided into two main classes of approaches, namely, measures that assess non-lagged connectivity, such as factorization and microstate analysis, and measures that quantify lagged connectivity, such as lagged coherence and the phase locking index.

This choice of methodology implies very different understandings of what constitutes connectivity: non-lagged connectivity implies the simultaneous co-activation of network elements and disregards delayed interactions, whereas lagged connectivity implies sequential activation and excludes simultaneity. The approaches are therefore mutually exclusive in terms of what mathematically defines "being connected". We will structure our brief review on EEG resting state connectivity in schizophrenia along this division and later try to integrate the findings.

It is also important to note here that none of these measures allow to directly translate connectivity patterns among sensors into anatomically corresponding brain connectivity patterns [14]. Our overview is therefore limited to studies that have either used inverse solutions to explicitly estimate the activity of particular regions of interest, and then quantify the amount of similarity among these estimates using lagged indices of connectivity, or that make global statements about connectivity patterns that explicitly accommodate volume conduction. Unfortunately, the number of such studies is yet small.

27.2.1 Lagged Measures of EEG Resting State Connectivity in Schizophrenia

The first study comparing lagged coherence in inverse space among SCZ and HC was an MEG study published by Hinkley et al. [15]. For each voxel, the authors computed the mean lagged alpha band connectivity with all remaining voxels (global connectivity). They found increased global connectivity in SCZ in the right inferior frontal gyrus and the left occipital gyrus, whereas decreased global connectivity was found in the right superior temporal gyrus and the left middle frontal gyrus and the precentral gyrus.

A later study by Lehmann et al. [16] investigated only medication-naïve patients. Lagged connectivity was computed between inverse solutions estimated for regions of interest (ROI) and in different frequency bands. The authors reported patients to have decreased connectivity between anterior and posterior ROIs in the lower alpha band and right-lateralized increased connectivity between anterior and posterior ROIs in the delta band.

Di Lorenzo et al. [17] found increased lagged connectivity in medicated SCZ in the delta, theta and beta bands, and the affected connections again were those predominantly linking anterior and posterior regions. In the alpha band, there was a decrease of lagged connectivity, mostly affecting connections among frontal regions but also including parietal parts of the brain. A theta band increase in lagged connectivity in patients was also reported by Andreou et al. [18], but found to be predominantly left lateralized, whereas another study by Shreekantiah Umesh et al. [19] that reported theta band lagged connectivity increases in remitted patients found increases between bilateral parietal and frontal regions.

The consensus among these studies seems difficult to name in terms of the involved regions, which may partially be explained by quite different analysis methods employed, differences in the statistical power and thresholds used and differences in the patients' clinical state and medication. Interestingly, these studies, however, converge well on the affected frequency bands and in the direction of the changes of differences in frequency bands. Delta, theta and beta lagged connectivity seems to be increased in patients, whereas alpha lagged connectivity tended to decrease. This pattern is reminiscent of the pattern of abnormalities that results when comparing spectral power between SCZ and HC, where delta, theta and beta power consistently tended to be increased and alpha power was (not as consistently) found to be decreased [20].

27.2.2 Non-lagged Measures of EEG Resting State Connectivity in Schizophrenia

Within the non-lagged measures of EEG connectivity that take volume conduction into account, there are a few studies that used a very global approach to compare SCZ and controls. These studies merely quantified how well the entire multichannel data recorded during an EEG epoch can be accounted for by the activity of

network activity defined by simultaneous, non-lagged oscillations of neuronal activity. One of these measures, the so-called omega-complexity, estimates the number of independent processes [21] that account for the measured EEG, whereas each of these processes can be considered to result from the activity of a network consisting of simultaneously oscillating regions. Another such measure is global field synchronization (GFS) that estimates, in the frequency domain, how much of the total variance of the signal can be explained by the activity of a single network of this type [22].

Papers using such global measures found differences between SCZ and HC that correspond to the results of the studies on lagged connectivity in an interesting way. Studies based on omega-complexity, which is a broad-band measure, found increased complexity in SCZ as compared to HC [23–26], which was taken as evidence for a "loosened cooperativity… of the active brain processes" [26]. This disconnection could mostly be accounted for by activity recorded at frontal electrodes. On the other side, the two existing studies on GFS in schizophrenia found that non-lagged type of connectivity explained less variance of theta band activity in patients, yielding lower GFS values [22, 24].

Despite all the differences in patient characteristics and methodological choices, the overall pattern that seems to emerge is that there is a shift from a non-lagged type of connectivity in HC, which is accounted for by low omega-complexity and high GFS values, towards interactions with a time delay in SCZ, which increases measures of lagged connectivity. Within this overall pattern, it seems that processes appearing in the theta band were most consistently affected by this shift.

