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Нейрофизиологические маркёры как связующее звено между генами и поведением: примеры из редких генетических синдромов, ассоциированных с расстройством аутистического спектра

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АННОТАЦИЯ

С редкими генетическими синдромами, ассоциированными с расстройствами аутистического спектра, связаны ряд неинвазивных нейрофизиологических маркёров, которые могут быть сопоставлены с молекулярно-генетическими характеристиками и поведенческими особенностями при данных заболеваниях. Так, для недавно открытого синдрома Потоцки–Люпски, связываемого с нарушениями в сегменте 17p11.2, выявлена ранее не описанная эпилептиформная активность — пилообразная гиперсинхронизация на частоте 13 Гц, что может свидетельствовать об определённом типе нарушений баланса возбуждения/торможения в нейронных сетях. Для редкого случая микродупликации в гене *SHANK3*, также связываемого с синдромом Фелан–МакДермид, описана цепочка взаимосвязей от нарушения в функционировании белка SHANK3 через искажённое взаимодействие возбуждающих и тормозных нейронов, прежде всего связанных с гипофункцией N-метил-D-аспартат-рецепторов на тормозных нейронах, до сниженного временного разрешения слуховой коры, отражающегося в отсутствие ответа следования за 40 Гц слуховой стимуляции (40 Гц auditory steady-state response) и лежащего в основе проблем в речевом развитии. Для синдрома Ретта, вызванного аномалиями в гене *MECP2*, который имеет очень широкое влияние на многие другие гены, нейрофизиологические находки тоже многообразны. Среди самых многообещающих — изменения в сенсомоторном ритме, потенциально связанные с ключевым симптомом болезни (стереотипными движениями рук), а также более запоздалая латенция основных компонентов вызванных потенциалов мозга, что может оказывать каскадный эффект на обработку информации и влиять на восприятие базовой информации, включая и речевую. Данный обзор посвящён представлению концепции нейрофизиологического профиля, построение которого для подобных заболеваний может помочь не только объективизировать диагностику нарушений развития, но построить механистическую цепочку от гена к поведению.

Ключевые слова: расстройство аутистического спектра; неинвазивные нейрофизиологические маркёры; электроэнцефалография; ЭЭГ; вызванные потенциалы; ВП; синдром Ретта; синдром Фелан–МакДермид; синдром Потоцки–Люпски.

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Neurophysiological markers that link genes and behavior in humans: examples from rare genetic syndromes associated with autism spectrum disorders

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ABSTRACT

Rare genetic syndromes associated with autism spectrum disorders have several noninvasive neurophysiological markers that can be linked with molecular genetic characteristics and behavioral characteristics in these diseases. For the recently discovered Potocki–Lupski syndrome associated with disturbances on the 17p11.2 segment, a previously undescribed epileptiform activity was detected, characterized by a saw-like hypersynchronization at a frequency of 13 Hz, which may indicate a certain type of disturbance in the excitation/inhibition balance in neural networks. For a rare case of microduplication in *SH3* and ankyrin repeat domains 3 (*SHANK3*), also associated with the Phelan–McDermid syndrome, we described a pathway from a violation in the functioning of the SHANK3 protein, through a distorted interaction of excitatory and inhibitory neurons, primarily associated with hypofunction of N-methyl-D-aspartate receptors on inhibitory neurons, to reduced temporal resolution in the auditory cortex, reflected in the absence of response following 40 Hz auditory stimulation (40 Hz auditory steady-state response) and underlying problems in speech development. For the Rett syndrome, which is caused by a mutation in methyl CpG binding protein 2 (*MECP2*), which has a very wide influence on many other genes, the neurophysiological findings were also diverse. Among the most promising are changes in sensorimotor rhythm, potentially associated with a key symptom of the disease, namely, stereotyped hand movements, as well as more delayed latency of the main components of the event-related potentials, which can have a cascading effect on information processing and affect the perception of basic information, including speech.

