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Review

P300 as a Measure of Cognitive Dysfunction from Occupational and Environmental Insults

Jing-Bo PAN, Tatsuya TAKESHITA and Kanehisa MORIMOTO

Department of Social and Environmental Medicine Osaka University Graduate School of Medicine, Osaka

Abstract

The P300 component of the event-related brain potential (ERP) is a sensitive, non-invasive, and convenient measure of cognitive dysfunction resulting from a variety of etiological agents. Application-orientated research on using the P300 measure as a cognitive probe for a wide range of neurological and psychiatric situations has been expanding rapidly in the last decade.

The aim of this paper is to preview issues of application-oriented P300 research in occupational and environment medicine. Firstly, the neurophysiological background of the P300 is outlined. Secondly, the recent findings of P300 abnormalities following various occupational and environmental exposures are overviewed. Thirdly, the empirical issues for application-oriented research such as the potential causes of variability, limitation and difficulty are summarized, with suggestion for controlling them and for future standardization. Finally, it is concluded that P300 assessments demonstrate promising possibility as a sensitive marker for general cognitive dysfunction in occupational and environmental medicine.

Key words: cognitive dysfunction, event-related potential (ERP), neurotoxicology, occupational and environmental exposure, P300

Neurophysiological Background

P300 and Oddball Paradigm

The P300 [or P3; with P denoting positive-going, and 300 denoting its modal latency or 3 denoting its ordinal sequence [1]] is a large event-related potential (ERP) component, with its peak over central-parietal scalp sites and latency ranging 280-600 ms, depending upon the task, stimulus modality and subject's age (Fig. 1). It is sometimes also referred to as the "late positive component" (LPC) [1,2]. It can be further divided into P3a (frontal P300) and P3b (parietal P300). In most application-orientated studies, however, the main interest concerns P3b that is generally termed P300 [3,4].

The P300 is one of the most extensively studied ERP components (Fig. 2), because it may reflect cognitive processes, such as orientation, attention, signal perception and memory [1,5-10]. It can be elicited by visual, auditory, somatosensory, or olfactory stimuli in a variety of experimental settings [5,6,8,11,12]. In the most widely used target detection (task) "oddball paradigm", the target stimulus occurs randomly and infrequently (e.g., 20%) among the frequently delivered (e.g., 80%) non-target stimulus (Fig. 3) [13-15]. The subject is instructed to detect the target and indicate the detection by way of "count" and "show" (i.e., "button-press" or "finger-tap" so that his behavioral performance can be measured simultaneously. The count response (condition)

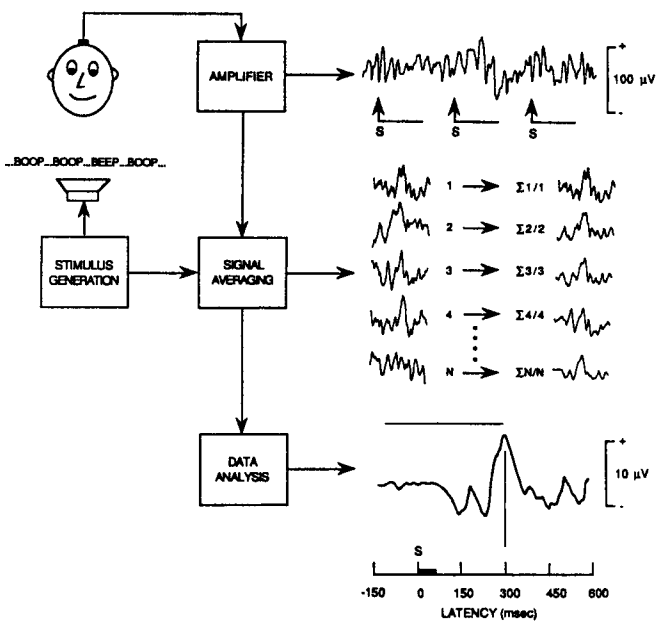

Fig. 1 The ERP recording system and flow charter of ERP signal-processing. It shows that the averaging process extracts ERP components from the background EEG signal ("S": stimulus-onset).

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Reprint requests to: Kanehisa MORIMOTO,
Department of Social and Environmental Medicine Osaka University Graduate School of Medicine 2-2 Yamada-Oka, Suita Osaka 565-0871, Japan
TEL: +81(6)6879-3920 FAX: +81(6)6879-3929
E-Mail: morimoto@envi.med.osaka-u.ac.jp

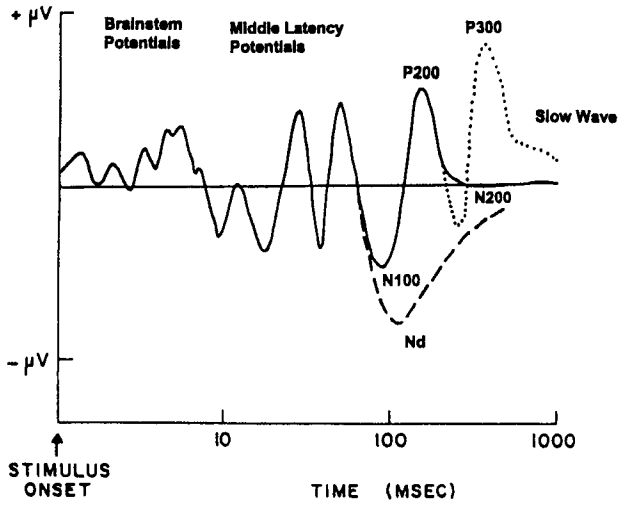

Fig. 2 Frequently recorded ERP components with their typical polarities, latencies, shapes and amplitudes (Reprinted with kind permission from J. Polich).

