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Effects of cold stress on early and late stimulus gating

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Abstract

The P50 component of the event-related potential (ERP) mainly reflects early pre-attentional processing. Along with P50, the N100 component and mismatch negativity (MMN) were postulated to represent a complex multistage and multi-component gating system. If some variable threshold or gating is exceeded by the MMN signal, the MMN is often followed by a relatively sharp fronto-central positive wave, the P3a component, which reflects an attentional switch to an environmental change. The P50 was shown to be affected by mental and cold stress, and the P3a amplitude was shown to be increased by the anticipation of threat. The aim of this study is to examine concurrently the early and late ERP indices of gating during acute stress. The ERPs to auditory stimuli in a passive oddball paradigm were recorded in 15 normal subjects during the cold pressor test and a control condition. The cold pressor test diminished P50 gating, increased N100 amplitude, elicited P3a responses and had no significant effect on MMN. Transient stress could impair early sensory gating and the ability to ignore irrelevant information that can cause passive attention switches indexed by the P3a component.

Keywords: Event-related potential; Mismatch negativity; Evoked potentials; Electrophysiology; Oddball paradigm; Stress

1. Introduction

Sensory gating is broadly defined as the ability of the brain to modulate its sensitivity to incoming sensory stimuli (Braff and Geyer, 1990). It reflects a complex multistage, multi-component process (Boutros and Belger, 1999). Sensory gating is commonly studied in paired click, oddball, and trains paradigms (Boutros et al., 1999). In the paired click paradigm, the effects of repetition on the amplitude of the P50 component of the event-related potential (ERP) is believed to reflect an automatic pre-attentive inhibitory capacity. In the oddball paradigm, on the other hand, increased amplitude of the P50 component to infrequent auditory stimuli has been shown to reflect pre-attentive recognition of novel stimuli or "gating in" of stimuli while decreased amplitude to frequent auditory stimuli reflects "gating out" of stimuli (Boutros et al., 1995).

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In the oddball paradigm, the subject is presented a sequence of repetitive "standard" (frequent) stimuli that are randomly, and with a low probability, replaced by a different deviant (infrequent) stimulus. In the passive (ignore) paradigm, attention is directed away from the acoustic stimuli to a concurrent (primary) task, usually involving another sensory modality, such as reading an interesting book or performing a challenging visual discrimination task. The passive oddball paradigm is used to study brain responses to ignored stimuli and to underlying involuntary discrimination of, and attention switches to, deviant stimuli (Näätänen, 1990). On the other hand, in the active oddball condition, the subject has to attend to all the stimuli to discriminate the deviant stimuli among them. Thus, the main interest is in the brain responses associated with attention.

Infrequent auditory stimuli deviating from a repetitive standard sound in some physical features, such as frequency, elicit the mismatch negativity (MMN) component of the ERP. MMN can be derived from a difference wave obtained by subtracting the standard stimulus ERP from the deviant stimulus ERP (Sams et al., 1985). MMN is thought to reflect the outcome of a mismatch process automatically registering the deviation of the current input from the neuronal representation of a repetitive stimulus in sensory memory (Näätänen, 1990).

MMN is often followed by a relatively sharp fronto-central positive wave that peaks at about 250 ms and is caused by the P3a component (Squires et al., 1975). The P3a component seems to be more easily elicited by the deviant stimulus when the magnitude of stimulus deviation is great, the interstimulus interval is short, and the primary task is not very demanding. The P3a component might reflect an attentional switch to an environmental change encoded by the cerebral process generating the MMN if some variable threshold is exceeded by this signal. Then a subsequent stage may be activated, resulting in the conscious detection of the deviant event. The P3a component might be the most sensitive cerebral indicator of an attentional switch (Schröger, 1997). However, in "attend" conditions when infrequent nontarget stimuli are inserted into the sequence of target and standard stimuli (three-stimuli oddball), the N2b–P3a complex is elicited in fronto-central and central scalp distributions to the infrequent nontarget stimuli (Courchesne et al., 1975; Squires et al., 1975).

