Cardiovascular Phase Relationships to the Cortical Event-Related Potential of Schizophrenic, Depressed, and Normal Subjects

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Cardiovascular phase, especially diastole, influences attention and the event-related potential (ERP) of the right hemisphere of the brain. Depression and schizophrenia are characterized by attentional deficits, unique lateralization of brain function, and deviant phase relationships of biological oscillators. In the present study, the ERP was recorded during stimulation triggered by diastole and systole in control (n = 16), depressed (n = 16), and schizophrenic (n = 9) subjects. Fifty tones were presented and subjects were instructed to count them silently. Previous findings were supported of delayed latencies and increased amplitude in depressed patients and decreased amplitudes and delayed latencies in schizophrenics. An exaggerated effect of diastole on the ERP in the right hemisphere was observed in depressed patients, however, no cardiovascular effect on the ERP was apparent in schizophrenic patients. Results suggested that heart/brain networks are tightly coupled in normal controls, perhaps "overdriven" in depressed patients, and uncoupled in schizophrenics.

Introduction

Relationships between cardiovascular and brain phase may be sensitive biological markers of psychopathology. There is substantial evidence that behavior and perceptual efficiency vary with cardiovascular phase, particularly diastole. For example, attention and perceptual threshold are related to decelerating heart rate and the diastolic phase of the cardiac cycle (Lacey 1959; Lacey et al 1963; Lacey 1967; Lacey and Lacey 1974). Accelerating heart rate and the systolic phase have been related to decision making and complex problem-solving (Birren et al 1963; Cacioppo and Sandman 1978; Sandman et al 1977; Saari and Pappas 1976). Furthermore, stimulation synchronized with diastole, but not systole, produces enhanced visual and auditory event-related potentials (ERP's) (Sandman 1984; Walker and Sandman 1979, 1982).
Cardiovascular and brain-phase interactions appear to be lateralized to the right hemisphere. For example, stimuli synchronized with diastole, or low heart rate, resulted in larger ERPs (especially N1), only in the right hemisphere of normal subjects (Sandman 1984; Walker and Sandman 1979, 1982). In careful studies of the direction of heart–brain interaction, Hatfield et al (1987) concluded that heart rate influenced the electroencephalogram (EEG) primarily in the right hemisphere and Hugdahl et al (1983) found a temporary anticipatory increase in heart rate, only when the right hemisphere of the brain was initially visually stimulated.

Flor-Henry's (1983) extensive literature review describes hemispheric differences in the ERPs of schizophrenic and depressed patients. Schizophrenics were reported to have ERP changes in the left hemisphere, whereas depressed patients tended to have changes in the right hemisphere (Buchsbaum 1979a, 1979b; Connelly et al 1985; Flor-Henry 1983; Gruzelier 1984; Sandman et al 1987).

Thus, cardiovascular phase, especially diastole, influences the ERP in the right hemisphere and appears to regulate attention. Although attentional deficits and unique lateralization of brain activity characterize schizophrenic and depressed patients, little is known about their cardiac–brain cycle interactions. Because pacemaker networks in the central nervous system (CNS) influence the generation of EEG rhythms (Carpenter 1982a, 1982b; Flor-Henry 1983; Winfree 1987a, 1987b), it is possible that heart–brain coupling is disorganized in psychopathology. The present study was designed to examine this possibility in depressed and schizophrenic patients.

Method

Subjects

Twenty-five right-handed psychiatric inpatients and 16 right-handed healthy paid volunteers were tested. All subjects volunteered for the study and provided written informed consent. The groups did not differ significantly in age: controls—mean 23.7 ± 3.88 years, schizophrenics—mean 31.6 ± 8.12 years, and depressed—mean 30.1 ± 8.05 years, and none reported loss of auditory acuity. Healthy normal controls were obtained from the University of California; Irvine students and staff and patients were obtained from the university inpatient psychiatric ward. All patients were diagnosed by two independent psychiatrists using the DSM-III and Research Diagnostic Criteria. The Schedule for Affective Disorders (SADS) was administered by a trained, experienced research assistant. Criteria were met for either major depressive episode with melancholia without psychotic features (n = 16), or schizophrenic disorder, chronic (n = 9).