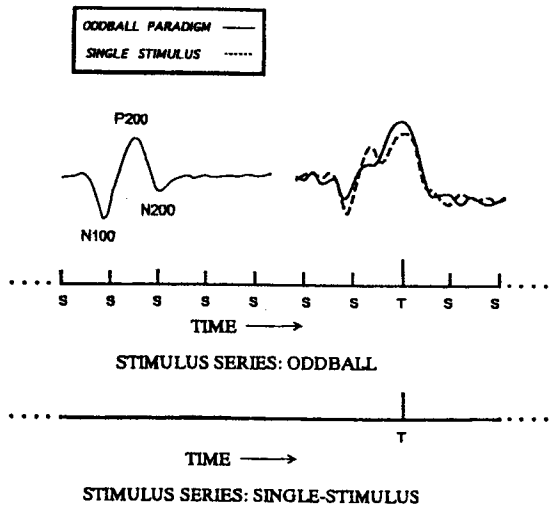

Fig. 3 Schematic of the oddball and single-stimulus paradigm ("T": target stimulus; "S": non-target stimulus). The ERP waves from the two paradigams are superimposed to indicate that they are similar (Reprinted with kind permission from J. Polich).

is sometimes too demanding to be followed by subjects especially those from patient populations because of the extra burden on calculation and memorization. The finger-tap is the easiest of the three, and an alternative for the clinical setting [14]. However, the P300 parameters and hence its sensitivity elicited by count response and show response may be different [16-18].

Neurophysiological Basis

The neurophysiological basis of the P300 is as yet unclear [9-11, 14, 19, 20] and a source of debate [21, 22] despite a large number of studies in normal, pathological human subjects [19, 23-27], as well as in surgical patients using implanted intracranial electrodes [28-30]. Furthermore, P300-like potentials have also been extensively studied in non-human mammal models such as rats, rabbits, cats, and monkeys [31-35]. Several candidate neurogenerators of P300, including the hippocampus, etc., have been proposed [19, 23, 28, 30]. Nevertheless, more recent approaches have suggested multiple generator sources of P300 elicitation [20, 24, 37-42]. These findings indicate that the P300 component of the ERP appears to reflect the activity of a widely distributed, complex neural network composed of many diverse cortical and subcortical structures, which are affected by the stimulus-event related attention and memory processing [20, 37-40]. Taken together, the recent multiple-neural-contribution proposition of the P300 generation implies that the P300 component is a result of the "net" effect of the cognitive process for the eliciting event. It may play a more fundamental role in cognition that is broad-based rather than reflecting just a single or specific cognitive function. This, therefore, seems to predispose the P300 as a probe of general cognitive disturbance. It also means that P300 measures can offer little help in locating the neurological damage.

P300 Associated Cognitive Processes

In general, voluntary detection of an infrequent, task-relevant stimulus elicits a P300 (P3b), which appears to index the attention and memory processes that are engaged in the task performance [14, 41]. The amplitude of P300 seems to reflect the allocation of attention resources (e.g., phasic attention and working memory) for a given task [14, 20, 41] and is associated with superior memory performance [20, 43]. P300 latency is thought to indicate the timing of perceptual processing [7, 11, 44], although some studies suggest that postperceptual effects were also involved [3]. Nevertheless, P300 latency from the averaging procedure reflects mainly premotoric or perceptual processing and is unaffected by motoric processes [45]. For instance, the P300 component is influenced by perceptual demands — a difficult discrimination task and/or longer categorization of the target will cause a delay in P300 latency [11, 44-46]. Thus, P300 measures can be used to index cognitive functioning that reflects the integrity of the brain and is especially sensitive to disorders that affect attention allocation and immediate memory [14].

In this context, the mainstream psychological/behavioral tests suffer from several drawbacks. They are subjective and culture-dependent since the scores are based directly upon the subjects' answers that are apt to be affected by factors such as motivation, test anxiety, etc. In contrast, the P300 component is objective, culture-free, and quantifiable. A subject's task performance can be evaluated objectively with the target stimulus hit-rate, so that both the tester and subject biases can be controlled more effectively [47-49]. Hence, P300 has inspired a wide range of research efforts to explore its utility as a cognitive probe of various central nervous system abnormalities. For example, P300 latency is negatively correlated with the cognitive mental capability affected or compromised by various physiological as well as etiological conditions [2, 50] — delayed P300 latency may reflect a cognitive slowing [51] and has been applied to study cognitive alterations related to aging [52], alcohol [53], smoking [54], Alzheimer's [55] and Parkinson's diseases [56], schizophrenia [57], and HIV-epidemiology [58], etc.

Taken together, the P300 offers many attractions as an objective maker of general cognitive alteration. It is certain that some cognitive processing in the brain has changed if there is a change in the P300 measures. However, it cannot be concluded that nothing has changed in the brain simply because we have failed to find a significant change in the P300 measures. Furthermore, caution must be taken to explain what exactly the

cognitive disturbance is and what location in the brain is involved, because the P300 cannot provide a precise description of what exactly is happening and where its main generator is located in the brain.

The diagnostic power of the P300 seems to lie in that it is a sensitive and objective marker (compared with psychological tests) and that its sensitivity in the time domain is better than other objective neuroimaging methods such as (f)MRI and PET.

300 Changes from Occupational and Environmental Exposure

Outlined in Table 1 are the recently available studies that show that changes in P300 could reflect the neurological and neurotoxicological impacts of various occupational and environmental exposures (chemical as well as physical etiologies). In some cases, the P300 changes have even been found in individuals who have been exposed only to below "safe" dosage levels, or before any pre-clinical manifestation could be observed. In other cases, it appeared to be able to reflect the detoxification procedures. These findings suggest that P300 may also be helpful in assessing the therapeutic effect as well as in defining "safe" exposure levels. Each of the major categories are previewed and critiqued below.

