Central and peripheral correlates of eye movements in selected mood disorders

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Abstract

OBJECTIVES: Abnormalities and disturbances of saccadic and pursuit eye movements were studied in several mental disorders and diseases. Certain irregularities in the particular oculomotor behaviour have been proposed they may correspond with specific type of mental disorder. It was our aim to contribute to this question by analyzing the bioelectrical correlates of the visual-oculomotor integration in patients suffering from panic disorder and from depressive symptoms.
METHODS: The horizontal saccadic eye movements, optokinetic nystagmus, saccadic eye movement evoked potentials as well as saccadic eye movement related potentials we recorded in the groups of outpatients suffering from depressive symptoms and panic disorder respectively. Groups of healthy volunteers served as control.
RESULTS: Saccadic eye movements were found to be significantly more inaccurate as compared to healthy subjects. The gain of the optokinetic nystagmus at middle and high velocities was significantly lower in panic patients. Preparation of motor plan for a saccade as well as the time of the maximal recruitment of the oculomotor muscle units was delayed in both groups of patients and their oculomotor event-related potentials were of the overall longer duration and higher variability as well.
CONCLUSION: The changes in oculomotor behavior as well as in its EEG correlates in the groups of above mentioned patients can not be taken as specific for the given disorder. On the other hand, they may help to follow up the course of the complex therapy.

ORIGINAL ARTICLE

INTRODUCTION

Several parallel anatomic circuits linking the frontal cortex regions to subcortical centers – extrapyramidal nuclei and thalamus first of all – were described to take an important role in neuropsychiatric disorders (Mega & Cummings 1994). Dysfunction of these circuits, which originate in prefrontal cortex mainly, includes impaired executive function, disinhibition, apathy, depression, obsessive-compulsive disorder and even schizophrenia (Mega & Cummings 2002). It is accepted that the prefrontal cortex is critical to regulation and execution of thinking, emotions and those

action which utilize relevant judgment, flexibility and attention (Arnsten & Robbins 2002) and its disturbances affect the cognitive control substantially.

It has been suggested (Koechlin *et al.* 2003) that the cognitive control involves at least three nesting levels of processing implemented in distinct frontal regions. Sensory control involved in selecting motor actions, contextual control of premotor representations according to external contextual signals and episodic control related to events that previously occurred or to ongoing signal. This model of cognitive controls assumes a cascade of top-down controls originating in caudal prefrontal and premotor regions. The results of studies by Bodner *et al.* (1996), Fuster *et al.* (2000), Moghaddam & Homayoun (2008), Levy & Goldman Rakic (2000) and Williams *et al.* (2001) can be summarized that the connectivity of the prefrontal regions, physiological properties of their neurons and the neuroplasticity as such suggest strongly their role in integration of sensory and memory information and in the representation and control of actions and behaviour.

The so-called oculomotor circuit connecting the frontal eye fields (FEF) and the posterior parietal cortex (PPC; parietal eye fields) via the nc.caudatus, globus pallidus, substantia nigra and thalamus is one of the above mentioned frontal-subcortical circuits. Moreover, the FEF are reciprocally connected with the dorsolateral part of the prefrontal cortex (DLPFC). It points to the important role of the visual-oculomotor integration in the overall behaviour of humans. The visual-oculomotor integration represents the most tight and precise integration of sensory and motor functions. It is generally accepted that the irregularities in the particular oculomotor behaviour reflect defects in the corresponding neural circuitry. It has been frequently proposed that they may correspond also with specific type of mental disorders. The saccadic eye movements (SEM), smooth pursuit eye movements (PEM) as also the optokinetic nystagmus (OKN) can be mentioned in this relation. The SEM, PEM and OKN are easily recorded, their physiological dynamic properties are well described their brain substrate is well delineated and the basic mechanisms of their cognitive control are suggested as well (Barnes 2008; Hutton 2008). It is no wonder that there exists a durative aim to develop and use simple oculomotor tests as noninvasive methods for diagnosing neuropsychiatric diseases and disorders. Several conclusive results may be found in the neurological, neuro-ophtalmological and otolaryngological praxis mainly (Boleas-Aguirre *et al.* 2007; Straube & Büttner 2008; Wong 2008). As for the mental disorders and diseases the situation is not so clear.

