Dopaminergic Activity as a Moderator of ERN Amplitude

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Abstract

Spontaneous eye-blink rates provide a noninvasive measure of functional brain dopamine (DA) activity, as dopamine agonists evoke a dose-related increase in blink-rates and DA depletion decreases blink rates. The dopaminergic reinforcement-learning model of the Error Related Negativity (ERN) generation (Holroyd & Coles, 2002), which posits that ERN generation results from a reduction of dopaminergic input to the anterior cingulate cortex, might therefore predict that greater tonic DA activity (indexed by higher blink-rate) would result in a larger phasic reduction in DA input, and thus a larger ERN. Spontaneous eye-blink rate during a 6-minute resting baseline was obtained for 58 participants, who then engaged in a forced choice discrimination task, from which ERN was obtained. ERN was calculated as a difference between Error trials and Correct trials. Results indicated that higher spontaneous eye-blink rates were related to ERN amplitudes at both the Fz and Cz sites, with more eye-blinks being correlated with a larger, more negative ERN ($p < .01$). The role of dopaminergic activity as a moderator is consistent with the dopaminergic reinforcement-learning model of ERN formation, and also suggests that individual differences in functional DA activity may be an important factor underlying individual differences in ERN amplitude.

Introduction

Moderators & Mediators

Mediators are variables that may reflect a possible mechanism underlying the relationship between the independent and dependent variables, in this case between error monitoring and ERN magnitude. In the ERN literature, possible mediators may include:

- ❑ Error detection (Falkenstein et al. 1990); Gehring et al. 1993)
- ❑ Response Conflict (Carter et al. 1998; Van Veen & Carter 2002)
- ❑ Error-force magnitude (Gehring et al. 1993)

Moderators, on the other hand, are variables that influence the relationship between the independent and dependent variable. These may include:

- ❑ Emphasizing speed over accuracy (Gehring et al. 1993)
- ❑ Presence of obsessive-compulsive tendencies or other anxiety traits (Hajcak & Simons 2002)
- ❑ Trait levels of positive and negative affect (Hajcak et al. in press; Luu et al. 2000)
- ❑ Socialization status (Dikman & Allen 2000)
- ❑ Schizophrenia (Mathalon et al. 2002)

Reinforcement Learning Model

The Reinforcement Learning model of ERN production (Holroyd & Coles, 2002) takes into account that a medial-frontal negativity seems to be seen whenever the outcome of a task is worse than expected, whether the task examines error commission or negative feedback. In particular, they claim that a reduction of dopaminergic input to the anterior cingulate cortex occurs in response to an error, thus generating the negativity. Therefore it would follow that greater tonic DA activity would result in a larger phasic reduction in DA input, and thus a larger ERN. Currently there is mixed evidence in the literature for this model:

- ❑ Parkinson's patients and the elderly, both thought to have lower tonic levels of dopaminergic activity, exhibit smaller ERNs than controls (Falkenstein et al. 2001; West & Alain 1999)
- ❑ Schizophrenia patients, thought to have an over-activity of the dopaminergic system, also exhibit smaller ERNs than controls (Mathalon et al. 2002)

Current Study

Despite the mixed evidence, it is reasonable to suspect that dopaminergic activity may act as a moderator for ERN magnitude. Although ideally a direct measure of functional dopaminergic activity would be required, spontaneous eye blinks can provide a non-invasive method of measuring tonic dopaminergic activity.

- ❑ DA agonists evoke a dose-related increase in blink rate (Depue et al. 1994; Karson, 1983; Kleven & Koek, 1996).
- ❑ DA depletion decreases blink rates (Taylor et al. 1999)

In fact, Allen et al. (2004) found a trend suggesting that a higher rate of spontaneous eye blinks was related to larger ERNs. The relationship in that study did not reach significance, but the sample size was relatively small and there was a modest effect size. Therefore, the present study aimed to clarify the possible role of tonic dopaminergic activity levels on ERN magnitude.