Table 1 Reported P300 changes from occupational & environmental exposure.

STUDY	INSULTS	LATENCY	AMPLITUDE
CHEMICAL			
Lindgren et al. (1997)	Organic Solvents		+[a]
Steinhauer et al. (1997)		+	-
Morrow et al. (1996)		+	+
Kumar et al. (1996)		+	-
Morrow et al. (1992)		+	-
Chen et al. (1994)	Polychlorinated Biphenyls (PCBs)	+	+
Murata et al. (1997)	Organophosphate Compounds (OPs)	+	-
Estrin et al. (1990)	Ethylene Oxide (EtO)	-	+
Wasch et al. (1989)	Hydrogen Sulfide (H_2S)	+	-
Fowler et al. (1993)	Nitrous Oxide (N_2O)	+	-,+[b]
Fowler et al. (1993)		+	-
Fowler et al. (1990)		+	-
Fowler et al. (1988)		+	+[c]
Estrin et al. (1988)		+	+
Solliway et al. (1995)	Lead (Pb)	+	+
Solliway et al. (1994)		+	+
Murata et al. (1993)		+	-
Araki et al. (1992)		+	-
Wennberg et al. (1992)	Manganese (Mn)	+	-
PHYSICAL			
Hirata et al. (1995)	Vibration	+	-
Wada et al. (1991)	Hyperbarism	+	-
Værnes et al. (1989)		+	-
Fowler et al. (1992)	Hypoxia	+	-
Fowler et al. (1992)		+	+-[d]
Fowler et al. (1988)		+	-
Danos et al. (1994)	Sleep deprivation	+	+
Morris et al. (1992)		+	+
Fowler et al. (1994)	Workload	+	-
Kramer et al. (1987)		-	+

+: significant change (latency prolonged, or amplitude decreased)
-: no significant change found
[a]: from patients of solvent-induced toxic encephalopathy
[b]: "-" from visual oddball, but "+" from auditory oddball
[c]: only up to 25% N_2O, not for >25%-35% N_2O
[d]: marginal decrease

Chemical Etiology

Organic solvents

Male patients of chronic solvent-toxic-encephalopathy (with at least 5 years of daily exposure to a mixture of fat-soluble substances such as white spirits, thinners and degreasers) showed markedly smaller P300 amplitudes, and lower signal detection performance in the relatively complex dual-task settings [59].

Research on aliphatic-and-aromatic-organic-solvent-toxic-encephalopathy revealed delayed P300 latencies and decreased P300 amplitudes [60]. These longer P300 latencies were positively associated with poorer cognitive performance [the Pittsburgh Occupational Exposures Test (POET) battery]. The attentional factor on the counting task alone ($F=11.9$, $P=0.002$), or lower intelligence scores on choice reaction task alone ($F=15.4$, $P=0.0005$) accounted for 30% of the latency variance]. The reduced P300 amplitudes were strongly associated with higher levels of psychiatric symptomatology [Global Severity Index accounted for 24% ($F=8.9$, $P=0.006$) or 35% ($F=15.1$, $P=0.0006$) of the amplitude variance on the counting or the choice reaction time task, respectively]. It was also associated with a slower reaction time [17% ($F=8.2$, $P=0.007$) or 16% ($F=8.7$, $P=0.006$) of the variance on the counting or the choice reaction task, respectively]. In an earlier report [61], the same group found significantly delayed P300 latencies and significant correlation between these latencies and the length of exposure [correlation coefficient is 0.80 for the counting task and 0.64 for the choice reaction task, respectively; $P<0.05$]. In addition, that the duration of exposure accounted for 64% of the variance on P300 delay implies that P300 prolongation is associated with increased exposure.

Research on paint-and-solvent exposed journeymen painters has found significantly delayed P300 latencies only from recently (within 1-66 hours) exposed painters and not from those who were free from exposure at least 4 days. Therefore, the authors mentioned the possibility that the delayed P300 latencies in younger workers was reversible and might return to normal range simply after cessation of exposure [62].

P300 latency prolongation has also been reported among rubber factory workers exposed to vapors of multiple organic solvents [63]. Taken together, these results imply that P300 measures may be a useful assessment of CNS integrity following neurotoxic exposure.

Polychlorinated biphenyls (PCBs)

Children of PCBs-victim mothers showed apparently prolonged P300 latencies, and significantly reduced P300 amplitudes [64]. Further, the delayed latencies were inversely related to their low full-scale intelligence quotient (FIQ) from Wechsler Intelligence Scale for Children-Revised Test (correlation coefficient: $r=-0.6$, $P=0.003$ at Cz; and $r=-0.5$, $P=0.005$ at Pz). These reflect the long-term neurotoxic effects of PCBs on the cognitive function of prenatal-exposed children, and demonstrated the potential of P300 in detecting such kind of subtle cognitive deficits.

Organophosphate compounds (OPs)

Exposure to OP components such as nerve gas and pesticides will result in anxiety, abnormal EEGs, and cognitive disruptions [65-68]. Significantly prolonged P300 latencies have been found on the victims of the Tokyo Subway Sarin Attack even 6-8 months later, which indicates that sarin exposure produced a longer, persistent neurotoxic effect even after the recovery of brain cholinesterase (ChE) activity and the disappearance of all obvious clinical abnormalities [69]. P300 latency also has been prolonged among workers engaged in spraying fenthion pesticide, together with significant changes in cognitive functions (Benton Visual Retention Test, and Alexander Passalong Test) and significantly lowered serum ChE level [70]. Thus, P300 latency may indicate both acute brain-toxic deficits and asymptomatic sequelae of OPs exposure.