Abnormalities and disturbances of SEM and PEM were studied in schizophrenics, bipolar disorder patients, dementias, patients suffering from depressive symptoms, attention deficit disorders, autism and some others also (Deijen *et al.* 1993; Goldberg *et al.* 2002; Holzman *et al.* 1974; Kathmann *et al.* 2003; Munoz *et al.* 2003; Schewe *et al.* 2009). Nevertheless, one important question persists whether oculomotor diagnostic tools could offer a specific outcome for a particular mental disorder or disease or whether they could help in assessing the effect of ongoing treatment. They may reflect namely several abnormal brain functions concerning early information processing or oculomotor response organization as well as a disorder of the integrative higher brain functions, e.g. the attention, memory and others. It was our aim to contribute to this question by analyzing the bioelectrical correlates of the visual-oculomotor integration in patients suffering from panic disorder or from depressive symptoms.

METHODS

Subjects

Altogether, 30 panic disorder (PD) outpatients (12 men, 18 women, mean age 32 yrs) according to Diagnostic and Statistical Manual of Mental Disorders – DSM IV (diagnosed and treated in the II. Neurological Clinic, Medical Faculty of Comenius University – MFCU, in Bratislava), within the interparoxysmal period, working regularly in their occupations, were examined. All the PD outpatients were without specific medications for more than 6 months. The examinations were done in the time period without panic attacks lasting more than 1 year. Further, the group of 10 outpatients suffering from depressive symptoms (DS) very closely related to the erectile dysfunction treated at the Psychiatric Clinic of MFCU. They were treated with minor tranquilizers and small doses of neuroleptics in combination with agovirin and vitamins. Groups of 30 healthy volunteers (14 men, 16 women, mean age 24 yrs) without neurological and psychiatric problems in anamnesis, served as controls.

All the subjects had normal or corrected-to-normal vision. The participants gave informed consent before the examinations, according to Helsinki Declaration and they obtained detailed information on the purpose of the study. The healthy participants got a small monetary reward. The whole experimental procedure was approved by the local ethical committee. The examinations were performed in a sound-attenuating and partially electrically shielded room. The whole examination lasted about one hour, including pauses, electrode placement, and removal.

Saccadic and optokinetic stimuli and procedures

The horizontal eye movements were recorded electro-oculographically by means of two Beckman type electrodes placed at outer canthi of the eyes. The subjects were seated in a comfortable armchair with a headrest.

In the saccadic eye movement task subjects had to catch as fast and accurate as possible the circular visual target (0.3 deg) appearing suddenly at panoramic screen (95° × 35°) located at 114 cm from the eyes. The intervals between the successive target presentations

were randomized within the time window from 5 to 15 seconds.

The optokinetic nystagmus (OKN) was elicited by the random dots pattern. The white circular targets of 1° in diameter each on black background were projected onto a panoramic screen Forty targets in average were moving on the screen either to the right or to the left. The pattern was presented for 1 min periods at 30°, 60° and 90°/sec angular velocities moving to the right and to the left, respectively. The intervals between two consecutive stimuli projections were adjusted according to the particular patient´s demands. The angular velocity of the slow nystagmic phase (AV-OKN) was automatically calculated by means of pooling the amplitudes of 10° calibration saccades to the right and to the left. The specialized computer program developed at our laboratory (ANALOKN) was used for data collection and analysis.

EEG recordings and analysis

Saccadic eye movement evoked potentials (SEMEPs) and the saccadic eye movement-related potentials (ERP – P3 wave) were registered over the frontal eye fields, the posterior parietal as well as inferotemporal cortices. The onset of a saccade served as a trigger for averaging. At least, 50 sweeps were taken into account. Each sweep was of 2 seconds duration, 500 ms before the saccadic onset.

The Beckmann type electrodes were affixed over the particular cortical areas referenced to linked mastoids. Electrode impedances were kept below 5 kΩ. The EEG was amplified by Bioscript 2000 amplifiers and after A/D data processing our special PC program ANALERP was used for off-line EEG analysis. For the analysis the artefact-free EEG segments were used. The time window was set to 2000 ms with 500 ms before the onset of a saccade.

