EEG Correlates of Startle Reflex with Reactivity to Eye Opening in Psychiatric Disorders: Preliminary Results

Kemal Arikan, Nash N. Boutros, Erol Bozhuyuk, B. Cagri Poyraz, B. Mert Savrun, Reha Bayar, Aysegul Gunduz, Feray Karaali-Savrun and Mehmet Yaman

Clin EEG Neurosci 2006 37: 230
DOI: 10.1177/155005940603700313

EEG Correlates of Startle Reflex With Reactivity to Eye Opening in Psychiatric Disorders: Preliminary Results

Kemal Arikan, Nash N. Boutros, Erol Bozhuyuk, B. Cagri Poyraz, B. Mert Savrun, Reha Bayar, Aysegul Gunduz, Feray Karaali-Savrun and Mehmet Yaman

Key Words
Electroencephalography
Eyeblink Reflex, Eye-Opening
Generalized Anxiety Disorder
Major Depressive Disorder
Panic Disorder
Posttraumatic Stress Disorder
Schizophrenia
Startle Reaction

ABSTRACT

Previous studies have shown alterations of eyeblink reflex in patients with various psychiatric disorders. It has previously been demonstrated by our group that EEG measures of the reactivity to eye opening could effectively predict patient-reported startle response in patients with acute stress reaction.

In our present study, EEG spectral power analysis and eyeblink electrical startle responses were acquired from a total of 39 patients diagnosed with various psychiatric disorders: 7 patients with schizophrenia, 10 patients with major depressive disorder (MDD), 10 patients with panic disorder, 5 patients with posttraumatic stress disorder (PTSD) and 7 patients with generalized anxiety disorder (GAD). EEG percent power data of each frequency band (delta, theta, alpha, beta) obtained from the 19 leads under open or closed eyelid conditions were used to calculate the arithmetical difference between eyes-open and eyes-closed states as representative of "EEG reactivity to eye opening." Data was analyzed separately for each diagnostic group.

For all of the disorders, right-sided R2c (contralateral secondary component) latency was the single eyeblink startle measure that was found to be significantly correlated with EEG reactivity to eye opening. The correlation was most significant for right temporal theta frequency in schizophrenia, right temporal theta frequency in MDD, left central beta frequency in panic disorder, left parietotemporal delta frequency in PTSD and right occipital alpha frequency in GAD. Findings showed a newly identified pattern that has potential scientific and clinical value with respect to psychiatric medicine.

INTRODUCTION

Startle reflex is a rapid, generalized motor response to abrupt and intense stimulation.[1] It consists of "a rapid sequential muscle contraction with the likely purpose of fascilitating the flight reaction and/or to protect the body from a sudden attack." "Baseline" startle or startle reactivity in absence of any experimental manipulation is measured by recording the eyeblink reflex, reportedly the most consistent component of startle pattern. Eyeblink reflex consists of an abrupt contraction of the orbicularis oculi muscle, which is innervated by facial nerve. Such a startle response can be elicited by brief and intense auditory, visual, or tactile stimuli. The eyeblink startle has an onset latency depending on the subject's emotional/motivational state.[2] A substantial amount of literature suggests that startle reaction is altered in a wide spectrum of psychiatric disorders.

Schizophrenia

Baseline startle reactivity has been shown to be altered in subgroups of schizophrenia. It has also been suggested that startle might serve to identify individuals with schizophrenia suffering from specific symptoms. Affective modulation of startle and prepulse inhibition paradigms have particularly been employed for this purpose.[2]

Major Depressive Disorder

Overall startle reactivity was found to be significantly reduced in depressed patients compared to the controls.[2]

Panic Disorder

In a study testing startle response during a verbal threat of shock in panic disorder patients, "baseline" startle was found to be increased in a younger age group, and

K. Arikan, B. C. Poyraz, B. M. Savrun, E. Bozhuyuk and R. Bayar are from the Department of Psychiatry, and A. Gunduz and F. Karaali-Savrun are from the Department of Neurology, Cerrahpasa Medical Faculty, University of Istanbul, Turkey.

Nash N. Boutros is from Wayne State University, School of Medicine, Detroit, Michigan, USA.