This review focuses on the presentation of the concept of a neurophysiological profile, the construction of which can help not only to objectify the diagnosis of developmental disorders, but also in the construction of a mechanistic chain from gene to behavior.

Keywords: autism spectrum disorder; noninvasive neurophysiological marker; electroencephalography; EEG; event-related potentials; ERP; Rett syndrome; Phelan–McDermid syndrome; Potocki–Lupski syndrome.

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PROMISES OF NEUROPHYSIOLOGICAL CHARACTERISTICS

It is a great challenge to assess sensory and cognitive functions in a person who cannot speak and cannot follow instructions. Fortunately, most people have these inabilities only quite early in life, limiting this challenging period to early childhood. The problems persist in many cases of neurodevelopmental disorders, in which deficits in voluntary actions and behavior can be quite dramatic. This is especially the case in the rare genetic syndromes, in which most psychological standardized tools for assessment cognitive and sensory functions are not working properly. Additionally, some subtle dysfunctions in basic sensory or cognitive processes might be undetectable with available behavioral tools, but can be revealed with neurophysiological methods (e.g., EEG). Electrophysiology (EEG), a method for noninvasive recording of neuronal activity, has great potential to reveal brain mechanisms underlying neurodevelopmental problems and can be used as a diagnostic tool [1, 2]. The inspiring example of the universal application of EEG in the early diagnostics of hearing disorder (brain stem auditory evoked potentials) has resulted in provision of the necessary treatment for early stages of hearing loss to thousands of children, thereby preventing a massive yearly burden of public health impairment that would otherwise result from untreated early hearing deficits. Unfortunately, reliable biomarkers of neurodevelopmental disorders that might constitute direct targets of intervention in the clinical setting have not been developed yet, although some potential neurophysiological biomarkers, related to basic sensory functions, have been proposed [3–7]. A high temporal resolution of EEG enables the assessment of the subtle dynamics of neuronal processes related to sensory and cognitive functions. Another advantage of EEG is that the abnormal sensory event-related potential (ERP) components can be recorded even in populations with problems of communication.

One of the most common forms of developmental disorders in childhood is autism spectrum disorders (ASD), characterized by pronounced changes in social interaction and communication, as well as problems in the sensorimotor system, stereotyped behavior, and difficulties with motor regulation. Studies of ASD are hindered by the difficulties of diagnosis due to the high etiological heterogeneity of the disease. Development of an effective neurophysiological marker can contribute to solving the problem of heterogeneity by forming groups of patients with similar parameters of brain activity, which may have a similar etiology of the disease. In this context, it becomes especially relevant to study the pathophysiology of rare genetic syndromes associated with ASD, such as Rett syndrome (RS), Phelan–McDermid syndrome (PMS), Potocki–Lupski syndrome (PTLS), the etiology of which has already been documented to some extent. Recently, more and more genetic mutations/rare genetic variants that underlie human developmental disorders have been identified, and new genetic syndromes have appeared in medical nosologies. However, despite all these breakthroughs, we still do not understand the mechanistic relationship between genes, brain processes, and behavior. The study of the systemic processes of the brain, as an intermediate link reflecting the work of neural networks and closely related with mental processes can help in understanding these complex genes and behavior interactions.

The importance of studying genetic syndromes is also emphasized by the direct possibility of creating an animal model of these disorders by modifying the known gene or genes and exploring the process at a deeper neurobiological level. These animal models usually show the behavioral phenotype that corresponds to ASD symptoms. The psychophysiological phenotype might be a better option for translation between animals and humans as it has more similarity between animals and humans than generally subjectively assessed behavioral characteristics. As all pharmacological treatment options for ASD are first examined in animals, having an objective reliable phenotype that can be translated from animals into humans and back is crucial for the progress in the field.

In this paper, I provide some examples of the application of the above-mentioned approach to neurodevelopmental disorders caused by abnormalities in molecular genetic pathways, primarily associated with the transcriptional protein methyl CpG binding protein 2 *(MECP2)*, observed in RS, as well as associated with the structure-forming protein of the postsynaptic membrane SH3 and ankyrin repeat domain *(SHANK3)*, observed in PMS, and PTLS.