The data suggest a specific role for noradrenaline in the modulation of sensory processing in humans and rats (Adler et al., 1988; Stevens et al., 1991; Miyazoto et al., 2000) and in the modulation of automatic attentional processing (Missonnier et al., 1999). Increased noradrenergic neuronal transmission in the central nervous system (CNS) induced by the alpha-2 noradrenergic antagonist yohimbine in normal controls can cause a transient impairment in auditory sensory gating (Adler et al., 1988; Stevens et al., 1993). Combat veterans with posttraumatic stress disorder (PTSD) exhibited decreased habituation of the P1 (P50) mid-latency auditory evoked potential (Neylan et al., 1999; Skinner et al., 1999).

Cerebral events underlying the P3a component probably participate in the sequence of processes leading to the release of an autonomic nervous system (ANS) response pattern typical of the orienting response (Näätänen and Gaillard, 1983). The integrity of the locus ceruleus (LC) and its ascending fibers was shown to be important in the generation and modulation of surface-recorded P300-like activity (Swick et al., 1994).

The prefrontal cortex seems to be a common generator site of P50 and P3a components of the ERP. Both components have been shown to be affected by prefrontal lesions (Knight, 1984; Knight et al., 1989).

In this study, we examined the effects of sympathetic nervous system processes induced by a cold pressor test on sensory gating, pre-attentive deviance detection, and attentional shifts. A modified passive oddball paradigm was used to assure that the interstimulus interval (ISI) between the deviant stimuli would be long enough to allow recovery from the effects of the preceding deviant stimulus and to delineate the effects of stress on sensory gating, pre-attentive deviance detection and attentional switch.

2. Methods

2.1. Subjects

Fifteen healthy volunteers (8 men and 7 women), who ranged in age from 19 to 46 years (mean = 26.3, S.D. = 8) and who were without hypertension, were included in the study. Two of the subjects were smokers (2–4 cigarettes/day). All subjects were either students or employees of the university. They were clinically interviewed and examined by one of the authors (MNE). None of the subjects had a history of psychiatric, neurological or hearing problems.

2.2. Cold pressor test

Although the cold pressor test traditionally involves water at temperatures of 2–4 °C, with brief, usually 1-min exposure, 10 °C water was chosen here to enable longer hand immersion while still eliciting a pressor response (Winzer et al., 1999). The volunteers were required to alternately submerge each hand to the wrist in two blocks of 10 °C water for 5 min. Arterial blood pressure and heart rates were measured from the contralateral arm at the beginning and the end of the cold pressor test.

Distress ratings were obtained by asking participants to locate on a 10-cm line the level of pain they were experiencing between points of no distress (0) and extreme distress (10) in the baseline room temperature water and the 10 °C water. The subjects were also tested for subjective rating of 2 °C water.

2.3. ERP recording

Electroencephalographic activity was measured at the Fz, F3, F4, FCz, Cz, and Pz recording sites with silver/silver chloride disk electrodes referenced to linked ear lobes. Electro-oculographic (EOG) activity was measured by bipolar recording with electrodes placed at the outer left canthus and below the left eye. All data were amplified (Psylab EEG amplifier) with band-pass filters set at 0.1 and 40 Hz. The signals were sampled at a rate of 400 points/s.

Stimulus duration was 50 ms with a sound intensity of 70 dB SPL, as measured at the subject's ear by a sound meter. The standards were 1000-Hz tones, and the deviants were 1250-Hz tones. The probabilities of the deviant and standard stimuli were 20% and 80%, respectively. Stimuli were presented with 2-s interstimulus intervals (ISIs). Infrequent stimuli did not occur in direct succession. Artifacts were eliminated by manual off-line selective averaging, taking into consideration the EOG. For each condition, 40 deviant and 40 standard stimuli were averaged.

