EEG-biofeedback u pacientů se schizofrenií: další možnost ovlivnění kognitivního deficitu?

EEG biofeedback in patients with schizophrenia: another possibility to influence cognitive deficit?

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Souhrn: Přehledový článek pojednává o aplikaci EEG-biofeedbacku u pacientů se schizofrenií se zaměřením na oblast kognitivních funkcí. EEG-biofeedback je forma neurofeedbacku, při kterém dochází k záměrnému ovlivňování mozkové aktivity prostřednictvím jejího reálného záznamu za pomoci EEG. Pacient je aktivním účastníkem při léčbě, což hraje svou roli při kognitivní remediaci. Je zde předkládán přehled abnormalit v oblasti EEG záznamů u pacientů se schizofrenií. Současně předkládáme podrobný popis dosavadních studií věnujících se aplikaci EEG-biofeedbacku u schizofrenie i jiných neuropsychiatrických poruch a pozornost je věnována i nedostatkům těchto studí. V závěru se snažíme shrnout přínosy aplikace této metody.

Summary: This paper reviews the application of the EEG-biofeedback in the treatment of schizophrenia, with a focus on cognitive function. EEG biofeedback is a type of neurofeedback, that allows the deliberate influence brain activity through real EEG record. The patient is an active participant in his own treatment, which is an important fact for cognitive remediation. We present the summary of abnormalities in EEG record in schizophrenia patients. We also bring forward detailed description of up to date studies using the EEG-biofeedback in schizophrenia and other neuropsychiatric disorders, and we focus on the drawbacks of these studies. At the end of the review we try to summarize the benefits of EEG-biofeedback.

Klíčová slova: biofeedback, neurofeedback, elektroencefalografie, schizofrenie, kognitivní remediace

Keywords: biofeedback, neurofeedback, electroencephalography, schizophrenia, cognitive remediation

Introduction

One of the long-lasting symptoms of schizhophrenia is cognitive deficit. Even in cases when both positive and negative symptoms are succesfully treated, patients with schizophrenia exhibit difficulties – especially in connection with memory process, attention and verbal abilities (van Erp et al., 2015; Loughland et al., 2007; Fioravanti et al., 2005), this complicates their attempts to return to daily functioning and succesfull integration into employment is nearly impossible for them. As a result, cognitive deficit can negatively affect patients‘ compliance during treatment (El-Missiryet al., 2015) and lower their quality of life (Savilla et al., 2008; Ritsner, 2007). It is appropriate to search for new posibilities that would contribute in strenghtening weakened areas and offer a new way to live a full life.

At the moment, there are attempts to pharmacologically modulate cognitive deficit, mostly by using second generation antipsychotics (so-called atypical neuroleptics). Despite the encouraging results of some of the studies, the resulting clinical effect is insufficiently robust (Keefe et al., 2007). Non-pharmagolocial methods are also in development. Cognitive remediation/cognitive trainings are a standart part of treatments for schizophrenia (McGurk, 2009, Wykes 2011). Patients work in groups or individually and they do exercises that target the weakened areas using either pen-paper method or computers. An important precondition for the success of these exercises is their regularity, even after hospitalization. Using modern devices, such as computers, as mentioned before, or tablets for example, the patients can exercise even when they are at home. The impact of cognitive deficit can also be reduced by activities, which are not primarily focused on it. Among these activities belong individual or family psychotherapy, psychoeducational programs, training social skills, etc. In this case, the main factor is probably patient’s increased self-acceptance and self-confidence and development of metacognitive thinking. Although there are studies that confirm the efectiveness of cognitive remediation (O'Reilly et al. 2016; Deste et al., 2015; Bowie et al. 2014), it is still necessary to search for new possibilities that could deepen the process, especially from the long-term point of view.