The P3 wave was elicited by visual targets in Go-NoGo paradigm which offers a simple possibility to investigate the brain activation during operations such as error processing, response competition and response inhibition. The latter was our case. The visual targets differed in color and were randomly presented within the range of 2 to 5 sec. Their direction (left/right) was randomized as well. The ANALERP program was used for the analysis.

Both the above PC programs (ANALOKN and ANALERP) were written in the source code. For the SEMs accuracy the nonparametric, non-paired statistical tests were used to assess the significance of differences obtained. The characteristics of the SEMEPs components and P3 wave, that is their latencies and amplitudes, were submitted to repeated measures of variance.

RESULTS

The accuracy of visually evoked 10° saccades as well as of saccades used for triggering the SEMEPs was used for EOG calibration also. In healthy subjects the number of inaccurate SEMs did not exceed the value of 5% in average (the inaccuracy being within the range of 0.3–0.5°). Contrarily, the saccades of PD patients were found to be inaccurate in more than 50% of record-

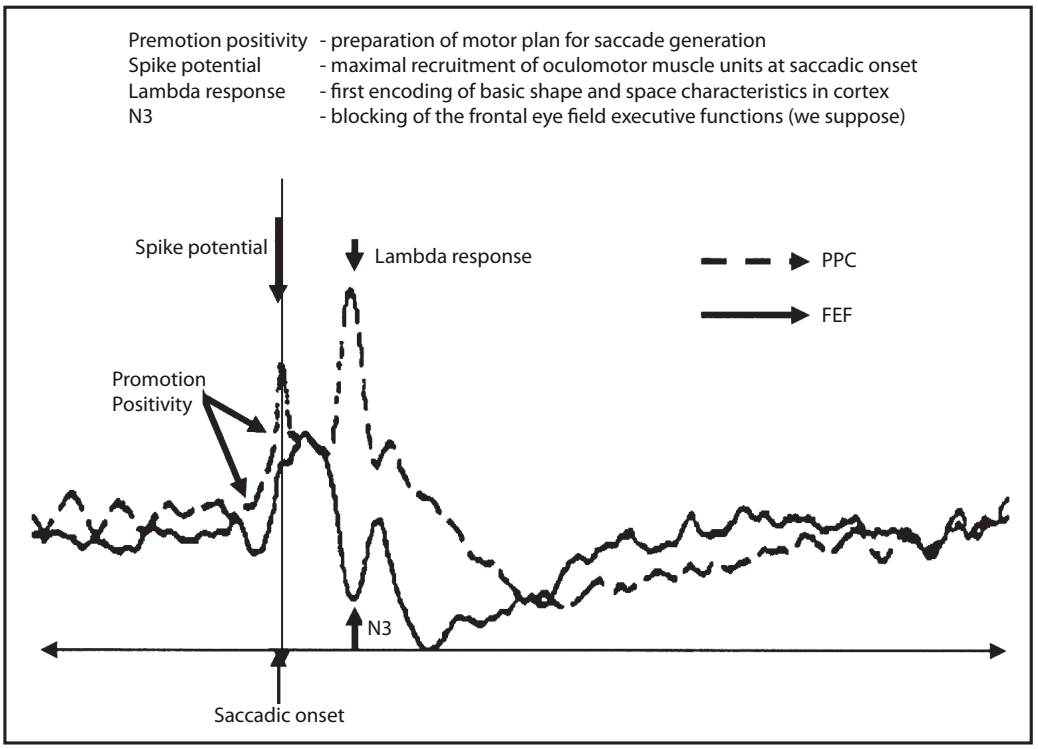

Fig. 1. Saccadic eye movement evoked potentials recorded in healthy subjects over the frontal eye fields (thick curve) and over the posterior parietal areas (dashed curve).

ings with interindividually as well as intraindividually greater inaccuracy (1–8°, $p<0.01$). The same value was found in patients with DS.

The average angular velocity of the slow (pursuit) nystagmic phase of PD patients with optokinetic stimuli moving at 30°.s^{-1} did not differ from those registered in healthy subjects (27°.s^{-1}). The main difference as compared to the AV-OKN registered in healthy subjects was the greater interindividual variability found in PD patients (15–45°.s^{-1}: 26–30°.s^{-1}, $p<0.001$).