The hypothesis that there may be an increased variance in the timing of neuronal connectivity in SCZ is interesting from several perspectives. Firstly, non-lagged type of neuronal co-activation is a candidate mechanism to account for the fact that multifaceted representations of environmental and mental information can apparently be perceived as something unitary, like seeing eyes and a nose and a mouth results in the unitary percept of a face. This "binding phenomenon" may be explained by time-locked activity of all local mechanisms that encode partial aspects of the mental representation, and the unity of the experience is encoded by the simultaneity of activation across the local processes [27]. If this apparent loosening of synchronicity indeed entails less unity on the level of the mental phenomenology, the hypothesis may help to account for the nature of some of the prominent positive symptoms, such as thought disorders, experiences of derealization and ego disturbances. Secondly, ERP responses to a broad range of stimuli are typically blunted in SCZ, which may be a result of increased variance in the timing of the activation of task-relevant processing resources, leading, as others have also suggested, to an increased cancellation of ERP signals by averaging. Finally, the fact that such a hypothesis makes statements about the organization of activity among network elements rather than the functioning of particular elements is supported by the limited success of trying to tie the diagnosis of schizophrenia to a localized structural or functional brain abnormality.

Despite this explanatory potential, the proposal that there may be an increased variance in the timing of neuronal co-activation in SCZ remains very global and is

uninformative about the kind of networks that may be primarily affected. In order to come to more specific conclusions, it is necessary and feasible to parse the measurements of brain activity into subcomponents that are defined by sufficiently similar dynamics of the involved processes. While several solutions to this problem exist, a coherent body of evidence on resting state EEG in schizophrenia has so far relied on the identification of so-called microstates [28]. EEG microstates represent subsecond time periods that can largely be accounted for by the activity of synchronous but potentially distributed activity in the brain. EEG microstates were found to cluster into a small set of highly replicable spatial configurations that have well-defined temporal parameters, such as their mean duration, their occurrence and the total time covered by each type of configuration.

The first report that a specific type of microstates was altered in schizophrenia was related to a microstate class labelled "D" that was later related to fronto-parietal executive control network functions [29]. This type of microstates was found to be shortened in medication-naïve acute SCZ as compared to HC [9]. This shortening was also correlated with the presence of paranoid-hallucinatory symptoms. The authors suggested that microstates of class D may have a protective role against psychotic experiences that is impaired when these states are shortened. A later study that compared EEG microstates in frequently hallucinating patients in time periods with vs without hallucinations could confirm the link of the shorting of this class D with the presence of hallucinations [30]. Microstate class D was also found to increase in patients that responded well to antipsychotic treatment, whereas no shortening of microstate class D before treatment and no increase of microstate class D duration were found in patients with a poor drug response [31].

Several studies found an increased count and an increased overall time spent in another type of microstates, the so-called class C, as recently summarized by a meta-analysis on microstate studies in schizophrenia [32]. This microstate class C appears to be related to salience processing [29]. Interestingly, the increase of microstate class C has also been found in adolescents with the 22q11 deletion syndrome, who have a 30 times higher risk to develop psychosis. The authors of this study suggested that this deviant microstate pattern may be related to aberrant salience mapping or to processes that are activated to compensate such deficits [33], which correspond well with the fact that antipsychotic medication typically interferes with neurotransmitter systems strongly involved in salience processing.

The pattern of alterations in EEG resting state microstates in SCZ reported so far and the patterns of EEG resting state microstate changes observed in studies investigating HC under different conditions allow us to draw a series of tentative explanations of these alterations. Firstly, in a large developmental study including subjects between 6 and 80 years of age, late adolescence was the time when microstate class C was found to be most frequent, and microstate class D least frequent [34]. This coincides with the typical age of onset of schizophrenia and supports the view that schizophrenia may be related to late neurodevelopmental problems. The other interesting aspect in the overall picture is that there seems to be a balance between microstates of classes C and D that is not only shifted in the favour of C during schizophrenia but also relates to particular state changes in HC in certain conditions. An overview of these observations can be found in the meta-analysis by

Rieger et al. [32]. In summary, the authors showed that this balance between microstates of classes C and D was consistently shifted towards C in HC when these subjects entered states that are characterized by reduced reality testing and monitoring of the self within its physical environment. The states found to be related to such shifts from D to C were, namely, hypnosis and sleep. These are states where attention-related updating of mental content from external-reality-close information, as assumingly observable through the presence of microstates of class D, is reduced, whereas the experiences reported by subjects often are characterized to be particularly salient, which are assumingly observable by the presence of microstate class C.