Method

Subjects

- ❑ 58 University of Arizona students (25 Female) participated

Physiological Recording

- ❑ EEG
  - ❑ Recorded from 25 scalp sites using a standard electrode cap
  - ❑ Amplified 20,000 times and continuously digitized at 256 Hz
  - ❑ Filtered online at 0.1 Hz and 100 Hz
- ❑ EOG was recorded from above and below each eye, and at the nasion
- ❑ EEG and EOG were both referenced online to A1, and referenced offline to linked mastoids

EEG Analysis

- ❑ Artifacts were removed after visual inspection
- ❑ Files were digitally filtered with a 15-Hz low-pass (96 dB/octave) filter.
- ❑ Eye blinks were corrected using a regression algorithm (Semlitsch et al. 1986)
- ❑ 1,500 ms epochs were created and baseline corrected, beginning 500 ms before response
- ❑ ERN amplitude was quantified by subtracting the correct trial waveforms from the incorrect trial waveforms, and selecting the minimum value in the 40-120 ms window after response

Procedure

- ❑ Subjects were chosen on the basis of the Levenson self-report Psychopathy Scale (M. R. Levenson et al. 1995; LSRP)
  - ❑ Subjects did not show a significantly different ERN based on the LSRP; therefore these scores were disregarded in the subsequent analysis
- ❑ Spontaneous eye blinks were measured during a 6 minute baseline EEG recording: 3 minutes with eyes open and 3 minutes with eyes closed
- ❑ An eye blink was identified in the EEG data as all of the following:
  - ❑ A positive deflection of at least 50 microvolts at FP1 and FP2
  - ❑ Polarity reversal between Nasion and VEOG
  - ❑ Lasting for a 250-450 ms duration
  - ❑ Additionally, a double blink was counted if the second peak (positive deflection) was at least 50 microvolts
- ❑ ERN was recorded during a subsequent Eriksen Flankers task (Eriksen & Eriksen, 1974)
  - ❑ Errors made during half of the trials resulted in a loud tone (Punishment condition; PUN), while errors made during the other half of the task resulted in a reward being withheld (Reward condition; REW)

Data Analysis

- ❑ Pearson Correlations were performed on the average number of blinks (across several blink raters), and the ERN sites Fz and Cz respectively
- ❑ A Paired-Samples t-test was used to compare the overall ERN in the PUN condition and the REW condition

Results

Reliability of Blink Counts

❑Independent raters counted blinks from each subject

❑Inter-Rater Intraclass Correlation for eye blink rate was .94

Grand Average Error-Correct waveforms

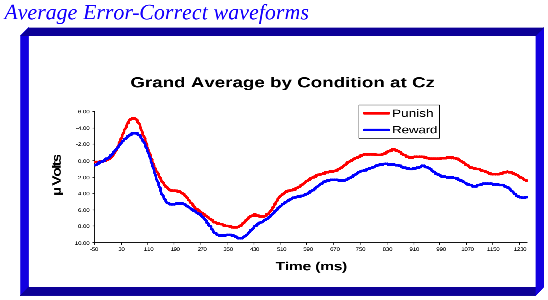

Figure 1. Error-Correct Response-locked ERP at Site CZ (above)

A clear ERN was observed on error trials. The ERN elicited during the PUN task was not significantly greater than during the REW task, but it demonstrated a trend in that direction at site Cz (p=.086).

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Results (cont.)

Relationship of Spontaneous Blinks to ERN amplitudes

The hypothesis that higher blink rates would be associated with larger ERN amplitudes was supported. Across reward and punishment conditions, higher blink rates were associated with more negative ERN amplitudes at site Fz (r=-.46) and Cz (r=-.40). Examining the REW and PUN conditions separately, the correlations were significant for PUN (r=-.46 and -.41 for Fz and Cz) but not for REW (r=-.25 and r=-.24 for Fz and Cz); the difference between these two conditions was not significant.