When using the stimuli moving at 60°.sec^{-1} the significant lagging down of the average AV-OKN in PD patients was found comparing to those in healthy subjects (40–45°.s^{-1} : 54–56°.s^{-1}, $p<0.01$). The interindividual variability of PD patients was found to be significantly greater as well (20–60°.s^{-1}: 51–58°.s^{-1}, $p<0.001$).

The same but more pronounced results were obtained when using optokinetic stimuli moving at 90°.s^{-1}: 40–44°.s^{-1} : 78–82°.s^{-1}, $p<0.001$, interindividual variability within the range of 15–85°.s^{-1} (as compared to 76–85°.s^{-1}, $p<0.001$). No left-right differences in AV-OKN of PD patients were found in all three stimuli velocities used.

The SEMEPs recorded over the FEF were found to be of longer duration in PD patients as compared to healthy subjects (450 ± 11.8 ms : 400 ± 9.0 ms, $p<0.01$). In parietally recorded SEMEPs the premotion positivity (PMP) of PD patients – reflecting the preparation for eye movements – was found to be of longer latency (105 ± 9.8 ms: 70 ± 7.1 ms, $p<0.02$) and also the latency of the spike potential (SP) reflecting the maximal recruitment of the eye muscles at the onset of a saccade (7.9 ± 1.7 ms: 7.0 ± 1.2 ms, $p<0.02$). On the other hand, the latency of the lambda response (LR) peak in the parietal SEMEPS of PD patients that is the time of the first encoding of the basic characteristics of the new visual stimulus did not differ from healthy volunteers. Similar results were found in patients with DS (Figures 1 and 2).

The SEMEPs in PD patients recorded over frontal eye fields were substantially affected by the corrective eye movements after the inaccurate saccade. There was no possibility to assess their morphology and time course as well (Figure 3)

The overall duration of ERP recorded for P3 wave analysis parietally were found to be of 280 to 660 ms including the average P3 peak latency of 296 ms with SD of ± 15 ms in healthy subjects. The P3 component reflects individual cognitive capability in both normal and patients population. The duration of the same potentials registered in PD patients was significantly more variable (260 to 850 ms, $p<0.01$) with significantly delayed average P3 peak latency of 348 ms ($p<0.01$) and more pronounced SD of ± 73 ms ($p<0.01$). When recorded over the FEF these potentials were of the overall duration from 115 to 570 ms in healthy subjects as compared to 87–759 ms ($p<0.01$) in PD patients with delayed average P3 peak latency (305 ms with SD of ± 21 ms as compared to 372 ms ± 81 ms ($p<0.01$). Similar results were found in patients with DS.

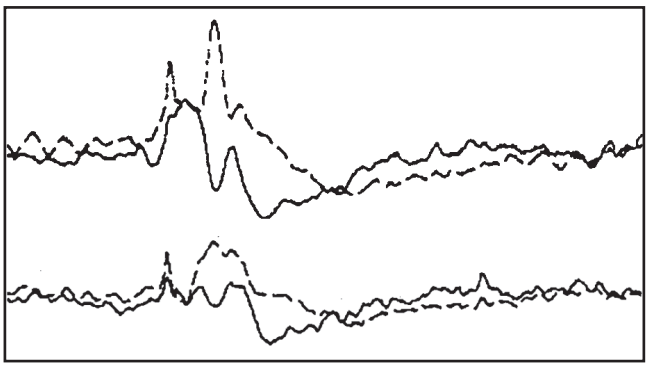

Fig.2. Upper curves illustrate the saccadic eye movement evoked potentials from healthy subjects, lower ones from examined patients. The potentials over the frontal eye fields (full lines) are more affected in patients as compared to potentials over the posterior parietal cortex (dashed lines).

