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Content

Animal Models of Schizophrenia with a Focus on Models Targeting NMDA Receptors

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Abstract

Schizophrenia is a serious and often devastating disease, affecting approximately 1% of worldwide population. Animal models represent a suitable way for investigating serious brain diseases in preclinical research. Animal models of schizophrenia can be generally divided into several categories that include pharmacological, genetic and neurodevelopmental models. Pharmacological models are usually based on application of specific receptor ligands for neurotransmitters. Genetic models are created by genetic manipulations (mutations; often in laboratory mice). Neurodevelopmental models are induced by manipulations in early stages of life of the laboratory animal. They are manifested later in juvenile or adult age by phenotypes that are similar to schizophrenia symptoms. This review summarizes and discusses pharmacological models of schizophrenia based on application of NMDA receptor antagonists; furthermore, the study focuses on selected genetic and neurodevelopmental models.

Keywords

Schizophrenia, animal models, pharmacological models, genetic models, neurodevelopmental models, preclinical studies

Schizophrenia is a serious, complex and devastating mental disease that affects about 1% of the worldwide population (Sartorius et al., 1986). It usually manifests in late adolescence, generally earlier in men than in women (Castle et al., 1998). Many patients show deficits in areas such as social behavior (Allen et al., 2005), intellectual abilities (Amminger et al., 2000) and motor functions (Rosso et al., 2000). The symptoms of schizophrenia can be divided into positive (hallucinations, delusions, thought disorders), negative (disorder in social interactions, motivation, disorder of natural speech, anhedonia) and cognitive impairment which includes difficulties with attention, working memory, visual retrieval and intelligence (Andreasen, 1995).

Modeling human neuropsychiatric diseases such as schizophrenia is difficult partly because of the complexity of the disease but mainly because the psychological states typical for human diseases are hard to observe in animals or are not accessible at all. Therefore, researchers often focus on changes in behavior or cerebral physiology or try to derive analogies that with a certain degree of simplification reflect the clinical symptoms in patients. Currently, there is no animal model that would encompass all the features and symptoms of schizophrenia. However, a series of pharmacological neurodevelopmental and genetic models that mimic certain states of the disease and are used for developing potential antipsychotic medication have been developed (Jones et al, 2011). The most common animal models are the rodents, but primates such as capuchins (Shiigi and Casey, 1999), squirrel monkeys (Boyce et al., 1991) or vervets (Ridley et al., 1982) can also be used. The interesting fact is that some pharmacological models that used blockers of N-methyl-D-aspartate (NMDA) receptors were tested even in aquarium fish, namely in zebrafish (Danio rerio) (Seibt et al., 2011).

All animal models should have adequate validity. The validity should be phenomenological, which specifies to what extent the changes in behavior in an animal are similar to changes in a human, constructive,

which reflects the theoretical and neurobiological findings and pathology, and predictive, which show the expected pharmacological response to the treatment, that is used in clinical practice (Jones et al., 2011). In the following text a brief overview of the most common models will be provided.

Pharmacological animal models

Pharmacological models are based on acute or chronic application of substances modulating the neurotransmitter (receptor) systems. Among the most used belong e. g. the dopamine agonists such as amphetamine (Ellison et al., 1981) or apomorphine (Swerdlow and Geyer, 1993), selective agonists of serotonin receptors such as 8-OH-DPAT (Arvidsson et al., 1981), selective antagonists of serotonin receptors including also (S)-WAY 100135 (Cliffe et al., 1993), WAY- 100635 (Mathis et al., 1994) or M100907 (Schimdt et al., 1992), or antagonists of NMDA receptors such as phencyclidine (PCP) (Noda et al., 1995), ketamine (Krystal et al., 1994), MK-801 (Andino et al., 1999) and D-AP5 (Hauber and Schimdt, 1989). This paper will henceforward focus on glutamatergic animal models of schizophrenia.

Glutamatergic models

Glutamatergic hypothesis of schizophrenia posits that the endogenous dysfunction of neurotransmission mediated by NMDA receptors may contribute to the pathogenesis of schizophrenia. It is believed that low doses of PCP and ketamine selectively and non-competitively block NMDA receptors so that they bind to a site in the ion pore that is associated with these receptors (Javitt and Zukin, 1991). As mentioned before, the psychopharmacological studies in humans (Krystal et al., 1994) and behavioral studies in laboratory animals (Koek et al., 1988) suggest that the antagonists of NMDA receptors induce schizophrenia-like symptoms (Javitt and Zukin, 1991) on which the model is based. Ketamine (Swerdlow et al., 1998), PCP and MK-801 reduce the prepulse inhibition in laboratory animals (Mansbach and Geyer, 1989); furthermore, the antagonists of NMDA receptors affect also certain aspects of sensory processing (Sillito et al., 1990).