M. Yaman is from the Faculty of Medicine, Afyon Kocatepe University, Afyon, Turkey.

Presented in part at the 2nd ECNS/ISNIP Joint Meeting, September 2005, Munich, Germany.

Address requests for reprints to Prof. Dr. M. Kemal Arikan, Psikıyatri ABD, Cerrahpasa Tip Fakultesi, Kocamustafapaşa, Istanbul, Turkey.

Email: mkarikan@istanbul.edu.tr

Received: November 7, 2005; accepted: December 27, 2005.

Table 1

Mean age and male-to-female ratios for diagnostic groups studied

Diagnosis	Mean Age	Male/Female Ratio
Schizophrenia n=7	27	2.5
Major Depressive Disorder n=10	29.1	0.4
Panic Disorder n=10	32.9	0.6
Posttraumatic Stress Disorder n=5	43.4	All males
Generalized Anxiety Disorder n=7	45	1.3

reduced in an older age group compared to respective control subjects. Authors interpreted the finding in the context of studies performed in Vietnam veterans with early posttraumatic stress disorder (less than 5 years) and concluded that excessive anticipatory anxiety to threatening contexts (i.e, contextual fear) might be responsible for the exaggerated startle in panic disorder.[2]

Posttraumatic Stress Disorder

Exaggerated startle reflex has historically been an important symptom experienced by combat veterans with combat-related psychiatric sequelae. Although exaggerated startle is no longer viewed as a cardinal symptom of PTSD, the large majority of studies in recent PTSD (less than 5 years) confirms the symptom of exaggerated startle.[2]

Generalized Anxiety Disorder

Although there is no published startle study specifically addressing the population with generalized anxiety disorder (GAD), "generalized anxiety induced by diffuse contextual cues" opposed to the situational fear such as phobias results in a more sustained elevation in startle reactivity. Such increases might be compartively more pronounced in the "baseline" startle activity.[2]

In general, findings suggest that the excitatory and inhibitory systems of the central nervous system (CNS) at least partially have some significance in eliciting abnormal startle response.[3,4] Elsewhere, findings during eyes-open state were reported to be closely related with hyperexcitability in the CNS.[3] In a previous study, Arikan et al[1] reported that patient-reported startle phenomena in subjects with acute stress reaction could effectively be predicted by EEG reactivity to eye opening and closing, recorded from the occipital leads. Nevertheless, no confirmation of the finding with the measurable parameters of the startle response, i.e., eyeblink reflex, was done. In the present study, we aimed to assess whether in various psychiatric disorders (i.e., schizophrenia, major depressive disorder, panic disorder, posttraumatic stress disorder and generalized anxiety disorder) cortical reactivity to eye opening as measured by EEG spectral power analysis is associated with the data provided by the "gold standard" test of startle response, i.e., eyeblink reflex.

MATERIALS AND METHODS

A total of 39 patients diagnosed with a DSM-IV (American Psychiatric Association, 1994) diagnosis (schizophrenia n=7, unipolar major depressive disorder (MDD) n=10, panic disorder n=10, posttraumatic stress disorder (PTSD) n=5 and generalized anxiety disorder (GAD) n=7) were enrolled into the study via recruitment in the outpatient clinic at the Psychiatry Department, Cerrahpasa Medical Faculty, Istanbul. Inclusion criteria were being free of any centrally acting medications for at least 1 week, and exhibiting no concomitant psychiatric (including alcohol/drug abuse) disorders, clinically significant physical/neurological conditions or laboratory abnormalities, or significant visual problems. Subjects with MDD scored 18 or higher on the 17-item Turkish version of Hamilton Depression Scale (HAM-D).[5] For subjects with PTSD, duration of disease was less than 3 years. All interviews were done by a fully-trained research psychiatrist. All subjects signed an informed consent before the study. Mean age and male-to-female ratios are summarized in Table 1.