Nicotine and caffeine were not allowed for 12 h before recording because of their effects on the P50 component. The subjects were asked to read an interesting book of their choice and to ignore all stimuli. Reading was controlled through examination of horizontal eye movements from the EOG. Recordings were made in four blocks (150 stimuli 30/120), alternating hand immersion to the wrist for 5-min intervals: Two blocks were recorded during the cold presser test, and two blocks during the baseline recording while the hand of the participant was immersed in water at room temperature.

2.4. Data analysis

Averages of two blocks for the cold pressor condition and two blocks for the control condition were taken for analysis. ERPs to deviant and standard stimuli were averaged. The P50 and N1 waves were measured in averaged standard and deviant ERPs (the former as the largest positive peak between 30 and 70 ms and the latter as the largest negative peak between 80 and 130 ms). The P50 amplitude responses to deviant minus standard tones and the P50 ratio (P50 deviant/P50 standard $\times$ 100) were also assessed for early pre-attentive gating function.

The MMN and P3a components were assessed by subtracting the averaged standard responses from the averaged deviant responses. The mean amplitude and latency of MMN was measured in the time window between 100 and 200 ms, and the mean amplitude and latency of P3a was measured in the 200- to 300-ms time window.

2.5. Statistical analysis

The data were subjected to multivariate analysis of variance with repeated measures and paired *t*-tests. Reduced degrees of freedom (Greenhouse–Geisser) were used to counter violations of the sphericity assumption where necessary.

The amplitude of P50 and the amplitude and latency of N100 were examined by three-way analysis of variance (ANOVA) for repeated measures, condition (control, cold stress) $\times$ stimuli (standard, deviant) $\times$ electrode site (Fz, F3, F4, FCz, Cz). The amplitude and latency of P50, P50 ratio (deviant/standard), P50 difference (deviant – standard), MMN and P3a were analyzed with two-way ANOVAs, condition (control, cold stress) × electrode site (Fz, F3, F4, FCz, Cz). For P3a, the Pz electrode site was also included in the analysis. Pearson's test was used for correlation analysis.

3. Results

3.1. Heart rate and arterial pressure

All data are shown in Table 1. Baseline and cold pressor test data were compared by paired *t*-tests. Systolic arterial tension recordings were significantly higher in the cold pressor test than the baseline recordings ($P<0.01$). There was no significant effect of the cold pressor test on pulse and diastolic arterial tension.

3.2. Self-rating

Self-ratings of distress increased as a result of water temperature in the cold pressor test in a simple factorial ANOVA ($F=88.48$, $df=2,42$, $P<0.001$). The cold pressor test at 2 °C was significantly more distressing than the baseline ($P<0.001$) and 10 °C temperature, and the 10 °C temperature was significantly more distressing than the baseline ($P<0.001$).

Table 1
Mean amplitude and latency of ERP components at Fz, and means of systolic blood pressure, diastolic blood pressure, heart rate and subjective distress ratings of 15 subjects

Component	Measures	Cold stress		Control	
		Mean	S.D.	Mean	S.D.
P50 (deviants)	Amplitude (μV)	1.65	0.95	1.76	0.7
P50 (standards)	Amplitude (μV)	1.52	0.90	0.81	0.47
P50 difference	Amplitude (μV)	−0.25	0.7	0.95	0.63
P50 ratio		86.30	38.80	249.30	111.20
N100 (deviants)	Amplitude (μV)	−7.31	4.23	−6.03	1.37
N100 (standards)	Amplitude (μV)	−7.56	3.41	5.34	1.48
N100 (deviants)	Latency (ms)	103.2	4.63	102.86	2.74
N100 (standards)	Latency (ms)	101.73	5.62	102.40	4.48
MMN	Amplitude (μV)	−2.79	1.15	−2.43	1.24
MMN	Latency (ms)	142.53	51.58	137.39	17.46
SBP	mmHg	115.20	10.37	106.00	5.90
DBP	mmHg	69.40	9.48	66.13	8.22
HR	Beat/min	73.66	6.96	73.73	5.73
Distress rating	Subjective	3.26	1.43	0.6	0.51