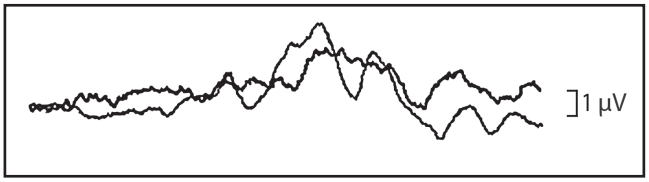

Fig.3. The overall time course of the frontal saccadic eye movement evoked potentials of patients suffering from panic disorder (thick line) are substantially affected by great number of corrective saccades

DISCUSSION

In the last two decades several abnormalities and disturbances of the saccadic as also of the oculomotor smooth pursuit systems were described in various neurological and psychiatric disorders and diseases. As Hutton pointed out (2008) the saccadic eye movement system provides a powerful tool for exploring the cognitive control of behavior. The oculomotor system with its limited output can be measured with exceptional precision and its input can be controlled and manipulated with the higher precision. The dorsolateral prefrontal cortex (DLPFC) is known to be strongly involved in cortical control of saccadic eye movements (Pierrot-Desseiligny *et al.* 2003; 2005). These studies point also to the fact that according to the demands the FEF can inhibit reflexive saccades to the suddenly appeared new visual targets controlled by the parietal eye fields. The anterior cingulate cortex (ACC) (Decety & Jackson 2004; Jackson *et al.* 2006) as well as posterior parts of the cingulate cortex forming the so-called cingulate eye fields are involved in preparation of intentional saccades (Pierrot-Deseilligny *et al.* 2006). On one hand, several neuropsychological studies suggest that the critical cortical region for cognitive control is the prefrontal cortex, on the other hand, neuroimaging studies emphasize the interplay of prefrontal and parietal cor-

tices. It was also documented that dysfunctions within the frontal-subcortical circuits play a significant role in several neuropsychiatric disorders (Tekin & Cummings 2002). Concerning the oculomotor regulations the dorsolateral prefrontal circuit lesions affect their executive functions.

The inaccuracy of visually guided saccades as well as the consequent great number of corrective saccades point to the disordered interplay of the DLPFC and PPC areas. Such situation does not allow adjust the cognitive control over the oculomotor behavior in proper way. More precisely, cognitive control processes in our patients did not render possible adjustment of the oculomotor behavior to changing demands. On the other hand, the parieto-frontal connections serve to alert the brain and to keep the attention on the optimal level (Sarter *et al.* 2001). It was shown that affecting this connection may influence the accuracy of saccadic eye movements (Jagla *et al.* 2009) It can be supposed also that the oculomotor behaviour could be more influenced by oscillation of patient´s attention between their subjective status and the experimental demands.

In this study we have shown that the accuracy of visually guided saccades is strongly impaired in outpatients suffering from depressive symptoms as also from panic disorder. The inaccuracy of saccades affects the latencies and amplitudes of SEMEP components. In healthy subject these potentials parietally reflect: 1. the preparation of motor program for a saccade as the so-called premotor positivity starting approximately 100 ms before the onset of a saccade (Armington 1978; Jagla & Zikmund 1994), 2. the maximal recruitment of the oculomotor muscle units at the onset of the saccadic movements of the eye as seen as the spike potential peaking some ms after the saccadic onset (Thickbroom & Mastaglia 1986) which by several authors may reflect the activation of different neuronal structures of central generator (Weinstein *et al.* 1991), 3. the time of the first encoding the basic space and shape characteristics of the visual stimulus in the brain cortex designated as the positive lambda complex peaking at about 140–160 ms after starting the saccadic eye movement (Marton *et al.* 1983). When recorded over the FEF the most prominent negative component of these potentials reflect also, according to our proposal, the blocking the eye movement execution during the encoding the basic visual information from new fixation (Jagla *et al.* 1994). In our patients, the analysis revealed that the formulation of the motor plan for a saccade was prolonged and the time of the maximal recruitment of the eye muscle units was delayed. It should be taken in mind that programming of saccades is a complex, perceptual, volitional, cognitive process in which the integration of overall visual, acoustic, somesthetic information as well as of cognitive demands takes place.

The corrective saccades accompanied at about 50% of primary saccades. Their amplitudes were within the range of 1–8°. In healthy subjects only 5% of visually evoked saccades are accompanied with corrective ones. Moreover, their amplitude does not exceed 0.5°. It is known that the saccade with amplitude at about 1° evokes a typical SEMEP (Armington 1978). This could explain the manifestation of the overall longer motor program formulation for saccades as also the delay of maximal recruitment of oculomotor muscle units in our patients. The basic encoding of visual information was not disturbed as revealed by latency of lambda responses which was the same in healthy volunteers and examined patients. The dysmetric visually guided saccades and increased rate of saccadic intrusions into the oculomotor responses point to disturbances in the integrative mechanisms subserved by the interplay between the prefrontal and parietal cortices.