A 19 channel (FP1, F7, T3, T5, F3, C3, P3, O1, FZ, CZ, PZ, F4, C4, P4, O2, FP2, F8, T4, T6) resting EEG was performed using silver chloride electrodes applied with collodion according to the International 10-20 System. Referential linked ear electrodes were used. Impedances were kept below 5kOhm. The activity derived from the leads was recorded in a shielded room (highpass filter 2 Hz, sampling rate: 128 Hz, gain: 16000, notch filter on, 50 microV/cm). A room temperature of 23° C was maintained to avoid excessive perspiration. During the recordings, the subjects were seated on a comfortable chair, and their vigilance level was kept as constant as possible by verbal commands. The EEGs were recorded for 50 epochs with eyes closed, 50 epochs with eyes open; epoch length was 4 seconds. Fast Fourier Transformation was applied to artifact free epochs.

The mean power spectrum was obtained from each subject in each different eyelid condition (open-O; or closed-C). Data obtained from each channel was stored for further analysis. The following frequency bands of the mean power spectra were considered: delta (2-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-16 Hz). Activity below 2 Hz was excluded to avoid misleading results due to eye movements. EEG percent power data of each frequency band (delta, theta, alpha, beta) obtained from the 19 leads under open (O) or closed (C) eyelid conditions were used to calculate the aritmetical difference between eyes-open

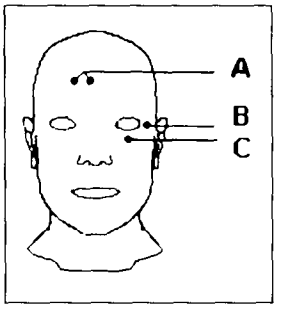

Figure 1.
Illustration of how right-sided R2c (contralateral secondary component) of the eyeblink reflex was recorded. A: Percutaneous electrical stimuli applied to the right supraorbital nerve. B: Reference electrode attached to the left temple. C: Active electrode attached to left lower eyelid.

and eyes-closed states (abbreviated as CO). CO data were used for subsequent analysis.

On the same day immediately before the EEG recordings for each patient, electrical eyeblink responses were measured following the protocols described widely elsewhere.[6] Briefly, the patient lay on an examination bed and environmental noise was eliminated. Stimulus duration was 0.2-0.5 msec using a constant current stimulator. The stimuli were administered via supraorbital nerve (V1) randomly between 45 and 60 sec to avoid habituation. Electromyographic activity was recorded from surface electrodes placed bilaterally on the midline of the patient's lower lid and on the temple. The ground electrode was placed under the chin. Five rectified responses were obtained from each side. For each patient, latencies for R1 (primary component), R2i (ipsilateral secondary component) and R2c (contralateral secondary component) responses were acquired for use in further analysis. R2i and R2c are acknowledged in this text as "right-sided" or "left-sided" with regard to the supraorbital nerve that is stimulated. Hence, for instance, *right-sided* R2c is recorded when *right* supraorbital nerve is stimulated.

RESULTS

Stepwise linear regression analysis was conducted between the eyeblink and EEG parameters. Data were analyzed separately for each diagnostic group.

Schizophrenia

A strong negative linear relationship was found between right-sided R2c component of eyeblink response and T4 theta frequency change in response to eye opening (p=0.001; r: 0.969 r^2: 0.939; beta: -0.969).

Major Depressive Disorder

There was a strong positive linear relationship between right-sided R2c component of eyeblink response and T6 theta frequency change in response to eye opening (p=0.006; r: 0.823 r^2: 0.678; beta: 0.823).

Panic Disorder

A strong negative linear relationship occurred between right-sided R2c component of eyeblink response and C3 beta frequency change in response to eye opening (p=0.002; r: 0.877 r^2: 0.769; beta: -0.877).

Posttraumatic Stress Disorder

It was found that there was a strong positive linear relationship between right-sided R2c component of eyeblink response and P3 delta frequency change in response to eye opening (p=0.003; r: 0.980 r^2: 0.960; beta: 0.980).

Generalized Anxiety Disorder

A strong negative linear relationship was shown between right-sided R2c component of eyeblink response and O2 alpha frequency change in response to eye opening (p=0.007; r: 0.893 r^2: 0.797; beta: -0.893).

For all of the diagnostic groups, no correlation of significant degree could be observed between the other eyeblink reflex parameters (latencies for right-sided and left-sided R1, right-sided and left-sided R2i, and left-sided R2c) and the rest of CO data. Although the findings of highly significant relationships were limited to one scalp electrode location in each diagnostic group, in fact the F-Values multivariate analysis of other electrodes has shown some spread to other areas even if not at the level of significance.