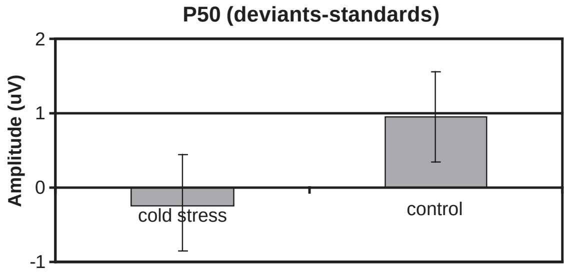

Fig. 1. Mean P50 difference (± S.D.) (deviant − standard) in cold pressor test and control conditions. Bars indicate ± S.D.

3.3. P50 and N100 components

Three-way ANOVAs, two conditions (cold pressor test vs. baseline) × two stimuli type (deviant × standard) × 5 electrodes (Fz, F3, F4, FCz, Cz), were applied to the amplitude of P50, and to the amplitude and latency values of N100.

P50 amplitude showed significant condition and stimulus effects. P50 amplitudes were larger in the cold pressor test condition than in the control condition ($F=7.0$, $df=1,14$, $P<0.02$), and P50 amplitudes to deviant stimuli were larger than P50 amplitudes to standard stimuli ($F=34.8$, $P<0.001$). The condition × stimulus type interaction was also significant ($F=8.9$, $df=1,14$, $P<0.01$). Paired *t*-tests showed that P50 amplitude to standard stimuli in the control condition was smaller than both the P50 amplitude to deviant tones in the control condition ($t=-5.8$, $df=14$, $P<0.001$, two-tailed), and P50 amplitudes to deviant and standard tones in the cold pressor test condition ($t=-3.4$, $df=14$, $P<0.003$, two-tailed; $t=-3.3$, $df=14$, $P<0.004$, two-tailed) (Fig. 1). Electrode site had no main effect on P50 amplitude.

Condition had a significant main effect on N1 amplitudes ($F=11.2$, $df=1,14$, $P<0.005$). There were no main effects of stimulus and channel on N1 amplitude. N1 latency was not significantly affected (Fig. 2).

3.4. P50 ratio, P50 difference

P50 amplitude ratio (infrequent / frequent) showed a significant main effect for condition ($F=16.68$, $df=1,14$, $P<0.001$). The P50 ratio was significantly smaller in the cold pressor test condition than in the control condition. The P50 amplitude difference (infre-

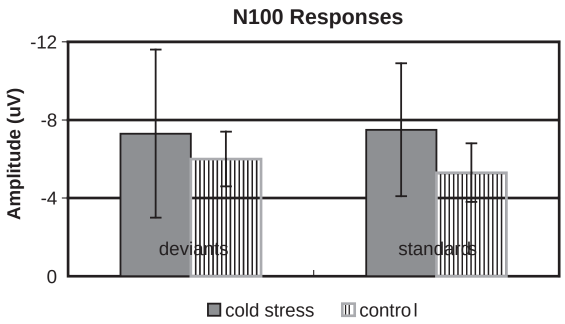

Fig. 2. Mean N100 response amplitudes (± S.D.) to deviant and standard stimuli in cold pressor test and control conditions. Bars indicate ± S.D.

quent – frequent) also showed a significant main effect for condition ($F=10.85$, $df=1,14$, $P<0.005$). The P50 amplitude difference was smaller in the cold pressor test than in the control condition, where there was no significant effect of electrode site. The P50 difference (deviant – standard) correlated significantly with N100 responses to standards ($r=0.4$, $P<0.01$, two-tailed) and N100 responses to deviants ($r=0.3$, $P<0.01$, two-tailed).