Modern stimulation methods are curently more and more often used to support the effectiveness of cognitive remediation. Their main advantage is, that thay are noninvasive, painless and with minimal side effects. Among the most frequently applied belong for example repetitive magnetic stimulation (rTMS; Fitzgerald et al., 2008, Mohr et al., 2006) or direct current stimulation (tDCS; Hoy et al. 2014). Another option is using EEG-biofeedback, which proved to be effective for other psychiatric disorders as well, e.g. obsessive-compulsive disorder (Kopřivová et. al, 2013; Xiaopeng et al., 2014) or depression (Siepmann 2008; Walker, Lawson, 2013). There are several reasons for using EEG-biofeedback during cognitive remediation. Similarly to stimulation methods, biofeedback is a simple and noninvasive method with minimal side effects. However, unlike with tDCS or rTMS, where the patient is usually a passive receiver, during EEG-biofeedback, the patient is engaged in the process. During the session, the patient is active and their self-awareness is being deepened in connection to the development of metacognition. The remaining question is, whether the schizophrenia patients are suitable adepts for this method and whether it can actually be benefitial for them. We are attempting tofind an answer by comparing results of researches that used this method and were conducted on schizophrenia patients or patients with other psychiatric disorders.

Cognitive deficit in schizophrenia

Cognitive deficit is one of the core symptoms of schizophrenia (Harvey, Gold, 1993; Wilk et al., 2005). According to meta-analysis Mesholam-Gately et al. (2009), during the first episode, there is a noticable deficit in all neuropsychological domains, which causes an overall decrease in cognition. At first, the most affected are verbal memory and speed of information processing. Fattourous-Bergmann et al. (2014) came to a similar conclusion in their meta-analysis focused on patients who did not receive treatment. These patients too experienced impairment of verbal memory, working memory and speed of information processing. Neuropsychological profile of chronic forms is similar to first episodes (Saykin et al., 1994). Fioravanti et al. (2005, 2012) created a meta-analysis, which included all the studies from the years 1900-2010, which were focused on evaluating cognitive functions of schizophrenia patients. It was very difficult for the authors to process all the data in regards to the stage of the illness since each study defines e.g. a chronic patient by different criteria. Therefore, they decided to include all the studies, regardless of the stage of illness. Despite the high heterogeneity of the specimen, the authors came to similar conclusions. They describe a cognition decline in all areas. The areas that exhibited the most significant difference in comparison to the control groups were memory, verbal skills and attention. Although the cognitive deficit persists even after the acute stage of the illness is over, its resulting form is influenced by the chosen type of medication. Atypical antipsychotics have more global effect on cognition in comparison to classical antipsychotics. Specific improvements were observed in the areas of learning and speed of information processing (Woodward, et al. 2005). Besides the type of medication, another important factor is the severity of negative symptomatology or the premorbid level of intellect (Fitzgerald et al., 2004).

EEG-biofeedback

Biofeedback is an umbrella term, which labels all influencing of autonomic reactions of the body. From galvanic skin tension to body temperature and heart rate. In recent years, the term neurofeedback has emerged and it refers to modulation of brain activity, e.g. using magnetic resonance or EEG. Using neurofeedback can support normal brain functioning, as shown in studies conducted on ADHD/ADD syndrome patients (Lubar, 1991; Thompson, Thompson, 1998). The neurofeedback method is based on the process of learning – in particular mostly on the principle of operant conditioning (Surmeli et al., 2012). Patients immediately receive information

about their brain activity in the form of visual or audio record, usually through a game (e.g. controlling a rocket). If they manage to alter their brain activity, they are rewarded with audio or visual record (e.g. they earn points). Operant conditioning is a universal mechanism of learning appearing everywhere in the animal kingdom (Kandel, 2001). Thus, the induced changes should become permanent. Specifically for EEG-biofeedback, the brain activity modification is achieved by using EEG. The electrical brain activity is recorded with an electroencephalograph. The recording is a result of spatial and temporal summation of postsynaptic potentials, which are generated by neurons. The results are recorded with great temporal accuracy (Bareš et al. 2006). Current innovations in this field are new methods of quantitative electroencephalography (QEEG), which uses computers to convert continuous analog signal into a digital form (Šóš, 2013). The advantage of such biofeedback is the possibility to either train several areas simultaneously or to focus on functional connectivity. On the other hand, the institutions that use this new method must have all the necessary equipment at their disposal, but it is far more expensive than the equipment for the „standard" EEG-biofeedback.