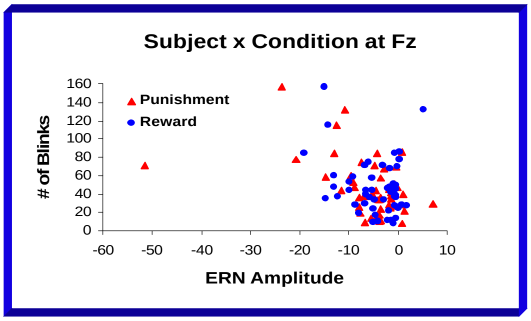

Figure 2. Scatterplot of Spontaneous Blinks and ERN Amplitude at Site Fz (above)

The outlier with extremely large ERN amplitude under the PUN condition serves only to attenuate the correlation. With the outlier removed, the overall correlation increases in magnitude from -.45 to -.49.

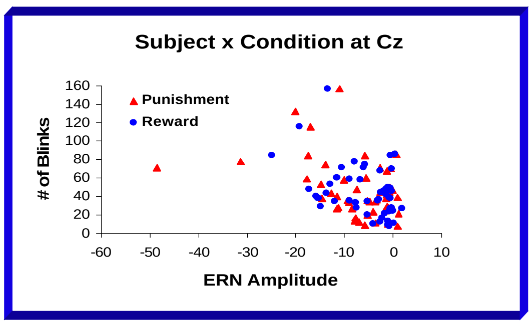

Figure 3. Scatterplot of Spontaneous Blinks and ERN Amplitude at Site Fz (above)

The outlier with extremely large ERN amplitude under the PUN condition again serves only to attenuate the correlation. With the outlier removed, the overall correlation increases in magnitude from -.40 to -.41.

Discussion

Learning Reinforcement Model

Overall, higher blink rates, serving as a proxy for functional dopaminergic activity, were associated with larger ERN magnitude. Although these results are consistent with the Learning Reinforcement Model, they should be interpreted cautiously because blink rate is an indirect measure of functional dopaminergic activity.

- ❑ A recent study has suggested that blink rate is not as good of an indicator of dopamine as previously thought.
- ❑ van der Post et al. (2004) found administration of either a D_2-agonist, -antagonist, or placebo did not affect blink rates
- ❑ However, in the van der Post et al. study, blinks were counted while subjects were watching an aquarium scene, which will reflect not only spontaneous blinks, but those that reflect attention-related processes

The smaller ERNs seen in schizophrenia patients are also left unexplained. A few possible explanations for this inconsistency in the literature include:

- ❑ Schizophrenia patients may have action monitoring deficits (Malenka, 1986; Frith et al. 2000)
- ❑ There may be a dysregulation in the dopaminergic system of schizophrenia patients (Kegeles, 2000)

Punishment and Reward Conditions

The relationship between blink rate and ERN magnitude was, descriptively, stronger in the PUN condition than in the REW condition.

- ❑ The PUN condition presented two negative events (error and punishment), whereas the reward condition arguably presented only one truly negative event (error and failure to receive reward)
- ❑ While it is adaptive to learn from both successes and failures, it may be reasonable to suggest that quickly learning about negative consequences is more adaptive
  - ❑ Consistent with this line of reasoning was the finding that average ERN in the PUN condition was descriptively larger than the ERN in the REW condition

Future Directions

In the future, studies examining the relationship between dopamine and error monitoring should use a more direct measure of dopaminergic activity, such as the administration of a dopaminergic agonist or antagonist before an ERN task.

- ❑ Zirnheld et al. (2004) found that subjects given Haloperidol, a dopamine antagonist, demonstrated a smaller ERN
  - ❑ It is also import to consider that Haloperidol is a relatively older and more non-specific drug

These results are nonetheless consistent with the Reinforcement Learning model of ERN postulated by Holroyd and Coles (2002), and suggest that within the general population, individual differences in functional dopamine activity may influence ERN amplitude. These findings suggest the promise of further research examining the relationship between functional dopaminergic activity and error monitoring.

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