Neuropsychology and neuropharmacology of P3a and P3b

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Received 10 December 2005; received in revised form 23 December 2005; accepted 23 December 2005

Available online 28 February 2006

Abstract

Perspectives on the P300 event-related brain potential (ERP) are reviewed by outlining the distinction between the P3a and P3b subcomponents. The critical factor for eliciting P3a is how target/standard discrimination difficulty rather than novelty modulates task processing. The neural loci of P3a and P3b generation are sketched and a theoretical model is developed. P3a originates from stimulus-driven disruption of frontal attention engagement during task processing. P3b originates when temporal–parietal mechanisms process the stimulus information for memory storage. The neuropharmacological implications of this view are then outlined by evaluating how acute and chronic use of ethanol, marijuana, and nicotine affect P3a and P3b. The findings suggest that the circuit underlying ERP generation is influenced in a different ways for acute intake and varies between chronic use levels across drugs. Theoretical implications are assessed.

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Keywords: P300; P3a; P3b; ERP; Oddball task; 3-stimulus paradigm; Memory updating; Attention resource allocation; Memory; Normal variability; Neuropsychology

1. Introduction

The P300 was discovered over 40 years ago and has provided much fundamental information on the neural underpinnings of cognition (Sutton et al., 1965; for a superb review of the original work, see Bashore and van der Molen, 1991). Despite many studies, the usefulness of P300 as a practical assessment tool has been limited because its neural generators are still unclear. However, recent advances on the underlying processing mechanisms of the P3a and P3b subcomponents have suggested a plausible approach. The present paper reviews these issues and outlines how human neuropharmacological findings can contribute to P300 theory. The paper is organized into sections: First, a theoretical overview for P300 is presented. Second, the neuropsychological background of the P3a and P3b subcomponent distinction is sketched. Third, the effects of neuropharmacological challenges on P3a and P3b are outlined. Fourth, the implications of the neuropharmacological associations are highlighted for alcohol, marijuana, and tobacco. The findings are discussed in terms of underlying mechanisms.

2. P300 theory

Fig. 1 schematically illustrates variants of the “oddball” paradigm, which is often used to elicit the P300. In the single-stimulus task, the target is presented infrequently in time with no other stimuli (top). In the traditional two-stimulus oddball, an infrequent target occurs in a background of frequent standard stimuli (middle). In the three-stimulus oddball, the target is presented infrequently in a background of frequently occurring standard stimuli and infrequently occurring distractor stimuli (bottom). The subject is required to respond mentally or physically to the target stimulus and not to respond to any other stimuli. In each case, the target elicits a large positive-going potential that increases in amplitude from the frontal to parietal electrodes and has a peak latency of about 300 ms for auditory and 400 ms for visual stimuli in young adults (Johnson, 1993; Mertens and Polich, 1997a; Polich, 2004).

The major interpretation of P300 amplitude is that it indexes brain actions when the mental representation of the stimulus environment is updated (Donchin, 1981). This theory has its roots in Sokolov’s model of the orienting response that was derived from habituation and dishabituation effects (Sokolov, 1977), which also have been found to affect P300 (Polich, 1989; Ravden and Polich, 1999). After initial sensory processing, the current
stimulus is compared to the previous oddball stimulus in working memory. If no stimulus attribute change is detected, the old stimulus “schema” is maintained, with sensory evoked potentials recorded. If a new stimulus is processed, attention mechanisms are engaged that cascade an “update” of the memory representation for the stimulus context to elicit the P300 (Donchin et al., 1986). These events are thought to be associated with long-term storage, as larger P300 amplitudes occur for remembered previous stimuli (Paller et al., 1988a; Johnson, 1995).

P300 latency is considered to be a measure of stimulus classification speed unrelated to response selection processes (Kutas et al., 1977; McCarthy and Donchin, 1981), such that its timing is generally independent of although related to response time (Duncan-Johnson, 1981; Pfefferbaum et al., 1986; Verleger, 1997). Peak latency is associated with cognitive efficiency. Component latency is negatively correlated with superior performance on neuropsychological tests of immediate memory in normal subjects (Polich et al., 1983, 1990b; Polish and Martin, 1992; Stelmack and Houlihan, 1994; Houlihan et al., 1998; Reinvang, 1999). P300 latency increases with normal aging (Polich, 1996; Fjell and Walhovd, 2001), and peak timing increases as mental capability is compromised by dementia (Polich et al., 1986, 1990a; O'Donnell et al., 1992; Potter and Barrett, 1999; Polish and Corey-Bloom, 2005).