EEG-biofeedback and psychiatric disorders

The EEG-biofeedback method has been applied during treatments of many different psychiatric disorders. Historically, research was most often conducted on ADHD patients. Review article Arns et al. (2013) focuses mainly on the most recent research. According to the authors, until 2009 there was a large number of presented studies that confirmed that biofeedback has a positive effect, especially on attention and impulsivity. However, it was not before the following years that studies which included comparison where placebo started to appear. Only after considering this aspect, it can be said that the standard protocols of biofeedback, such as modulation of theta/beta waves, training sensorimotor waves (SMR) and slow cortical potentials, can be considered clinically effective on ADHD patients. Review article Hammond (2005) includes several studies that describe a positive effect of neurobeedback on reducing anxiety and depression levels. Xiaopeng et al. (2014) applied EEG-biofeedback on 40 patients with OCD and they tracked changes in clinical manifestation (assessed according to The Yale Brown Obssessive Compulsive Scale) and in cognition (RBANS). The research took 8 weeks with the interval 5 sessions per week, each session was 24 minutes long. At the beginning, the probands were acquainted with the machine. In each session, they were reminded about the relaxation techniques, which were supposed to allow them to better concentrate on brain activity modulation, in particular on alpha and theta waves and SMR. The comparison of the results from the beginning and from after the research showed that 86,5% of probands achieved clinical improvement. Statistically significant differences were observed in the following areas (RBANS): longterm memory, attention and total score. The authors assume that improvement of cognition is a result of clinical improvement of the OCD symptoms. Thompson et al. (2009) focus on abnormalities in EEG recordings from Asperger syndrome patients. They conducted an extensive study using QEEG and they neuroanatomically compared the results with the symptoms described for this disorder. The authors then followed up by using EEG-biofeedback on Asperger syndrome patients (Thompson et al., 2010). It was 40-60 sessions in combination with metacognitive training focused on e.g. social understanding or spatial imagination. The patients had to give them feedback about the level of relaxation and whether they were able to focus well. The authors describe significant improvements in the area of attention (T.O.V.A and IVA) and in clinical symptoms of this disorder (assessed: Australian Scale for Asperger's Syndrome, Conners' Global Index, SNAP version of the DSM-IV criteria for ADHD, and the ADD-Q). At the same time, the probands reached on average 9 points more than before in the total score of Wechsler's intelligence test. We were not able to find any other similar study concerning schizophrenia patients.

EEG-biofeedback and schizophrenia

Abnormalities in EEG recordings of schizophrenia patients

In a normal recording of an adult person who is fully awake (relaxed with their eyes closed), there are characteristic alpha waves over the rear quadrants, as well as beta activity of central and frontal areas and also theta activity, which is less prominent and it is mostly in temporal areas. The EEG recordings of schizophrenia patients show a great amount of abnormalities. These abnormalities get associated with aspects relevant to the illness (type of medication, treatment duration, number of suffered episodes, etc.). Some abnormalities can already be observed during the first episodes of the illness and thus it can be considered to be a result of neurological changes caused by schizophrenia. In connection to cognitive deficit, it is often mentioned that there is lower amount of gray matter in the frontal and temporal lobe areas.