Ethylene oxide (EtO)

Chronic, low-level EtO exposed hospital workers demonstrated significantly low P300 amplitude, although their P300 latency delays were not statistically reliable [71].

Hydrogen sulfide (H_2S)

Abnormally prolonged P300 latency combined with neuropsychological testing has suggested persistent cognitive impairment caused by incidental-and-discrete cases of acute H_2S exposure [72].

Nitrous oxide (N_2O)

Research on sub-anaesthetic doses of N_2O has shown that P300 measures, especially delayed P300 latency, may sensitively index the transient, dose-dependent cognitive disturbance produced by N_2O narcosis [73-77]. These prolonged latencies were strongly related to the increased reaction time (RT) (correlation coefficient ranged from 0.49 to 0.73 in reference 74, and from 0.60 to 0.82 in reference [75].

Heavy metals

P300 latencies from lead-zinc-copper-exposed gun metal factory workers [78, 79], and low-level-lead-exposed battery factory workers [80, 81] were significantly prolonged. The prolongation positively correlated with their blood lead (correlation coefficient: $r=0.447$, $P<0.05$ in reference 78 and 79, or $r=0.40$ $P<0.002$ in reference 80 and 81), urinary lead ($r=0.507$, $P<0.05$ in reference 78 and 79), urinary δ -aminolevulinic acid ($r=0.34$, $P<0.001$ in reference 80 and 81), and working years ($r=0.492$, $P<0.05$ in reference 79).

The findings of prolonged P300 latency from low-level manganese exposed steel smelting workers has been taken to mean that P300 may reveal early and subclinical cerebral dysfunction as a "serious sign of low-level but unacceptable occupational manganese exposure" [82].

Physiological Etiology

Vibration

Significantly delayed P300 latencies were observed in vibration-exposed ex-workers with severe cognitive (mainly memory and judgment) dysfunction. The latencies were negatively related to the duration of abstaining from the exposure [$r=-0.455$ (age-adjusted), $P<0.01$ at Cz and $r=-0.382$ (age-adjusted), $P<0.05$ at Pz]. These findings implied that vibration affects cognitive process and P300 latency [83]. It seems unlikely that the delay was directly caused by aging, smoking and drinking alcohol, since these factors were evenly met in controls. Nevertheless, it is still unknown whether such factors as exposure to noise, dust and workload have contributed to the P300 prolongation because they were not evenly met although the pertinent subjects might be unavailable. Studies on currently vibration-exposed workers may help to further clarify whether vibration is the main cause of the cognitive delay indicted by the prolonged P300.

Hyperbarism (chamber diving)

Hyperbaric helium-oxygen chamber saturation diving corresponding to 70 — 180 [84], and 354 [85] meter below sea surface level or meters of seawater (msw), could cause a clearly prolonged P300 latency on professional divers. When the depth reached 360 msw, P300 could not be recorded. These results suggest that P300 may be useful for detecting early cognitive alteration and early signs of high-pressure nervous syndrome (HPNS).

Hypoxia

Increased visual response time (RT) is believed to be one of the predominant features of hypoxia. Hypoxia delayed either visual or auditory P300 latency and RT [86-88]. Compared with response time, P300 latency is non-intrusive and less sensitive to response-related variability. So it is potentially a more stable and sensitive measure of hypoxia-induced cognitive impairment.

Sleep deprivation

The fact that a night of sleep deprivation has caused significantly decreased P300 amplitude and increased P300 latency [89, 90] suggests that P300 is a more sensitive cognitive measure of sleep deprivation than the routinely used behavior measure — response time (RT). One possible explanation lies in that RT is to a greater extent composed of the time for making a "physical action". Therefore, the determinant portion of RT is much slower, and longer than the duration for just a mental process (i.e., the P300 latency). Thus, any changes reflecting only early or slight abnormalities in the domain of time will be "buried" in the RT and invisible.

Workload

The workload effect on P300 has been studied under different complex dual-task paradigms. In a simulated flight mission (main) task that changed the wind-speed and the direction as the workload-manipulation, the amplitude of the P300 (elicited by using auditory oddball as a secondary task) decreased monotonically with the increase of the workload [91]. In a simulated aircraft-landing task that changed the turbulence and hypoxia as workload manipulation, visual and auditory P300 latencies increased clearly and systematically with the increase of workload and the decrease of performance [92]. The complex resource-competition between the main task and the second task has made the explanation difficult, because (as described earlier) the P300 component seems to reflect the "net effect" of cognitive activity. Therefore, the P300 amplitude decrease means that the workload-manipulation of the first study primarily produced a net decline in the attention resource allocation, while the delayed P300 latency of the second study reflected a major slowdown in perceptual capability. Taken together, the obvious discrepancy in the processing demands of the main tasks and the resulted resource-competition between the main and the secondary task resulted in different P300 alteration. It suggested that P300

measures are selectively sensitive to the task-relevant attributes of the workload.

Empirical Considerations in P300 Application

Except for etiological insults, empirical observation and research have revealed that many biological/physiological factors such as age, body-temperature and food-take (Tab. 2 of reference 14) and technical parameters such as stimulus intensity, inter-stimulus-interval (ISI) and target deliver probability may also potentially cause variations in the P300 measurement [14, 93, 94]. (For a comprehensive review of these factors, please see reference 14 and 93.) It is, therefore, essential to base the diagnostic utility of P300 measurements on an empirically demonstrated basis and combine P300 measures with other pathological evidence such as the history of exposure to improve its diagnostic specificity.