POTOCKI–LUPSKI AND UNIQUE CLINICAL EEG MARKERS: SAW-LIKE SHARP WAVES WITH A FREQUENCY OF 13 HZ

Potocki–Lupski syndrome is one of the recently described genetic disorders [8]. It occurs approximately 1 in 25,000 live births. Its main cause is interstitial duplication in 17p11.2 (length of about 3.7 Mb). This region includes several genes, such as *RAI1*, *SREBF1*, *DRG2*, *LLGL1*, *SHMT1*, and *ZFP179* [9, 10]. There is no clear understanding of which gene/genes contribute to the disorder, although some animal models have already been examined [11].

As summarized in recent reviews [12, scoping review part in 13], PTLS is characterized by a wide range of congenital abnormalities, including mild dysmorphic features, hypotonia, failure-to-thrive in infancy, as well as ophthalmic, orthopedic, cardiovascular, oropharyngeal, and renal anomalies. At the behavioral level, PTLS might cause developmental delay, speech and language disorders, and borderline to

severe intellectual disability (ID). Other features include deficits in executive functions and aggressivity, anxiety, withdrawal, and features of attention-deficit/hyperactivity disorder. The prevalence of the ASD phenotype in PTLS ranges from 38 to 80% and some researchers propose the 17p11.2 as a new region implicated in the genetics of ASD [14, 15].

At the brain level, history of seizures, and microcephaly are reported in PTLS, whereas EEG phenotype was not extensively studied [13]. Particularly, sporadic paroxysmal EEG abnormalities without clinical correlates were reported in 12–45% of cases [8, 16–18].

As PTLS patients are very rare, even one patient with PTLS might provide useful insights into gene-brain-behavior interaction. In this paper, I cite recent case reports of a 13-year-old Russian female child with confirmed *de novo* duplication 17p11.2 [13, 19]. The extensive examination of her resting state by the expert in clinical EEG interpretation revealed two types of atypical paroxysmal EEG abnormalities, which had not been previously reported in patients with the same pathology. One was the very unique pattern — saw-like sharp waves with a frequency of 13 Hz — had not been seen previously by the clinician who performed the analysis as well as her colleagues — all with multi years' experience in clinical EEG, and, to the best of our knowledge, were not reported in the literature known to us either in ASD-associated syndromes in particular or for neurodevelopmental disorders in general. However, a more comprehensive and systematic investigation of this issue in the literature is certainly required. Whether this unique EEG pattern can be related to the particular gene affected and what the mechanistic link between this neurophysiological feature and molecular genetic functioning calls for further examination.

Also, this recent study, in addition to the above-described pattern, revealed another quite rare feature in clinical EEG — the atypical peak–slow wave patterns. This EEG abnormality was previously reported in girls with RS associated with the later onset of the disease [20]. We shall discuss this finding further in the section related to RS. As for the case-report of the PTLS patient, the power spectral density of the resting state EEG did not show considerable differences between the present patient and the cohort of her healthy peers. The values of nonlinear features such as Hjorth parameters and Fractal Dimension were noticeably lower in this PTLS patient than in her peers. Such non-stationary departures of the EEG signal, although not commonly applied in EEG practice, indicate a promise for the future research in the clinical population [21–23].

PHELAN–MCDERMID SYNDROME AND 40 HZ AUDITORY STEADY-STATE RESPONSE (ASSR)

Phelan–McDermid syndrome also known as 22q13 deletion syndrome, is a neurodevelopmental disorder, associated with ASD [24]. Its estimated prevalence is between 1:15000 and 1:8000 [25]. The affected 22q13 locus contains several genes with *SHANK3* being the major candidate gene. The protein product of *SHANK3* is a scaffolding protein in postsynaptic glutamate receptors, including mGluRs (metabotropic glutamate receptors), N-methyl-D-aspartate (NMDA), and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors [26, 27]. There is a link between *SHANK3* deletion and parvalbumin (PV) expression and functioning of the GABAergic interneurons for the PMS phenotype [28–31], confirming the crucial role of inhibition in the development of PMS. The severity of symptoms positively correlates with deletion sizes [25].

