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Cognitive and biological determinants of P300: an integrative review

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Abstract

The P300 event-related brain potential (ERP) is thought to reflect neuroelectric activity related to cognitive processes such as attention allocation and activation of immediate memory. However, recent studies have provided evidence that the P300 also is influenced by biological processes such as fluctuations in the arousal state of subjects. The effects of natural (circadian, ultradian, seasonal, menstrual) and environmentally induced (exercise, fatigue, drugs) state variables on the P300 are reviewed. The findings suggest that these factors contribute to P300 measures and are discussed in terms of their theoretical and applied implications.

Keywords: P300; Event-related potential; Arousal; Biological determinants

1. Introduction

The P300 component of the event-related brain potential (ERP) is considered a 'cognitive' neuroelectric phenomenon because it is generated in psychological tasks when subjects attend and discriminate stimuli that differ from one another on some dimension. Such a discrimination produces a relatively large (ca. 10–20 μV), positive-going waveform with a modal latency of about 300 ms when elicited with auditory stimuli in young adults. First reported 30 years ago (Sutton, Braren, Zubin and John, 1965), explanations of the P300 center around the basic information processing mechanisms of attention allocation and immediate memory. Hence, interest

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in the P300 has expanded dramatically because of its significance as a means to assess cognitive function in a variety of basic (see below) and applied circumstances (e.g., Donchin, Kramer and Wickens, 1986; Polich, 1993a; Pritchard, 1986; Alexander et al., 1994; Fabiani, Gratton, Karis and Donchin, 1987; Karniski and Blair, 1989; Polich, 1986b; Segalowitz and Barnes, 1993).

Although the P300 usually is viewed in this cognitive context, recent findings have suggested that a substantial portion of P300 variation appears to be caused by factors not only related to alterations of the task structure but also to fluctuations in the arousal state of the subject. State fluctuations may occur spontaneously or may be induced by environmental factors — variables that can be characterized as 'biological determinants'. Use of this phrase is not meant to imply that there is a rigid dichotomy between 'cognitive' and 'biological' systems, but rather to emphasize that parameters contributing to P300 production also are sensitive to the 'energetical' or 'intensive' factors that are not necessarily induced by the task (Hockey, Gaillard and Coles, 1986; Kok, 1990). In this framework, the term biological can be taken to mean those factors that affect the organism's physiological state as a whole and, therefore, affect its capability to engage in cognitive operations. However, it is assumed that neurophysiological operations underlie both cognitive and biological influences on the P300, but that the relationship between these influences has not been addressed adequately. Indeed, it is not unreasonable to assert that despite some acknowledgement in the early stages of ERP research (see below), until relatively recently these intensive aspects have been underestimated in the information processing models of most P300 studies.

The present review was undertaken to provide a systematic description and evaluation of P300's biological determinants in normal subjects by using the concept of arousal as an explanatory mechanism. The review consists of three themes: First, the methodological and theoretical background of the P300 will be sketched, with the issues surrounding its neurophysiological origins and functional significance outlined and suggestions proffered on how fluctuations in biological state contribute to component generation. Second, two major classes of variables known to affect P300 measures will be reviewed: natural and environmentally induced variables. Third, the import of these effects for P300 theoretical implications in the light of the concept of arousal will be discussed. As a general tactic to facilitate the goal of providing an accessible overview of these topics, the pertinent data will focus on variables that can affect the outcomes of ERP studies in general, with other, less germane factors acknowledged and references provided. Finally, to promote clarity, the relevant effects will be illustrated graphically whenever feasible. Thus, the major purpose of this review is to present the case for considering biological factors as necessary for the understanding of the P300 event-related potential.

2. Theoretical perspective

2.1. P300 and cognition

The theoretical interpretation of the P300 is based on: (1) neurophysiological investigations of the brain mechanisms that underlie its generation, (2) evidence

from experimental studies that manipulate psychological variables, and (3) biological influences on central nervous system (CNS) function. After consideration of methodological issues, the major findings concerning P300 neural origins and psychological theory are summarized, with biological determinants reviewed subsequently (for additional perspectives, see Bashore and van der Molen, 1991; Donchin, Karis, Bashore, Coles and Gratton, 1986; Hillyard and Picton, 1986; Johnson, 1986; Picton, 1992; Polich, 1993b; Pritchard, 1981).

2.1.1. Methodological issues

The P300 component often is elicited with a simple discrimination task. This procedure has been dubbed the 'oddball paradigm', since two stimuli are presented in a random series such that one of them occurs relatively infrequently — i.e. the oddball. The auditory version of this task uses two different tones, with the target stimulus typically occurring less frequently than the non-target or standard stimulus (e.g., with probabilities of 0.20 and 0.80, respectively). The subject is required to distinguish between the tones by noting the occurrence of the target (e.g., mentally counting, pressing a button, etc.) and not responding to the standard. This task has been used to study a wide variety of information processing issues (e.g., Duncan-Johnson and Donchin, 1977; Polich, 1986a,b, 1987a,b, 1989a,b; Squires, Wickens, Squires and Donchin, 1976; Verleger and Berg, 1991; Woodward, Brown, Marsh and Dawson, 1991).

The P300 component is measured by assessing its amplitude (size) and latency (timing). Amplitude (μV) is defined as the voltage difference between a prestimulus baseline and the largest positive-going peak of the ERP waveform within a latency window (e.g., 250–400 ms, although the range can vary depending on stimulus modality, subject age, task conditions, etc.). Latency (ms) is defined as the time from stimulus onset to the point of maximum positive amplitude within the latency window. In addition, P300 scalp distribution is defined as the change in component amplitude across the midline recording sites (Fz, Cz, Pz), which typically increases in magnitude from the frontal to parietal electrodes. Scalp distribution effects are of considerable import, since variation in amplitude from the manipulation of task or subject variables has been used to infer information about P300 neural generators (for an insightful review, see Johnson, 1993).

A sometimes complicating factor, however, stems from the observation that particularly alerting or novel stimuli will produce an earlier positive-going component. This early peak has been labeled the 'P3a' (Snyder and Hillyard, 1976; Squires, Squires and Hillyard, 1975), with the later peak, sometimes called 'P3b' — i.e. the canonical P300 related to information processing operations that are reviewed below. The P3a is generally larger in amplitude over the frontal and central electrode sites and appears to reflect an initial orienting process (Courchesne, Hillyard and Galambos, 1975; Roth, 1973), which may originate in the frontal cortex (cf. Knight, 1984, 1990; Nasman and Durio, 1993). However, other studies have used high intensity, forcefully alerting stimuli to elicit P300 components that have a more central-parietal maximum amplitude (Putnam and Roth, 1990; Roth, Dorato and Kopell, 1984). These findings suggest that several types of components may be generated in

response to relatively intrusive stimuli that appear to depend on the particulars of stimulus and task conditions. In addition, the P3a may be more sensitive than the P3b to individual differences in cognitive function (cf. O'Donnell, Friedman, Squires, Maloon, Drachman and Swearer, 1990; Polich, Howard and Starr, 1983), but this issue has not been well studied (cf. Johnson and Donchin, 1985; Ruchkin, Johnson, Canoune, Ritter and Hammer, 1990) because the P3a is observed readily in only about 20% of normal subjects (Polich, 1988). Since these factors are incompletely understood, the relationship between the P3a and P3b is not yet clear.

2.1.2. Neural and psychological mechanisms

Depth electrode recordings in humans originally suggested that at least some aspect of the P300 is generated in the hippocampal portion of the medial temporal lobe (Halgren, Squires, Wilson, Rohrbaugh, Babb and Crandall, 1980; McCarthy, Wood, Williamson and Spencer, 1989; Smith et al., 1990). However, subsequent studies on individuals who have undergone temporal lobectomy (Johnson, 1988a; Smith and Halgren, 1989), stroke patients (Knight, 1990; Onofrj, Gambi, Fulgente, Bazzano and Colamartino, 1991; Onofrj et al., 1992), and monkeys (Paller, Zola-Morgan and Squire, 1988; Paller, McCarthy, Roessler, Allison and Wood, 1992) have indicated that the hippocampal formation influences P300 measures relatively little (Polich and Squire, 1993). Important in this context are findings that implicate the temporal-parietal junction in P300 generation (Knight, Scabini, Woods and Clayworth, 1989; Verleger, Heide, Butt and Kömpf, 1994; Yamaguchi and Knight, 1991, 1992). These results imply that P300-related ERP activity recorded at the scalp is primarily a cortical process, such that systematic changes in component amplitude over the scalp have been taken to reflect the differential activation of P300's neural substrates (Johnson, 1993; Scherg and Picton, 1991). Whether P300 activity represents a unitary event or is a summation of several distinct processes is a still unresolved issue, although the thrust of the evidence suggests that the P300 stems from multiple neural sources that contribute to the observed scalp topography (Johnson, 1989a,b; Knight et al., 1989).

A major theoretical interpretation of P300 amplitude is that it indexes brain actions stemming from 'tasks that are required in the maintenance of working memory' (Donchin et al., 1986, p. 256) when the mental model or context of the stimulus environment is updated (Donchin, 1981; Donchin and Coles, 1988). Recent theoretical extensions of the updating view have provided the basis for impressive gains in the understanding of basic P300 phenomena (cf. Johnson, 1986, 1988, 1993; Matt, Leuthold and Sommer, 1992; Sommer and Matt, 1990; Sommer, Matt and Leuthold, 1990). An alternative hypothesis suggests that the P300 ERP component is related to the 'closure' of perceptual events (Desmedt, 1981; Verleger, 1988), but this approach generally has not gained widespread support. Thus, even though the final chapter has not been written on the theoretical meaning of the P300 ERP, the majority of data are consistent with some form of context updating, and this viewpoint will be adopted here.

The context updating theory has been supported by demonstrations that larger P300 amplitudes are associated with superior memory performance in normal sub-

jects (e.g., Fabiani, Karis and Donchin, 1990; Noldy, Stelmack and Campbell, 1990) and has its roots in Sokolov's (1977) model of the orienting response, which also has been postulated to result from a change in the organism's internal neural representation (Donchin, Ritter and McCallum, 1978; Polich, 1989a; Roth, 1983). Additional studies have indicated that P300 amplitude is related to how the stimulus deliveries its task-relevant information (Johnson, 1988b; Ruchkin et al., 1990), and that it is proportional to the amount of attentional resources in terms of processing capacity that is employed in a given task (Kramer and Strayer, 1988; Polich, 1987b; Wickens, Kramer, Vanasse and Donchin, 1983). Indeed, P300 habituation suggests that the resources allocated to a new stimulus are reduced with repeated elicitations of the ERP (Kramer, Schneider, Fisk and Donchin, 1986; Polich, 1989a; Siddle, 1991) — effects that appear sensitive to attentional influences (Geisler and Polich, 1994a; Kenemans, Verbaten, Melis and Slangen, 1992; Koelega, Verbaten, van Leeuwen, Kenemans, Kemner and Sjouw, 1992). Thus, the P300 can be considered as a manifestation of CNS activity involved with the processing of new information when attention is engaged to update memory representations.

The usual interpretation of P300 latency is that it is a metric of stimulus classification speed (Kutas, McCarthy and Donchin, 1977; Magliero, Bashore, Coles and Donchin, 1984) and is generally unrelated to response selection processes (Duncan-Johnson, 1981; McCarthy and Donchin, 1981; Ritter, Simson, Vaughan and Macht, 1983), although these assertions are debated (Pfefferbaum, Christensen, Ford and Kopell, 1986; Ragot, 1984; Ragot and Fiori, 1994). In this context, it is important to note that P300 latency is correlated negatively with mental function in normal subjects, such that shorter latencies are related to superior cognitive performance (Emmerson, Dustman, Shearer and Turner, 1989; Howard and Polich, 1985; Johnson, Pfefferbaum and Kopell, 1985; O'Donnell et al., 1990; Polich and Martin, 1992; Polich, Howard and Starr, 1983). The neuropsychological tests that produce the strongest correlation between P300 latency and mental performance are those that assess how rapidly subjects can allocate and maintain attentional resources — a view that is consistent with the observation that P300 latency increases systematically as cognitive capability decreases because of dementing illness (Brown, Marsh and LaRue, 1982; Homberg, Hefter, Granseyerer, Strauss, Lange and Hennerici, 1986; O'Donnell, Squires, Martz, Chen and Phay, 1987; Polich, Ehlers, Otis, Mandell and Bloom, 1986). Given these findings, it is reasonable to conclude that individual differences in P300 values obtained from a simple stimulus discrimination task provide a reliable indication of individual variability in neuroelectric processing capability and speed.