27.2.3 Future Directions

The present state of knowledge indicates that there are consistent abnormalities in EEG connectivity measures related to schizophrenia and that these findings can to some degree be interpreted within a common framework. The picture we have so far requires however further clarification in two aspects. Firstly, there is a broad variety of methodological approaches to EEG that use terms like "connectivity" but refer to mathematically very different and even incompatible concepts. This needs, on the long run, an overarching theoretical and empirical framework that permits us to differentiate patient groups not only in terms of more or less connectivity of a particular type but also in terms of changes of the type of connectivity that is observed and to draw conclusions about what type of connectivity is beneficial or detrimental for a healthy functioning. The second shortcoming of the current state of knowledge about EEG connectivity differences related to abnormalities in schizophrenia is that across the studies presented so far, there is a considerable heterogeneity of symptoms among the patients, which is yet to be insufficiently taken into account but must be expected to systematically relate to specific networks [35]. The current body of evidence gives hope that with EEG models of brain connectivity that can simultaneously account for non-lagged and lagged connectivity, combined with patient assessment approaches that are oriented towards biologically meaningful diagnostic entities, we may substantially increase our understanding of this disorder in the future.

27.3 Electrophysiological Markers of Transition to Psychosis

Yuko Higuchi and Tomiki Sumiyoshi

27.3.1 Introduction

Schizophrenia usually develops around the adolescence period, with the whole life risk of about 0.85%. It disturbs patients not only by positive symptoms (hallucinations, delusions, etc.) but also causing deterioration of daily/social functions and

seriously affecting patients' life. Early intervention into psychosis is a comprehensive and evidence-based approach aiming at detection and treatment of psychotic symptoms in their early stages, reducing the long-term adverse impact of psychosis and preventing relapses [36]. Shorter duration of untreated psychosis (DUP) has been associated with a greater response to antipsychotic drugs in terms of symptoms and quality of life. Contrary, prolonged DUP is associated with decreased levels of social functions, for example, work function and communication skills, as well as longer hospitalization [37, 38]. In this context, efforts have been directed to detect and immediately treat patients who are in early stage of psychosis. Recently, the importance of intervention to "prodromal stage" of schizophrenia has been also recognized. Operationalized criteria to detect putative prodromal symptoms of psychosis have been largely tested and used worldwide. These criteria are known as ultrahigh risk (UHR), clinical high risk (CHR) and at-risk mental states (ARMS) and allow the identification of subjects with about 30% risk of developing psychosis over a 2-year period [39], mostly schizophrenia-spectrum disorders. For early diagnosis, objective biomarkers, particularly those based on brain morphology, neurophysiology and neuropsychology, have been proposed to provide information [40–42]. However, reliable measurement tools are not confirmed. Therefore, much effort is going on to detect biological markers for diagnosing psychotic disease. In this section, we describe neurophysiological findings, particularly event-related potentials.

27.3.2 Event-Related Potentials (ERPs)

ERP is one of the methods to assess the brain function using EEG. It occurs in response to an internal or external event. We can get quantitatively information about some aspects of cognitive disturbance, by measuring parameters such as amplitude or the latency of ERPs. The ERPs are recorded using an electroencephalograph and a stimulator (e.g. auditory or visual). It is a simple and noninvasive procedure, and efforts on patients are minimum. Recently, some ERPs are thought to be useful as trait markers of schizophrenia. Especially, P300 and mismatch negativity (MMN) have been widely used for this purpose.

P300 recordings are performed usually as follows: EEG is recorded in electrical and sound shield room, and low-probability (around 10–20%) target stimuli are presented intermixed with frequent standard stimuli. Target stimuli differ from standard ones in physical characteristics (tones of different frequencies, e.g. 1000 vs 2000 Hz, or durations, e.g. 50 vs 100 ms, different pictures and so on). For P300, subjects are requested to pay attention to the target stimuli carefully and perform a task, (e.g. to press a button promptly in response to infrequent target stimuli), while for MMN subjects have to ignore the stimuli. Thus, while P300 indexes task-related attentional and categorization processes, MMN is a sensory memory-based brain response to any discriminable change occurring in a stream of stimuli, in the absence of attention [43], indexing pre-attentive change detection. In patients with psychosis, both ERP components are altered. Furthermore, using the MMN recording

paradigm, a further component can be elicited: the P3a, a component indexing the automatic allocation of attention to changes in the environment.