Core features of PMS include ID ranging from mild to severe, delayed or absent expressive speech, and moderate to profound developmental delay [32, 33]. Patients also show decreased sensitivity and hyporeactivity [34]. The prevalence of autism in PMS is very high and varies from 50 to 75% [25, 32]. Other characteristics of PMS are hypotonia, gait disturbances, minor dysmorphic features as well as gastrointestinal, renal, and cardiac problems.

At neurophysiological level, patients with PMS have a high risk of developing seizures with a reported prevalence of 40–63% [35, 36], and an even higher occurrence of epileptiform and disorganized activity, with a general slowing of background EEG [37, 38]. Spectral EEG changes in PMS include generalized slowing of activity, reduced occipital α rhythm [38–41], and decreased β and γ rhythms [42]. In studies of evoked potentials, patients show a decrease in the amplitude of the early components (P50 and P60-N75) in the auditory and visual modalities, as well as a decrease in the amplitude of P2 and a stronger habituation in response to repeated tones [34].

The most interesting result that directly map into molecular genetics, cellular, and systematic studies is the link between 40 Hz ASSR and SHANK3 abnormalities. This response is visible on the EEG as a rhythm that matches the frequency of stimulation, thus, indexing temporal resolution of the auditory cortex. At cellular and molecular levels, it is related to a disruption in the functioning of NMDA receptors on parvalbumin interneurons [43]. In this paper, I review a case-report of a 15-year-old girl with a rare partial *SHANK3* duplication (the first seven exons of the *SHANK3* gene (22q13.33)) [6]. Her phenotype includes microcephaly, mild mental retardation, and learning disabilities, dysgraphia, dyslexia, and smaller vocabulary than that of typically developing peers, as well as mild autistic symptoms that were below the threshold for ASD diagnosis. This description resembles the PMS phenotype as well as that of previously described patients with 22q13.33 microduplications (≈30 cases reported so far). Whereas this patient had no structural brain abnormalities evident at magnetic resonance imaging scans, no seizures, and relatively preserved auditory ERP with slightly attenuated P1, her 40 Hz ASSR was totally absent. Thus, the following path, relating speech perception

problems and SHANK3 abnormalities, can be suggested: *SHANK3* gene abnormalities — deviation in SHANK3 protein (key scaffolding protein of the postsynaptic density of the excitatory neurons) — dysregulation within excitatory synapses — abnormal interaction of excitatory and inhibitory interneurons (e.g., hypofunctioning of NMDA receptor of the PV+ interneurons) — absence of 40 Hz ASSR — reduction in temporal resolution of auditory cortex — language problems.

RETT SYNDROME — SET OF NEUROPHYSIOLOGICAL MARKERS

Rett syndrome is a neurodevelopmental disorder with a prevalence of about 1 in 15000 live births. It is mainly caused by mutations in the *MECP2* gene located on the X chromosome. Its protein product, MECP2 protein, interacts with a repressor complex of HDACs (Histone deacetylases) and SIN3A proteins to repress gene transcription [44, 45] and also acts as a transcriptional activator [46]. *MECP2* affects the activity of more than 60 molecular pathways, including those involved in spine morphology, dendritic complexity, and mTOR (mammalian target of rapamycin) signaling vital for cell growth and metabolism [46]. *MECP2* disruption in GABAergic neurons only seems enough to cause symptoms in mice models [47], pointing to the crucial role of inhibition in the development of RS. Similar findings were recorded in our previous work [34].