All subjects were free of tricyclic and amphetamine medication for at least 2 weeks prior to admission. Over 80% of the patients were followed as outpatients by one of the authors prior to hospitalization and entered the hospital medication-free for several weeks. The remaining 20% of the patients reported being medication-free for at least 1 week prior to admission and were observed to be medication-free for at least 2 days before testing. No patients were medicated between the time of their admission and their test date. Normal subjects (n = 16) denied the use of medications, drug abuse, and any history of mental or physical disorders.
ERP Procedure

Subjects reclined in a comfortable chair while transducers were applied for recording EEG from each hemisphere of the brain. Grass Ag/AgCl cup electrodes were attached to the scalp overlying the right and left hemispheres of the brain according to the International 10–20 system. Monopolar placements at C3 and C4 were referenced to linked mastoids (Sandman 1984). The electrode sites were swabbed with acetone and the electrodes filled with Grass EEG creme and affixed to the scalp with nonflexible collodion. Electrodes with an impedance of greater than 5,000 ohms were replaced. Most importantly, electrodes with differences between the left and right hemisphere of greater than 1000 ohms were corrected. The EEG signal was amplified by a Grass polygraph using AC preamplifiers with the low-frequency filter set at 0.3 Hz and the high-frequency filter set at 35 Hz.

The subjects were fitted with headphones (Senheiser HD 400) for pure tone auditory stimulation (600 Hz, 90db SPL against 72db white noise, 250 msec duration). Stimulation was triggered by cerebral pulse pressure waves [not the electrocardiogram (EKG)], ranging from 667 msec to 1 sec, and reflecting normal heart rates between 1 Hz and 1.5 Hz. Interstimulus intervals were random. Trials triggered by diastole or systole were separated (i.e., not done during the same EKG event). No subjects had abnormal heart rates or rhythms during testing. Subjects were instructed to count the stimuli. This task was easily comprehended and was used to direct attention without requiring an overt motor response that resulted in small but visually evident late component (P300) activity.

On-line averaging of the EEG by a PDP 11/34 computer interfaced with the amplifiers provided a refreshed, running average as well as the EEG sample from which the average was computed. The ERP was analyzed by sampling the EEG at 200 Hz for 640 msec. The 500 msec poststimulus sampling period was zeroed by averaging the preceding 140 msec prestimulus epoch. All waveforms were shifted so that the prestimulus baseline was zeroed. Fifty ERPs to tones synchronized with diastole and systole were averaged for each subject. The waveform triggers for each ERP were separated by at least three pulse pressure waves. The latencies and peak-to-peak amplitudes (i.e., absolute differences) of the major components were identified. The entire ERP waveforms, including the prestimulus segments, were evaluated by a trained technician to identify the prominent peaks within specific, standardized latency windows (P1, 30–80 msecs; N1, 70–150 msecs; P2, 130–250 msecs; N2, 180–320 msecs; P3, 250–600 msecs).

A semiautomated scoring program displayed the ERPs on a cathode ray tube and placed cursors at the points of greatest positivity and negativity. A spectral interpolation technique was applied for measurement of the latency of waveform peaks. The waveform was approximated as a sum of sinusoids (Fourier coefficients) resulting in unlimited temporal resolution. Components were described accurately up to 25Hz (Nyquist frequency). The peak-to-peak amplitude (for determination of absolute differences) was computed automatically. Peak amplitude was determined by subtracting immediately preceding peaks from target peaks (i.e., N1 amplitude = N1 − P1).

Artifact Rejection

All subjects were studied under eyes-closed conditions so that electrooculogram (EOG) contamination of data epochs was minimized and were observed through a closed-circuit
television monitor. Even though the subjects were tested with eyes closed in the auditory procedure, eye movement and eye blink artifact were eliminated automatically by the computer software. The accuracy of the rejection was determined by separately testing subjects asked to make lateral eye movements (eyes closed) to a series of 10 tones in each condition. Eye movement was verified by electrodes attached to the outer canthus and suborbit referenced to linked mastoids. The software system correctly identified 98.4% of the lateral eye movements in the EEG. Eye blinks in response to the tone were detected on 100% of the trials. Contaminated trials were repeated until 50 trials were averaged.