Ketamine

Ketamine is a dissociative anesthetic that was synthesized in 1962. During its administration in healthy volunteers in **subanesthetic** doses, short-term and temporary changes in behavior that are similar to positive, negative and even to cognitive symptoms of schizophrenia occur (Adler et al., 1999; Krystal et al. 1994). Ketamine also worsens the psychotic symptoms in schizophrenia patients (Lahti et al., 1995). In healthy subjects, psychotomimetic effects are significantly reduced by clozapine, the atypical antipsychotic. However, the effects are not blocked by conventional antipsychotics of older generation (Malhotra et al., 1997). In rodents, ketamine disrupts the prepulse inhibition (Swerdlow et al., 1998) and causes locomotor hyperactivity (Hetzler and Wautlet, 1985). On the contrary, one of the studies found a decrease in locomotor activity after ketamine administration in monkeys (Shiigi and Casey, 1999). Usefulness of the model with subchronic application of subanesthetic doses of ketamine was confirmed by Becker and his colleagues in their experiment. They found decreased binding of [^{3}H]L-glutamate on glutamate receptors in frontal cortex and increased binding of [^{3}H]L-spiroperidol on D2 receptor in hippocampus in brown rats that were administered with ketamine. Ketamine in low doses (10, 20, and 30 mg/kg) increases glutamate release in the prefrontal cortex (PFC), thereby it stimulates the postsynaptic non-NMDA receptors. This causes disruption of dopaminergic neurotransmission in PFC and in cognitive functions that are associated with this area. The same study found that ketamine has biphasic effect on the flow of glutamate in PFC. Low subanesthetic doses (30 mg/kg) increase the glutamate levels in PFC, whereas the anesthetic doses (200 mg/kg) reduce these levels (Moghaddam et al., 1997). In addition, the clinical studies have shown that subanesthetic doses of ketamine induce cognitive deficits in tasks that are dependent on PFC (Ghoneim et al., 1985) such as delayed verbal recall from memory

tests (Krystal et al., 1994). It is also important to mention that subanesthetic doses of ketamine induce rapid antidepressant effect which persists for a matter of days to weeks (Berman et al., 2000).

Phencyclidine

Phencyclidine is a noncompetitive antagonist of NMDA receptors which has a relatively high affinity for the D2 and 5-HT2 receptors (Kapur and Seeman, 2002). In humans, it induces a syndrome which seemingly resembles schizophrenia and which comprises both its positive and negative symptoms (Javitt and Zukin, 1991). In rodents, it primarily causes stereotyped behavior (Sams-Dodd, 1996), social withdrawal (Corbett et al., 1995), hyperactivity (Kalinichev et al., 2008) and it also disrupts prepulse inhibition (Mansbach and Geyer, 1989) and recognition memory (Egerton et al., 2005). In monkeys, the acute doses of PCP induce deficits in spatial (Boyce et al., 1991) and working memory (Baron and Wenger, 2001) and also in prepulse inhibition (Lynn and Javitt, 2001). Permanent cognitive deficit induced by sub-chronic PCP doses can be attenuated by atypical antipsychotics such as ziprasidone (a dose of 2.5 mg/kg), onlanzapine (a dose of 1.5 mg/kg) and clozapine (a dose of 5 mg/kg) (Abudl-Monim et al., 2006). The classical antipsychotics such as haloperidol (Abdul-Monim et al., 2003) and chlorpromazine have no effect on the deficit (Abdul-Monim et al., 2006).

Dizocilpine (MK-801)

Dizocilpine (MK-801) that was synthesized in 1982 is a phencyclidine-like substance. MK-801 induces hyperlocomotion and impairs cognitive functions. Unfortunately, there is only a small range of doses that can be applied in order to avoid overdosing. It then leads to neurotoxic effects (Olney et al., 1989). In rodents, subchronic exposure to high doses (≥10 mg/kg) induces cell death and neurodegeneration e.g. in olfactory bulbs, dentate gyrus and entorhinal cortex (so called Olney's lesions) (Bender et al., 2010). Likewise PCP, MK-801 also creates a spectrum of motor dysfunctions such as hyperactivity, stereotypy, cognitive deficit or ataxia (Koek et al., 1988) in various species including pigeons, rhesus monkeys and rodents.

In rats the systemic administration of MK-801 causes deterioration in various learning and memory processes, e.g. in passive place avoidance tasks (Ohno and Watanabe, 1996) or in spatial orientation tasks in radial maze (Pitkänen et al., 1995) and in water maze (Whishaw and Auer, 1989). One of the studies found that after MK-801 administration rats find the hidden platform in Morris water maze more slowly than control animals and that they exhibited increased thigmotaxis (they stay closer to the walls of the maze) (Lukoyanov and Paula-Barbosa, 2000). The results of another experiment showed that even a single dose of MK-801 (4 mg/kg) is capable of inducing changes in spatial learning in rats in Morris water maze. These changes subside within five days (Whishaw and Auer, 1989). Furthermore, it was found that the effects of systemic administration of MK-801 on spatial learning in the water maze are extremely difficult to separate from motor and sensory disorders (Ahlander et al., 1999). The results of another study show that when MK-801 is administered to naïve rats that are unfamiliar with the rules of spatial alternation task on rotating arena the working memory worsens and the efficiency of performance in this task is disrupted. However, in animals that undergo a pre-training before MK-801 administration (a dose of 0.12 mg/kg and 0.15 mg/kg) this deficit does not appear (Zemanova et al., 2013). Results of a different study showed that only the highest doses (0.2 mg/kg) of systemically administered dizocilpine induce significant deficit in active place avoidance task learning, while lower doses of MK-801 (0.1 mg/kg) do not affect performance in this task (Stuchlik et al., 2004). Another study found that even 0.15 mg/kg of MK-801 impairs spatial working memory in rodents which, when combined with other findings, suggests that NMDA receptors play a role rather in long-term storage of spatial information (White and Best, 1998). There is a number of studies that connect learning and memory with MK-801 animal model of schizophrenia. One of the studies tested the effect of MK-801 on behavioral (cognitive) flexibility in active place avoidance task and in Morris water maze tasks (MWM) in rats. It turned out that in this

schizophrenic behavior model the cognitive flexibility is impaired and that the active place avoidance task is more sensitive to this deficit (in this task the deficit was present already at the dose of 0.08 mg/kg) (Lobellova et al., 2013). Behavioral flexibility is the ability to adapt to the changes in close environment. In schizophrenia patients, this ability is often reduced which, among other things, proved the results of the patients suffering from schizophrenia in virtual decision-making tasks (Han et al., 2012). Changes in attention, behavioral flexibility and adaptation to the new conditions were also observed in animal models of schizophrenia in different experiments, e.g. after exposure to NMDA receptors in attention task (Amitai and Markou, 2010).