A variety of cognitive factors have been found to affect P300 measures such as stimulus information content, sequence probability structure, and task relevance/difficulty (Donchin and Coles, 1988; Johnson, 1988a; Verleger, 1988; Oken, 1997; Sommer et al., 1998). In addition, P300 is sensitive to the general and specific arousal effects that contribute to attention activation and information processing (Pribram and McGuinness, 1975; Kok, 1990). Tonic arousal changes occur in minutes or hours and are manifestations of relatively slow fluctuations in the energetic arousal state; phasic arousal responses indicate the organism’s energetic reaction to specific stimulus events. Thus, tonic and phasic arousal effects originate from spontaneous and situational factors that affect P300 measures, which can be controlled to reduce individual variation and increase experimental sensitivity (Polich and Kok, 1995; Polish, 2004).

The intra-subject test–retest correlation coefficient for P300 amplitude ranges from 0.50 to 0.80 and for peak latency from 0.40 to 0.70 (Polich, 1986; Fabiani et al., 1987; Segalowitz and Barnes, 1993). This test–retest variability stems in part from ultradian rhythms effects on ERP measures (Lin and Polish, 1999; Ravden and Polish, 1999). Despite this variation, P300 measures are as sensitive as most standard biomedical clinical assays, can measure individual cognitive capability for both normal and patient populations, and are relatively inexpensive to record (Polich and Herbst, 2000).

3. P3a and P3b

An infrequent tone presented with physically different frequent tones in the absence of a task can produce a positive waveform having a central/parietal maximum amplitude distribution and relatively short peak latency. This component has been dubbed the “P3a” to distinguish it from the task-relevant target “P3b” potential (Squires et al., 1975; Snyder and Hillyard, 1976). P3a from auditory stimuli can be observed directly during oddball task processing in 10–20% of normal young adults (Polich, 1988). Appropriately presented auditory and visual stimuli without a task also can produce a P3a-like potential (Mertens and Polish, 1997a; Jeon and Polish, 2001). Perceptually novel “distracter” stimuli (dog barks, color forms, etc.) that are not repeated and presented with target and standard stimuli (tones, letters, etc.) will elicit a “novelty P300” that has a frontal/central maximum amplitude distribution, short peak latency, and habituates relatively rapidly (Courcechesne et al., 1975; Knight, 1984). This potential has been interpreted in terms of frontal lobe activation (Friedman and Simpson, 1994; Knight, 1997b) and is observed across modalities (Yamaguchi and Knight, 1991; Fabiani et al., 1998). These characteristics suggest that the novelty P300 is associated with the redirection of attention monitoring (Knight, 1997a; Barcelo et al., 2000; Spencer et al., 2001).

Most P3a and novelty P300 tasks have employed easy stimulus discrimination tasks to facilitate target detection.
Katayama and Polich (1998) used an auditory three-stimulus paradigm and manipulated perceptual target/standard discrimination task difficulty to vary the level of attention required for task performance. For the easy task with a discrepant tone distractor, P300 amplitude was largest over the parietal locations for both target and distracter stimuli. For the difficult task, P300 for the distracter was largest over the central electrodes similar to P3a and novelty P3, and P300 for the target was largest over the parietal electrodes as normally found. Comerchero and Polich (1998, 1999) evaluated auditory and visual non-novel distracter stimuli across task difficulty and observed that such distracters produced central maximum P3a-like potentials for the hard task, with the largest amplitudes obtained for the high salience distracters. Taken together, these results imply that the generic P300 is composed of subcomponents that can be elicited separately by specific stimulus and task conditions (Polich, 2003).