Apparatus

Physiological recordings were obtained with a Grass, model 79 polygraph equipped with appropriate preamplifiers and driver amplifiers. Cerebral pulse pressure waves were measured with plethysmographs containing light-emitting diodes and narrow band emitting infrared radiation with a wave length of 0.74 µm placed over the supraorbital notch (just temporal of the nasium), thereby triggering the auditory stimulus with either the systolic or diastolic phase of the pulse pressure wave (and not the EKG). The signal was amplified by the Grass AC preamplifier with a time constant of 0.08 sec and a half amplitude high-frequency filter of 5 Hz. Peak systole and the trough of diastole were detected by Schmidt triggers and delivered to the digital 11/34 computer to initiate averaging of the EEG.

Data Analysis

The ERP was analyzed by sampling the EEG at 200 Hz for 640 msecs. The sampling period was initiated by detection of systole or diastole at the supraorbital notch. Amplitudes and latencies of ERP components were subjected to a 3 (normal × depressed × schizophrenic) × 2 (left/right hemisphere × 2 (systole/diastole) analysis of variance with repeated measures of the last two factors. Simple effects tests (Student-Newman-Keuls) for posthoc analyses of interactions and within group differences were performed for latencies and amplitudes with significant main effects and interactions.

Results

ERP Component Latency

*Diagnosis.* As summarized in Table 1 and illustrated in Figures 1 and 2, the main effect of diagnosis was evident in significantly delayed latencies of P1, N1, P2, and N2 in depressed (D) and schizophrenic (S) patients compared to normals (N). Although the latencies for these components were delayed for both patient groups, the largest differences occurred between the schizophrenic patients and normals for N1 and N2, and between the depressed patients and normals for P2.

*Cardiac Phase.* As illustrated in Figures 2 and 3, the mean latency of N1 was increased 

\[ F = 4.71, \text{df} = 1,30, p < 0.05 \]

during diastole (115.0 msec) versus systole (110.7 msec) for all three groups. Two-way analysis of variance (ANOVAS) indicated that the delayed latency of N1 during diastole (112.3 msec) versus systole (107.3 msec) was significant in normals and depressed subjects 

\[ F = 5.48, \text{df} = 1,30, p < 0.05 \]

but not
Table 1. Mean Latency and Amplitude

| Component | Norm (N) | Depr (D) | Schi (S) |
|-----------|----------|----------|----------|
| Mean P1 Lat \(^{a,d}\) | 56.0 ms | 64.0 ms | 80.8 msec |
| Mean N1 Lat \(^{a,d}\) | 101.4 ms | 118.2 ms | 123.8 msec |
| Mean P2 Lat \(^{a,d}\) | 181.7 ms | 199.8 ms | 197.4 msec |
| Mean N2 Lat \(^{a,d}\) | 288.6 ms | 301.0 ms | 315.1 msec |
| Mean P1 Amp \(^{a,c}\) | .891 uv | 3.00 uv | 1.24 uv |
| Mean N1 Amp | 10.8 uv | 12.6 uv | 7.36 uv |
| Mean P2 Amp \(^{b,c}\) | 23.0 uv | 23.7 uv | 16.1 uv |
| Mean N2 Amp \(^{b,c}\) | 17.2 uv | 20.6 uv | 12.6 uv |

\(^{a} N \times D p < 0.05; \)
\(^{b} N \times S p < 0.05; \)
\(^{c} D \times S p < 0.05; \)
\(^{d} N \times D \times S p < 0.05. \)

Figure 1. Left and right hemisphere grand average ERPs from controls, depressed, and schizophrenic subjects during stimulation synchronized with systole and diastole from cerebral pulse pressure waves. Waveforms illustrate differences among the diagnostic groups.
schizophrenic patients. The apparent delay of P3 during systole in schizophrenics in Figure 2 was not reliable.

_Lateralization._ As illustrated in Figures 2 and 3, the mean latency of P2 was delayed in the right hemisphere (193.0 msec) compared to the left hemisphere (191.5 msec), in the three-way ANOVA. Although significant ($F = 4.73$, 1,38 df, $p < 0.05$), the differences were small across all three groups. However, Student-Newman-Keuls revealed that delayed latency of P2 in the right hemisphere of depressed patients (199.8 msec) versus normals (181.7) was primarily responsible for the significant main effect ($F = 4.80$, df = 1,30, alpha <0.025).