Mice in which an animal model of psychosis using MK-801 was induced replaced the components of behavior such as sniffing or pawing by monotonous locomotion. This fact corresponds to the positive symptoms in schizophrenia (stereotypy) and it is associated with excessive dopaminergic activity in the mesolimbic areas (Nilsson et al., 2001). The authors described the changes as overall behavioral primitivization (Nilsson et al., 2001). There is a difference is sensitivity to MK-801 between the sexes: the female rats are more sensitive to this substance probably due to the fact that MK-801 is metabolized in liver and females have lower efficiency of metabolic system (Andino et al., 1999). For the same reason, the females are more sensitive to PCP which leads to its higher concentration in plasma and brain (Nabeshima et al., 1984). It was proved that female rats show 4 to 10 times stronger behavior induced by MK-801 and up to 25 times greater serum and brain concentration of MK-801 than male rats (Andino et al., 1999).

In terms of molecular changes, one study found that MK-801 modifies the expression of NR1 splice variants and NR2 subunits of NMDA (Rujescu et al., 2006) in a similar manner that was observed in schizophrenia (Gao et al., 2000). The study also noted relatively decreased amount of GABAeric parvalbumin-positive interneurons (Rujescu et al., 2006) which is parallel to the changes that were observed in the brains of patients suffering from schizophrenia (Zhang and Reynolds, 2002). In rats, the chronic exposure to MK-801 leads to increased quantity of intracellular glutamate in hippocampus, while in the extra-hippocampal regions no change in concentration was observed (Genius et al., 2013).

It was found that the administration of 5-HT2A/2C receptor antagonists such as ritanserin and risperidone (which is also the D2 receptor antagonist) blocks the cognitive impairments induced by MK-801, while haloperidol, the D2 receptor antagonist, is not able to sufficiently correct the deficit in active place avoidance task in Carousel Maze (formerly known as Active Alothetic Place Avoidance, AAPA). This deficit is induced by MK-801 administration but it effectively blocks hyperlocomotion (Bubenikova-Valešova et al., 2008). Interestingly, after administration of risperidone and haloperidol in intact rats an impaired performance in AAPA could be observed. However, this performance impairment did not occur after ritanserin administration (Bubenikova-Valešova et al., 2008). It turned out that neuroleptics (the antipsychotic agents used for clinical purposes) antagonize behavior induced by MK-801 (Tiedtke et al., 1990) as well as PCP (Sturgeon et al., 1981). This indicates that the behavior induced by NMDA receptor antagonists can be used as complementary model of psychosis in search of new and more effective antipsychotic in schizophrenia treatment.

Neurodevelopmental animal models

Neurodevelopmental animal models are based on neurodevelopmental hypothesis of the emergence of schizophrenia. This hypothesis supposes that a disruption in prenatal or perinatal period of brain development causes dysfunctions of brain connectivity that are manifested by schizophrenia outbreak in early adulthood. This hypothesis is confirmed by e.g. studies aimed at inhibition of NMDA receptors that show that exposure to MK-801 (Harris et al., 2003) and PCP in late fetal or early postnatal period in rats increases the risk of brain

damage (Wang et al., 2001). Chronic blockade of NMDA receptors by both MK-801 (Gorter and Bruin, 1992) and PCP during this period causes cognitive deficit and impairs spatial memory in adulthood (Sircar and Rudy, 1998). The time when the inhibition of NMDA receptors increases the cell damage correlates with maximal expression of these receptors. In humans, this period corresponds to the third semester of pregnancy (Lee and Choi, 1992), in rats to the first two weeks of postnatal life (Colwell et al., 1998). Neurodegenerative changes caused by hypofunction of NMDA receptors may serve as models for pharmacotherapy of schizophrenia research (Olney and Farber, 1995).

To the neurodevelopmental models belong also the malnutrition models that address the issue of prenatal malnutrition on brain development (Llorente et al., 2007), models of viral infections (Takei et al., 1995), stress during pregnancy (Fride and Weinstock, 1988), neonatal brain lesions (Lipska and Weinberger, 1993) and other neuronal damages such as postnatal hypoxia after which changes in gene expression of NMDA receptor subunits and reduced prepulse inhibition were observed (Schmitt et al., 2007).

To create a structural model of psychosis in animals the neonatal hippocampal lesions (Lipska and Weinberger, 1993) or medial prefrontal cortex lesions (Jaskiw et al., 1990) are used. The best described neurodevelopmental animal model of psychosis was designed by Lipska and Weinberger. The model consists in performing neonatal excitotoxic ventral hippocampal lesion (Lipska and Weinberger, 1993; 1995). After amphetamine application, this lesion causes changes in behavior such as hyperlokomotion (Lipska and Weinberger, 1993). Experimental manipulations with ventral hippocampal lesions are in rats performed on the seventh postnatal day and they result in both temporary (Lipska et al., 2002b) and permanent (Lipska et al, 1993) inactivation of the ventral hippocampus. As a result of these manipulations, hyperactivity (Lipska et al., 2022b), changes in gene expression (Lillrand et al., 1996), deficits in working memory (Lipska et al., 2002b) and impaired prepulse inhibition (Daenen et al., 2003) can be observed in adult rats. It turned out that even temporary inactivation of ventral hippocampus during critical period can trigger behavioral changes similar to those that can be observed in animals with permanent excitotoxic lesions. Since the neonatal disconnection of ventral hippocampus changes the PFC development and plasticity and creates cellular changes that mimic the symptoms of schizophrenia it can represent a potential new model for studying schizophrenia (Lipska, 2004).