The utility of P300 can also be enhanced by taking measures to minimize the effects of biological/physiological factors [14, 93]. For example, three kinds of measures are proposed to reduce biological-factor-induced inter-group variability and hypothesis-test error: (a) controlling circadian, ultradian and seasonal differences by measuring body-temperature, recency of food-intake, and fatigue, etc.; (b) matching aging, gender, and handedness, etc.; (c) taking biological factors as independent variables in data analysis. Table 2 presents some recommended technical parameters for recording oddball P300 [14]. They may offer help to control the technical variability in P300 recording.

Another major obstacle of P300 application is the insufficient standardization of the P300 recording. This problem is complicated by suggestions that the sensitivity of the P300 elicited by different paradigms and response conditions are different [16-18]. These findings provided further evidences to support use more than one paradigm and/or response to the same pathological population so as to improve the sensitivity of the P300 and to reveal abnormalities as much as possible. This, therefore, imposes an extra burden on the proposed standardization since it means that more than one paradigm and/or response should be standardized in order to meet the future requirements on differential diagnosis. On the other hand, the P300 application would also benefit from the rich diagnostic capacity reserved in its eliciting paradigms and/or responses. Although an unclear neurophysiological basis of the P300 means that it can hardly offer much help now, it will not prevent the proposed standardization from progressing along an empirical-oriented or parametric path like that of the electroencephalography (EEG). Therefore, the standardization would benefit greatly if future application-oriented studies could make major progress in characterizing the P300 changes resulted from various etiological and biological factors under different eliciting conditions. In this respect, there is still a long way to accomplish.

Table 2 Recommended parameters for auditory and visual clinical P300 paradigms [Reprinted from J. Polich[14] 1998, with kind permission from Lippincott-Ravan Publishers, 12107 Insurance Way, Hagerstown, MD 21740, USA].

Parameter	Comment	
Stimulus factors	Auditory	Visual
Target	1,000Hz	X
Standard	2,000Hz	O
Duration	10-ms rise/fall time, 50-ms plateau	100ms
Intensity	70-dB nHL	Moderate
Interstimulus Interval	2-3s	2-3s
Subject and task		
Seated position	Lying down is acceptable if necessary	
Eyes open	Eyes closed acceptable if subject makes too many movements	
Finger-tap/button-press task	Avoide count task because it is too difficult	
Target probability at 0.20	Probability at 0.10 is acceptable but time-consuming	
Electrophysiological recording		
Electrodes Fz, Cz, Pz, EOG	Midline recordings a minimal configuration	
Reference A1/A2	Nosetip is acceptable	
Ground forehead	Fp1 or Fp2 can also be used	
Bandpass 0.01-30Hz	High pass of 0.1-0.5Hz acceptable; the lower the better	
Epoch length 800-1000ms	Length may be longer for other ERPs (e.g., CNV)	
Artifact rejection ± 100 μV	50 μV more conservative	
20 + correct target trials	25 + in average best	
Replication of two blocks	Facilitates component identification	

EOG, elecrooculogram; ERP, event-related potential; CNV, contingent negative variation.

The recent report of a "good to excellent inter-laboratory P300 measures consistency" across many differently distributed laboratories brought us one step further towards the standardization of P300 testing [95, 96]. It provides us with quantitative evidence for the promotion of this method since it had demonstrated that P300 was reliable and replicable. It also laid the foundation for future large-scale cross-laboratory studies in order to establish a numerical diagnostic calibration based upon a sufficiently large sample of scores from various populations.

One more potential problem with P300 application comes from the report of failure in recording recognizable P300 from some clinical populations [94], partly because the eliciting paradigm and/or task is too demanding for their compromised cognitive capabilities. When the easiest finger-raising task is still too demanding for them, alternative paradigms could provide a choice. It is demonstrated recently that both active and passive "single-stimulus" paradigms may yield comparable P300 measures to that from a typical oddball paradigm [97-100]. In these paradigms, only the target stimuli are presented. The frequent standard stimuli are omitted or replaced with either "silence" in auditory modality or "blank screen" in visual modality (Fig. 3). Hence, the mental demands on the subject and the relevant technical requirements are minimized. Such methodologies may offer alternatives in assessing the cognitively impaired, young children, elderly patients, and the uncooperative. Nevertheless, caution should be taken in explaining the date since the sensitivity of these tests may be different from that of typical oddball paradigm. Further studies are needed.

Conclusion

Observations and interest in using the P300 component to assess cognitive dysfunction from occupational and environmental insults have increased substantially in the last decade. The available data have shown that prolonged latency and/or decreased amplitude of P300 may sensitively reflect the cognitive disturbances caused by various occupational and environmental-related neurological and neurotoxicological agents. More importantly, the P300 component may be sensitive to profile the "dynamic course" of the exposure as well as the detoxification process.

Taken together, the currently rapid expending of application-oriented P300 research has benefited considerably from the sophistication of P300 techniques, including the

improved control of previously ignored variability. The P300 may become a subclinical marker of general cognitive disturbance in occupational and environmental medicine if its measures can be further characterized and standardized by studies. At the present stage, it can be used as an objective indicator of general cognitive alternations by associating with standard neuropsychological tests and other pathological evidence such as history of exposure.