Light et al. [44] in their large consortium study (about 1000 SCZ) obtained reliable MMN/P3a measurements by using a simple two-channel recording system, in relatively modest recording conditions (e.g. usually lacking sound proofing and/or electrical shielding of recording rooms with often little local expertise in electrophysiology). They concluded that MMN/P3a recording can be added as biomarkers to multisite clinical studies without specialized EEG research centres. For this reason, widely clinical application is expected in the future.

27.3.3 P300 in Psychotic Disorders

SCZ show smaller amplitudes of P300 than HC. Meta-analysis showed that the effect size for the P300 amplitude reduction in schizophrenia was 0.85 and for the P300 latency augmentation was −0.57 [45]. Further, Ozgurdal et al. [46] indicated that reduction of P300 amplitudes has been also noted in subjects with ARMS. Frommann et al. [47] also report that smaller P300 amplitudes are present prior to a putative onset of psychosis in high-risk individuals, and the abnormalities of late initial prodromal state (LIPS) were more severe than early initial prodromal state (EIPS) for psychosis. Thus, some evidences indicate that P300 is useful as biomarker of psychotic disorders.

However, several confounds should be taken into account when using P300 as a biomarker. It requires vigilance and motivation might influence the results. For example, if a patient is in an acute catatonic stupor state, or has severe symptoms, which prevent collaboration, P300 cannot be recorded. Furthermore, some studies have reported that P300 amplitude is affected by various factors, including medication, e.g. olanzapine, clozapine and perospirone [48–50]. Bramon et al. [45] also described in their meta-analysis (1) the P300 amplitude was significantly more abnormal in drug-free than in medicated patients and (2) on the contrary, the presence/absence of antipsychotic treatment did not have a significant effect on the P300 latency. Other studies and a meta-analysis did not report any effect of medication status on P300 amplitude [51].

27.3.4 P300 in Subjects at Risk for Psychosis

There are few studies about P300 for electrophysiological marker of transition to psychosis. van Tricht et al. [52] found that P300 amplitudes at Pz were significantly smaller in UHR-T (who later made the transition to overt psychosis) patients compared to UHR-NT (who did not make the transition) subjects. On the other hand, Bramon et al. [53] described that compared to the cases remaining at risk, the individuals making a transition to psychosis did not significantly differ in their P300 or N100 amplitudes and latencies. We also measured P300 in HC, ARMS subjects and SCZ. The mean amplitudes were smaller in schizophrenia group compared to other

groups. There were no significant differences in latency. Both P300 parameters were not statistically different between ARMS converter and non-converter.

27.3.5 MMN in Schizophrenia Patients

As for P300, abnormalities of MMN in SCZ were repeatedly reported. There are about 200 articles in peer-reviewed international journals reporting a MMN amplitude reduction in SCZ, and the effect size is over 0.95 [54]. Several other psychiatric disorders (i.e. bipolar disorder with psychotic features, major depressive disorder, borderline personality disorder, Alzheimer's disease) show none or smaller reductions in MMN than schizophrenia [55–57] even when cognitive impairment or psychotic symptoms were more severe than in the schizophrenia group [55]. Recent meta-analysis, including affective disorders, indicates high specificity of schizophrenia [54].

Unlike P300, MMN has several advantages: (1) no or minimal collaboration is required from subjects, so the influence of their motivation and ability is small, (2) drowsiness (even at stage REM) does not impede the recording of MMN, and (3) the influence of psychotropic drugs commonly used for schizophrenia is little (e.g. dopamine antagonists, benzodiazepines) [58, 59].

There are several types of MMNs, such as duration MMN (dMMN) and frequency MMN (fMMN), based on the mode of presentation of target stimuli. The impairment of dMMN for schizophrenia is greater than that of fMMN [60], with the latter emerging only in the chronic, but not early stage of schizophrenia [61]. Thus, dMMN can be a more sensitive marker than fMMN, in the context of early psychosis. Haigh et al. [61] demonstrated in their meta-analysis that in subjects at disease onset, no reduction of fMMN was found compared to HC (Cohen's $d < 0.04$), whereas small-to-medium reduction of dMMN was found (Cohen's $d = 0.47$) [61]. Generally, dMMN appears to mainly index the trait aspect of schizophrenia, whereas fMMN may be more closely related to the state aspect of the pathological process [62]. Several studies also showed that the dMMN amplitude of chronic schizophrenia was lower than in first-episode schizophrenia [63, 64]. Thus, dMMN amplitude also is gradually reduced by the progress of clinical stage.