Selected genetic animal models

Genetic animal models of schizophrenia slowly displace pharmacological and neurodevelopmental models. The main advantage of these models is the fact that they have potentially grated construct validity (Harrison et al., 2012). There is a wide variety of genes that are, as expected, involved in the pathophysiology of schizophrenia and that can be explored. It is worth mentioning that a number of genetic manipulations aimed at variety of genes are presented as schizophrenia endophenotypes, i.e. isolatable phenotypic characteristics that are bound to a disease, frequently hereditary and often present in healthy blood relatives of these subjects (e.g. Willi et al., 2010).

One of the genes that is associated with schizophrenia is NRG1 (Neuregulin 1) located at chromosome 8p13 (in humans). 30cM region around 8p21.1-22 on the chromosome 8p is considered a locus comprising of one or more genes that are co-responsible for the onset of schizophrenia (Pulver at al., 1995). Neuregulins represent a family of growth and differentiation factors encoded by four different genes (NRG-1 to NRG-4) that are bound to ErbB family of tyrosine kinase transmembrane receptors (Papaleo et al., 2012). NRG1 modulates neuronal precursors and cell migration using radial glial cells (Schmid et al., 2003) and increases neuronal survival (Vaskovsky et al., 2000). One of the studies showed that heterozygous mice for NRG-1 receptor of ErbB4 exhibit similar abnormalities in behavior as patients suffering from schizophrenia – e.g. hyperactivity

(Gerlai et al., 2000) and that these changes can be partially reversed by clozapine (Stefansson et al., 2002). Recently, the possibility that NRG1 path may be interconnected with NMDA receptors is being considered. The connecting link between these two systems is the fact that ErbB4 receptor is bound to a postsynaptic scaffold protein PSD-95 (Huang et al., 2000) which interacts with NMDA receptors (Kornau et al., 1995).

In vitro stimulation of NRG1 was able to suppress the currents in prefrontal pyramidal neurons induced by NMDA receptors (Gu et al., 2005). Also, the activation of NMDA receptors in prefrontal cortex was significantly suppressed in patients with schizophrenia that exhibited a greater degree of Erb4 – PSD-95 signaling compared to healthy individuals. It follows that more intensive NRG1 signaling may contribute to the hypofunction of NMDA receptors (Hahn et al., 2006). An experiment investigating the short- and long-term effects of chronic blockade of NMDA receptors in the interaction between prefrontal cortex and hippocampus was carried out. 24 hours after the last injection of MK-801 the interactions of ErbB4, PSD-95 and NMDA receptors in PFC were increased. However, 12 days after the last dose these effects were not visible, indicating the reversibility of these changes. These results suggest that NRG-ErbB4 signaling may be modulated by repeated blockage of NMDA receptors and provide further evidence of interconnection of these two signaling pathways (Li et al., 2013).

Another possibility for the research is the genetic modification of the NMDA receptors themselves. The receptors are composed of a number of NR1, NR2A-D, NR3A-B subunits (Dingledine et al., 1999). An example of genetic animal model for NMDA receptor hypofunction is the NMDA receptor hypomorphic mouse that has significantly reduced the NR1 subunit (Mohn et al., 1999). These mice exhibit reduced motor activity, deficits in social interactions (Mohn et al., 1999), decreased metabolic activity in the medial prefrontal cortex and hippocampus (Duncan et al., 2002) and prepulse inhibition deficits of an acoustic startle response (Duncan et al., 2004). It was found that clozapine and haloperidol mitigate prepulse inhibition deficits in NR1 hypomorphic mice (Duncan et al., 2006a) and olanzapine reduces their locomotor hyperactivity (Duncan et al., 2006b). The significance of this model for schizophrenia is being challenged because the evidence for abnormalities in genes that cause expression of the NMDA receptor subunits has not been found yet (Nishiguchi et al., 2000). In addition, these animals showed response neither to PCP nor to MK-801 which is contrary to the conclusions that have been found in schizophrenia patients (Krystal et al., 1994). Furthermore, two lines of mouse animal model with a point mutation of glycine binding site on NR1 subunit were created: Grin1 (D481N) and Grin1 (K483Q). The second phenotype confirmed the essential role of NMDA receptor activation in neonatal survival (Kew et al., 2000). The Grin 1D481N/K483Q heterozygous mice exhibited NMDA receptor hypofunction, hyperlocomotion, stereotyped behavior and impaired performance in finding visible platform task in Morris water maze (Ballard et al., 2002). Except that, the NR2 subunit (GluRepsilon1) can also be eliminated. In these mice, NMDA receptors are malfunctioning and mice exhibit hyperlocomotion again (Miyamoto et al., 2001).

Conclusion

The aim of this study was to summarize the findings of hypoglutamatergic animal models of schizophrenia-like behavior. The main reason for this was the fact that the neurodevelopmental hypothesis of glutamate NMDA receptors hypofunction has been recently gaining interest. Currently, the non-competitive antagonists of NMDA receptors such as ketamine, phencyclidine and MK-801 are used for schizophrenia-like behavior modeling in animals. These models have a great potential even though they do not reflect all the symptoms of schizophrenia. These non-competitive antagonists bind to a site on the NMDA receptor ion channel; thereby they block and disrupt their proper functions. Chronic blockade of NMDA receptors can also be caused by application of NMDA receptor non-competitive antagonists in late fetal or early postnatal period. This results in poor brain development and onset of schizophrenia-like behavior in adult animals. In animal

models, these antagonists induce a broad spectrum of symptoms relevant to schizophrenia such as locomotor hyperactivity, stereotyped behavior, impaired recognition, and ataxia, deficits in spatial and working memory, reduced prepulse inhibition, changes in glutamate release, and also social withdrawal which is induced by low doses of MK-801. Another promising option that allows researches dealing with NMDA receptors responsibility for the onset of schizophrenia is creating genetically modified animals which exhibit similar behavioral and pharmacological changes as patients suffering from schizophrenia. The contribution of these animal models to schizophrenia research is undeniable; however, knowledge about the origin, etiology and neuropathology of the disease still remains scarce, since due to its complexity a single "ideal" and "universal" animal model that would contain all the symptoms cannot be created. Models can however mimic several important aspects and symptoms of schizophrenia. This fact is also important in finding a safer and more effective medication for the disease.