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References

1) Hillyard SA, Kutas M. Electrophysiology of cognitive processing. Ann Rev Psychol 1983; 34: 33-61.
2) Goodin DS, Squires KC, Starr A. Long latency event-related components of the auditory evoked potential in dementia. Brain 1978; 101: 635-48.
3) Verleger R. On the utility of P3 latency as an index of mental chronometry. Psychophysiol 1997; 34: 131-56.
4) Verbaten MN, Huyben MA, Kemner C. Processing capacity and frontal P3. Int J Psychophysiol 1997; 25: 237-48.
5) Sutton S, Tueting P, Zubin J, John ER. Information delivery and the sensory evoked potential. Science 1967; 55: 1436-9.
6) Chapman RM, Bragdom HR. Evoked responses to numerical and non-numerical visual stimuli while problem solving. Nature 1964; 203: 1155-7.
7) Kutas M, McCarth G, Dunchin E. Augmental mental chronometry: The P300 as a measure of stimulus evaluation time. Science 1977; 197: 792-5.
8) McCarthy G, Dunchin E. A metric for thought: a comparison of P300 latency and reaction time. Science 1981; 211: 77-9.
9) Kutas M. Prophecies come true: What's new in event-related brain potentials (ERP) research since 1984. In: Barber C, et al (eds) Evoked potentials review No. 4. Nortingham: IEPS publications, 1991: 73-91.
10) Mangun GR, Hillyard SA. Mechanisms and models of selective attention. In: Rugg MD & Coles MGH, (eds) Electrophysiology of mind: event-related brain potentials and cognition. Oxford: Oxford University Press, 1995: 40-85.
11) Coles MGH, Smid HGOM, Scheffers MK, Otten LJ. Mental chronometry and the study of human information processing. In: Rugg MD & Coles MGH (eds) Electrophysiology of mind: event-related brain potentials and cognition. Oxford: Oxford University Press, 1995: 86-131.
12) Hillyard SA, Squires KC, Bauer JW, Lindsay PH. Evoked potential correlates of auditory signal detection. Science 1971; 172: 1357-60.
13) Polich J. P300, probability, and inter-stimulus interval. Psychophysiol 1990; 27: 396-403.
14) Polich J. P300 clinical utility and control of variability. J Clin Neurophysiol 1998; 15: 12-33.
15) Verleger R, Berg P. The waltzing oddball. Psychophysiol 1991; 28: 468-77.
16) Mertens R, Polich J. P300 from a single-stimulus paradigm: passive vs. active tasks and stimulus modality. Electroenceph Clin Neurophysiol 1997; 104: 488-97.
17) Polich J. Resoponse mode and P300 from auditory stimuli. Biol Psychol 1987; 25: 61-71.
18) Filipovic SR, Kostic VS. Utility of auditory P300 in detection of presenile dementia. J Neurol Sci 1995; 131: 150-5.
19) Picton TW. The P300 wave of the human event-related potential. J Cognit Neurophysiol 1992; 9: 456-79.
20) Johnson RJr. Event-related potential insights into the neurobiology of memory systems. In: Boller F, et al (eds) Handbook of neuropsychology, Vol. 10. Amsterdam: Elsevier, 1995: 135-63.
21) Verleger R. Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of P300. Behav Brain Sci 1988; 11: 343-427.
22) Donchin E, Coles MGH. Precommentary: is the P300 component a manifestation of context updating? Behav Brain Sci 1988; 11: 355-425.
23) Johnson RJr. Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. Brain 1988; 111: 1517-29.
24) Johnson RJr. Auditory and visual P300 s in temporal lobectomy patients: evidence for modality-dependent generators. Psychol 1989; 26: 633-50.
25) Onofrj M, Fulgente T, Nobiolio D, et al. P300 recordings in patients with bilateral temporal lobe lesions. Neurol 1992; 42; 1762-7.
26) Polich J, Squire L. P300 from amnesic patients with bilateral hippocampal lesions. Electroenceph Clin Neurophysiol 1993; 86: 408-17.
27) Verleger R, Heide W, Butt C, Kompf D. Reduction of P3b in Patients with temporo-parietal lesions. Cogn Brain Res 1994; 2: 103-16.
28) Halgren E, Baudena P, Clarke JM, et al. Intracerebral potentials to rare target and distractor auditory and visual stimuli: I. Superior temporal plane and parietal lobe. Electroenceph Clin Neurophysiol 1995; 94: 191-220.
29) Halgren E, Baudena P, Clarke JM, et al. Intracerebral potentials to rare target and distractor auditory and visual stimuli: II. Medial, lateral and posterior temporal lobe. Electroenceph Clin Neurophysiol 1995; 94: 229-50.
30) Kiss I, Dashieff RM, Lordeon P. A parieto-occipital generator for P300:) evidence from human intracranial recordings. Int J Neurosci 1989; 49: 133-9.
31) Paller KA, McCarthy G, Rossler E, Allison T, Wood CC. Potentials evoked in human and monkey medial temporal lobe during auditory and visual oddball paradigms. Electroenceph Clin Neurophysiol 1992; 84: 269-79.
32) Pineda JA, Westerfield M, Kronenberg BM, Kubrin J.