3.5. MMN and P3a components

There was no significant effect of condition and electrode placement on MMN amplitude and latency.

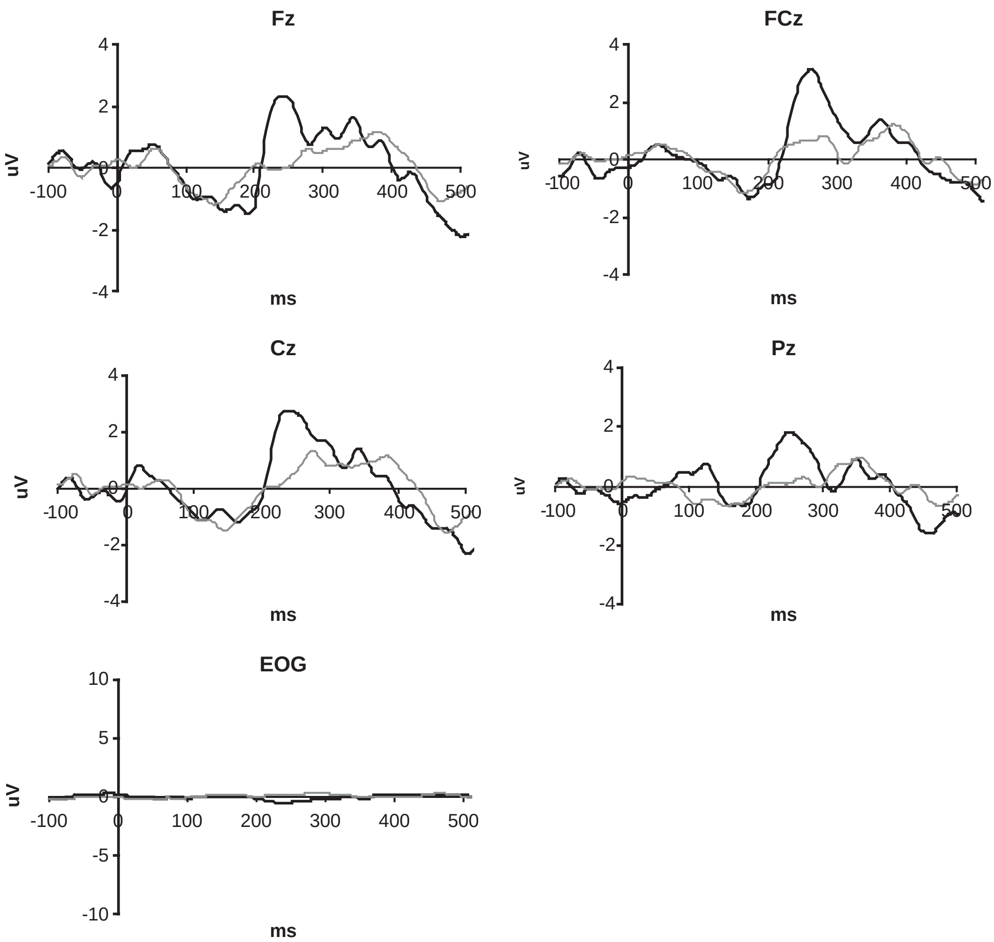

Fig. 3. Grand average difference waveforms obtained by subtracting ERPs to standard tones from those to deviants. Black line = cold pressor test; gray line = baseline condition.