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Go/NoGo continuous performance task in the psychophysiological research

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Abstract

Introduction: Go/NoGo continuous performance task (CPT) is a neuropsychological test designed for measurement of attention and impulsivity and very often associated with attention deficit hyperactivity disorder (ADHD). The aim of this study was to provide current view of test with its application in future psychophysiological research and clinical practise.

Methods: The studies regarding CPT were collected using scientific databases (PUBMed, Medline, SCOPUS). The heart rate variability (HRV) as an index of parasympathetic activity and electrodermal activity (EDA) as a noninvasive index of sympathetic arousal were applied in ADHD and depression during Go/NoGo CPT.

Conclusion: In psychophysiological research, the altered HRV and EDA could represent a noninvasive biomarkers for internalizing/externalizing psychopathology. It seems that Go/NoGo CPT could be used as an important diagnostic tool in mental disorders, however future research is needed.

Key words: Go/NoGo continuous performance task, heart rate variability, ADHD, electrodermal response

Introduction

Stress can be generally defined as a response to demands (usually noxious) on the body (Selye, 1936) or as alterations in psychophysiological homeostatic processes (Burchfield, 1979). The stimulus disrupting homeostasis is called a stressor. Stressors may be divided into several categories: *e.g.* physical *(e.g.* heat, cold), metabolic (*e.g.* hypoxia, hypoglycemia) and mental stressors (*e.g*. public speaking) (Mravec and Zucha, 2006). Stress leads to various changes in nervous system and the complex effect of mental stress depends on cognitive processing by cortical (mainly orbitofrontal and medial prefrontal) areas in cooperation with limbic system (Mravec et al., 2009). Nevertheless, autonomic nervous system (ANS) is very sensitive to mental stressors and its reactivity has been shown associated with physical, behavioral and mental health symptoms (El-Sheikh et al., 2009; Obradovic et al., 2010). Therefore, the ANS reactivity is extremely sensitive to laboratory stressors, such as Stroop and the mental arithmetic tests. Mental stress alters immediately and completely the sympathetic/parasympathetic balance (Martinez-Lavin, 2007), and the effect depends on receptor type

(McCorry, 2007). For example, active stress is linked with higher heart rate, mediated through β-adrenergic activation and passive stress causes changes in blood pressure predominantly through the activation of α-receptors (Chi et al., 1993; Delahanty et al., 1996).

One of the examples of active mental stressor is Go/NoGo continuous performance task (Go/NoGo CPT), which is designed as a neuropsychological test to measure attention and impulsivity. In following proposal, we describe the characteristic of test.

Variants of Go/NoGo CPT

In the traditional Go/NoGo CPT, participants are instructed to respond rapidly, generally with a button-press, to presentation of Go stimuli only, and response inhibition is measured by the ability to appropriately withhold responding to NoGo stimuli. Several variations of Go/NoGo stimuli have been used in various studies, for example the faces with emotions (Yu et al., 2014), coloured circles and geometric shapes (Thomalla et al., 2014), airplanes (as Go stimulus) and bombs (as a NoGo stimulus) (Rubia et al., 2001), numbers (Nelson et al., 1998), as well as the letters or its auditory modalities (Shucard et al., 2008). The example of test using Go/NoGo paradigm with letters stimuli is the Conners´Continuous Performance Test (CCPT). Traditional CCPT requires the subject to press a computer key only after X is presented and the modern version – the CCPT-II requires subject to press the computer key immediately after every letter except the X (Conner, 2000).

The differences in Go/NoGo paradigms are not only in the stimuli but also in the task designs. More traditional is using a simple format of test with a single Go stimulus and single NoGo stimulus. The example of more complex design is a version of the task where X and Y are alternately presented on the screen, and there is a two-letter repeat, which is the NoGo signal: if X is presented, Y will become Go signal and X the NoGo signal, and *vice versa* (Garavan et al., 1999).

The Go/NoGo parameters

Performance efficiency is generally expressed in terms of correct detections, commission and ommission errors and reaction time (Table 1.). From the psychological context, the errors of omisssion are assumed to reflect symptoms of innattention, while errors of commisssion are supposed to reflect impulsivity (Barkley, 1991; Halperin et al., 1991). Computerized RT measures, as a valuable indicator of cognitive performance have gained renewed attention, because the recognition that reaction time variability (RTV) may convey unique information (Berkson and Baumeister, 1967; Barrett et al., 1986; Jensen, 1992). RTV has been discussed as a potentially important index of the stability/instability of an individual´s nervous system (Karalunas et al., 2014). Several studies have used standard deviation (SDRT) to quantify RTV (Geurts et al., 2009; Sinzig et al., 2008). Alternatively, RTV is calculated as a coeficient of variation: SDTR/mean RT or by ex-gaussian decomposition, in which τ reflect both the mean reaction time and standard deviation of the exponential portion of the distribution. However, the ideal metrics of RTV are not yet clear (Karalunas et al., 2014).