DISCUSSION

In this study we found that right-sided R2c (contralateral secondary component) latency was substantially related with eye opening reactivity in EEG for all of the diagnostic groups. Latency for the secondary component (R2) of eyeblink reflex is reported to show more variability compared with the primary component (R1), and its susceptibility to modulation also differs greatly. See Figure 1 illustrating how right-sided R2c of the eyeblink reflex was elicited. Reflex arc of R2 response is reportedly multisynaptic, while the reflex circuit of R1 is in an oligosynaptic organization with three neurons.[6] This might explain, at least in part, why R2 is more prone to alteration due to effects in the CNS and why in this study this measure has been the sole eyeblink parameter found to be correlated with EEG data. On the other hand, the significance of our finding of lack of relationship between other R2 latencies (right and left R2i, and left R2c) and EEG data remains to be concluded.

Startle reaction has been well documented to be of value in the study of emotional disturbances.[2] It has been reported that the EEG changes observed in the group with startle reaction symptoms may theoretically indicate hyperexcitability in the CNS.[7] In our previous study, we have demonstrated that startle response reported by the patients with acute stress reaction (ASR) could be predicted by EEG reactivity to eye opening recorded from the occipital leads. In that study, reduced delta power response to eye opening was found to be the most substantial indicator for that purpose.[1] Current study demonstrates that the magnitude of eye opening reactivity at several cortical regions can be plotted as indicators of startle reflex (latencies) elicited in subjects with different psychiatric disorders. As no single EEG localization and frequency has been found to be determining across various disorders, it would be most prudent to discuss findings separately for each disorder.

Schizophrenia

In our study, we found that in schizophrenia latency for the right-sided contralateral secondary component (R2c) of the eyeblink reflex is inversely correlated with eye opening reactivity in the theta range measured at the right anterior temporal region. In other words, increased de-stability in the theta band has been found to be closely related with "exaggerated startle response" (decreased startle reaction latency) in this group. We could postulate that relative theta stability in the left side compared to the right side might indicate a left-sided dysfunction in schizophrenia and startle-related increased-theta response in the right side might indicate that the theta rhythm, when it occurs in the right temporal region of schizophrenic subjects, is a kind of alpha (even perhaps beta) variant that is prone to supression by eye closure. On the other hand, there is a line of proof from EEG studies that theta activity in awake subjects is related to higher brain functions such as cognition and memory, and the origin of this activity is reportedly in the anteromedial cortex.[8] Augmented low frequency and diminished alpha-band power reported in schizophrenic patients has been linked with dysfunction in the thalamo-cortical circuits. Involvement of these networks could lead to both symptomatology and information-processing deficits evident in schizophrenia.[9] Involvement of thalamo-cortical circuits in schizophrenia might well have its effects reflected as alterations of the startle response, hence our finding of correlation between EEG spectral data of the right anterior temporal region and that of eyeblink reflex latency.

Major Depressive Disorder (MDD)

In the current study, magnitude of the theta change in the right side shows linear correlation with latency for the right-sided contralateral secondary component (R2c) of the eyeblink reflex. This indicates an inverse relationship between the magnitude of right temporal theta response to eye opening and startle reaction. We also found that in MDD, theta response to eye opening in the left side was comparatively less than the one in the right side. Considering the increased (T5-theta-closed (mean): 23.5 and T6-theta-closed (mean): 22.1) and persistent theta frequency in the left side, we concluded that the left side is more dysfunctional compared to the right side. Since startle reaction has been found to be reduced in depression,[2] and depression has been linked to left hemispheric dysfunction,[10] our findings are consistent with the current literature.

Panic Disorder

Latency for the right-sided contralateral secondary component (R2c) of the eyeblink reflex was inversely correlated with eye opening reactivity in the beta range measured at the left central region of panic patients included in the study. Therefore, high beta reactivity at left central area might be an indicator of increased startle reaction. In consensus with our findings, one study reported relative beta power to be related to self-rating of anxiety.[11]

Posttraumatic Stress Disorder

In this group, latency for the right-sided contralateral secondary component (R2c) of the eyeblink reflex is correlated with eye opening reactivity in the delta range measured at the left parietotemporal region. In agreement with our previous finding in patients with acute stress reaction (ASR),[1] reduced delta power response to eye opening seems directly related with "exaggerated" startle reaction. Our current study shows that parietotemporal (as opposed to occipital in ASR) eye opening reactivity in the delta range might be utilized for this purpose in subjects with PTSD.