Rett syndrome is characterized by a typical development for 18–36 months before a regression. During regression, motor and speech skills may be lost, and epilepsy may develop. One of the core features of RS are characteristic stereotypic hand movements (e.g., washing movements). Other characteristics include hypotonia, breathing irregularities, and intellectual disabilities. Autistic symptoms occur in 60% of patients [48], whereas, before the onset of severe motor impairment, children with RS may be diagnosed with autism, and autistic features are more pronounced with milder motor symptoms [49]. Among the above-described syndromes, RS has the most severe phenotype with just a few patients being able to walk independently or speak after the regression stage, having also drastic problems with voluntary hand movements. Thus, the degree of preservation of sensory, perceptual, and cognitive functioning is hard to assess, making it even more crucial to search for neurophysiological markers that might shed more light on this question.

At the brain level, microcephaly is often reported, whereas no structural brain abnormalities are generally established. About 50–90% patients with RS are diagnosed with epilepsy [7]. Semiology of seizures varies with the most common being generalized seizures, tonic-clonic seizures, and complex partial seizures. Centro temporal spikes (CTS) is one of the most frequent epileptiform abnormalities in RS that might reflect alternation of excitation/inhibition balance in the perisylvian cortical areas contributing to motor disturbances and speech disturbances observed in these patients [50–53]. One of the properties of the CTS in RS is its suppression by hand movements linking it to the mu-rhythm activity. Mu-rhythm is a sensorimotor rhythm at the frequency of 9–13 Hz that is related to motor function, imitation, and cognitive control [54–57]. During typical development it has maximum over the central sites and attenuates in response to active or passive hand movements. Patients with RS show a similar pattern of response, but their mu-rhythm has abnormally low frequency [57, 58]. Recent large scale clinical EEG study of RS supplemented with longitudinal case-report [20] introduced a new index to assess sensorimotor rhythm abnormalities in clinical EEG — frequency rate index. It is measured as the ratio between high- and low frequency power of sensorimotor rhythm and reflects the range of variability of the frequencies of this rhythm. This index is low in RS, indicating an attenuation in the proportion of the upper band of sensorimotor rhythm in RS. Additionally, this novel sensory-motor index showed a significant relationship with severity of disease both in longitudinal case and group analysis, suggesting that they are clinically relevant neurophysiological parameters. Whether abnormalities in this index indicate only the RS group or also other neurodevelopmental disorders requires further examination. This study also confirms general slowing of background EEG in RS. Other finding extends the knowledge of quantitative EEG abnormalities into long-range temporal correlation; it was attenuated in RS, resembling ASD findings as well as those in other neurodevelopmental disorders [59].

The rare atypical peak–slow wave patterns recorded in a 13-year-old Russian female child with confirmed *de novo* duplication 17p11.2 (PTLS) [16] was also observed in a patient with RS, associated with the later onset of the disease [20]. We can speculate that such atypical peak–slow wave patterns are associated with atypical facial movements looking like a grimace as they were observed in both of these cases. As the molecular genetic paths of RS and PTLS have no clear-cut link, there is need for bioinformatic analysis to capitalize on the reported neurophysiological findings.

There are potential biomarkers of RS among the characteristics of ERP. ERP components are generally delayed across all sensory modalities both in RS patients and in its animal models [2]. This abnormality might underlie the perceptual and cognitive deficits observed in RS, and can have cascading effects. Interpretation of neurophysiological phenotype is not straightforward as studies on RS animal models show that even similar ERP alterations in auditory and visual domains might have a diverse neural basis. One of the ERP abnormalities is auditory ERP in response to tones and phonemes [60]. Their early components are preserved, whereas the later ones (P2 and N2) are impaired. These deficits characterize the ERP in response to both tone and phonemes. Problems with neurophysiological differentiation of tones (absence of mismatch negativity response), presented at slow rates, have been observed in RS patients,

suggesting atypically quick fading of neuronal representation of stimuli and fast neuronal adaptation [61].

In summary, neurophysiological markers can be classified into the common or specific to particular neurodevelopmental disorders, which constellations allows to characterize individual cases of the disorder and ideally link them to the treatment strategy.