The high intrusion of corrective saccades affected the EEG recording in such extent that the SEMEPs could not be reliable evaluated (Jagla *et al.* 2003). We decided then to use the randomized blocking of the reflexive saccade within a train of visually guided saccadic eye movements. Only the EEG segments time-locked to the blocked saccades were analyzed and the typical cognitive P3 wave appeared. It was markedly influenced by the inability of patients to filter out the irrelevant stimuli. This points to the fact that stimulus classification and processing capacity is prolonged and more variable in patients with mood disorders. Korunka *et al.* (1993) stressed the possibility that the PD patients and healthy subjects should differ more in processing emotionally neutral stimuli. These findings persisting also after treatment suggest the considerable fluctuation in the overall activation level of those neuronal loops which participate also in the oculomotor circuits.

The general imbalance of the tonus within the oculomotor circuits was reflected also in the changes of angular velocity of the optokinetic nystagmus of PD patients. In previous studies we have shown that the selection of moving visual stimuli may be under the influence of functional brain asymmetry, biological significance of moving objects as well as upon the external and internal factors which was documented in examinations with interfering mental activity (Zikmund & Jagla 1978; Jagla & Zikmund 1994; 1980). The very surprising finding concerns the inability of PD patients to pursuit accurately the moving visual stimuli even at their moderate velocity. It documents the disorder of visual-oculomotor (sensory-motor) integration reflecting the alterations in information processing, particularly the inability to suppress or gate the irrelevant information.

In the relevant literature two kind of theories – cognitive behavioural and neurobiological – are used to explain the pathophysiological mechanisms of neuropsychiatric disorders and diseases. The forebrain regions and the several neurotransmitter neuronal loops in brain stem represent typical example for such explanations concerning the panic disorder. The downstream effects of hierarchically higher neuro-

nal loops engaged in disorders with depressive symptoms may also affect the oculomotor circuitry within the brain stem. Our results are more associated with neurobiological approaches to panic disorder and depressions. Our pilot study of changes in biochemical sweet parameters in PD patients supports it as well (Kukumberg *et al.* 2009).

The fundamental brain functions as receiving, processing, storing information and creating proper answers accordingly lead to functional and structural changes within the brain. These processes, described as the neuroplasticity, enable subjects to adapt his/her behavior according to external and internal conditions. Disregulation of plasticity is supposed to play a role in variety of neuropsychiatric disorders as mood disorders, depressive symptoms and major depression, panic disorder as a kind of anxiety disorders and even schizophrenia including (Drewets 2000; Moghaddam & Homayoun 2008; Pittenger & Duman 2008). It can explain also the disordered visuo-oculomotor integration in our subjects and can be taken as an argument why the above oculomotor findings can not be assumed as specific for a particular neuropsychiatric disorder. Up to now there is no knowledge on how the specific neuroplasticity changes as such look like. On the other hand, the disorders of neuroplasticity may not evoke the same effects within different brain regions (Fišar & Hroudová 2010).

The ability of the brain to manage constantly neural communication and to rearrange existing one through our lifetime is the result of many complex processes. Without neuroplasticity the disordered brain functions as well as their regulatory mechanisms could be never regained. As mentioned above the plastic changes are present also in patients suffering from mood disorders. Several studies pointed recently to the genes playing possible role in synaptic plasticity and synaptic remodeling in anxiety disorders (Gratacòs *et al.* 2007). On the other hand, Manji *et al.* (2000; 2002) have shown that the structural changes in such patients are reversible also due to the proper pharmacological therapy. In conclusion, it may be supposed that the changes in oculomotor behavior as well as of its EEG correlates in subjects suffering from depressive symptoms and panic disorder may help to follow up the course of the complex therapy. Similar point of view was formulated by Trillenberg *et al.* (2004) and Reilly *at al*. (2008) as for the eye movement control examinations by schizophrenia, affective disorders, attention deficit hyperactivity disorder, Parkinson's disease, and Huntington's disease.

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