Additionally, P300 amplitude and latency also are correlated negatively (Polich, 1986b, 1992). This outcome appears to originate at least in part from the nature of the signal averaging process, which necessarily includes in the final ERP waveform individual trials that may vary considerably with respect to P300's peak latency across trials. This so-called 'latency jitter' can contribute significantly to the observed amplitude differences between experimental conditions and among individuals (cf. Karniski and Blair, 1989; Michalewski, Prasher and Starr, 1986). Furthermore, delays in P300 latency may be caused by factors that affect the related

underlying cognitive events but also can result from processes that precede component generation (e.g., Duncan-Johnson and Kopell, 1981; Polich, 1987b; Ritter et al., 1983). These effects can sometimes be dissociated as in the case of age-related changes for P300 latency (Goodin, Squires, Henderson and Starr, 1978; Pfefferbaum, Ford, Wenegrat, Roth and Kopell, 1984; Picton, Stuss, Champagne and Nelson, 1984; Polich, Howard and Starr, 1985; for a review, see Polich, 1995), but they need to be considered in conjunction with the possible influence of latency jitter when interpreting delays in component peaks.

2.2. The role of arousal

As the above synopsis indicates, the P300 component reflects neural activity related to basic aspects of cognition. However, because the P300 is derived from neural activity it is necessarily affected by the physical state of its underlying physiology. A major influence that governs general biological state is subsumed under the rubric of arousal. This broad-based concept can be defined in terms of its verb form as meaning 'to excite'. However, as Gale and Edwards cogently point out in their comprehensive analysis, 'arousal is used by different voices as a source of stimulation, as a trait or state threshold for response, as a response to stimulation, as endogenous variation, as experienced drowsiness or alertness, as a correlate or as a consequence of action, as a measure of intensity of action, or as a drive or motivator of action' (1986, p. 492). Hence, more than several of these definitional approaches appear applicable to P300 phenomena, although a complete model of the relationship between a unitary arousal concept and this ERP has not been proffered. The present review attempts to provide an inchoative outline for the importance of arousal in relation to the P300 from normal subjects. These issues are considered next.

2.2.1. Arousal and information processing

Early views of arousal conceived of variation in an organism's activity level as a non-specific unitary process, originating from the reticular activating system (Lindsley, 1961). Broadbent (1971) was one of the first who advocated assessing the relationship between physiological arousal and psychological states. The arousal concept was initially used to account for the observation that task performance often could be characterized as an inverted U-shaped function of arousal (Yerkes and Dodson, 1908). However, subsequent approaches posited that arousal has two kinds of effects on performance: (1) a general arousing effect and (2) a specific or idiosyncratic effect that contributes to a complex pattern of activation that modulates information processing and therefore performance. For example, it has been suggested that a general 'arousal' system facilitates the alerting effects of sensory processes, while a more specific 'activation' system functions to control efferent or motor processes. In addition, 'effort' is considered as a third mechanism that is assumed to be responsible for regulation of the balance between arousal and activation (Pribram and McGuiness, 1975; Sanders, 1983; Tucker and Williamson, 1984). Thus, arousal appears to affect cognition in a more focused way than can be explained with a general diffuse view of biological energy state.

The use of arousal as an explanatory backdrop for ERP findings is not new. It was initially invoked as a means to account for the supposed differential attentional states produced when signal and non-signal stimuli were presented sequentially. However, with paradigm refinement and delineation of the major controlling variables for P300 measures, arousal-based explanations for specific experimental findings became much less tenable as cognitive-based theories emerged (cf. Karlin, 1970; Pritchard, 1981). Hence, the association between specific arousal states and cognitive performance has rekindled the need for considering energetical concepts, since the limitations of information processing models that do not attempt to account for variability in human behavior arising from biological state are becoming increasingly apparent (Kok, 1990). Variation in the state of the organism can occur because of endogenous as well as exogenous energetic factors and can be assessed by using physiological, performance, or self-report measures (Hockey, 1983; Hockey et al., 1986). A schematic illustration of these factors is presented in Fig. 1, the implications of which will be amplified below.

One plausible connection between bodily state and cognition may be derived from the well known psychophysiological differentiation between tonic and phasic changes in arousal. Measures of *tonic changes* usually involve time periods of the order of minutes or hours and are manifestations of relatively slow fluctuations in

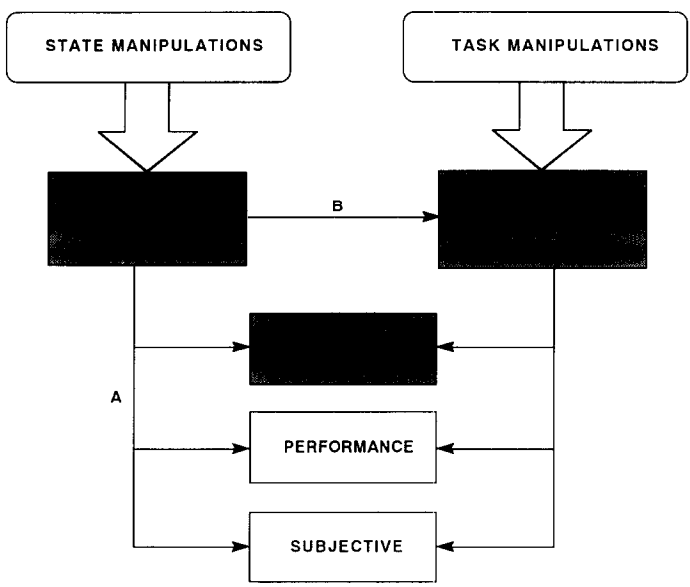

Fig. 1. Theoretical influences of biological factors on psychological variables for the P300 event-related brain potential. Pathway A represents the general effect of biological determinants on P300 processes. The resulting effects are global in nature because they result from overall or tonic changes in arousal level. Pathway B represents the indirect effect of biological determinants that influence relatively specific cognitive operations, which produce more specific influences on P300 measures because they result from relatively short-term or phasic changes in arousal level.

the general or non-specific background arousal state of the individual (e.g., heart rate, electroencephalographic activity, endocrine cycles). In contrast, *phasic responses* reflect the organism's energetic reaction (e.g., orienting response, ERPs, skin conductance, etc.) to specific stimulus events. Although the relationship between tonic and phasic influences and arousal level depends on the strength and time-constant of the psychophysiological variables under investigation, variations in biological state — whether they originate from situational or spontaneous factors — can affect information processing in important ways. For example, the suboptimal state that results from typical 'stressors' like sleep deprivation or noise can interfere severely with information processing efficiency (Broadbent, 1963, 1971; Kahneman, 1973; Hockey, 1986). This holds also for cognitive operations like attention and memory updating — i.e., the same processes that are assumed to be reflected by P300 (Hockey and Hamilton, 1983; Kok, 1990). Thus, both tonic and phasic bodily changes can contribute to arousal level and therefore affect the quality of mental activity.

Evaluation of P300 within this context must further consider whether changes in its amplitude and latency occur because of general or specific effects of biological state. A *general* state effect is assumed not to be restricted to the population of neurons influenced by P300-specific task variables. Fig. 1 illustrates this point by pathway A. Such an effect could occur if the set of P300 generators is larger than the subset that is activated by the stimulus and task of a particular experiment. These non-specific factors could be related to the activation of extended or deeper subcortical (thalamic) or brainstem sources (Kroptotov and Ponomarev, 1991; Onofrj et al., 1992; Velasco, Velasco, Velasco, Almanza and Olvera, 1986; Yingling and Hosobuchi, 1984). A *specific* state effect means that biological conditions influence the same population of neurons that are engaged by the task variables crucial for the elicitation of P300, such as those involved in the oddball paradigm. Fig. 1 indicates this association by pathway B in which biological determinants directly affect the same neural structures and psychological mechanisms that are activated by the task. Assuming that multiple generator sources exist for P300 activity, state variables therefore also can produce a unique contribution to component scalp topography.

In this context, it is worth noting that a more cognitive-based alternative to a biological determinant view might be constructed in terms of dual-task effects on P300 amplitude (e.g., Kramer and Strayer, 1988; Wickens et al., 1983). Hence, for any task situation in which arousal was hypothesized to be operating, attentional processing resources would be allocated to that arousal source such that P300 amplitude would be altered relative to a non-arousal state. Although reasonable and likely applicable for several of the topics reviewed below, this approach sidesteps the main question of what is causing the reallocation of resources, viz. variation in the subject's biological state (Kahneman, 1973; Pribram and McGuiness, 1975). Thus, the present review attempts to consider the effects of arousal-mediated outcomes directly, rather than by invoking a cognitive construct secondarily related to the primary phenomenon.

2.2.2. Summary

As this overview indicates, the available evidence suggests that the P300 brain po-

tential reflects CNS activity related to cognitive operations. Performance studies have found that the same cognitive operations that are manifested by P300 — attention and memory updating — also are susceptible to fluctuations in the (arousal) state of the organism. These effects can originate from either general/tonic or specific/phasic sources. In the following sections, studies demonstrating how state fluctuations can affect P300 are considered.

3. P300 and biological state

The factors reviewed below have been organized into categories defined by the origins of the determinant: natural and environmentally induced changes in biological state. In general, *natural factors* have been derived from P300 results obtained with the classic auditory oddball paradigm. Since the oddball task is relatively easy to perform and elicits robust P300 effects, it is very suitable as a model ERP paradigm in both basic and applied research. Some of the studies reported in the *environmentally induced* section were based on the additive-factors method. This approach facilitates making inferences about the locus of biological determinants on specific information processing stages. The results of these reports will be examined by highlighting their contributions to the isolation of arousal effects. In addition, however, fluctuations in arousal state also can be induced by altering the task structure, for example, by manipulating stimulus intensity or task complexity. Although these stimulus and other task-induced effects can be considered as 'environmental', they typically occur in specific experimental conditions that are related to the attentional or resource requirements of the task itself (e.g., Johnson, 1986, 1988b; Kramer et al., 1986; Papanicolaou, Loring, Raz and Eisenberg, 1985; Polich, 1989b; Putnam and Roth, 1990; Sugg and Polich, 1995; Vesco, Ryan, Bone and Polich, 1993). Since the effects of these factors on the P300 have been considered elsewhere, they will not be reviewed here (cf. Donchin et al., 1986; Kramer and Spinks, 1991; Polich, 1993a, 1995).

3.1. Natural factors

Natural factors that influence the P300 are those that occur regardless of any experimenter-manipulated variables. They can vary continually and systematically or may exert their effects when the subject engages in particular activities that are related to naturally varying phenomena. The primary findings of this category will be presented with their relationship to the P300 described in terms of the theoretical perspective developed above.

3.1.1. Circadian rhythms

Mental performance is known to vary with time-of-day, although the effects depend on a mix of physiological and cognitive factors as well as individual differences (Folkard and Monk, 1983; Kerkhof, 1985). The general influences of time-of-day on specific ERP components have been reviewed previously (Wesensten and Badia, 1992). The findings suggest that just as the behavioral sequelae stemming

from physiological variation originating with circadian rhythms are imprecisely understood, how time-of-day contributes to ERP variation also is unclear. This conclusion derives from the weak effects of day-time circadian variation for P300 (Augirre and Broughton, 1987; Kerkhof, 1982) and electroencephalographic (EEG) measures (Torsvall and Akerstdet, 1987; Tsuji and Kobayashi, 1988).