Table 1. Standard evaluating parameters in Go/NoGO CPT

Correct detection	indicate the number of times the client responded to the target stimulus
Ommision errors	indicate the number of times the target was presented, but the client did not respond/click the button
Commision errors	indicate the number of times the client responded but no target was presented
Reaction times (RT)	this measure the amount of time between the presentation of the stimulus and the client´s response

CPT seems to be helpful in differencial diagnosis of mental disorders, in which the ability to supress inappropriate and unwanted actions is impaired. The most notable is attention deficit/hyperactivity disorder (ADHD) (Barkley, 1997). Karalunas et al. (2014) in their meta-analyse of several studies found increased RTV among individuals with ADHD compared with typically-developing controls. Moreover, this parameter has correlated with measures of behavioral inattention (Nigg, 1999; Wahlstedt, 2009; Wahlstedt et al. 2009), and it has to correlate with hyperactivity-impulsivity in other study (Gomez-Guerrero et al., 2011). However, the application of CPT, in particular RTV as a specific diagnostic tool remains questionable and without general acceptation as a „gold standard" in externalizing psychopatology (McGee, 2000; Gualtieri et Johnson; 2005). For example, higher RTV has been observed in other mental disorders such as autism (Verte et al., 2005), schizophrenia (Kaiser et al., 2008) and bipolar disorder with psychotic symptoms (Bora et al., 2006).

Physiological responses to Go/NoGo test

Brain activation

The Go/NoGo tasks are focused on executive functions, that refer to the ability to plan and execute behaviour (Simmonds et al., 2008). The ability to supress irrelevant stimuli or impulses is essential for normal thinking processes and ultimately for successful living. Inhibitory control of behaviour, composing of motor, emotional, cognitive, and social abilities, is phylogenetically one of the highest developed human self-control functions (Williams et al., 1999). The beginning of inhibitory abilities also marks an important milestone in cognitive development, and is considered as a characteristic of frontal lobe maturation (Diamond, 1990). Previous studies have investigated the neural correlates of response inhibition. For example, the human lesion studies

demonstrated the involvement of the frontal cortex (Drewe, 1975; Godefroy and Rousseaux, 1996), with more specific localization of the superior medial (Drewe, 1975; Floden and Stuss, 2006; Picton et al., 2006) and right inferior prefrontal cortical areas (Aron et al., 2003; Chambers et al., 2006). Recent studies using an objective neuroimaging methods found frontal lobe activation during Go/NoGo CPT (Garavan et al. 1999; Rubia et al. 2001). However, localization within the frontal cortex varies across studies depending on the task specificity (Mostofsky et al., 2003). It seems that the simple format of Go/NoGo task is examination of response inhibition under conditions in which other cognitive/behavioral processes are minimized, while more complex designs of Go/NoGo task demand also short term/working memory. The studies using simple format of Go/NoGo task demonstrated activation in the presupplementary motor area (pre-SMA) bilateral occipital regions and the precuneus, and the studies using the complex format of CPT found activation in the pre-SMA, right middle/inferior frontal gyrus, bilateral inferior parietal regions, bilateral putamen, bilateral insula, right middle temporal gyrus, left fusiform gyrus and the left middle gyrus. Moreover, both simple and complex Go/NoGo tasks evoked the activity of the pre-SMA suggesting that recruitment of the pre-SMA is critical to response inhibition irrespective of the task demands (Simmonds et al., 2008).

Autonomic nervous system

As mentioned in the beginning, Go/NoGo CPT as a mental stressor leads to the ANS response and alters the sympathetic/parasympathetic balance. Moreover, the complex analysis of ANS during CPT are rare.

Heart rate variability-index of parasympathetic activity

Cardiac function is extremely sensitive to autonomic influences. The heart rate variability (HRV), *i.e.,* the amount of the heart rate fluctuations around the mean heart rate, provides insight into the autonomic control of the heart and gives important information about cardiac sympathetic and parasympathetic interaction (Stein and Kleiger, 1999; Van Ravenswaaij-Arts et al., 1993). The mental arousal which follows a laboratory mental stress test produces a centrally induced shift of ANS balance towards the sympathetic activation associated with vagal withddrawal. Therefore, it can be used as an ideal model to study the magnitude and complex dynamics of heart rate autonomic regulatory inputs (Visnovcova, et al. 2014). HRV is traditionaly quantified by linear methods- time and frequency (spectral) domain analysis- providing the information about the heart rate variability magnitude and frequencies (Task Force, 1996). Spectral analysis of HRV allows to isolate the faster high frequency respiratory-coupled oscillations as an index of cardiac vagal function (Bertson et al., 1997; Martinmäki et al., 2006). Recently, nonlinear methods measuring qualitative characteristic of the cardiac time series, *i.e.* complexity, and other system dynamic features have been shown to be more suitable for a detailed description of heart rate autonomic control (Javorka et al., 2009; Porta et al., 2009). Moreover, series of neuroimaging studies have provided evidence that HRV has been related to the activity of the prefrontal cortex (Lane et al., 2009). Therefore, it is proposed that HRV is related to cognitive performance (Thayer et al., 2009), which was supported by findings that subject with high HRV had a significantly higher number of correct responses compared to subject with low HRV during Go/NoGo task (Hansen et al., 2003; Eisenberg and Richman, 2011).

In our study, we assessed HRV during Go/NoGo CPT in ADHD as an externalizing disorder, depressive patient as an internalizing disorder and control subject. Our protocol type sent two stimuli types, a target -green circle and non-target -red coloured letter. In control subject, HRV was decreased during test indicating a shift of ANS dynamic balance to vagal withdrawal and sympathetic arousal (Fig. 1). It indicates physiological response of autonomic flexibility and adaptability. On the other hand, we found different heart rate reactivity in mental disorders compared to controls indicating a potential alteration in cardiac autonomic flexibility in ADHD and

depression (Figures 2 and 3). It seems that HRV could represent an important predictive marker in psychophysiological research, however, this hypothesis is needed to validate in future longitudinal studies.