Several subsequent studies have supported the view that the P3a and novelty P300 are the same potential. Simons et al. (2001) carefully replicated the original non-novel stimulus auditory P3a (Squires et al., 1975) and novelty P300 (Courchesne et al., 1984) tasks and found no differences between the two components. The authors concluded that previous distinctions between the P3a and novelty P300 were not supported. Polich and Comerchero (2003) compared non-novel and novel distracters to replicate the original visual three-stimulus reports and manipulated task difficulty across conditions (Courchesne et al., 1975, 1978). Both non-novel and novel distracters produced virtually identical central maximum topographies in the hard but not easy discrimination condition, with the largest amplitudes obtained for high impact distracter stimuli. Additional results using a difficult task and non-novel distracters also have been reported (Goldstein et al., 2002; Bledowski et al., 2004a).

4. Theoretical considerations

Different stimulus/task conditions appear to determine P300 scalp topography outcomes in a fashion that suggests overlapping neural activations are engaged, with the functional distinction between an initial frontal/central P3a and subsequent parietal P3b emerging (He et al., 2001; Spencer et al., 2001; Gaeta et al., 2003; Yago et al., 2003). Stimulus context as defined by the degree of physical similarity between stimuli determines task difficulty (Demiralp et al., 2001; Hagen et al., 2006), such that the degree of attention focus engaged governs P3a generation (Knight, 1997b; Hartikainen and Knight, 2003). A subsequent memory comparison performed that evaluates the current stimulus in the context of the previous stimuli governs P3b generation. It is therefore reasonable to suppose that the initial processing of a new stimulus engages the early focal attention that underlies P3a production, whereas the subsequent memory comparison engages the operations associated with P3b production (Polich, 2003).

If stimulus discrimination demands increase the degree of focal attention required for task performance, the P3a system could index the operation of an automatic attention network that is responsive to stimulus deviance. Whether this process reflects top-down attention switching for incoming stimuli or bottom-up control over response processes to distracters is debated (Escera et al., 1998; Goldstein et al., 2002; Debener et al., 2005). However, both ERP (Daffner et al., 2000a,b,c; Suwazono et al., 2000) and fMRI (Kirino et al., 2000; Opitz, 2003; Bledowski et al., 2004b) studies suggest that a frontal attention mechanism governs neural responsivity to novelty thereby implying a top-down process (for a review, see Dien et al., 2004). Regardless, the role of stimulus characteristics and task demands appear to be critical determinants of distracter evaluation to determine the different topographic and timing outcomes observed at the scalp (Debener et al., 2002; Polich and Comerchero, 2003; Berti et al., 2004).

5. Neuropsychology of P300

The exact neural origins and neuropsychological meaning of the P300 are imprecisely known, even though appreciable progress has been made in the last 25 years (Soltani and Knight, 2000). Given the attention and memory operations associated with P300 generation, the first human studies on the neural origins of this ERP focused on the hippocampal formation using depth electrodes implanted to assess sources of epileptic foci in patients. These recordings suggested that at least some portion of the P300 (P3b) is generated in the hippocampal areas of the medial temporal lobe (Halgren et al., 1980; McCarthy et al., 1989). However, subsequent investigations using scalp recordings on individuals after temporal lobectomy (Johnson, 1988b; Smith and Halgren, 1989), experimental excisions in monkeys (Paller et al., 1988b, 1992), and patients with severe medial temporal lobe damage (Rugg et al., 1991; Onofrj et al., 1992) found that the hippocampal formation does not contribute directly to P300 generation (Molnar, 1994). Indeed, assessment of patients with bilateral hippocampal lesions demonstrated no statistically reliable P300 amplitude or latency differences relative to a matched control group (Polich and Squire, 1993).

Other lesion studies have found that the integrity of the temporal–parietal junction is involved with either generation or transmission processes subsequent to hippocampal activity and contributes to ERP measures (Knight et al., 1989; Yamaguchi and Knight, 1992; Johnson, 1993; Verleger et al., 1994). These findings imply that hippocampal absence does not eliminate the P300, but that the temporal–parietal junction does affect its production.