The modulatory nature of circadian influences on the P300 is illustrated in Fig. 2, which plots component data from an auditory oddball paradigm as a function of

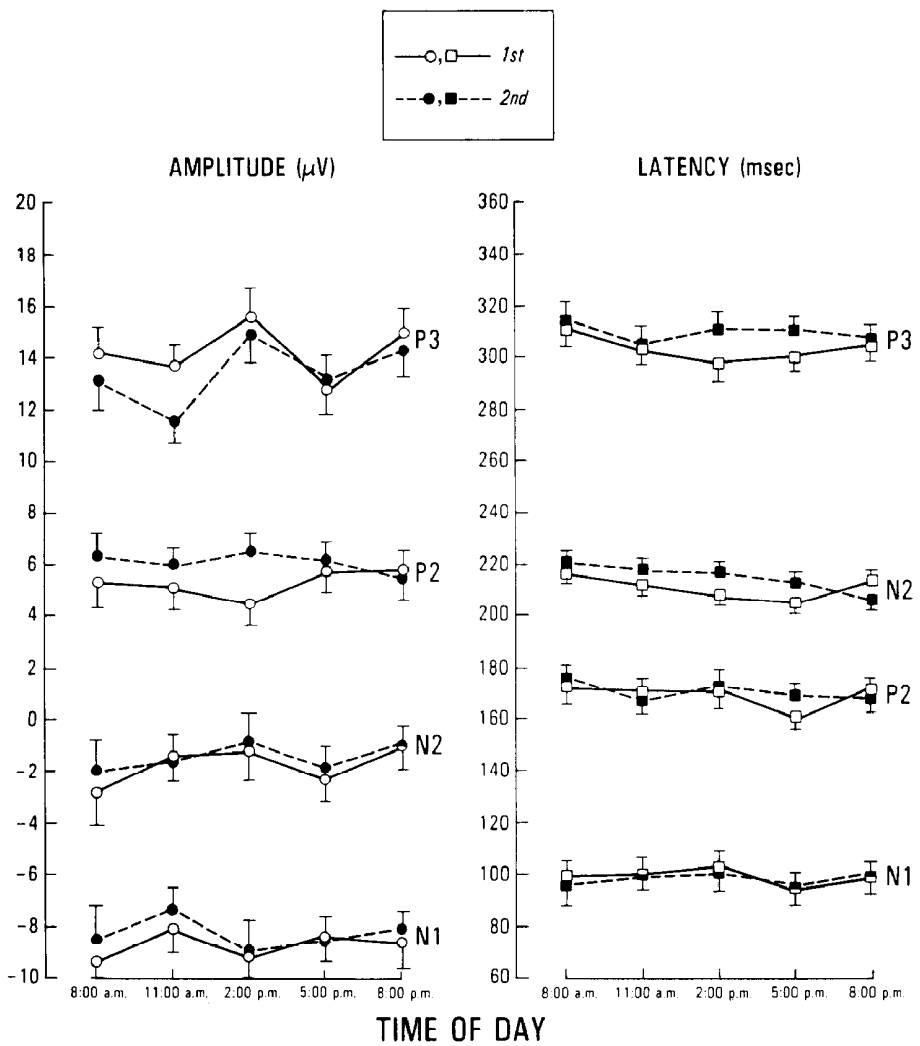

Fig. 2. P300 amplitude and latency (Pz) and N1, P2 and N2 amplitude and latency (Cz) as a function of time-of-day for the first and second administration time of the ERP paradigm, with $n = 24$/group at each testing time (after Geisler and Polich, 1990).

time-of-day for independent subject groups assessed at the different times (Geisler and Polich, 1990). ERPs were elicited once at the beginning (first) and at the end (second) of the testing session. Despite some variation, no statistically reliable time-of-day results were found for either P300 amplitude or latency. However, even though P300/circadian effects were not observed, the usual physiological/circadian changes were obtained: body temperature and heart rate increased during the course of the day across subjects and began their normal decline during early evening. These physiological measures were correlated with P300 latency as is illustrated in Fig. 3 so that time-of-day bodily changes related to variations in arousal level contributed indirectly to P300 peak latency values.

3.1.2. Food and morning/evening activity preferences

An additional indirect influence of circadian rhythms on the P300 has been found

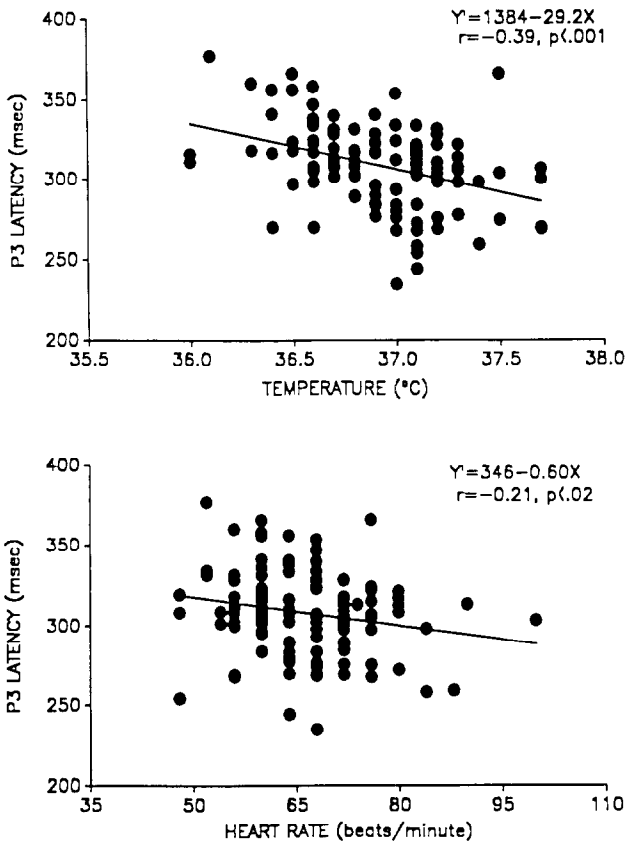

Fig. 3. P300 latency (Pz) as a function of body temperature and heart rate for $n = 120$ young adult subjects who were assessed at different times of the day (after Geisler and Polich, 1990).

for the recency of food consumption. All subjects of the P300/circadian study were told to maintain their regular eating habits, and a questionnaire was used to ascertain the recency of food ingestion and how much food was consumed. As suggested by Fig. 2, some differences were observed for P300 amplitude between the first and second measurement conditions, especially for subjects tested in the morning and early afternoon at times when food is normally consumed. An additional investigation was performed to characterize these effects (Geisler and Polich, 1992a), with the results summarized in Fig. 4: P300 amplitude is reduced when food has not been consumed recently and becomes larger when food is ingested; P300 latency is relatively unaffected by recency of food intake.

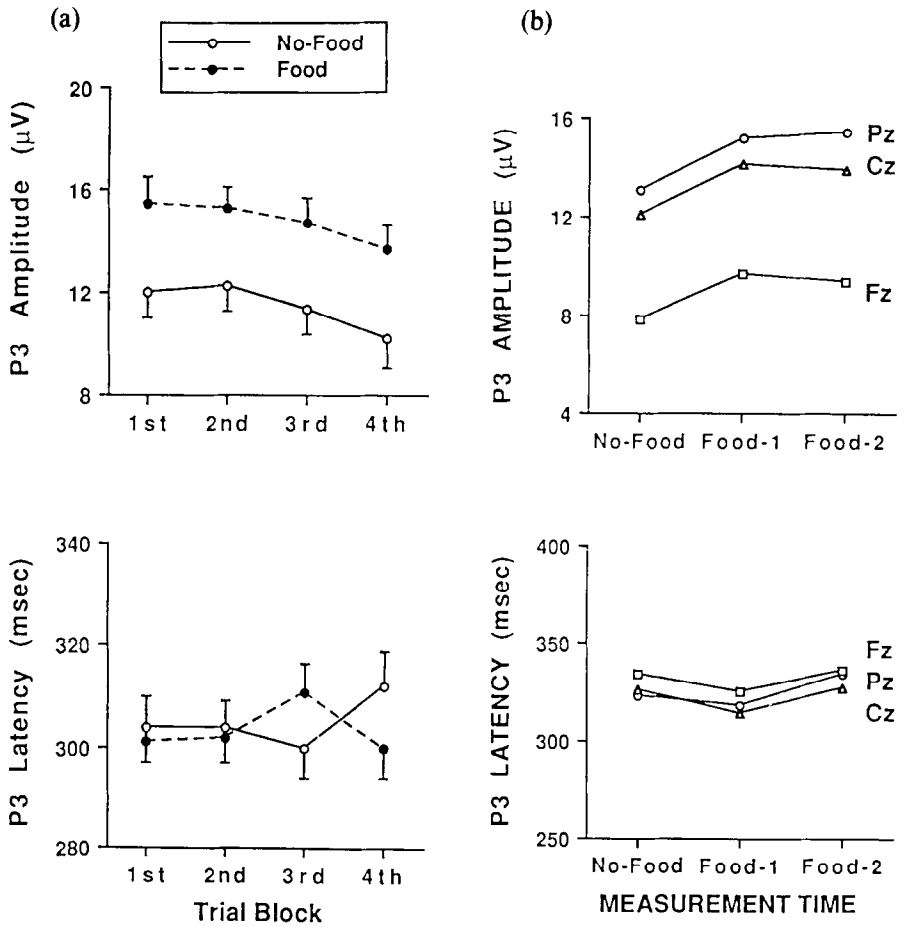

Fig. 4. (a) P300 amplitude and latency (Pz) as a function of trial block for subjects (n = 24/group) who had (Food) and who had not (No-Food) eaten within 6 h of testing. (b) P300 measures for the midline electrode sites as a function of measurement time with respect to when subjects (n = 24) had consumed food (after Geisler and Polich, 1992a).

The mechanism underlying the sensitivity of P300 amplitude to food is not known. Because food consumption produces an increase in blood glucose level, which contributes to the brain's neuroelectric activity (Blackman, Towle, Lewis, Spire and Polonsky, 1990; Jones et al., 1990), it was assumed initially that the glucose increase originating from food consumption was responsible for P300 amplitude changes. However, this hypothesis was not supported by correlational analyses or from a study that manipulated hyperglycemic states directly (Geisler and Polich 1992a, 1994b). Because glucose increase does not appear to affect ERPs, P300/food effects

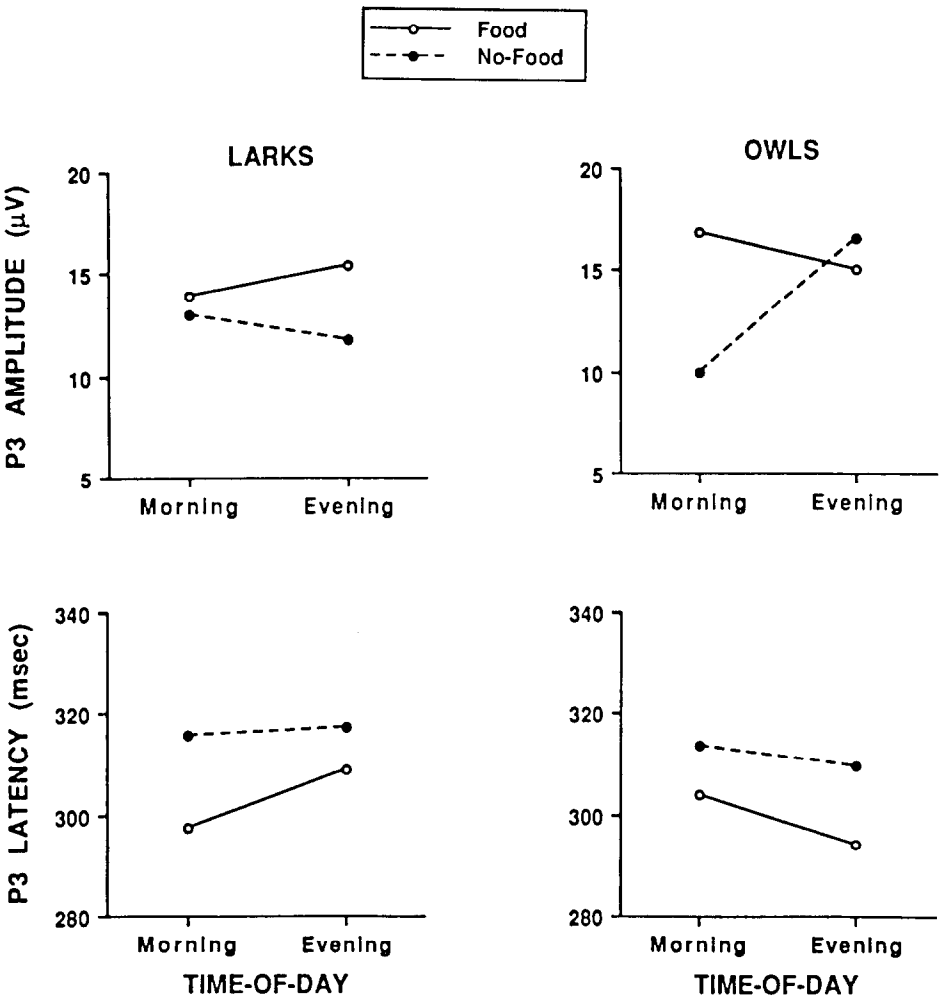

Fig. 5. P300 amplitude and latency (Pz) for the 'Larks' (morning-preferring) and 'Owls' (evening-preferring) subject groups as a function of whether individuals were assessed in the morning or evening and whether they had eaten (Food) or not eaten (No-Food) within 6 h of testing, with $n = 8$/group (after Geisler and Polich, 1992b).