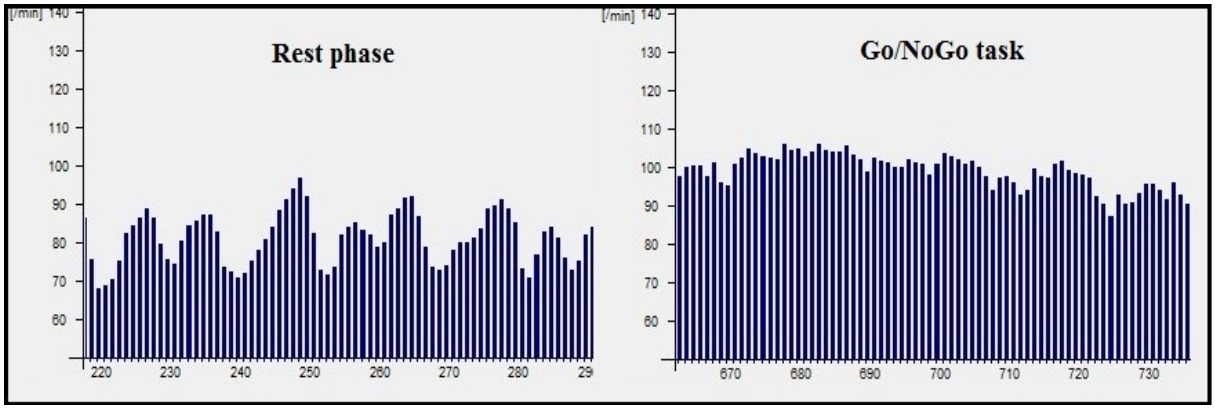

Fig. 1 HRV in rest phase and during CPT in healthy subject indicates a physiological response of ANS

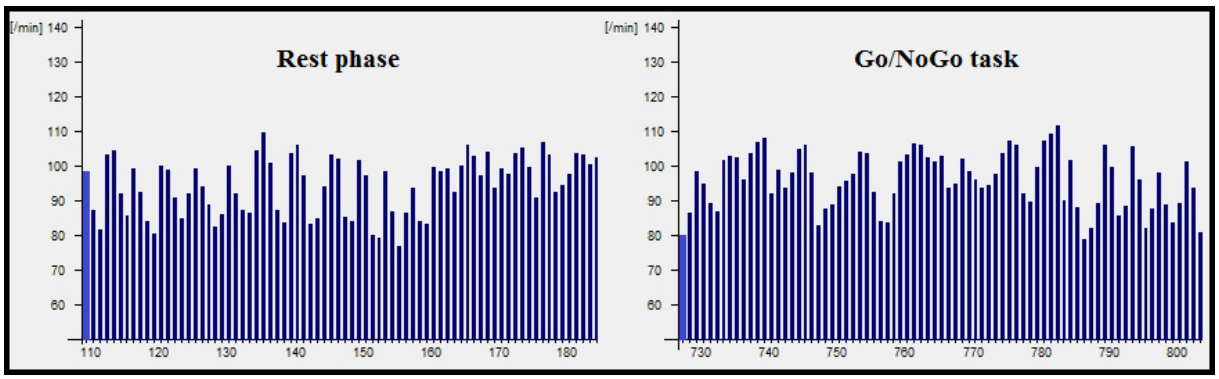

Fig. 2 Altered HRV in rest phase and during CPT in ADHD patient

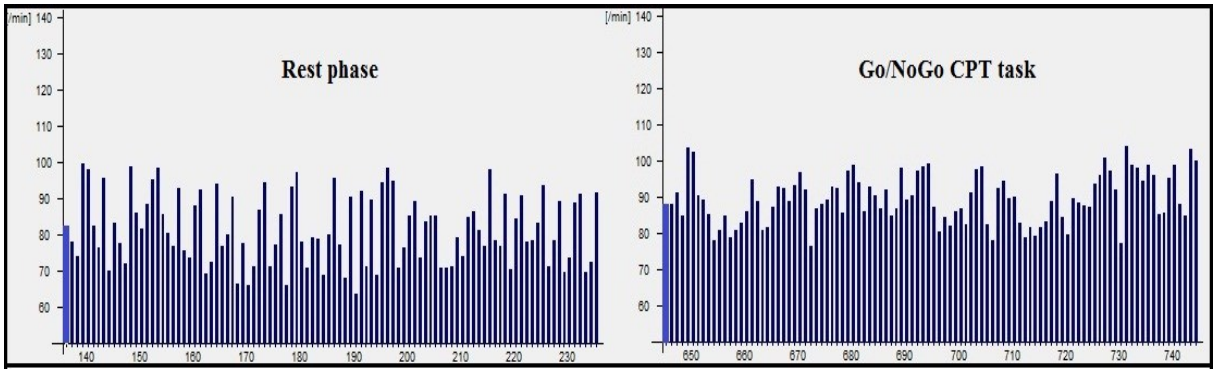

Fig. 3 Altered HRV in rest phase and during CPT in depressive patient

Electrodermal aktivity - index of sympathetic activity

Electrodermal activity (EDA) is accepted as a noninvasive marker of sympathetic arousal in response to stress in psychophysiological research (Ionescu-Tirgovişte and Pruna, 1993; Jacobs et al., 1994). Value of skin conductance depends of amount of sweat produced by ecrine sweat glands regulationg by sympathetic nervous system. When the sweat duct is filled with sweat, more conductive area originates on the nonconductive corneu (Dawson et al., 2007). In our study, we assesed EDA in response to CPT in the same patient mentioned above (Figures 4,5,6). EDA amplitude (μS) was evaluated in a percentage value from resting phase (5 min.) and the CPT response (5 min.). Our individual pilot results found the lowest EDA reactivity in ADHD patient (23,73%) compared to depression (58,06%) and heathy subject (65,49%) indicating a potential sympathetic underarousal typical for externalizing psychopathology. Therefore, we suggest that electrodermal response to CPT could represent a biomarker for externalizing/internalizing psychopathology differences.