In this paragraph, we will attempt to summarize all the areas that are usually associated with abnormalities in EEG recordings. Begić et. al (2000) focused their study on groups of patients whose dominating symptoms of schizophrenia were positive or negative. The only difference between these forms was in the delta and theta waves in the frontal area. Greater differences appeared in the comparison between patients and a healthy control group. The patients differed in delta, theta, alpha and beta 2 waves. Manchanda observed EEG abnormalities and their connection to the length of the illness after three (2008) and then after five years of treatment (2014). At the beginning of the treatment, there was no significant difference in the intensity of exhibited symptoms between the patients with normal, borderline and dysrhytmic EEG. During the treatment, the condition of all patients improved (evaluated according to SANS and SAPS scale). After five years, at the end of the study, the persisting negative and positive symptoms of patients with dysrhytmic EEG were statistically most significant. Based on these results, the authors presume that abnormal EEG of schizophrenia patients predicts a worse prognosis of the illness. The influence of medication is also an often discussed cause of abnormalities in EEG recordings. Amann et al. (2003) confirmed in their research that EEG abnormalities are strongly related to treatments with haloperidol and quetiapin. On the other hand, the newest olanzapine does not cause such significant changes, probably because of a different mechanism of action. The study by Ramos et al. (2001) states, that the different reaction to medication influences the EEG recording. The research group for their study consisted of ten pharmacoresistant patients, ten previously treated patients in remission and ten healthy probands (the control group). All of them were right handed men, paired based on their age and education. The patients placed in the pharmacoresistant group had to meet a certain condition – the symptoms of their illness must have been persistent for over two years. The results showed that EEG recordings of resistent and previously treated patients were different. Thus the authors presume that EEG recording might predict the patient‘s reaction to treatment. Shrivastava et al. (2014) focused on the influence of clozapine. They traced EEG abnormalities in two thirds of patients with their first schizophrenic episodes. After clozapine treatments, the number of patients with EEG abnormalities has increased significantly. At the beginning of the research, 40 % of the patients had abnormal EEG recording. At the end of the research, the number rose up to 75 %. Haloperidol treatments seem to cause a decrease of delta waves and an increase of theta and beta waves (Kemali et al. 1992). It is evident, that in a certain way, antipsychotic medication modulates the electrical activity in the brain. Assuming that schizophrenia causes weakening of connections in certain areas of the cortex which leads to functional damage, Jalili et al. (2010) analysed EEG synchronization of schizophrenia patients. EEG synchronization is a method that analyses signal and allows evaluation of changes in basic EEG activity in any frequency bands (Bočková, Rektor 2009). The most prominent desynchronization that the schizophrenia patients exhibited was in the area of alpha and beta waves, which correlated with the length of the illness and with the negative symptomatology (Jalili et al. 2010).

However, Sponheim et al. (1994) had not confirmed the existence of differences between EEG recordings of chronic patients and patients who experienced their first episode. Both groups showed increased delta and theta activity, while their alpha activity was decreased. Thus the results imply that certain EEG abnormalities do not depend on the type of medication or the length of illness. In connection to these findings, Itil et al. (1974) claims that abnormalities in case of untreated patients are a permanent feature of schizophrenic disorder. Clementz et al. (1994) focused on patients who experienced their first schizophrenic episode. In comparison to the control group, their delta and theta waves were increased, while the alpha waves were decreased. The authors consider these abnormalities to be permanent, but nonspecific. Patients with bipolar affective disorder show similar results. According to Clementz et al. (1994), these abnormalities are often interpreted as results of subcortical changes during schizophrenia development.

Very interesting are also researches dedicated to abnormalities in the gamma spectrum. Higher cognitive processes are often associated with the oscilation of gamma waves in the prefrontal cortex area. During processing of complex tasks, schizophrenia patients exhibit lower frequency of these waves (Spencer et al. 2004) as well as decreased synchronicity (Spencer et al. 2003). The authors associate these results with neuroanatomical and physiological changes described for schizophrenia, such as white matter deficit or decrease of excitatory impulses that enter pyramidal cells.

In conclusion, EEG abnormalities most often appear as decreased alpha activity (8-13 Hz) and increased delta and theta activity (1-8 Hz). These abnormalities can appear during the first episodes (of unmedicated patients), which is why it is probably connected to pathophysiological changes that accompany schizophrenic disorders. Most of the authors also confirm that the number of abnormalities (and desynchronization of signal) increases in connection to the chronicity of illness and type of medication. With a focus on the area of cognitive deficit of schizophrenia patients, the abnormalities in the gamma spectrum which are connected to the function of the prefrontal cortex seem to be the most important.

An overview of existing researches

We searched in EBSCO and PubMed databases. The following table contains an overview of the studies; we mostly drew from the Cothran, Larson (2012) comprehensive review article. The authors list only five studies dedicated to EEG-biofeedback of schizophrenia patients. Currently, the most discussed study is Surmeli et al. (2012), which proved that biofeedback has a longterm positive effect on treatment. Unfortunately, the authors in their article present an inaccurate description of the sessions. That makes their research hardly replicable and it is often a subject of criticism by other authors. There were 48 probands who participated in the study, their primary diagnosis was schizophrenia, medicated, previously hospitalized. At the beginning of the study, each proband got their EEG measured. In order to get the "cleanest" possible recordings, the patients got their medication suspended for a certain period of time. It is questionable whether suspending medication is ethical. The EEG recordings were processed and compared to the norm. The deviation from normal EEG was calculated for each patient. After that, all probands attended several EEG-biofeedback sessions (on average it was 58,5 sessions in 24-91 days). The aim was to get the EEG recording as close to normal as possible. 47 patients experienced an improvement of clinical signs (assessed according to PANSS scale). This result is very impressive, but as mentioned before, the study is missing a description of sessions and EEG-biofeedback application. In a study by Gruzelier et al. (1999), the patients were divided based on their hemispheric dominance to "active" with more active left hemisphere and to "withdrawn" with more active right hemisphere. Clinical picture of "active" patients showed prevailing positive symptoms of schizophrenia (qualitative cognitive impairment, hallucinations, emotional lability, hyperactivity). In case of "withdrawn" patients, the