may be related to more general changes in arousal level from recency of food ingestion, such that cognitive processing can be affected (cf. Baldeweg, Ullsperger, Pietrowsky, Fehm and Born, 1993; Pietrowsky, Specht, Fehm and Born, 1994).

Support for this latter hypothesis comes from a study in which innate arousal level was manipulated by comparing subjects who differed in their activity time-of-day preference (Geisler and Polich, 1992b). The results are presented in Fig. 5. Morning- (larks) or evening-preferring (owls) subjects who were measured at their preferred activity times evinced P300 amplitudes in the absence of food intake that were comparable to those when food had been consumed recently. P300 latency tended to be shorter with food consumption, but none of the effects were significant. Because individual differences in activity preference time have been linked to inter-subject variation in arousal level, these findings suggest further that P300/food effects originate from changes in bodily state (cf. Akerstedt and Froberg, 1976; Horne and Ostberg, 1976; Kerkhof, 1980, 1982; Monk and Leng, 1986).

3.1.3. Ultradian rhythms

Repeated presentation of an auditory oddball paradigm produces a decrease in P300 amplitude and an increase in latency (Kenemans et al., 1992; Lammers and Badia, 1989; Polich, 1989a; Wesensten, Badia and Harsh, 1990). Under some conditions repeated tasks have demonstrated cyclical patterns for P300 measures (Harsh, Stone and Leider, 1988; Lew and Polich, 1993). Given that EEG activity indexes ultradian fluctuations in arousal levels that occur in approximately 90-min cycles (Okawa, Matousek and Petersen, 1984; Tsuji and Kobayashi, 1988), it is not unreasonable to expect that the P300 component also might be affected by these cyclical changes. However, because P300 amplitude habituates over trial blocks, observing systematic variation in component measures can be masked by the decreased amplitude obtained with task repetition.

Lin and Polich (1995) attempted to overcome this problem by examining individual amplitude profiles when subjects were assessed every 10 min for ten successive trial blocks with an auditory oddball task. The results are portrayed in Fig. 6, which plots P300 amplitude and latency over the ten trial blocks for two subject groups who were designated as 'uppers' and 'downers' as defined by the change in their P300 amplitude from trial block one to two. Because individual variation in P300 has been linked to inter-subject differences in background EEG (Intriligator and Polich, 1995; Spencer and Polich, 1992), it was hypothesized that some subjects produced an amplitude increase while other subjects produced an amplitude decrease depending on when they were initially measured during their ultradian-driven EEG cycle (Lloyd and Stupfel, 1991; Ortega and Cabrera, 1990). For the present data, the P300 latency averages of these two subject groups demonstrated a complete cycle that occurred in approximately 90 min, with opposite phases for the upper and downer subject groups. These findings imply that fluctuations in neural electrophysiological activity that reflect changes in arousal level also can affect P300.

3.1.4. Seasonal variation

An additional natural influence on the P300 ERP stems from the amount of

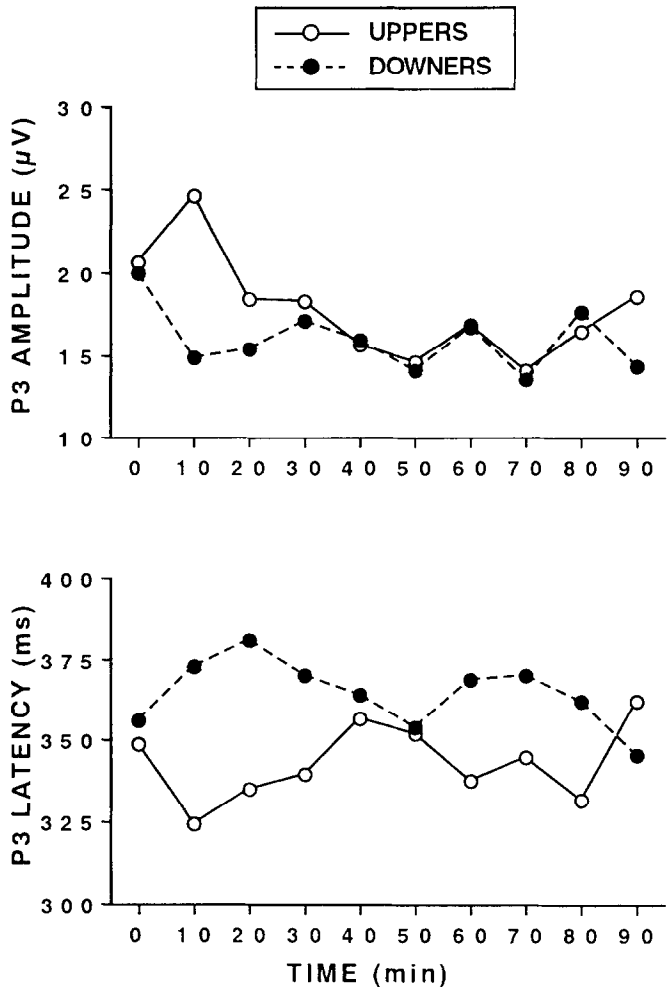

Fig. 6. P300 amplitude and latency (Pz) as a function of trial block for subjects whose amplitudes increased ('Uppers', $n = 13$) or decreased ('Downers', $n = 11$) from trial block 1 to trial block 2 — a categorization method that was derived from theoretical considerations of ultradian changes in background EEG (cf. Intriligator and Polich, 1995). Note that the cycles of P3 latency for the two subject groups are opposite in phase (after Lin and Polich, 1995).

daylight that varies with seasonal change. First reported in ERP studies of affective disorder, the primary findings are illustrated in Fig. 7. These P300 amplitude changes have been observed for ERPs elicited with auditory and visual stimuli, although no seasonal effects have been found for peak latency and different patterns of amplitude variation were observed between studies (cf. Deldin, Duncan and Miller, 1994; Polich and Geisler, 1990). It is unknown whether P300/seasonal changes are related to arousal, but seasons with more light might be conducive to

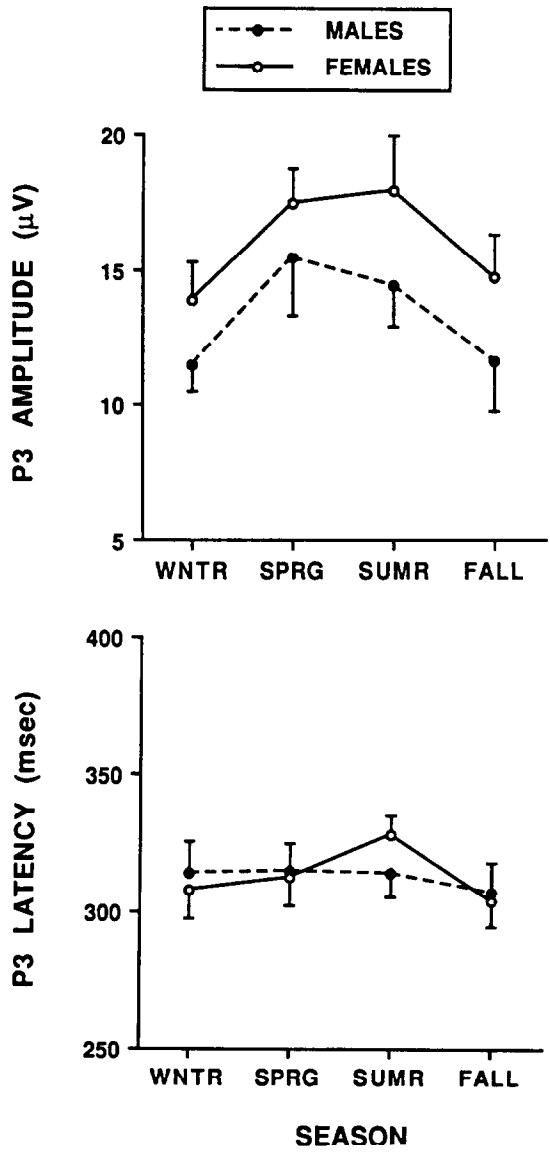

Fig. 7. P300 amplitude and latency (Pz) as a function of season of the year for male and female subjects, with $n = 20$ independent groups/season (after Polich and Geisler, 1991; see Deldin et al., 1994 for additional findings).

increased activity and greater overall arousal. This also could account for the inter-study differences, since the amount of light within each season varies considerably between the geographical locales in which seasonal effects have been assessed to date. More important, these effects suggest it is critical to obtain ERP data from dif-

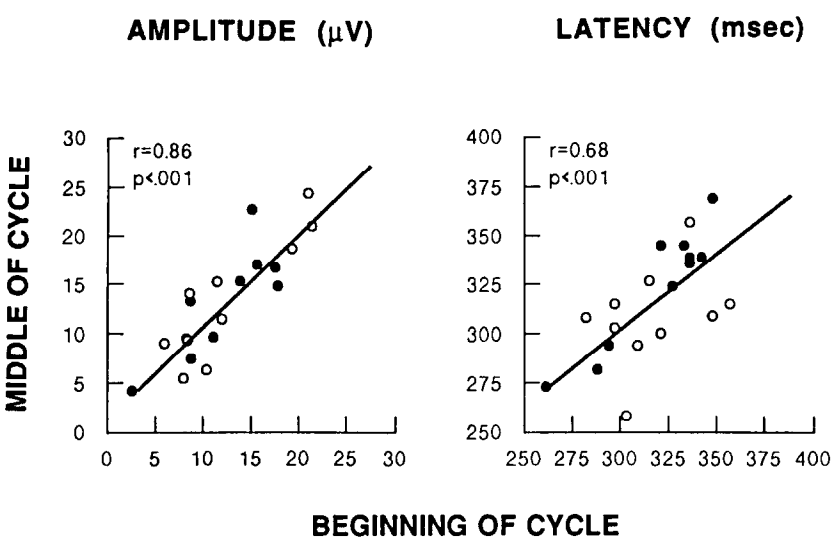

Fig. 8. P300 amplitude and latency (Pz) from women who were either spontaneous cyclers (O) or took birth control pills (●) assessed at the beginning and middle of their menstrual cycle, with $n = 10$/group (after Fleck and Polich, 1988).

ferent groups of subjects (e.g., patients and controls) at the same time of year to avoid confounding P300 amplitude by seasonal variability.