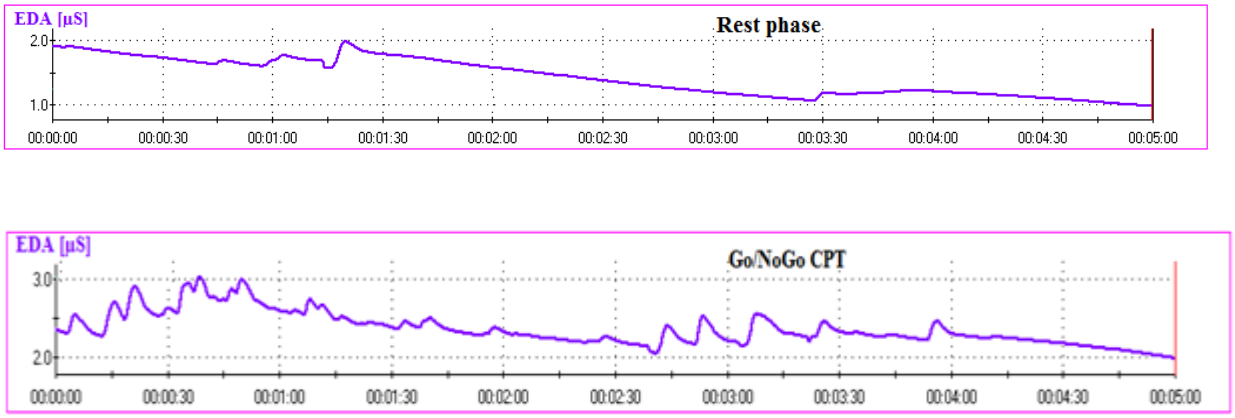

Fig. 4 Increased EDA in control subject indicating sympathetic arousal in response to stress

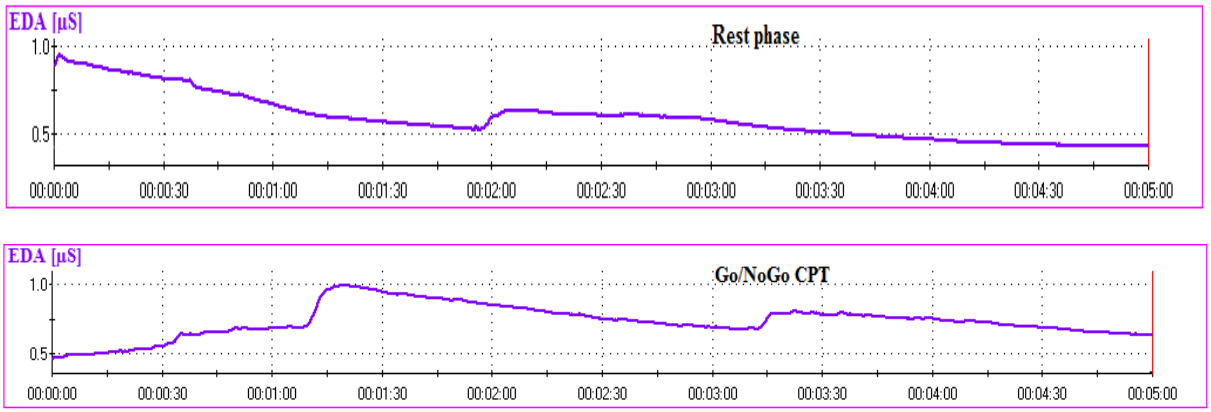

Fig. 5 EDA in ADHD patient indicating a potential sympathetic hypoarousal

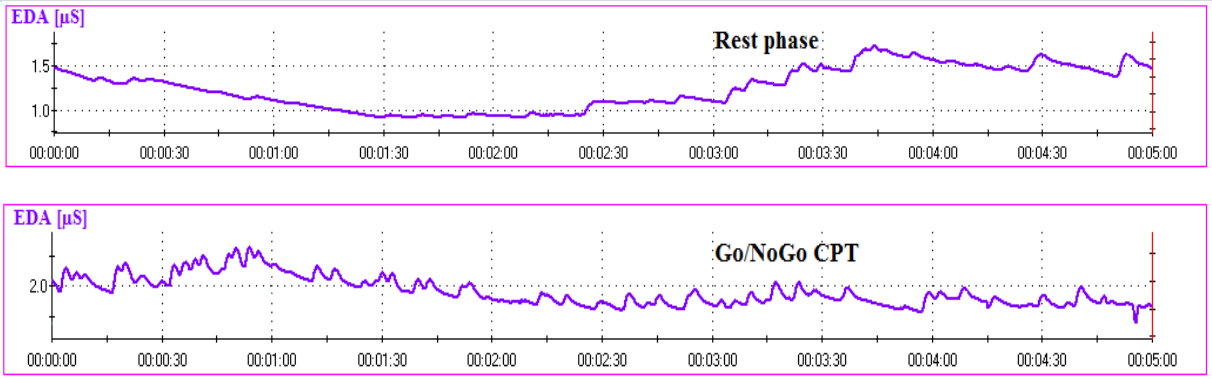

Fig. 6 EDA in depression patient indicating sympathetic arousal in response to stress

Conclusion

Go/NoGo CPT represents a neuropsychological test of vigilance and sustained attention, but it is not standard diagnostic tool in mental disorders. We suggest that diminished HRV and electrodermal activity in response to CPT could indicate abnormal autonomic regulation associated with higher risk of adverse health outcomes. It seems that complex psychophysiological approach may be useful in clinical application for differential diagnosis of mental disorders. Future research is needed.

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