27.3.6 MMN in Clinical High-Risk Subjects

Recently, several studies reported dMMN amplitude reduction already in the prodromal stage of schizophrenia. We measured dMMN/P3a/reorienting negativity complex in ARMS subjects, first-episode schizophrenia (FES) and 19 HC participants [63]. During the follow-up period (2.2 years), 4 out of the 19 ARMS subjects transitioned to schizophrenia (converters), while 15 did not (non-converters). Figure 27.2 indicates that dMMN amplitudes of converters were significantly smaller than those of non-converters before onset of the illness. dMMN amplitudes of non-converters did not differ from those of HC, while converters showed significantly smaller dMMN amplitudes compared to HC. Our data confirm that

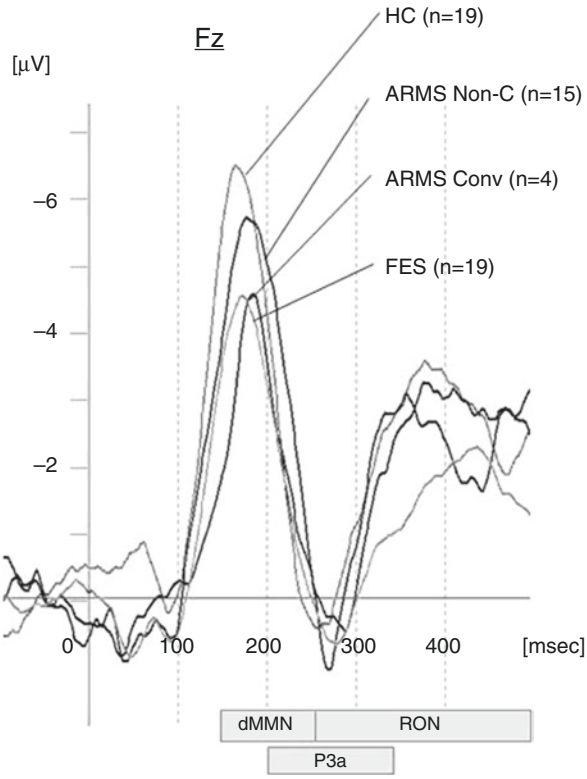

Fig. 27.2 Duration mismatch negativity (dMMN)/P3a/reorienting negativity (RON) complex waveforms at the Fz lead. Waveforms are represented for healthy controls (HC), ARMS converters (Conv) and non-converters (Non-C) and first-episode schizophrenia (FES). MMN, P3a and RON peaks were identified within the 150–250 ms, 200–350 ms and 250–500 ms search windows, respectively

diminished dMMN amplitudes provide a biomarker, which is present before and after the development of psychosis. There are some meta-analysis and review articles, which discussed this issue. Nagai et al. [65] reviewed MMN in schizophrenia and ARMS patients, considering both dMMN and fMMN. They concluded that dMMN amplitude reduces before the onset of psychosis and may be a significant predictor of the conversion to psychosis. Erickson et al. [54] showed, in their meta-analysis, that the CHR participants exhibited a modest effect size of 0.40 for differences with respect to HC. They also calculate a separate effect size for converters and non-converters that was 0.79 and 0.17, respectively, with converter showing significantly higher effect size.

As described above, several evidences about low dMMN amplitude of high-risk subjects accumulated. However, the question of whether we use dMMN as a biomarker of schizophrenia is still open. For example, Naatanen et al. [62] report that the transition may indicate a quantitative change on an illness dimension rather than categorical change from "healthy" to "ill", so a single time point recording of MMN to predict transition is unlikely to be an optimal approach. Moreover, MMN has some "interindividual" difference but is surprisingly stable "intra-individual", in longitudinal dMMN measurements. It was reported that MMN amplitude shows a reduction with aging [66]. If a subject does not have any trait of schizophrenia, MMN decline is not found across repeated measurements, except for the age-appropriate

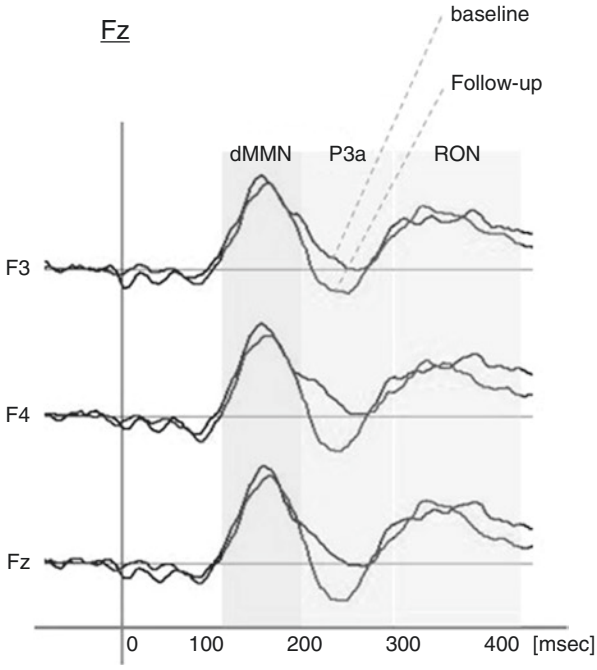

Fig. 27.3 Duration mismatch negativity (dMMN)/P3a complex grand-average waveforms (n = 15) at the Fz lead. Waveforms are represented for ARMS non-converter at baseline and follow-up [2.4 (±1.6) years later]