3.1.5. Menstrual cycle

Another natural cycle stems from menstrual hormonal changes. When simple auditory stimuli were used to elicit the P300 component first at the beginning of menses and then a second time 14 days later, no effects of menstruation have been found for either amplitude or latency measures (Fleck and Polich, 1988). The data are illustrated in Fig. 8 for both spontaneous cycling and oral contraception users. These results indicate that despite bodily changes due to menstruation (hormonal, temperature, etc.), P300 values from an oddball task are consistent. Some P300 latency effects have been found for late luteal phase dysphoric disorder irrespective of menstrual cycle changes (Ehlers, Phillips and Parry, 1995). Further, when more 'emotional' stimuli (nude males, babies, etc.) were employed, P300 amplitude was found to be larger during ovulation than at other times (Johnston and Wang, 1991). Thus, the affective or arousal quality of stimulus items can interact with hormonal changes and contribute to P300 variability when the eliciting stimulus is emotionally salient.

3.1.6. Summary: P300 and natural factors

As the above review indicates, the P300 ERP can be affected by variables that vary naturally with respect to intra- and extra-individual influences. The effects on P300 measures from these natural factors appear to be related directly to how each

variable contributes to overall arousal level. Although the exact structural or physiological mechanisms underlying these effects are not yet well understood, it appears that insofar as naturally occurring changes modulate arousal, so too will such factors modulate P300 measures to a proportional degree.

3.2. Environmentally induced factors

In this section biological changes that are produced by environmental factors, also referred to in the literature as stressors, will be considered. At the performance level, the influences of environmental stressors on mental operations have been relatively well documented (Broadbent, 1971; Hockey, Gaillard and Coles, 1986; Kahneman, 1973). How these variables alter ERPs has not been investigated systematically to date, primarily because the electrophysiological study of energetical influences on cognitive performance is a relatively new endeavor. Toward this end, the present section will focus on how changes of body state from exercise, sleep deprivation, mental fatigue, and 'common' drugs can affect the P300 component.

3.2.1. Exercise

Several reports have suggested that frequent physical exercise may have facilitatory effects on mental performance (Bashore and Goddard, 1993; Tomporowski and Ellis, 1986). In particular, cross-sectional studies have demonstrated that age-related differences in mental performance speed for some cognitive and neuropsychological tasks are attenuated in elderly subjects with high- compared to low-aerobic fitness (Spirduso, 1980; Baylor and Spirduso, 1988). These results could reflect factors other than physical fitness, since individuals who exercise regularly may be self-selected for variables that can affect mental performance. However, the findings taken at face value suggest that exercise can contribute to intellectual performance and imply that energetical activities affect the CNS and, therefore, cognitive function.

P300 electrophysiological measures have been employed in combination with behavioral performance to evaluate the effects of exercise and fitness on cognition more directly. Bashore (1989) used a stimulus-response compatibility task to compare young and old exercisers and nonexercisers. Both the old and young subjects showed a similar pattern in their behavioral responses, although when subject groups were differentiated on the basis of their fitness levels, as measured by VO_2 max (i.e., maximum oxygen volume intake — the greater the intake, the more physically fit an individual is), the low-fit older group produced a dramatic increase for response time in the incompatible condition relative to the high-fit group. More important, P300 amplitude was smaller and component latency was longer for the low- compared to high-fit subject groups across task variables. Thus, both behavioral and P300 data indicated that exercise facilitated complex performance in elderly subjects.

Additional support for this view comes from a comprehensive study by Dustman et al. (1990). Groups of young men and healthy older men were obtained such that half of the subjects were in good aerobic condition, and half were in poor aerobic

condition as determined by evaluating lifestyle activity and VO_2 max. All subjects completed a series of neurocognitive, EEG and ERP procedures, with the P300 component assessed using a simple visual oddball task. Compared to low-fit men, high-fit subjects had better neurocognitive and visual sensitivity functioning as well as shorter latencies. Furthermore, P300 latency was significantly longer in older compared to the younger subjects, but the age effect was attributable to the relatively long latencies of the low-fit older men; no P300 amplitude data were reported. In another study (Dustman et al., 1984), the impact of fitness training as an intervention technique was measured in an exercise group, a nonexercise group, and a group trained in nonaerobic physical exercise. The aerobic exercise subjects attained significant performance gains over the two other groups on various neuropsychological tests.

In contrast to these positive findings, Blumenthal and Madden (1988) assessed the effects of aerobic exercise training in middle-aged men on speed of short-term memory and found no performance advantage from exercise. Lijzenga, Kok and Hofman (1994) studied the role of aerobic fitness in a group of elderly men that were trained for a 3-month period, such that their VO_2 max levels increased significantly between pre- and post-test sessions. Subjects performed several visual ERP tasks that manipulated stimulus quality, target time uncertainty, and response compatibility. No significant effects of fitness training were obtained for either the response time or ERP measures from any experimental condition; P300 amplitude and latency topography profiles also were highly similar across pre- and post-test sessions. The different effects of exercise between studies may have resulted because the amount of aerobic intervention was not great enough to produce substantial CNS changes (for comprehensive reviews, see Bashore, 1989, 1990; Bashore and Goddard, 1993).

Taking a somewhat different approach, the short-term effects of autonomic arousal induced by exercise in young adult subjects of both sexes were investigated by Geisler and Squires (1992). ERPs were elicited with a simple auditory oddball task, and P300 measures were obtained before and after riding an exercise bike with moderate exertion for 3–5 min. The findings are illustrated in Fig. 9. P300 amplitude was found to increase and P300 latency to decrease significantly after exercise compared with a no-exercise control condition. The amplitude and latency changes were of the same magnitude across the midline electrode sites, suggesting that the P300/exercise effects were occurring in a global fashion related to increased general arousal level. When viewed in the context of the ERP/exercise studies reviewed above, these results strongly imply that tonic state is affected by exercise and, therefore, affects phasic P300 values.

3.2.2. Sleep deprivation

Whereas exercise is viewed as a positive energetic influence on cognition and can produce enhanced P300 amplitude measures, at the opposite end of the arousal continuum is the low arousal state resulting from sleep deprivation. Relatively few studies have assessed effects of sleep deprivation using ERPs. In general, however, P300 amplitude tends to decrease and latency increase as sleep begins (Wesensten and

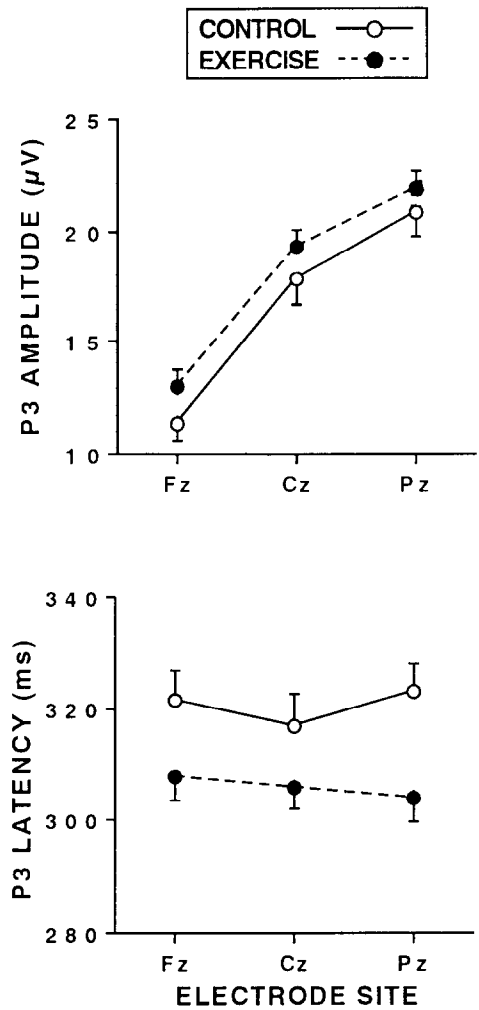

Fig. 9. P300 amplitude and latency as a function of the midline electrodes illustrating the effects of vigorous exercise, with $n = 16$ (after Geisler and Squires, 1992).

Badia, 1988), with sleep disorders that produce fatigue demonstrating similar results (Broughton and Aguirre, 1987; Walsleben, Squires and Rothenberger, 1989). Hence, changes in arousal level stemming from sleep and its disruption affect P300 in a manner consonant with other biological state effects.

Smulders (1993) recently has reported a study of sleep deprivation effects. Normal young subjects were tested twice, once after a night of restful sleep and once after one night of complete sleep deprivation. The task variables were stimulus degradation, target uncertainty, and stimulus-response compatibility, with time-on-task effects also evaluated. All subjects were tested between 15.00 h and 17.00 h, so that

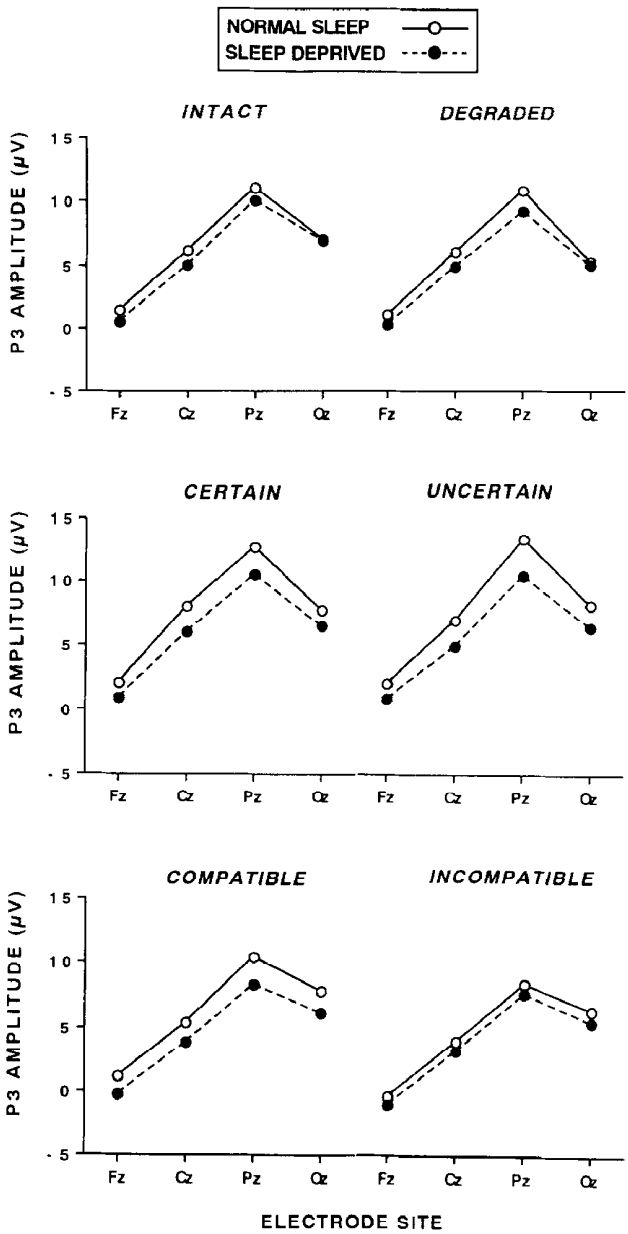

Fig. 10. P300 amplitude as a function of the midline electrodes for subjects who were either rested or physically fatigued from sleep deprivation for three task conditions that manipulated different information processing stages, with $n = 15$/group (after Smulders, 1993).

the sleep-deprived subjects were awake for over 40 h and physically very fatigued, whereas the rested subjects were assessed during the afternoon after typical daytime activities. Sleep-deprived subjects were slower and less accurate in their responses and produced appreciable increases in omission errors and longer task duration compared to rested subjects. The ERP results are illustrated in Fig. 10: P300 amplitude was smaller and peak latency tended to be longer after sleep deprivation across all variables. Note that P300 amplitude was smaller in about the same degree for all task manipulations with sleep deprivation across electrode sites. This global pattern suggests that P300/sleep deprivation effects result from non-specific factors related to a decrease in general arousal.