As outlined above, the P3a is produced when the attention focus required for the primary discrimination task is interrupted by an infrequent nontarget stimulus event, which does not have to be perceptually novel. ERP studies on humans with frontal lobe lesions have found that patients produced a clear diminution of the P3a from the distracter stimulus, with a parietal maximum for the P3b from the target stimulus (Knight, 1984). Frontal lobe engagement is therefore necessary for P3a generation and mechanisms of attention control (Knight, 1990, 1997b; Knight et al., 1995). In addition, the hippocampal formation is also involved in “novelty” information processing, as patients with focal hippocampal lesions demonstrate reduced P3a amplitude from distracters but normal P3b components from targets.
relative to controls (Knight, 1996). P3a amplitude from novel auditory distracter stimuli was virtually eliminated over frontal electrode sites for lesion patients compared to controls, whereas P3b amplitude from the target stimulus was generally similar between the groups at the parietal site.

Fig. 2a schematically illustrates these implications with a neuropsychological model for P3a and P3b production. Discrimination between target and standard stimuli in an oddball paradigm is hypothesized to initiate frontal lobe activity that engages the attention focus demanded by task performance (Posner and Petersen, 1990; Pardo et al., 1991; Posner, 1992). ERP and fMRI findings have demonstrated frontal lobe activity for the detection of rare or alerting stimuli (Potts et al., 1996; McCarthy et al., 1997; Verbaten et al., 1997). P3a appears related to the neural changes in the anterior cingulate when incoming stimuli replace the contents of working memory, and communication of this representational change is transmitted to infero-temporal lobe representation maintenance mechanisms (Desimone et al., 1995). P3b results from memory storage operations that are initiated in the hippocampal formation with the updated output transmitted to parietal cortex (Knight, 1996; Squire and Kandel, 1999). Thus, P3a is produced when a demanding stimulus commands frontal lobe attention; P3b is produced when attention resources are allocated for memory updating in association cortex.

As the model suggests, the neuroelectric events that underlie P300 generation stem from the interaction between frontal lobe and hippocampal/temporal–parietal function (Knight, 1996; Kirino et al., 2000). ERP and fMRI studies using oddball tasks have obtained patterns consistent with this frontal-to-temporal and parietal lobe activation pattern (Mecklinger et al., 1998; Opitz et al., 1999; Spencer et al., 1999; He et al., 2001; Kiehl et al., 2001). Further support comes from magnetic resonance imaging (MRI) of gray matter volumes that suggest individual variation in P3a amplitude from distracter stimuli is correlated with frontal lobe area size, whereas P3b amplitude from target stimuli is correlated with parietal area size (Ford et al., 1994). Such results may underlie individual P3a and P3b variability (Squires et al., 1975; Polich, 1988; Bledowski et al., 2004a,b).

Initial neural activation during auditory oddball discrimination may originate from right frontal cortex (Polich et al., 1997), as P300 amplitude is larger over the right compared to left frontal/central areas (Alexander et al., 1995, 1996; Mertens and Polich, 1997b). After frontal processing of the incoming stimulus, activity appears to propagate between the cerebral hemispheres across the corpus callosum (Baudena et al., 1995;...
Satomi et al., 1995; Barcelo et al., 2000). This hypothesis is supported by evidence that larger callosal fiber tracts are associated with larger P300 amplitudes and shorter latencies for left- compared to right-handed individuals (Alexander and Polich, 1995, 1997; Polich and Hoffman, 1998), since these groups differ in their corpus callosum size (Witelson, 1992; Driesen and Raz, 1995).

6. Neuropharmacology and P300

The neurotransmitters systems underlying P300 generation are as yet unclear, although various mechanisms have been implicated (Frodl-Bauch et al., 1999; Hansenne, 2000). Given distinct P3a and P3b neuropsychological origins, different neurotransmitters may be engaged for each constituent subcomponent under specific stimulus/task processing requirements. Available data suggest that dopaminergic/frontal processes for P3a and locus-coeruleus–norepinephrine/parietal activity for P3b are reasonable to propose. This dual-transmitter P300 hypothesis is speculative but appears to account for a variety of findings and provides a useful framework for evaluating drug effects. These considerations and a strategy for evaluating acute and chronic drug-use effects are reviewed next.