FUTURE PERSPECTIVE AND CHALLENGES

Understanding the relationship between genes and the psyche is vital as it can provide new perspectives in the diagnosis and treatment of various neurological and psychiatric diseases. Psychophysiology can serve as a response to the great challenges of society in understanding the neurophysiological foundations of developmental disorders. The study of rare genetic diseases in which the pathophysiological process is most pronounced will allow understanding of the mechanism that is only partially involved in other pathologies. Disorders with various etiologies can be hidden under the "umbrella" of ASD. Identifying patterns of neurophysiological processes of syndromes associated with autism will enable identification of subtypes of ASD and development of personalized medicine rooted in understanding the disturbed biological pathway based on objective biomarkers.

Noninvasive brain mapping techniques, such as EEG, allow objective measures of brain function, identifying underlying cortical network dynamics, and provide biomarkers for assessment of sensory and cognitive functions at which information flow may be breaking down. A combination of EEG/ERP parameters allows building of a psychophysiological portrait of developmental disorders of various etiologies. Modern analytical algorithms (clustering, machine learning, and artificial neural networks) can be used to identify the most important parameters of the electrophysiological profile, e.g., related to acoustic perception to differentiate developmental disorders determined by various molecular genetic pathways and the typically developing group in a multidimensional psychophysiological space. The obtained psychophysiological profiles and aggregate electrophysiological measures will potentially be used in clinical trials to evaluate treatment efficiency as objective quantitative measures of brain function (i.e., neuromarkers) that can be tracked in a noninvasive and unbiased manner.

However, several obstacles prevent direct implementation of the above-described approach in clinical practice. Firstly, the experimental procedures should be refined to improve their usability for individual-level testing in a clinical setting and ideally for infants. Currently, there are no translational neurophysiological characteristics that can be measured noninvasively and are linked to known underlying molecular genetic mechanisms. In this study, I emphasized importance of the 40 Hz ASSR, described above, and a recently developed paradigm, to track ERP changes related to long-term potentiation phenomena (LTP) studied originally in animals at the molecular/cellular level [62–65]. Such a paradigm includes a short period of sensory tetanization, presentation of click at a rate of about 13 Hz in auditory and 9 Hz at visual modality that induce LTP-like changes in ERP [66–68]. Although current results on this paradigm are inconsistent and unimpressive, the approach that uses the experimental paradigm for human studies from already established approaches in animals seems promising. Additionally, there is a need for assessment of the distribution/heritability of the biomarkers of risk in the general population. Furthermore, there is a need for common experimental protocols as well as analytical approaches that were agreed to be used across multiple research or clinical groups.

One of the tools that can be used to fulfill this goal is a recently developed crowdsourcing platform for Automatic Labeling of Independent Components in Electroencephalography, ALICE, http://alice.adase.org/ [69]). A toolbox automatically classifies independent EEG components. The ALICE system has been tested on several datasets obtained from various age groups and various data markers. ALICE allows marking and detecting artifacts (eye movements, linear noise, channel artifact, heartbeat artifact, muscle activity), as well as brain activity (alpha rhythm, mu-rhythm). ALICE's long-term goal is to unite the efforts of experts from neuroscience, neurophysiology, and other related areas, that are vital in developing a machine learning model that could be used in EEG studies for the objective assessment of various artifacts as well as identification of clinically relevant features (e.g., epileptiform activity or mu- alpha rhythm ICA components differentiation). Overall, for a rapid implementation of the idea of neurophysiological profiles in clinical practice, a large multisite consortium is needed.

CONCLUSION

This article introduced the concept of a neurophysiological profile, which combines noninvasive neurophysiological markers with molecular genetic underpinnings and behavioral characteristics. The development and implementation of this approach still require substantial effort, but the above described neurophysiological markers of rare genetic syndromes associated with ASD provides the first step into this endeavor.

ADDITIONAL INFORMATION

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