3.2.3. 'Common' drugs

Drugs can be considered as an environmentally induced biological determinant in the sense that they alter neurochemical activity and therefore physical as well as psychological state. A wide range of pharmaceutical agents have been assessed with ERPs in humans and other animals. Such studies typically manipulate drug ingestion in the context of information processing tasks, such that the drug's effects can be discerned under tightly controlled conditions and often for applied purposes (e.g., Brumaghim, Klorman, Strauss, Levine and Goldstein, 1987; Callaway, 1983; Duncan and Kaye, 1987; Halliday, Naylor, Brandeis, Callaway, Yano and Herzig, 1994; Martin, Siddle, Gourley, Taylor and Dick, 1992; Meador, Loring, Huh, Gallagher and King, 1990; Rockstroh, Elbert, Lutzenberger and Altenmüller, 1991). Because the present paper's purpose is to assess biological factors that contribute to P300 findings in general, and since drug/ERP reports are quite variegated in their content and findings, only the effects of the 'common' drugs, caffeine, nicotine, and alcohol will be reviewed here. The influence of these common drugs on ERPs has been evaluated primarily with respect to their psychoactive properties rather than for their energetical contributions. The extant ERP data will be presented by considering how these substances influence arousal and P300 values.

Caffeine. Snel (1993) has comprehensively reviewed the behavioral effects of caffeine and concludes: 'The general balance in arousal of several concurrently active systems in the nervous system determines the efficacy of caffeine, i.e. the lower the arousal the greater the effect' (p. 263). Hence, the contribution of caffeine as an influence on P300 needs to be considered in the context of fluctuating arousal levels originating from sleep/wake cycles, fatigue, other drugs, etc. Assessment of caffeine with the P300 is just beginning, but the findings appear to be consistent with other biological factors that modify arousal level.

Lorist, Snel and Kok (1994a) investigated caffeine and mental fatigue effects with a response time task that varied stimulus degradation, target uncertainty and stimulus-response compatibility. Young adults served as subjects and mental fatigue was manipulated between groups. The fatigue group was kept awake during the night in the lab and tested at about 04:00 h. It was assumed that this approach would maximize cognitive fatigue without inducing severe physical fatigue (cf. Smulders, 1993), since most subjects normally reported being mentally depleted towards the end of a sleepless night. The rested group was tested at about 10:00 h after a night

of normal sleep at home. Subjects were given a placebo or caffeine in a double blind and deceptive design, with normally brewed decaffeinated coffee as a vehicle.

All subjects reported that they felt more energetic in the caffeine than in the placebo condition. Behaviorally, fatigued subjects were less accurate in their responses than rested subjects, and caffeine produced a stronger improvement in performance for fatigued compared to rested subjects. As illustrated in Fig. 11, mentally fatigued subjects demonstrated decreased P300 amplitudes in all task conditions. Note that the P300/mental fatigue scalp distribution had a more specific posterior focus than that produced by P300/sleep deprivation (Fig. 10). Caffeine in-

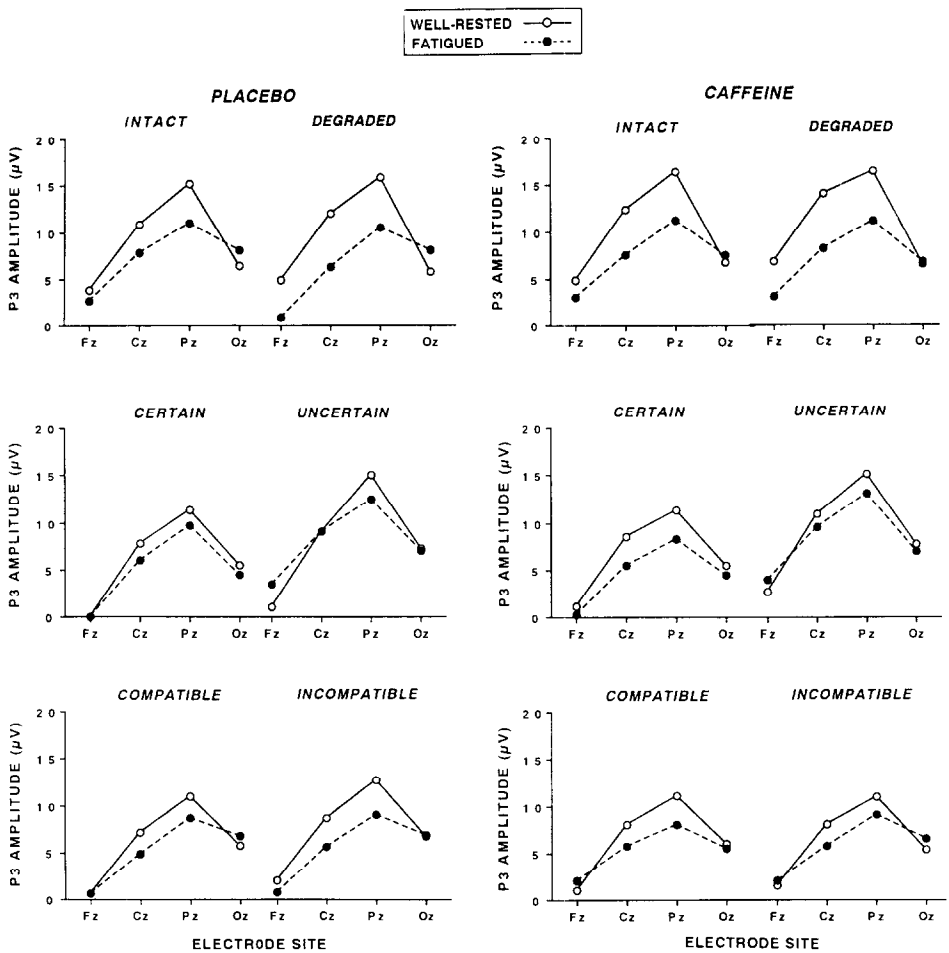

Fig. 11. P300 amplitude as a function of the midline electrodes for subjects who were either rested or mentally fatigued and who drank either a placebo or caffeinated beverage for three task conditions that manipulated different information processing stages, with n = 12/group (after Lorist et al., 1994a).

duced a small increase in P300 amplitude in all task conditions, with the enhancement at posterior sites attributed to increases in phasic cortical arousal. P300 latency was not significantly affected by caffeine.

In a second study, caffeine effects were assessed using the same basic drug and placebo design with mental fatigue manipulated as before (Lorist, Snel, Kok and Mulder, 1994b). Subjects performed a visual selection search task that required them to make a button press response to target letters designated as relevant and to ignore irrelevant stimuli. Subjects responded faster in the caffeine than in the placebo condition, although performance accuracy was the same in both conditions. Mental fatigue produced a significant reduction in P300 component amplitude and prolongation of peak latency. Caffeine was found to increase P300 amplitude, with the strongest effect observed for the fatigued rather than rested subjects. Caffeine also eliminated the difference in P300 latency between the fatigued and rested subjects observed in the placebo condition. As in the first study, these results were more pronounced at the central and parietal electrodes.

In sum, caffeine affects P300 amplitude and to a lesser extent peak latency depending on the level of mental fatigue. The additive factors methodology employed suggests that these effects are central in their information processing locus and are manifested primarily at the central/parietal recording sites. Whether or not caffeine changes P300 values as a function of daily intake amount, frequency, or cessation of abstinence is not known. However, when taken together with the available behavioral and ERP data, these findings suggest that P300/caffeine effects are influenced by arousal level (Lorist et al., 1994a,b; Snel, 1993).

Nicotine. Tobacco smoke contains nicotine, which produces most of the immediate pharmacological effects of smoking on bodily functions, including addiction. Indeed, the ability of nicotine to act as a positively reinforcing stimulus is at the core of tobacco addiction and has been traced to the mesolimbic system (Reavill, 1991; Stolerman and Shoaib, 1991). The common finding of smoking-enhanced task performance has been attributed to nicotine-induced increases in arousal state, a hypothesis that has received substantial support from behavioral and neuroelectric results (Edwards and Warburton, 1983; Wesnes and Warburton, 1983). Many of the electrophysiological studies have used EEG rather than ERP measures, with the general finding that tobacco deprivation produces slowing of alpha frequency while theta activity increases (Pritchard, 1991; Knott, 1991; Herning, Brigham, Stitzer, Glover, Pickworth and Henningfield, 1990) — a biological state that is consistent with reports of fatigue and sleepiness. As a whole, these effects strongly implicate a relationship between nicotine and changes in arousal level.

Relatively few studies have employed the P300 component in the assessment of nicotine. Edwards, Wesnes, Warburton and Gale (1985) investigated how smoking cigarettes affects response time and P300 using a rapid visual information processing task in which nicotine-deprived male smokers were required to detect three consecutive odd or even digits. After smoking, the number of correct detections increased and response time decreased compared with baseline and nonsmoking conditions. P300 amplitude was not affected by smoking, but P300 latency to correct detections was significantly shorter after smoking compared with nonsmoking. Similar post-

smoking effects were reported when ERPs were elicited with a grammatical reasoning task. P300 amplitude or latency did not change between non-smokers and smokers (non-deprived) for the test stimuli, but P300 latency elicited by the warning stimulus was shorter for the smokers after smoking (Landers, Lindhold, Crews and Koriath, 1990). Thus, nicotine use by smokers affects speed of information processing as reflected by P300 latency in some task situations.

Other nicotine studies have found increases for P300 amplitude after smoking, although the effects appear to be related to specific biological and task conditions such as the pre- vs. post-smoking CO levels, stimulus modality, and stimulus 'noise' conditions (Hasenfratz, Michel, Nil and Battig, 1989; Michel, Nil, Buzzi, Woodson and Battig, 1987; Pritchard, 1993). These mixed results for smoking and P300 amplitude changes may reflect a variety of experimental measures, including nicotine dosage level. Norton, Howard and Brown (1991) elicited ERPs with an auditory oddball task and found that nicotine affected P300 amplitude as a function of dose: low nicotine doses produced an enhancement of amplitude to the rare stimuli, while high doses resulted in an amplitude decrease. It is noteworthy that the data from a stress-arousal checklist used in this study suggested that both subjective and P300 measures were reflecting the same underlying arousal mechanisms. Herning and Pickworth (1985) also manipulated nicotine dosage level and found similar P300 effects from an auditory oddball task.

Taken together, the P300/nicotine results suggest that tobacco can affect both amplitude and latency measures, although the results are difficult to characterize precisely. The influence of nicotine may be relatively gross so that it can be observed more readily with global EEG measures (Pritchard, 1991; Knott, 1991; Herning, Hunt and Jones, 1983). It also may be the case that ERP assessment of nicotine requires paradigms specifically designed to elicit controlled attentional preparation such as that indexed by the contingent negative variation or CNV (for a review, see Knott, 1989). However, it may be suggested tentatively that nicotine contributes to electro-cortical activity most likely by affecting arousal level, and that these changes influence P300 amplitude and latency depending on the dosage level and task.

Alcohol. Many reports have employed quantitative EEG to assess CNS responses to alcohol. In general, acute ethanol ingestion reduces power in the theta and alpha frequency bands, with drinking history and risk-for-alcoholism contributing to the strength of the effects (Ehlers, Wall and Schuckit, 1989; Pollock et al., 1983). These results are consistent with alcohol-induced physiological changes related to decreased arousal and slowing of cognitive function (for reviews, see Begleiter and Porjesz, 1988; Porjesz and Begleiter, 1981). Hence, it is reasonable to expect that alcohol's influence on CNS function would affect the P300 component.