Table 2
Mean amplitude and latency of the P3a components of the event-related potential at Fz, F3, F4, FCz, Cz, and Pz of 15 subjects

Channel	Measures	Cold stress		Baseline	
		Mean	S.D.	Mean	S.D.
Fz	Amplitude (μV)	2.15	0.94	3.90	2.30
F3	Amplitude (μV)	2.10	0.97	3.31	1.16
F4	Amplitude (μV)	2.00	1.03	3.88	2.14
FCz	Amplitude (μV)	2.38	1.30	4.26	2.30
Cz	Amplitude (μV)	2.10	1.29	4.17	2.48
Pz	Amplitude (μV)	1.64	0.98	2.80	1.17
Fz	Latency (ms)	265.7	35	247.3	41.2
F3	Latency (ms)	260.5	28.7	247.4	43.1
F4	Latency (ms)	250.9	30.8	248.6	43.1
FCz	Latency (ms)	260.3	29.5	244.0	40.6
Cz	Latency (ms)	279.5	28.6	265.5	40.2
Pz	Latency (ms)	277.4	25.7	277.3	29.6

P3a amplitude displayed significant condition (F=16.26, df=1, 14, P<0.001) and electrode site effects (F=3.98, df=2.4, 43.1, P<0.01, ε=0.615). P3a amplitudes were significantly larger in the cold pressor test than in the control condition (Fig. 3). The Bonferroni test confirmed that P3a amplitude at Pz electrode site was significantly smaller than P3a amplitude at FCz and Cz (P<0.02, P<0.04, respectively). There was no significant condition × electrode site for P3a amplitude.

P3a latency showed a significant electrode site effect (F=12.2, df=2.4, 43.1, P<0.001, ε=0.486). The Bonferroni test confirmed that P3a latency was significantly longer at the Cz and Pz electrode sites than at the other channels (Fz, F3, F4, FCz) (P<0.02) (Table 2). There was no significant condition × electrode site interaction for P3a latency.

P3a showed a moderate but significant correlation with P50 difference (r=−0.3, P<0.01, two-tailed) and P50 ratio (r=−0.3; P<0.01, two-tailed). P3a also significantly correlated with N100 response to standard tones (r=−0.4, P<0.01, two-tailed) and N100 response to deviant tones (r=−0.4, P<0.01, two-tailed).

4. Discussion

The results of the blood pressure measurements and analog subjective ratings suggest that the cold pressor test used in our study induced milder stress in comparison to the stress induced by the conventional test. Because the capacitance vessels (veins) reach maximal constriction at a lower sympathetic stimulation frequency than do resistance vessels (Berne and Levy, 1998), we obtained only a systolic pressure increase, which is mostly determined by cardiac output, and no significant change in diastolic pressure, which is determined by arterial peripheral resistance.

In the oddball paradigm, sensory gating is operationally defined as the ratio of the amplitude of the response to the infrequent stimulus divided by the amplitude of the response to frequent stimulus (Boutros et al., 1995). Higher ratios can either reflect lower amplitudes in response to frequent stimuli, and thus stronger inhibition with repetition, or higher amplitudes in response to infrequent stimuli and, thus, stronger response to rare stimuli (Boutros et al., 1995). In this study, the P50 amplitude to deviants was significantly higher than the P50 amplitude to standards in the control condition as previously demonstrated in the oddball paradigm with the same ISI (Boutros and Belger, 1999). Decreased P50 difference and decreased P50 ratio during the cold pressor test as a result of increased P50 amplitude to standard tones suggest that cold stress impaired auditory sensory gating in normal subjects. Our data also support the findings of impaired gating obtained with the cold pressor test (Johnson and Adler, 1993) and with mental arithmetic stress (White and Yee, 1997) in the double click paradigm.

N100 response amplitudes to both standard and deviant tones were significantly increased in the cold pressor test, where there was no significant stimulus effect. At relatively long ISIs, such as the 2-s ISI in our study, N1 amplitudes for standard and deviant stimuli usually differ little or not at all (Näätänen and Picton, 1987). Because of the relatively longer ISI in our study, and the moderate correlations between P50 difference and N100 responses, as well as the correlations between P50 ratio, P3a and N100 responses, our data did not rule out a gating function of N100. Reduced serotoninergic activity has been shown to increase the slope of the auditory evoked potential as a function of stimulus intensity. Because stimulus intensity did not differ among the stimuli in our study, the increase in N100 amplitudes to both standard and deviant stimuli suggests that increased noradrenergic activity during the acute cold stress might have led to increased amplitudes of N100, perhaps as an effect of decreased recovery time of the N100 generators.