decline. The key information is coming from the potential change of MMN versus the individual baseline, thus giving an index of a trajectory of individual illness progression [62]. We measured dMMN longitudinally in ARMS subjects (preliminary data, Fig. 27.3). All subjects received interventions, including CBT and/or antipsychotic drugs. All subjects did not convert to overt psychosis including schizophrenia during the observation period (2.4 ± 1.6 years). dMMN reduced little and didn't reach significance. On the other hand, P3a amplitudes were increased at frontal leads.

In summary, ARMS subjects without reductions of dMMN amplitudes are unlikely to develop psychosis, indicating usefulness as a trait marker. On the other hand, P3a amplitudes are subject to change according to clinical status. Further investigation is needed to examine the role for MMN/P3a/RON complex in the prediction of transition to psychosis.

27.3.7 Conclusions

P300 amplitude is reduced and its latency is prolonged in schizophrenia. P300 amplitude might be affected by medication and patients' condition, so caution is needed when using P300 as biomarker of schizophrenia risk. On the other hand, MMN is considered to be relatively free from these confounding factors. Reduction of MMN amplitude in schizophrenia is robust, and evidence for diminished dMMN amplitude

in ARMS has accumulated. Thus, reduction in dMMN amplitudes before the onset of psychosis may provide a more robust marker of the conversion to psychosis.

27.4 Electrophysiological Alterations and Psychopathological Dimensions in Schizophrenia

Annarita Vignapiano, Giulia Maria Giordano, Antonella Amodio, and Armida Mucci

27.4.1 Introduction

Reflecting the progress in the conceptualization of schizophrenia as heterogeneous syndrome, DSM-V places emphasis on its psychopathological dimensions. Many factor-analytic studies of psychopathological ratings allowed to identify negative, positive, disorganization dimensions that do not appear to be affected by age, severity of symptoms and chronicity of the illness.

Numerous studies revealed abnormalities of ERPs in subjects with schizophrenia that might be related to different symptom dimensions and presumably contribute to the psychopathology of the disease [67, 68].

ERPs are indices of the physiological underpinning of different functions such as early perception and attention (P50, N100, P200), automatic allocation of attention (P3a), task-related effortful processes (P3b; Fig. 27.4), automatic or preconscious processes (MMN), semantic memory (N400) and anticipation [contingent negative variation (CNV), stimulus-preceding negativity (SPN)] or evaluation [feedback-related negativity (FRN)] of reward.

Several studies have used ERPs to investigate the neurobiological basis of symptom dimensions in schizophrenia, particularly the positive, negative and disorganized dimensions, but the findings are inconsistent.

In the next sections of this paragraph, we will overview the electrophysiological correlates of the different symptom dimensions and review the pathophysiological hypotheses related to these correlates.

27.4.2 Electrophysiological Alterations and Positive Dimension

Delusions and hallucinations are considered hallmark symptoms of schizophrenia. These symptoms can become chronic, causing an impaired quality of life. Current treatments, including antipsychotics, exhibit variable effectiveness against them.

P50, N100, P300, MMN and N400 are ERP components more frequently investigated in association with positive symptoms.

According to the hypothesis that positive symptoms in schizophrenia might be underpinned by information overload due to sensory gating deficits, several ERP components related to gating and early attentive processes, such as P50 and N100, were investigated.