The basic findings for acute ethanol ingestion and P300 have been summarized well by Oscar-Berman (1987): P300 is altered most consistently in comparison with other late ERP components (N100, P200, N200) under the acute influence of ethanol as well as in abstinent chronic alcoholics. The basic nature of these acute effects are illustrated in an elegant study by Rohrbaugh et al. (1987), which assessed ethanol intoxication with a visual vigilance task in young adult male social drinkers. Subjects monitored a sequence of digits for the occasional presentation of a target digit when

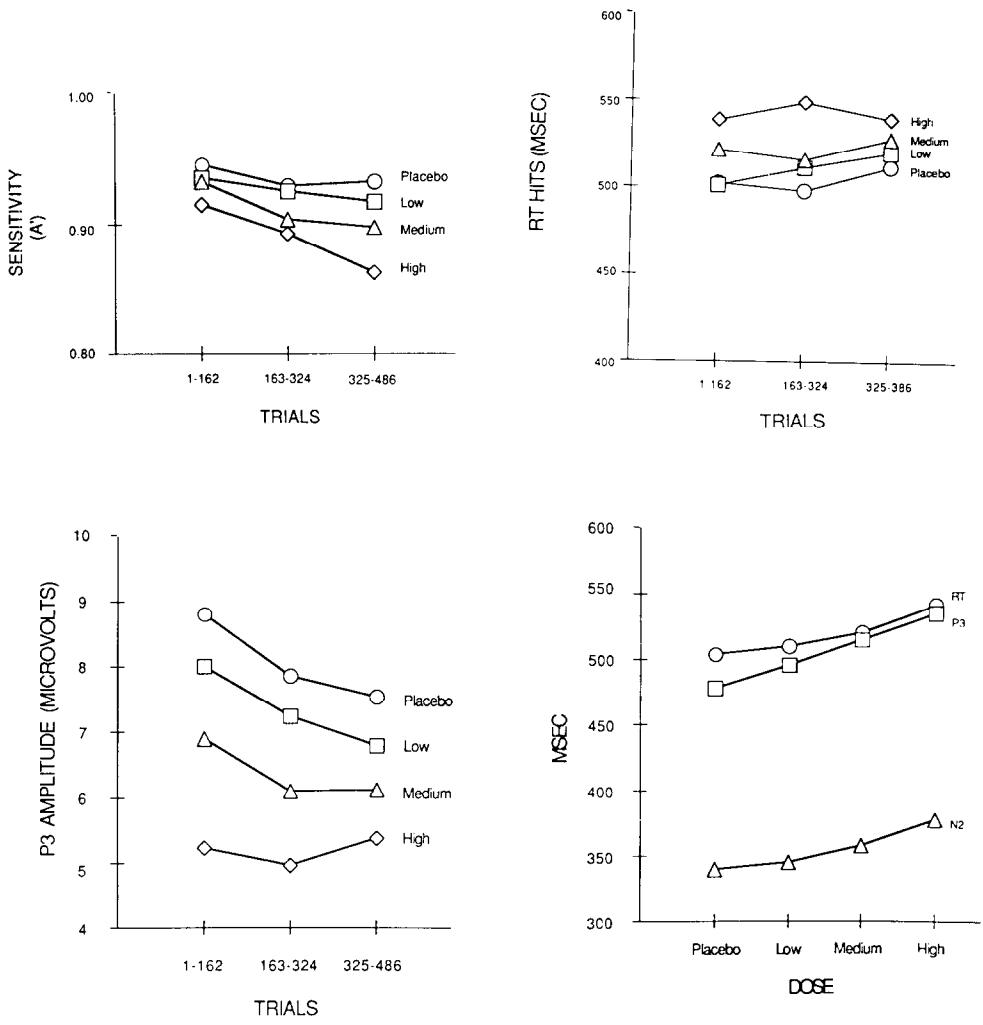

Fig. 12. Behavioral and P300 measures (Pz) to placebo, low, medium and high doses of ethanol, with $n = 12$ male subjects (after Rohrbaugh et al., 1987).

the rapidly presented stimuli were blurred. The findings are summarized in Fig. 12. Detection performance deteriorated as a function of time-on-task and ethanol dose relative to the placebo condition. P300 amplitude decreased with increases in dose and time-on-task. The smaller P300 components after ethanol intake were interpreted as reflecting a reduction in the amount of available processing capacity. Ethanol also produced dose-related delays in P300 latency that paralleled response time increases.

Other P300/acute alcohol studies generally have confirmed these results (Oscar-

Berman, 1987; Roth, Tinklenberg and Kopell, 1977; Teo and Ferguson, 1986). There is some suggestion that difficult processing tasks demonstrate less P300 amplitude reduction with alcohol ingestion — perhaps because of the modulating influence of resource allocation or increased arousal level induced by task difficulty (Campbell and Lowick, 1987; Campbell, Marois and Arand, 1984; Sommer, Leuthold and Hermanutz, 1993). Further, these findings have been extended with topographic brain mapping methods applied to ERP data from an auditory oddball task by Lukas, Mendelson, Kouri, Bolduc and Amass (1990). Acute ethanol ingestion was associated with reduced P300 amplitude and delayed latency as observed previously, with the additional finding from dipole source analysis that a theoretical neural generator of the P300 shifted to a more inferior position in the brain after ethanol intake. Finally, additional studies have suggested that the decrease in P300 amplitude observed with alcohol ingestion is greater over the right compared to left hemisphere (Daruna, Goist, West and Sutker, 1987; Porjesz and Begleiter, 1985), although these and other amplitude effects are not always found (Campbell and Lowick, 1987; Pfefferbaum, Hovrath, Roth, Clifford and Kopell, 1980). Overall, despite some variability across studies, the consensus of these reports is that alcohol ingestion reduces P300 amplitude and increases its peak latency.

The chronic effects of alcohol on ERPs also have received some attention. Based on neuropsychological findings indicating that social alcohol consumption may produce cognitive deficits under sober testing conditions (Alterman, Bridges and Tarter, 1986; Hill and Ryan, 1985; Parker, Birnbaum, Boyd and Nobel, 1980; Schaeffer and Parsons, 1986), several P300 studies have noted reductions in amplitude and increases in latency as a function of the reported amount of alcohol typically consumed (Neville and Schmidt, 1985; Polich and Bloom, 1985). However, subsequent reports did not confirm these results (Baribeau, Ethier and Braun, 1987; Polich, Burns and Bloom, 1988; Pfefferbaum, Ford, White and Mathalon, 1991). A study by Maritz, Snel, Zeef and Kok (1994) is illustrative. A visual selection task that also varied memory load was used to compare different groups of male subjects who varied in age and drinking history: lifetime non-drinkers aged 30–40, social drinkers aged 30–40, lifetime non-drinkers aged 50–60, and social drinkers aged 50–60. If chronic alcohol use induces premature neurocognitive aging, lifetime middle-aged social drinkers and elderly non-drinkers should show the same behavioral performance and ERP profiles. The results are illustrated in Fig. 13. Only nonsignificant effects of social drinking were observed for P300 amplitude and latency, and no evidence was found for accelerated cognitive aging in social drinkers. Given the inconsistency of previous studies, these data imply that P300 does not change reliably because of social alcohol consumption.

In sum, acute alcohol ingestion reduces P300 amplitude and increases peak latency in most task situations, with some indications of greater amplitude reduction over the right compared to left hemisphere. The amount of alcohol consumed by social drinkers does not change P300 measures. It also should be noted that P300/acute alcohol effects appear to be different for individuals who are at genetic risk for alcoholism but who are not alcoholic themselves (Schuckit, Gold, Croot, Finn and Polich, 1988) in a manner similar to behavioral reports (O'Malley and Maisto, 1985;

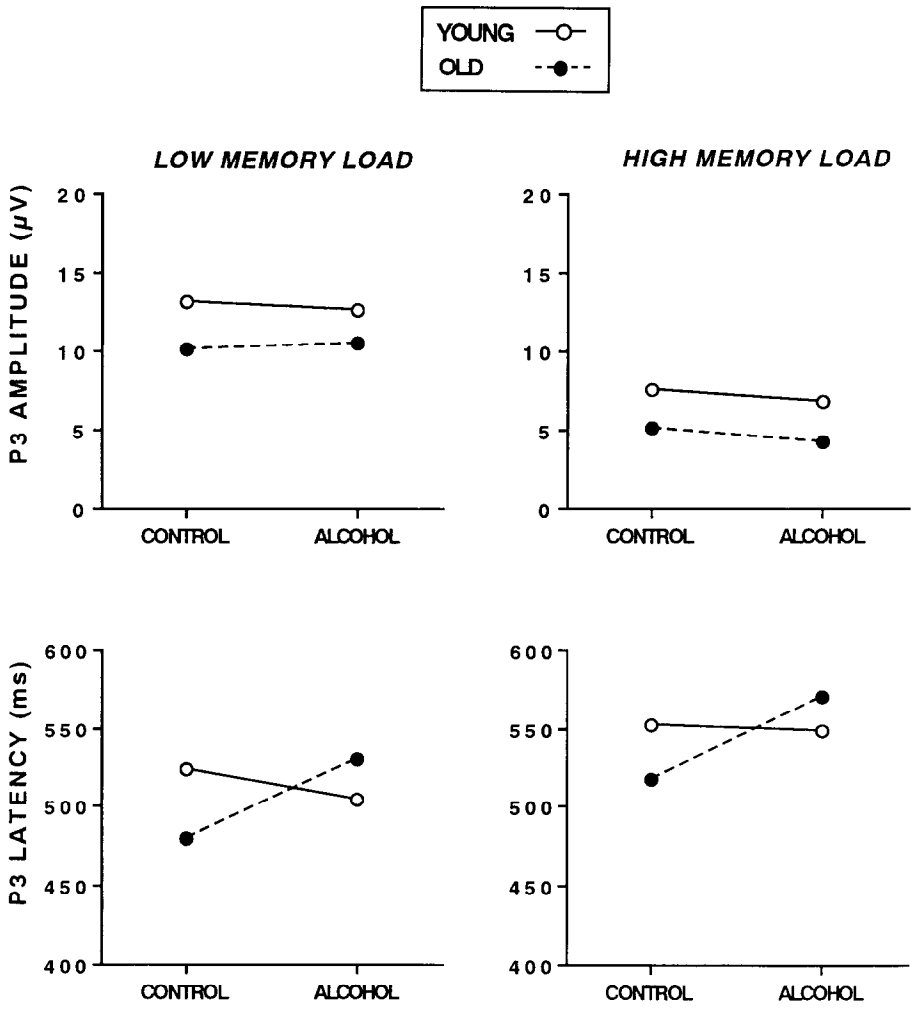

Fig. 13. P300 amplitude and latency (Pz) as a function of social alcohol consumption for young (30–40 years) and elderly subjects (50–60 years) in high and low memory load conditions, with $n = 12$/group. None of the effects of social drinking were statistically reliable (after Maritz et al., 1994).

Schuckit, 1985; Tarter and Edwards, 1988). However, it is unlikely that the P300 is a biological marker for the inheritability of alcoholism since the influence of family history is observed reliably only under rather specific stimulus, task, and subject age conditions (for a review, see Polich, Pollock and Bloom, 1994).

3.2.4. Summary: environmentally induced factors

In general, the effects of environmentally induced variables on P300 amplitude and latency appear to be more heterogeneous than those derived from naturally in-

duced variation. Although environmental factors often affect overall arousal directly (e.g., tonic exercise, sleep deprivation, alcohol, etc.), they do so in ways that can influence specific P300 parameters rather than the component as a whole (e.g., chronic exercise, fatigue, nicotine, etc.). The reasons for this sometimes observed specificity are unknown. As information concerning the influence of these factors is obtained, the underlying physiological mechanisms also will become more apparent and the reasons for the specific effects made more clear.

4. Discussion

The biological contributions to P300 amplitude and latency from natural and environmentally induced state factors have been surveyed and their import outlined. In this final section, an overview of the findings will be presented and the theoretical framework will be revisited to incorporate the contribution of biological determinants.

4.1. Theoretical implications

Table 1 summarizes the biological determinants reviewed above and indicates that most natural and environmental state factors have significant effects on P300 amplitude and latency. The global pattern of effects implies that when arousal is increased by food intake, high body temperature, ultradian cycles and normal sleep, P300 amplitude increases and latency decreases, with the opposite pattern observed when arousal is decreased by lack of food, sleep deprivation and alcohol ingestion. These results suggest that natural and induced factors modulate the CNS to affect P300 measures in a non-specific fashion, since P300 amplitude scalp topography usually did not interact with fluctuations in biological state. This global effect of state fluctuations is represented in Fig. 1 by pathway A, wherein biological determinants affect measurement processes directly but with global outcomes. Hence, the P300 findings are in general accordance with performance data showing that time-of-day and sleep deprivation are accompanied by an overall or tonic change in arousal level (Broadbent, 1971; Hockey et al., 1986). As suggested above, such non-specific influences could be related to the activation of extended or subcortical sources that affect P300 neural generators in a diffuse fashion.