Elicitation of the P3a component is dependent on a variable threshold and specific stimuli and ISI conditions in the passive oddball paradigm; a short ISI and a large physical difference between deviant and standard stimuli are important. If the stimulus deviation is great, the P3a may be preceded by the N2b. In our data, the N2b component could not be isolated in the individual recordings. In our recording conditions, ISI and deviant standard deviation magnitude were not typical for eliciting P3a as can be seen in the control condition P3a responses. In that case, the significant increase in P3a response amplitude during the cold pressor test seems to be related to a change in the variable threshold. The finding of no change in MMN amplitude supports this suggestion. The P3a component is elicited as a result of a deviance detection process indexed by MMN that surpasses the variable threshold (Schröger, 1997). The variable threshold might function as a gate to a limited capacity system.

It can also be argued that a significant increase of P3a amplitude might be caused by attention to the auditory stimuli because of cold stress. In attend conditions, N2 and P3b ERP components were elicited along with exogenous components and P3b was maximally positive at Pz. Its amplitude reflects the amount of allocation of attention to the stimulus processing, whereas P3a is detected at an earlier latency and is maximally positive fronto-centrally (Ritter and Ruchkin, 1992). Significantly lower P3 amplitude at the Pz electrode site and the lack of an apparent N2 component suggest that increased amplitudes of P3a during cold stress did not result from the subjects' attention to the stimuli.

In a three-stimuli active oddball paradigm, increased P3a amplitudes were found in patients with panic disorder and posttraumatic stress disorder (Clark et al., 1996; Kimble et al., 2000). In a passive condition with a three-stimuli oddball paradigm, P3a amplitude was found to be increased during anxiety induced by anticipation of shock (Grillon and Ameli, 1994). It seems that some subjects with anxiety disorders have defective filtering or gating of stimuli at the end point of the preconscious cognitive processing that directs attention to the physical changes in the stimulus array. That may lead to difficulty in adapting to novelty and unnecessary allocation of resources (Clark et al., 1996). The proposed abnormalities of noradrenergic functioning in these disorders (Nutt et al., 1999; Southwick et al., 1997) and the role of noradrenalin in stress induced by both the cold pressor test (Sherwood et al., 1986) and attention (Selden et al., 1990) suggest the importance of the noradrenergic system in the variable threshold that, when low, may cause attentional switches indexed by the P3a component.

P3a is most clearly evoked in medial frontal structures such as the frontal gyrus pars triangularis, anterior cingulate gyrus and dorsolateral frontal cortex (Baudena et al., 1995). These areas are strongly interconnected, and together they have been hypothesized to constitute the cerebral network for the orientation of attention (Baudena et al., 1995). In a functional magnetic resonance imaging study, innocuous thermal related activations were located mainly in the anterior part of the anterior cingulate cortex, which was proposed to be a non-specific attention/arousal system (Kwan et al., 2000). Knight (1984) found that P3a to novel sounds was greatly decreased in subjects with frontal lobe lesions. P50 responses were also found to be increased in frontal lesions, indicating disturbed gating (Knight et al., 1989).

Moderate but significant correlations between P50 difference, N100, and P3a suggest that these ERP components can be associated in the multi-component, multistage gating system. The data indicate that in a mildly stressed brain, induced by the cold pressor test, the ability to filter out irrelevant sensory information is lost along with the ability to ignore irrelevant information that can cause a passive attention switch (breakthrough of the unattended) as indexed by P3a. The findings show that inducing acute stress using a cold pressor test during ERP recordings in a passive oddball condition with 2-s ISIs can provide important information about the early and late filtering (gating) of auditory stimuli.

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