_Interactions._ No significant interactions for latency were found across all three diagnostic groups. Between group two-way ANOVAs revealed significant hemisphere $\times$ diagnosis ($F = 4.80$, df = 1,30, $p < 0.05$) and condition $\times$ hemisphere ($F = 4.83$, df = 1,30, $p < 0.05$) interactions only for P2 in depressed and normals, as illustrated in Figure 2. Student-Newman-Keuls tests indicated that these interactions were due to
the increased latency of P2 in the right hemisphere of depressed patients compared to normals (as described in the previous section). The largest delays of P2 latency occurred in the right hemisphere during diastole in depressed patients (203.3 msec) compared to the right hemisphere during diastole of normals (182.1 msec) and the left hemisphere during diastole of normals (183.1 msec) ($F = 4.81, df = 1, 30$, alpha < 0.025).

**ERP Amplitude Measures**

*Diagnosis.* As illustrated in Table 1 and Figures 1 and 4, the mean amplitudes of P1 and N2 were significantly different across all three diagnostic groups. Two-way ANOVAs indicated that the largest differences in P1 were between depressed patients and normals and that the largest differences in N2 were between schizophrenic and depressed patients. P1 amplitude was largest in depressed and smallest in normal subjects. The N2 component was also largest in depressed patients but smallest in schizophrenics. We also found decreased amplitudes of P2 and N2 in schizophrenics compared to depressed patients and controls.

*Cardiac Phase.* No main effects of cardiovascular phase were found on ERP amplitude.

*Laterazation.* No main effects of lateralization of ERP amplitude were found in the central analysis. Two-way ANOVAs between normals and schizophrenics revealed small but significant ($p < 0.01$) decreases in the amplitudes of N1 (left = 9.78 uv, right =
Amplitudes of the major ERP components for control, depressed, and schizophrenic subjects.

9.33 μV), P2 (left = 21.0 μV, right = 20.1 μV), and N2 (left = 16.0 μV, right = 15.1 μV) in the right hemisphere.

Interactions. There were no significant interactions for ERP amplitude across all three groups. A significant hemisphere × diagnosis interaction was found for N2 (F = 5.04, df = 1.23, p < 0.05) between normals and schizophrenics. Student-Newman-Keuls revealed that the largest differences occurred between the left hemisphere in normals (17.8 μV) and the right hemisphere in schizophrenics (12.5 μV) (F = 5.04, df = 1.23, alpha < 0.025).

Discussion

Replication of Noncardiac Studies

The results of this study confirmed and extended earlier findings that did not use cardiovascular phase-locked procedures. For example: (a) depressed, and especially schizophrenic, patients had delayed latencies of the major ERP components (Baribeau-Braum
et al 1983; Sandman et al 1987; Shagass et al 1977; Shagass et al 1980; Shagass and Schwartz 1964); (b) the ERP in schizophrenics was severely dampened (Baribeau-Braum et al 1983; Buchsbaum 1979b; Davis et al 1980, Flor-Henry 1983; Sandman et al 1987; Shagass and Schwartz 1964; and (c) the ERP in depressed patients was augmented (Flor-Henry 1983; Shagass et al 1980).

The finding of delayed P2 only in the right hemisphere is consistent with earlier results (Peronnet and Michel 1977; Desmedt et al 1984) that lateralized electrical signs most often are of positive polarity. Results in depressed and normal subjects also support the findings that P2 is delayed in nonpsychotic, depressed patients (Plooij-van-Gorsel 1984). Against the background of these replicated results the effect of cardiovascular phase on the ERP can be evaluated.

**Diastole-ERP Interactions**

Earlier studies indicated that stimulation synchronized with diastole produces a 10%–20% change in the auditory ERP response (Sandman 1984). Of the ERP components studied, those components related to attention (e.g., N1-P2; Picton et al 1974; Picton and Hillyard 1977) have been the most susceptible to cardiac influence (Sandman 1984; Walker and Sandman 1979, 1982). Similar results were found for controls and depressed patients in the present study. The influence of diastole on N1 in control subjects was apparent only as a trend ($p = 0.052$) in the present study, however, this influence was identical to our findings in our previous study (Sandman 1984). Failure to exactly replicate N1 amplitude augmentation is probably related to the complexity of the task in the different studies.