Human and monkey P3-like responses in a mixed modality paradigm: effects of context and context-dependent noradrenergic influences. Int J Psychophysiol 1997; 27: 223-40.
33) Shinba T. Event-related potentials of the rat during active and passive auditory oddball paradigms. Electroenceph Clin Neurophysiol 1997; 104: 447-52.
34) Wang Y, Nakashima K, Shiraishi Y, Kawai Y, Ohama E, Takahashi K. P300-like potential disappears in rabbits with lesions in the nucleus basalis of Meynert. Exp Brain Res. 1997; 114: 288-92.
35) Wilder MB, Farley GR, Starr A. Endogenous late positive component of the evoked potentials in cats corresponding to P300 in humans. Science 1981; 211: 605-7.
36) Halgren E, Squires NK, Wilson C, Rohrbaugh J, Babb T, Crandall P. Endogenous potentials in the human hippocampal formation and amygdala by infrequent events. Science 1980; 211: 803-5.
37) Ruchkin DS, Johnson RJr, Canoune HL, Ritter W, Hammer M. Multiple sources of P3b associated with different types of information. Psychol 1990; 27: 157-76.
38) Johnson RJr. On the neural generators of the P300 component of the event-related potential. Psychophysiol 1993; 30: 90-7.
39) Goodin DS. Cognitive event-related potentials. J Clin Neurophysiol 1998; 15: 2.
40) Knight RT. Distributed cortical network for visual stimulus detection. J Cogn Neurosci 1997; 9: 75-91.
41) Knight RT, Scabini D. Anatomic bases of event-related potentials and their relationship to novelty detection in humans. J Clin Neurophysiol 1998; 15: 3-13.
42) Knight RT. Contribution of human hippocampal region to novelty detection. Nature 1996; 383: 256-9.
43) Fabiani M, Karis D, Dunchin E. Effects of mnemonic strategy manipulation in a Von Restorff paradigm. Electroenceph Clin Neurophysiol 1990; 75: 22-35.
44) Leuthold H, Sommer W. Postperceptual effects and P300 latency. Psychophysiol 1997; 35: 34-45.
45) Smulders FTY, Kok A, Kenemans JL, Bashore TR. The temporal selectivity of additive factor effects on the reaction process revealed in erp component latencies. Acta Psychol 1995; 90: 97-109.
46) Kok A. Event-related-potential (ERP) reflections of mental resources: a review and synthesis. Biol Psychol 1997; 45: 19-56.
47) Harbin TJ. The late positive component of the evoked cortical potential: application to neurotoxicity testing. Neurobehav Toxicol Teratol 1985; 7: 339-44.
48) Rebert CS. Multisensory evoked potentials in experimental and applied neurotoxicology. Neurobav Toxicol Teratol 1983; 5: 659-71.
49) Rebert CS, Andreassi JL. Editorial comment: evoked potentials in neurotoxicology. Int J Psychophysiol 1993; 14: 1-3.
50) Goodin DS, Aminoff MJ. Evaluation of dementia by event-related potentials. J Clin Neurophysiol 1992; 9: 521-5.
51) Polich J, Ehlers CL, Otis S, Mandell AJ, Bloom FE. P300 latency reflects the degree of cognitive decline in dementing illness. Electroenceph Clin Neurophysiol 1986; 63: 138-44.
52) Polich J. EEG and ERPs in normal aging. Electroenceph Clin Neurophysiol 1997; 104: 228-43.
53) Polich J, Burns T, Bloom FE. P300 and the risk for alcoholism: family history, task difficulty, and gender. Alcohol Clin Exp Res 1988); 12: 248-54.
54) Ewards JA, Wesnes K Warburton DM, Gale A. Evidence of more rapid stimulus evaluation following cigarette smoking. Addict Behav 1985; 10: 113-26.
55) Polich J, Ladish C, Bloom FE. P300 assessment of early Alzheimer's disease. Electroenceph Clin Neurophysiol 1990; 77: 179-89.
56) Aotsuka A, Weate SJ, Drake ME, Paulson GW. Event-related potentials in Parkinson's disease. Electromyogr Clin Neurophysiol 1997; 36: 215-20.
57) Boutros N, Nasrallah H, Leighty R, Torello M, Tueting P, Olson S. Auditory evoked potential, clinical vs. research applications. Psychiatry Res 1997; 69: 183-95.
58) Ollo C, Johnson RJr, Grafman J. Signs of cognitive change in HIV disease: an event-related brain potential study. Neurol 1991; 41: 209-15.
59) Lindgren M, Osterberg K, Orbaek P, Rosen I. Solvent-induced toxic encephalopathy: electrophysiological data in relation to neuropsychological findings. J Clin Neuropsychol 1997; 19: 772-83.
60) Morrow LA, Steinhauer SR, Condray R. Differential associations of P300 amplitude and latency with cognitive and psychiatric function in solvent-exposed adults. J Neuropsychiatry 1996; 4: 446-9.
61) Morrow LA, Steinhauer SR, Hodgson MJ. Delay in P300 latency in patients with organic solvent exposure. Arch Neurol 1992; 49: 315-20.
62) Steinhauer SR, Morrow LA, Condray R, Dougherty GG Jr. Event-related potentials in workers with ongoing occupational exposure. Biol Psychiatry 1997; 42: 854-8.
63) Kumar V, Tandon OP. Auditory event-related potentials (P300) in rubber factory workers-a preliminary study. Indian J Physiol Pharmacol 1996; 40: 274-6.
64) Chen YJ, Hsu CC. Effects of prenatal exposure to PCBs on the neurological function of children: a neuropsychological and neurophysiological study. Develop Med Child Neurol 1994; 36: 312-20.
65) Burchfiel JL, Duffy FH, Sim VM. Persistent effects of sarin and dieldrin upon the primate electroencephalogram. Toxicol Appl Pharmacol 1976; 35: 363-79.
66) Davies JE. Neurotoxic concerns of human pesticide exposures. Am J Ind Med 1990; 18: 327-31.
67) Duffy FH, Burchfiel JL, Bartels PH, Gaon M, Sim VM. Long-term effects of an organophosphate upon the human electroencephalogram. Toxicol Appl Pharmacol 1979; 47: 161-76.
68) Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypoole K. the Pesticide Health Effects Study Group. Chronic central nervous system effects of acute organophosphate pesticide intoxication. Lancet 1991; 338: 223-37.
69) Murata K, Araki S, Yokayama K, et al. Asymptomatic sequelae to acute sarin poisoning in the central and autonomic nervous system 6 months after the Tokyo subway attack. J Neurol 1997; 244: 601-6.
70) Misra UK, Prasad M, Pandey CM. A study of cognitive functions and event-related potentials following organophosphate exposure. Electromyogr Clin Neurophysiol 1994; 34: 197-203.