prevailing symptoms were negative, such as emotional bluntness, social withdrawal, motoric slowing. Then the probands completed biofeedback training (10 sessions, in each they got 60 tasks divided into 3 segments). The biofeedback was in a form of a game – controlling a rocket that moved according to activity of the desired hemisphere (and also suppressing activity of the dominant hemisphere). After completing all of the sessions, the authors noticed that anxiety and tension levels of the probands have decreased while reduction of positive symptoms was only minimal (assessed according to PANSS scale). The authors were mainly attempting to verify, if the patients themselves could influence interhemispheric asymmetry, which would help their treatment. All of the probands learnt how to control the rocket, but the authors did an analysis and found out that regardless of hemispheric dominance, the patients had different performance levels. They were divided into two groups – good and average. "Good" probands learnt how to suppress activity of the dominant hemisphere faster and easier (depending on activation of the opposing hemisphere). Then the authors focused on the performance levels of these groups during sessions. During the first and the second segment, the difference in performance between the two groups was minimal, but during the third segment of tasks, the difference was obvious. This is why the authors assume that the ability to learn of both groups is on the same level. The cause for the difference is probably connected to attention deficit. At the end of the session, the "average" patients had difficulty paying attention and their performance levels decreased. This led the authors to believe that negative symptomatology does not influence the ability to learn using biofeedback, because both groups included patients with good and average performance. The performance during sessions did not depend on their hemispheric dominance and set of clinical symptoms. The authors suppose that the difference is caused by different ways of experiencing anxiety during session, but it would be appropriate to further examine this area. In their overview, Schoenberg, Sierra, David (2012) list three studies dedicated to biofeedback and schizophrenia. One of the studies is Schneider, Pope (1982), which focuses on modulation of slow cortical potentials, see table 1. It confirms that patients are able to modulate their brain activity. However, the induced changes are not permanent, the learning effect has not been proved. The other two studies do not deal with EEG-biofeedback.

Discussion

As we stated in the introduction, the need to search for new possibilities that would lead to strenghtening of cognitive remediation is still great. There are several reasons why it is difficult to effectively modulate it. Meta-analysis (Bora, Murray) from 2014 included 25 studies, it was focused on patients who experienced their first schizophrenic episode and on a group of respondents with a great risk of possible development of the illness. This meta-analysis proves that cognitive deficit is already easily recognizable in prodromal phase. It is not a neurodegenerative disease and it is possible to train cognitive functions in a suitable way in an attempt to lower the negative impact of the disease. However, assessing the effectiveness of the methods used is very difficult considering the high number of variables. Ranging from personality, patient's motivation and external aspects (support from the family, social integration, course of the disease, effects of medication, etc.) to the influence of the examinators, whose behavior and attitude towards patients may of course differ. Interpretation of the results must be done with caution. It is not adequate to seek universally valid conclusions, but rather to try to specify the group of patients, who will benefit from the given method.

Conducted studies have proved that application of EEG-biofeedback in treatment of schizophrenia has its merits. Especially, it seems that in this regard, the ability to learn is not dependent on negative symptomatology (gruzelier et al., 1999). At the same time, it can improve patients' clinical state (Surmeli et al., 2012). However, the area of EEG-biofeedback application has also several fundamental deficiencies. On the neurological level, the description of certain characteristic neuropsychological profiles or neurological abnormalities is missing.