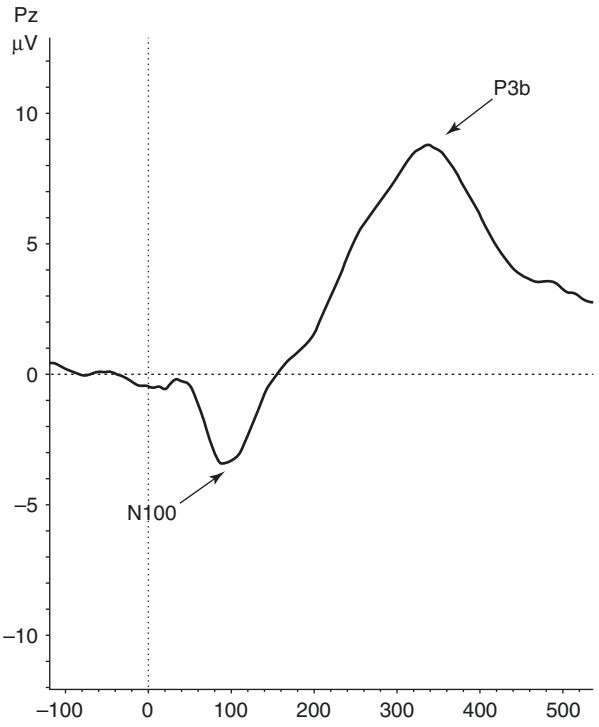

Fig. 27.4 Example of N100-P3b like waveform time-locked to the target stimulus at the Pz lead in healthy controls

P50 appears approximately 50 ms after the presentation of auditory stimuli; its amplitude reduction with stimuli repetition is thought to index sensory gating, known to be impaired in SCZ [68].

An association of P50 abnormalities with auditory hallucinations and delusional thoughts was reported in some but not all studies [69, 70].

N100 is a negative component that appears about 100 ms following an auditory stimulus (Fig. 27.4), generated from primary and secondary auditory cortical areas. Some studies revealed that N100 amplitude reduction in SCZ was related to the severity and experience of hallucinations [71, 72], suggesting a top-down stimulation of auditory cortex, which reduced the reactivity to external stimuli. N100 abnormalities might be related to abnormalities of the so-called corollary discharge, a neural signal involved in the recognition of self-generated signals [73, 74].

Pre-attentive sensory processing, as indexed by MMN abnormalities, is also impaired in SCZ (see the third paragraph of this chapter for information on the MMN). The reduction of MMN amplitude was related to the presence and severity of positive symptoms [75], particularly to auditory hallucinations [76]. These data suggest that impairment of early integration of information might subtend positive symptomatology.

P300 subcomponents abnormalities were consistently reported in schizophrenia [51] (see the third paragraph of this chapter for information on P300) and were

differently related to positive symptoms [77]. P3a amplitude was associated with the predisposition to auditory hallucination and their severity, while P3b was related to the presence and severity of hallucinations and delusions [74]. However, several studies failed to find any association between P3b amplitude and positive symptoms [68].

In addition to difficulties in early processes, SCZ showed an impairment of information integration and semantic memory as revealed by abnormalities of N400, a negativity peaking at approximately 400 ms, after presentation of any potentially meaningful stimulus [78]. According to some authors, this impairment might explain the persistence of the delusions despite the awareness of contradictory information [79].

In conclusion, the current literature suggests that positive symptoms might be related to an aberrant intrinsic organization of functional brain networks, leading to alterations of sensory gating, an incorrect perception of the environment due to reduced integration of information [80] and a failure in corollary discharge [74].

27.4.3 Electrophysiological Alterations and Negative Dimension

Negative symptoms have long been recognized as a core dimension of schizophrenia, have a strong impact on quality of life and social functioning and do not respond to pharmacological treatment. They can be grouped into two domains: a motivation-related domain, referred to as avolition, including apathy, anhedonia and asociality, and an expression-related domain, referred to as diminished expression, including alogia and blunted affect [81]. Negative symptoms represent a heterogeneous clinical construct, including primary symptoms and secondary symptoms caused by other factors, such as positive symptoms, depression, social deprivation, substance abuse and antipsychotic medications [82, 83]. Primary and enduring negative symptoms, with distinct neurobiological and clinical correlates, characterize a schizophrenia subtype named deficit schizophrenia (DS) [83].

The findings concerning the associations of ERP abnormalities with negative symptoms have been controversial, in particular for P50-N100 sensory gating abnormalities and P300 or MMN amplitude reduction [67, 84].

Recent research was devoted to the study of negative symptom domains. Avolition is related to a deficit of motivation, and several aspects of this complex construct were found impaired in SCZ, with the exception of the hedonic experience [85]. In particular, SCZ seem to have difficulties in the anticipation and evaluation of reward [86] that were partially reflected by abnormalities in CNV, SPN and FRN [87, 88]. The CNV is a slow negative wave, related to preparatory attention, motivation and anticipation of salient stimuli. Two independent studies did not find any relationship between early and late components of CNV and anhedonia or negative symptoms [88, 89]. Moreover, in the latter study, during a monetary incentive delay task, the authors found an association of early P300 abnormalities with social anhedonia but not with the negative symptom domains. These findings suggested that negative symptoms might have multiple pathophysiological mechanisms and that motivation and anhedonia might be partially independent constructs.