71) Estrin WJ, Bowler RM, Lash A, Becker CE. Neurotoxicological evaluation of hospital sterilizer workers exposed to ethylene oxide. J Toxi Clin Toxicol 1990; 28: 1-20.
72) Wasch HH, Estrin WJ, Yip P, Bowler R, Cone JE. Prolongation of the P300 latency associated with hydrogen sulfide exposure. Arch Neurol 1989; 46: 902-4.
73) Estrin WJ, Moore P, Letz R, Wasch HH. The P-300 event-related potential in experimental nitrous oxide exposure. Clin Pharmacol Ther 1988; 43: 86-90.
74) Fowler B, Kelso B, Landolt J, Porlier G. The effects of nitrous oxide on P300 and reaction time. Electroenceph Clin Neurophysiol 1988; 69: 171-8.
75) Fowler B, Pogue J, porlier G. P300 latency indexes nitrogen narcosis. Electroenceph Clin Neurophysiol 1990; 75: 221-9.
76) Fowler B, Adams J. Dissociation of the effects of alcohol and amphetamine on inert gas narcosis using reaction time and P300 latency. Aviat Space Environ Med 1993; 62: 493-9.
77) Fowler B, Hamel R, Lindeis AE. Relationship between the event-related brain potential P300 and inert gas narcosis. Undersea Hyperb Med 1993; l20: 49-61
78) Araki S, Murata K, Yokoyama K, Uchida E. Auditory event-related potential (P300) in relation to peripheral nerve conduction in workers exposed to lead, zinc, and copper: effects of lead on cognitive function and central nervous system. Am J Ind Med 1992; 21: 539-47.
79) Murata K, Araki S, Yokoyama K, Uchidqa E, Fujimura Y. Assessment of central, peripheral, and autonomic nervous system functions in lead workers: neuroelectrophysiological studies. Environ Res 1993; 61: 323-36.
80) Solliway BM, Schaffer A, Pratt H, Yannai S. A multidisciplinary study of lead-exposures subjects. Environ Res 1994; 67: 168-82.
81) Solliway BM, Schaffer A, Erez, Mittelman, Pratt H, Yannai S. The effect of lead exposure on target detection and memory scanning differs. J Neurol Sci 1995; 134: 171-7.
82) Wennberg A, Hagman M, Johansson L. Preclinical neurophysiological signs of Parkinsonism in occupational manganese exposure. Neuro Toxicol 1992; 13: 271-4.
83) Hirata M, Matsumoto T, Toibana N, Hashiguchi T, Harada N, Yamada S. Involvement of the central nervous system in vibration syndrome. Int Arch Occup Environ Health 1995; 67: 173-8.
84) Wada SI, Urasaki E, Kadoya C, Matsuoka S, Mohri M. Effects of Hyperbaric environment on the P300 component of event-related potentials. J UOEH 1991; 13: 143-8.
85) Værnes R, Hammerborg D. Evoked potential and other CNS reactions during a heliox dive to 360 msw. Aviat Space Environ Med 1989; 60: 550-7.
86) Fowler B, Kelso B, Landolt JP, Porlier G. The effects of hypoxia on P300 and reaction time. In: Electric and magnetic activity of the central nervous system: research and clinical applications in aerospace medicine. AGARD Conference Proceedings No.432. Neuilly Sur Seine, France: AGARD, 1988: 16-7.
87) Fowler B, Kelso B. The effects of hypoxia on components of the human event-related potential and relationship to reaction time. Aviat Space Environ Med 1993; 63: 510-6.
88) Fowler B, Lindeis AE. The effect of hypoxia on auditory reaction time and P300 latency. Aviat Space Environ Med 1992; 63: 976-81.
89) Danos P, Kasper S, Scholl HP, et al (1994) Clinical response to sleep deprivation and auditory-evoked potentials-preliminary results. Pharmacopsychiatry 27: 70-1.
90) Morris AM, So Y, Lee KA, Lash AA, Becker CE (1992) The P300 event-related potential: the effects of sleep deprivation. J Occup Med 34: 1143-52.
91) Kramer AF, Sirevaag E, Braune R. A psychophysiological assessment of operator workload during simulated flight missions. Human Factors 1987; 29: 145-60.
92) Fowler B. P300 as a measure of workload during a simulated aircraft landing task. Human Factors 1994; 36: 670-83.
93) Polich J, Kok A. Cognitive and biological determinants of P300: an integrative review. Biol Psychol 1995; 41: 103-46.
94) Goodin DS. Clinical utility of long latency 'cognitive' event-related potentials (P3): the pros. Electroenceph Clin Neurophysiol 1990; 76: 2-5.
95) Alexander JE, Polich J, Bloom FE, et al. P300 from an auditory oddball task: inter-laboratory consistency. Int J Psychophysiol 1994; 17: 35-46.
96) Cohen HL, Wang W, Porjesz B, et al. Visual P300: an interlaboratory consistency study. Alcohol 1994; 11: 583-7.
97) Cass M, Polich J. P300 from a single-stimulus paradigm: intensity and tone frequency effects. Biol Psychol 1997; 46: 51-65.
98) Polich J, Eischen SE, Collins GE. P300 from a single auditory stimulus. Electroenceph Clin Neurophysiol 1994; 92: 253-61.
99) Polich J, Heine MRD. P300 topography and modality effects from a single-stimulus paradigm. Psychophysiol 1996; 33: 747-52.
100) Polich J, Margala C. P300 and probability: comparison of oddball and single-stimulus paradigms. Int J Psychophysiol 1997; 25: 169-76.