Generalized Anxiety Disorder (GAD)

Finally, latency for the right-sided contralateral secondary component (R2c) of the eyeblink reflex is correlated with eye opening reactivity in the alpha range measured at the right occipital region of GAD patients. In other words, increased alpha reactivity to eye opening at this localization is closely related with exaggerated startle reactivity. Considering that lower frequency (delta) reactivity at the same localization has been reported by our group to be inversely related with subject-reported startle in acute stress reaction (ASR),[1] our current finding of positive correlation of alpha band reactivity with exaggerated startle reaction in subjects with GAD might be interpreted as replication of our previous study findings.

In general, the above data indicate that there is a diagnosis-specific relationship between eyeblink latency and eye opening reactivity to EEG measures. The relationship has certain characteristics. It is frequency- and localization-specific. It shows either negative or positive correlation. The pattern makes it possible to get the data from diagnosis-specific EEG findings together with data from neural mechanisms of the startle reactions. Besides, working with a subtracted list of "open eyes" and "closed eyes" EEG measures allows for having all EEG data together in a single statistical equation, thus permitting detailed analysis. Such a study design might enrich the method of EEG by providing certain independence. As this newly-encountered pattern has a highly preliminary nature, much more effort should be given for understanding its background.

Our study nevertheless has some limitations. Lack of longitudinal follow-up of the patients with respect to the measured parameters and clinical outcome has prevented us from concluding about the possible prognostic value of our findings. Lack of control subjects is the other shortcoming of this study. Finally, these preliminary findings have to be replicated by other studies with larger sample size and a possible longitudinal design.

ACKNOWLEDGEMENT

This work is supported by the Research Fund of the University of Istanbul.

REFERENCES

1. Arikan K, Uysal O, Oran O, Coban A, Tolun H, Kokrek Z. Earthquake related startle reaction and its EEG correlates. Clin Electroencephalogr 2001; 32(4): 205-209.
2. Grillon C, Baas J. A review of the modulation of the startle reflex by affective states and its application in psychiatry. Clin Neurophysiol 2003; 114: 1557-1579.
3. Matsumoto J, Hallett M. Startle syndromes. In: Marsden CD, Fahn S, (eds). Movement Disorders. Oxford: Butterworth Heinemann; 1994: 418-433.
4. Ciulla C, Takeda T, Endo H. MEG characterization of spontaneous alpha rhythm in the human brain. Brain Topogr 1999; 11(3): 211-222.
5. Akdemir A, Turkcapar MH, Orsel SD, Demirergi N, Dag I, Ozbay MH. Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. Compr Psychiatry 2001; 42(2): 161-165.
6. Esteban A. A neurophysiological approach to brainstem reflexes: blink reflex. Neurophysiol Clin 1999; 29: 7-38.
7. Rossini PM, Desiato MT, Lavoroni F, Caramia MD. Brain excitability and electroencephalographic activation: non-invasive evaluation in healthy humans via TMS. Brain Res 1991; 567(1): 111-119.
8. Koenig T, Lehmann D, Saito N, Kuginuki T, Kinoshita T, Koukkou M. Decreased functional connectivity of EEG theta-frequency activity in the first-episode, neuroleptic-naïve patients with schizophrenia: preliminary results. Schizophrenia Res 2001; 50: 55-60.
9. Sponheim SR, Clementz BA, Iacono WG, Beiser M. Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. Biol Psychiatry 2000; 48: 1088-1097.
10. Soares JC, Mann JJ. The anatomy of mood disorder-review of structural neuroimaging studies. Biol Psychiatry 1997; 41: 86.
11. Knott VJ, Bakish D, Lusk S, Barkely J, Perugini M. Quantitative EEG correlates of panic disorder. Psychiatry Res Neuroimaging 1996; 68(1): 31-39.