Delayed P2 in the right hemisphere during diastole of depressed patients is consistent with studies of normal subjects, which found that the major influence of cardiovascular phase on the ERP is during diastole in the right hemisphere (Sandman 1984; Walker and Sandman 1979, 1982). Coupled with earlier studies (Sandman et al 1982; Hugdahl et al 1983) these findings support the lateralized effect of diastole on the ERP in the right, rather than the left hemisphere of the brain.

**Cardiovascular Phase and the Lateralized ERP**

ERP changes in control subjects reflected the anatomy and physiology of the underlying pacemaker drive system. The latency delays and amplitude increases found in ERPs of depressed patients suggested that rhythms in the brain are “overdriven” by the heart and/or peripheral pacemaker networks. The “forced oscillator” resonance phenomenon, when one oscillating system overdrives another at the resonant frequency, results in maximization of amplitude (AHA 1981; Flor-Henry 1983; Hatfield et al 1987; Kennedy 1959; Sandman et al 1982; Walker and Walker 1983; Winfree 1987a, 1987b).

Pacemaker networks have been implicated in the generation of EEG rhythms, motor rhythms, sensory receptor physiology, and overt human behavior (Carpenter 1982a, 1982b; Wehr and Goodwin 1983; Winfree 1987a, 1987b; Wong and Schwartzkroin 1982). The major connection between the central and peripheral pacemaker networks is in the right sympathetic chain ganglia on the right side of the body. For example, the peripheral cardiac pacemaker and baroreceptor networks are connected to the central hypothalamic-pituitary–pineal pacemaker network through the dominant right-sided, sino-atrial node via cervical and thoracic ganglia (Carpenter 1972; Kashima et al 1981). Functionally,
this is reflected in the findings that the P–P interval is increased (decreased heart rate) with right, but not left, stellate ganglion block in normal volunteers (Kashima et al 1981). Our data suggest that this dextral orientation is reflected in connections between the heart and brain.

**EKG Artifact**

The question of EKG artifact in the ERP with our paradigm was addressed in earlier studies. Trials averaged on EKG “triggers” in normal subjects with the stimulus omitted failed to produce any effect on the EEG (Sandman et al 1982) Other laboratories also have addressed this issue. For example, Schandry et al (1986) presented evidence of stimulus-independent electrocortical events tightly coupled with cardiovascular activity, not related to EKG artifact. Thus, the effects of cardiovascular phase on the ERP does not appear to be due to EKG induced artifact.

**Drug-Effects**

Many schizophrenics have been treated with neuroleptics with a biological half life measured in months even though drug half life may only be days. The recent and remote effects of psychotropic drugs could influence the ERP, particularly latency in the current study. However, similar effects of the heart and brain were observed in previously medicated depressed patients and never-medicated controls. Moreover, earlier studies of psychotic patients indicated that neuroleptics did not have major effects on the brain potentials of the latencies reported here (Baribeau-Braum et al 1984; Sandman et al 1987).

**Conclusion**

As suggested earlier (Sandman et al 1982), ERP changes in depressed patients may result from tightly coupled central and peripheral “drive” systems. Interactions between the brain and heart in the normal state may be ordinarily expressed through a lateralized pacemaker structure that traverses the central and peripheral nervous systems with key connections among cortex, thalamus, reticular activating system, and sympathetic chain ganglia. The dextral preference of the cardiovascular–ERP cycle interactions corresponds with the anatomical lateralization of the pacemaker and sympathetic circuitry. Our ERP findings suggested that the underlying peripheral and CNS pacemaker networks in depression and schizophrenia are fundamentally different. The data from the present study suggest that the central pacemaker system of depressed patients may be “overdriven” by the heart and that of schizophrenics may be blocked, disorganized or, incompletely lateralized. The finding of a diastolic effect on the brain suggests that the pacemaker networks of the brain and the heart are tightly coupled in normals, even more tightly coupled in depressed patients, and perhaps loosely coupled, or even uncoupled, in schizophrenics.

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