Considering the unspecific recording of EEG activity of schizophrenia patients, it is appropriate to first compare EEG recordings from the research group with normal EEG recordings, and then determine which wavelenghts will be modulated specifically for the given group. Similarly, as it is for example in Kopřivová et al. (2013) study, where EEG-biofeedback was applied on OCD patients. Another thing that is missing is a deeper elaboration of cognitive profile in connection to EEG abnormalities. Contemporary studies do not include a specific description of the level of cognition before and after application of biofeedback. The research methodology is also very different. Future studies should either focus on patients with first schizophrenic episode or elaborate on more narrow problematics (e.g. abnormalities connected to medication, abnormalities of related patients). It is important to verify the effectiveness of EEG-biofeedback not only with tests, but also by attempting to connect it to imaging techniques that can confirm whether there are any functional changhes during application. That way, the method's effectiveness would not be proved merely on the basis of patient's subjective evaluation. Related research could then more closely specify what cognitive profile is suitable for the application and which areas can be expected to improve. The course of session should be emphasised during application of EEG-biofeedback. It is important that the patients trust the method and feel comfortable during the session to motivate them to cooperate. EEG-biofeedback could then become not only a tool for support of cognitive remediation, but also for development of patients' volitional components. As we stated in the introduction, during the session, the patient experiences a sense of control over their activity, which contributes to overall conscious control and may lead to development of metacognition.

Conclusion

EEG-biofeedback can be an effective supporting method during cognitive remediation of schizophrenia patients. Its use is painless and the patients actively participate in the treatment, which also increases their compliance. Improvement can be anticipated mostly in the area of self-control and metacognition, areas that affect patient's functioning in everyday life. In this context, one of the possibilities is modulation of gamma waves in prefrontal cortex area, which is responsible for higher cognitive processes, although this spectrum is not normally scanned. Application of EEG-biofeedback on different groups of patients seems to be effective. However, contemporary research about EEG-biofeedback and schizophrenia lacks deeper systematic elaboration. EEG abnormities of schizophrenia are nonspecific, which is why it is required to be more consistent when establishing the research plan. Focus should be not only on variables such as length of illness or type of medication, but neurological findings and the degree of cognitive deficit should be taken into consideration as well. For application of this method, it seems to be more suitable, when the condition of the patients has been stable for a long period of time. The best way to verify the effectiveness of this and other methods is using longitudinal research design. The principle of EEG-biofeedback is based on the process of learning, which is well preserved in most schizophrenia patients. With regards to this, it can be presumed that application of this method can be succesful. However finding a suitable scale for measuring the success of this method is problematic. If these shortcomings can be overcome, biofeedback could be applied as a supporting factor to the current cognitive remediation for schizophrenia.

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Table 1: overview of studies concerned with the effect of EEG-biofeedback on schizophrenia patients

Authors	Research group	Frequency of sessions	Research objective	Results	Duration of change
Schneider, Pope (1982)	9 schizophrenia patients	5 sessions	Brain activity was changed in a similar manner to when antipsychotics are used.	It is possible to modulate EEG activity.	Changes were observed only during sessions, but not in between sessions.
Schneider et al. (1992)	12 hospitalized medicated patients (men) and 12 healthy men .	20 sessions, each consisted of 110 tasks in consecutive days.	Influencing delta and theta waves (slow cortical potentials).	At the end of the study, the probands were able to modulate their brain activity in reaction to stimulus (same as the control group after 5 sessions).	The effect lasted only during sessions. No longterm effect.
Gruzelier et al. (1999)	16 patients divided according to their hemispheric dominance.	10 sessions, 60 tasks in each, divided into 3 segments.	Self-regulation using interhemispheric asymmetry.	Using interhemispheric asymmetry during biofeedback.	Partial – the authors suggest shorter but more intensive and individual sessions.
Boleo, 2010	70 patients with chronic schizophrenia.	130 sessions in 18 months. Length of sessions was 5 – 60 minutes.	Improvement of clinical condition, the author recommends strenhghtening alpha waves in the right parietal region and inhibiting delta and fast beta waves in frontal area.	70 patients experienced improvement in self-regulation, cognition and affectivity.	Improvements lasted even after two years.
Surmeli et al. (2012)	51 probands (25 men and 26 women, average age 28,82).	Average number of sessions was 58,5, the sessions were 60 minutes long. Duration 24 – 91 days.	Comparison of EEG recording with NxLink databasis.	3 patients did not complete all sessions, 47 out of 48 experienced improvement (according to PANNS scale).	Changes lasted even after stimulation – during the following 22 months 40 patients remained under observation.

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