SPN is a negative ERP component involved in anticipation of feedback, and it has been found to be correlated with trait anhedonia [88].

FRN is related to the brain activity in the anterior cingulate cortex; it is sensitive to the expectedness of the feedback as well as to feedback valence [87]. Horan et al. [90] reported that FRN amplitude difference between positive and negative feedback correlated with positive symptoms, a result probably due to the use of the Brief Psychiatric Rating Scale (BPRS) that does not evaluate the motivation-related domain of negative symptoms.

Few studies investigated ERPs in patients with deficit schizophrenia [91–93]. An amplitude reduction of P300 was found over the left temporal region in patients with NDS and in both this region and the right parietal region in patients with DS [93]. Mucci et al. [92] revealed a double dissociation of ERP abnormalities: patients with NDS showed a left-side reduction of the P300 component, while patients with DS showed a reduced amplitude of the N100 over the scalp central leads. In the study conducted by Li et al. [91], the authors found that NDS showed delayed latency of P3b and DS showed delayed point A in CNV that correlated with global functioning but not with individual negative symptoms. Furthermore, both DS and NDS showed similar abnormalities in N100, MMN, P3a, CNV amplitude and P50 gating. In conclusion, it is difficult to identify electrophysiological abnormalities associated with negative symptoms, probably due to their heterogeneity or to the tendency of different authors to examine one specific ERP component, rather than several components.

27.4.4 Electrophysiological Alterations and Disorganization Dimension

Disorganization has been recognized as a longitudinally stable symptom domain that is present since the earliest manifestation of the illness [94]. A variety of studies have reported different definitions, including heterogeneous symptoms, such as inappropriate affect, poverty of content of speech, positive and negative aspects of thought disorder, attentional deficits and sometimes bizarre behaviour [95].

Few neurophysiological studies have analysed ERP components, such as P50, N100, P200, P300 and N400, related to disorganization dimension, reporting inconsistent findings.

P50 sensory gating abnormalities have been associated with vigilance and sustained attention [96]. In SCZ and in schizotypal individuals, a significant relationship between disorganization and P50 suppression deficits was observed [97], suggesting that disorganization might be underpinned by difficulties in inhibiting information at early pre-attentive stage.

As regard to other ERP components, Williams et al. [98] found an association of disorganization with increased latency of N100, P200, P300 and decreased P200 amplitude, that might suggest a widespread disturbance in the control of information processing.

Moreover, an association of disorganization with a reduction of posterior P300 amplitude was found in young recent-onset SCZ [99]. Since the posterior P300

indicates the subsequent updating of memory of the current situation, these observations suggested that disorganization was related to an impairment in memory function, which occurred in the early stage of the disease [100].

Some studies focused on specific aspects of disorganization, such as disorganized speech, which was found related to an impairment in how concepts are elaborated in semantic memory, as indexed by abnormalities in N400 [78]. Some N400 studies observed that SCZ had deficits in the use of semantic context and hyperactivity of the semantic network, the last more prominent in presence of a formal thought disorder that might be described as a more general "conceptual disorganization" [78, 101]. These findings were not corroborated by other studies [102, 103].

Current literature is unable to clarify ERP abnormalities associated with disorganization probably due to the extremely heterogeneous aspects included in this dimension and the failure of instruments to detect its core aspects.

Conclusions

In this paragraph, we provided an overview of electrophysiological correlates of schizophrenia dimensions. The findings suggest that SCZ have ERP deficits from the early phase of sensory processing (i.e. P50, N100, N400) to the relatively late phase (i.e. P300, N400) and in the anticipation and evaluation of salient stimuli (CNV, SPN, FRN). These abnormalities have been found to correlate with different psychopathological symptom domains; however, no conclusion can be drawn as findings were inconsistent and conflicting [67, 68, 77]. Discrepancy in literature findings was partly due to heterogeneity in the definition and assessment of psychopathological dimensions, which represents a major obstacle to progress in schizophrenia research. Another possible reason for inconsistencies might be related to poor control of confounding variables, such as cognitive dysfunctions, often observed in SCZ and rarely assessed by the reviewed studies, which might contribute to different ERP abnormalities. Finally, the most recent pathophysiological models of schizophrenia indicate a diffuse disconnectivity and lack of coordination among neural networks, which might lead to different cognitive and behavioural manifestations and multiple ERP abnormalities. According to these models, schizophrenia involves substantial inter- and intra-individual variability. Future studies should better characterize symptom dimensions, systematically assess cognitive dysfunctions and study multiple components of the ERPs, as well as resting state dysfunctions and the relationships among them.

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