In contrast, more specific or phasic effects such as those observed for mental fatigue and caffeine (see Fig. 11) produce scalp topography profiles that may be reflecting comparatively direct activation of P300 neural generators related specifically to the alerting arousal system (Kahneman, 1973; Pineda et al., 1991; Pribram and McGuinness, 1975). These results illustrate an effect of biological state on P300 as suggested by pathway B. Note that in this case the hypothesized biological influence operates on psychological or cognitive determinants of P300 so that their ultimate effect is manifested in a relatively specific manner. Although these types of comparisons are not yet common in the ERP literature, their import is of considerable interest for both theoretical and empirical reasons (Johnson, 1993; Scherg and Picton, 1991).

Table 1
Summary of P300 amplitude and latency biological determinants

Factor	Amplitude	Latency	Comment
Natural			
Circadian	Indirect	Indirect	Time-of-day influences bodily functions that can affect P300 measures
Body temp.	No	Yes	Increased temperature, shorter P300 latency
Heart rate	No	Yes	Faster heart rate, shorter P300 latency
Food	Yes	No	Food intake increases P300 amplitude
Activity time	Yes	Some	Food interacts with activity preference time
Ultradian	Some	Yes	90 min cycle associated with cyclic P300 latency changes
Seasonal	Yes	No	Seasons with light, increases in P300 amplitude
Menstrual	No	No	Neutral stimuli, no effects; emotional stimuli, amplitude changes with cycle
Induced			
Exercise	Indirect	Direct	Affects overall arousal level; promotes pulmonary activity
Tonic	Yes	Yes	Increase amplitude, decrease latency
Chronic	No	Yes	Intervention: latency decreases, some variability across studies
Fatigue	Yes	Yes	Amplitude decreases, latency increases
Drugs (common)	Yes	Yes	Effects depend on specific drug, general arousal level, tonic/chronic use
Caffeine	Some	Yes	Amplitude increases if subject fatigued, latency generally decreases
Nicotine	Small	Yes	Amplitude effects weak, latency shortens after smoking tobacco
Alcohol			
Tonic	Yes	Yes	Amplitude decreases, latency increases
Chronic	No	No	Social drinking: no permanent long-term effects
Alcoholism risk	Yes	No	At risk/younger subjects have smaller amplitudes with difficult visual tasks

Unfortunately, the sources of these effects often are not readily apparent primarily because the neural origins of this ERP component are unknown. However, recent animal studies may shed some light on the the neural mechanisms that are involved in the modulation of P300 amplitude by arousal. These studies have demonstrated that higher cortical functions are affected by neurotransmitters with pronounced regional specialization. For example, some animal ERP studies have suggested that the noradrenergic locus coeruleus participates in arousal and alerting by sensitizing target neurons in the parietal cerebral cortex to enhance the matching of appropriate behaviors with unique, informative, or stressful stimuli (Pineda, Swick and Foote, 1991; Steriade and McCarley, 1990). Because these stimulus variables are similar to those involved in the elicitation of various manifestations of the P300 component (Courchesne et al., 1975; Johnson, 1988b; Polich, 1990; Ruchkin et al., 1990), it is not surprising that locus coeruleus lesions alter monkey P300-like ERPs (Neville and Foote, 1984). The animal studies also imply that the P300 is not reflecting undifferentiated arousal or neurotransmitter systems, but is associated with specific noradrenergic functions involved in the regulation of phasic input (Foote and Morrison, 1987). Thus, the locus coeruleus plays a crucial role in the generation of such potentials and may, therefore, contribute critically to the connection between the biological and psychological factors underlying the P300.

4.2. P300 and biological determinants: future studies

As the above theoretical speculations imply, the connection between the P300 component and its underlying neurophysiological mechanism(s) is not yet clear, so that a direct association between arousal and ERPs may be difficult to demonstrate because the former typically reflects tonic changes while the latter are phasic in origin. The present review has attempted to establish a basis for the relationship between arousal and P300 effects by illustrating how these psychophysiological phenomena may be manifested together in terms of natural and environmental variables. What is needed, however, are more systematic and direct manipulations of variables that affect each construct independently. In general, by observing how variation in arousal level produces differential effects on P300 measures, the pattern of interactions between task variables, state manipulations and scalp topography should reveal more about the underlying cause-and-effect relationships between arousal and ERPs such as those described above (e.g., Geisler and Polich, 1992b; Lorist et al., 1994a; Smulders, 1993). Similarly, more specific studies could be directed at assessing the various aspects of arousal by manipulating variables that directly affect its different components of 'alerting', 'activation', and 'effort' (Pribram and McGuiness, 1975; Tucker and Williamson, 1984). For example, task variables that facilitate stimulus input by virtue of their alerting qualities should demonstrate distinct patterns of P300 amplitude changes relative to those that contribute to response activation (Sanders, 1983). In addition, the role of 'effort' could be assessed by manipulating mental workload under conditions of relatively low and high general arousal, perhaps by using fatigue as a means to change biological state (Donchin et al., 1986; Kramer and Spinks, 1991). Approaches such as these would

provide a richer context that would help specify the more precise effects of 'arousal' on the P300 ERP.

Several arousal effects on P300 stem from natural causes. The sources of these influences often have been discovered serendipitously in studies designed to assess some other related biological variable. Given the seemingly consistent pattern of natural factors associated with variation in arousal level and their consequent effects on P300 measures, the search for additional biological determinants would seem to be a reasonable theoretical and empirical tactic to take. An example of this approach not reviewed above is to assess personality types that vary on an arousal-related dimension, such as high (trait) anxiety and introversion/extroversion. Individuals with an extreme extrovert personality — people who are thought to be cortically aroused by external stimuli (Eysenck, 1986) — yield larger P300 amplitudes than introverts under conditions that preclude component habituation (Cahill and Polich, 1992; Daruna, Karrer and Rosen, 1975; DiTraglia and Polich, 1991; Polich and Martin, 1992; Pritchard, 1989; for an extensive review, see Gales and Edward, 1986). In a related fashion, individual differences in activity time preferences also produce systematic differences in P300 measures when appropriate time-of-day and task variables have been assessed (Geisler and Polich, 1992; Kerkhof, 1982). Similarly, environmental factors that influence arousal can be used to delimit the degree of its effect on ERPs (e.g., drugs that manipulate heart rate, activity level, etc.). Assessment of these factors with respect to the different arousal components would help facilitate clarification of how arousal affects the P300 component.

4.3 Applied/clinical considerations

The practical implications of the findings outlined in Table 1 are summarized schematically in Fig. 14. Because ERP studies often use within-subject designs (top), most biologically based factors that affect the P300 component do not vary excessively within a 2- to 3-h testing session and their influence is usually assuaged by appropriate counterbalancing. However, when between-subjects designs are employed (middle), as often occurs in applied or clinical studies (patients vs. normals), biological factors become critical for reducing inter-group variability and the probability of hypothesis-testing error. In this case, individual P300 measures are assumed to be anchored around a mean that can be affected by variables that impact on CNS functions (e.g., state values independent of age, disease, etc.). Thus, ensuring that subjects are assessed similarly with respect to temporal variables (circadian, ultradian, seasonal, etc.) and measuring bodily functions (temperature, recency of food, fatigue, etc.) will help delimit extraneous variance and facilitate its control statistically.

Finally, the utility of using biological factors as independent variables should be mentioned (bottom), since this approach can reveal relationships of empirical and theoretical interest. Although not directly emphasized in the present review, the correlational associations between neuropsychological test performance and P300 latency mentioned above indicate that individual latency variability is related to behavioral measures of mental processing speed. This finding implies that stimulus

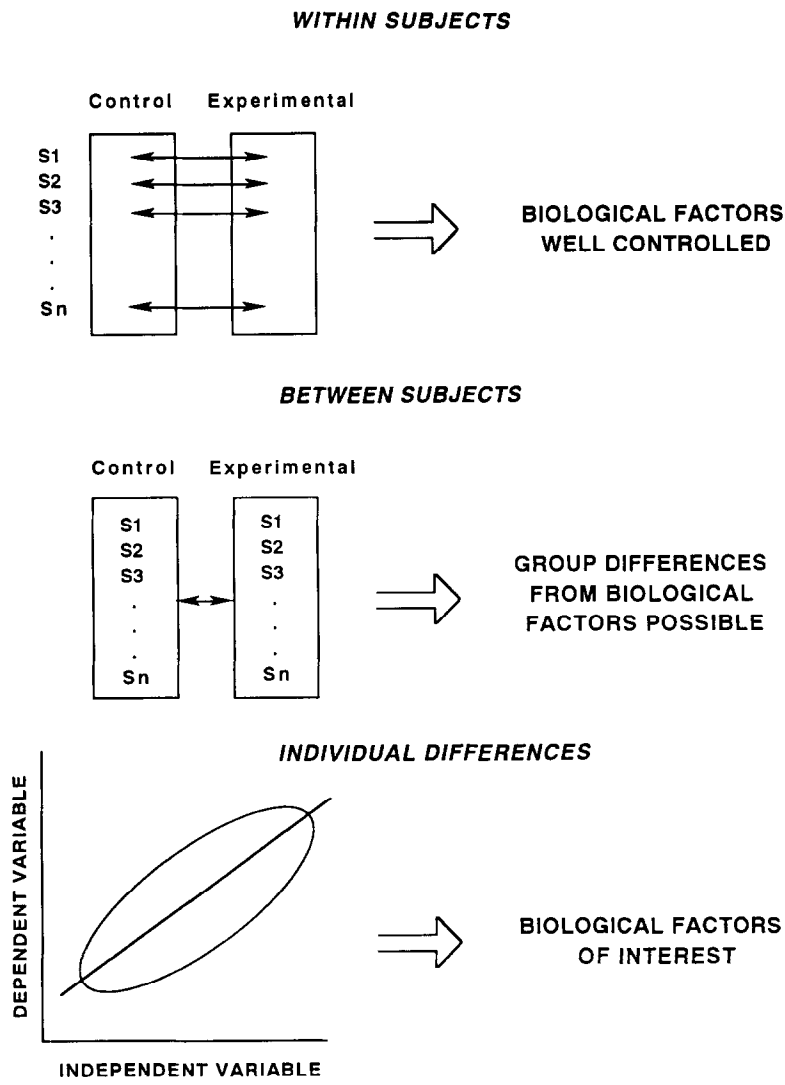

Fig. 14. Schematic representation of how biological determinants can contribute to experimental outcomes (see text for details).

classification time is affected by cognitive operations specific to perceptual and attentional processing capability rather than more general intellectual ability. By considering such neuropsychological differences as contributors to component variability and controlling or manipulating them, such biological factors could prove to be useful for investigating neuroelectric events that reflect cognitive information processing and contribute to P300 theoretical development (cf. Colet, Piera and

Pueyo, 1993; Eischen and Polich, 1994; Orlebeke, Kok and Zeillemaker, 1989; Pelosi, Holly, Slade, Hayward, Barrett and Blumhardt, 1992a,b; Polich and Burns, 1987; Polich and Martin, 1992; Rogers and Deary, 1991; Stelmack and Houlihan, 1994).

5. Conclusion

The P300 event-related brain potential is a complex phenomenon. In the past, most P300 studies have focused on the effects of alterations in task structure on component parameters and the underlying cognitive systems. In contrast, the present review has emphasized the important roles of natural and environmentally induced state variables in P300 research and the concept of arousal as a unifying theoretical mechanism. Although the causal connection between arousal and the P300 may be difficult to delineate directly, it is not unreasonable to conclude that arousal level does affect the P300 component in various task situations. Thus, the factors reviewed here in addition to others as yet undiscovered are necessary to consider if the puzzle that is the P300 will ever be solved.

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