Several lines of evidence imply catecholaminergic mediation for frontal P300 generation: (1) Parkinson patients who have decreased levels of dopamine demonstrate deficient P300 measures (Hansch et al., 1982; Stanzione et al., 1991). (2) The dopamine antagonist sulpiride increases P300 in low-amplitude subjects and decreases it in high-amplitude subjects (Takeshita and Ogura, 1994). (3) Pharmacological studies have found dopaminergic mediation of P300 amplitude and latency (Hansch et al., 1995; Wang et al., 2000). (4) Children at elevated risk for alcoholism evince dopamine-related genetic differences associated with P300 amplitude deficits (Hill et al., 1998), which may be related to dopamine level differences underlying an “endophenotype of alcoholism” (Hesselbrock et al., 2001). Although systematic amplitude topography comparisons of these effects have not been performed, the findings taken together suggest a frontal/central focus for the contribution of P3a to overall P300.

In addition, a review of the wide-ranging P300 neuropharmacology literature suggests that the locus-coeruleus–norepinephrine (LC–NE) system underlies parietal P300 generation in a simple target detection task (Nieuwenhuis et al., 2005). Since the neuropharmacological evidence stems primarily from ERPs elicited in rat, cat, and monkey populations, differences in paradigm and task performance need to be considered in evaluating these outcomes. However, the suggestion that LC–NE contributes to P300 generation is consistent with attention resource allocation and arousal-related effects in humans (Polich and Kok, 1995; Kok, 1997). The topographic LC–NE activation of temporal–parietal areas also implies P3b contribution to overall P300.

Fig. 2b illustrates a hypothetical model system based on these considerations. Given that P3a is related to focal attention mechanisms mediated by dopaminergic activity and that P3b requires temporal–parietal integrity where dense NE inputs are found, a dual transmitter hypothesis underlying P300 generation appears plausible. One approach to these issues in humans is to assay ERP effects before and after acute drug intake and compare individuals who have been selected based on their chronic drug-use frequency. If P3a and P3b topographic distributions vary as a function of acute and/or chronic drug use, development of a metric for assessing individual reactions to drug effects can be pursued.

Fig. 3 schematically outlines an “ERP Neuropharmacology Strategy” designed to characterize individual differences for drug use. Baseline, placebo, and drug challenge measures are obtained to compare low-use and high-use subject groups. If ERPs do not vary across experimental drug conditions (left panel), it is reasonable to infer that the underlying neurotransmitter systems are similar between the use groups. If ERP measures do vary across experimental drug conditions (right panel), it is reasonable to infer that the underlying neurotransmitter systems are different between the use groups. This approach permits the evaluation of acute and chronic drug use changes on the neurotransmitter systems that contribute to individual differences in ERP scalp recordings. Topographic changes in P3a and P3b from different drugs can then be developed to characterize how the central nervous system (CNS) is affected by short- and long-term changes to neurotransmitter systems.

7. Common drugs and P300

The ERP studies outlined below employed this approach by assessing young adults who were empirically defined as “low” or “high” use individuals for different substances based on normative data from thousands of drug-use surveys of the same population. Low-use and high-use generally reflect the bottom and upper 30% of each subject group in terms of various quantification measures. Additional criteria were employed to eliminate drug-dependent or substantial poly-drug users. Placebo and dose-related drug conditions were assessed on different days. Such studies require appreciable time to complete. The general
findings reported here reflect reliable outcomes, with detailed reports forthcoming.

Table 1 summarizes the paradigm parameters used across neuropharmacological challenge studies. This three-stimulus P3a/P3b paradigm has been applied in a consistent fashion to assess drug use in normal university students (e.g., Ilan and Polich, 2001; Reese and Polich, 2003; Lopez and Polich, 2004; Polich and Ochoa, 2004). The acute and chronic effects of alcohol, marijuana, and tobacco are outlined next for low-use and high-use individuals. The implications of the findings are discussed with respect to the likely neurotransmitter pathways.

Fig. 4 illustrates the mean P3a (left) and P3b (right) amplitudes as a function of baseline, placebo, and drug dose conditions for alcohol, marijuana, and tobacco subject groups. Drug manipulations were conducted under highly controlled conditions in low-use and high-use subjects (see figure caption). The order of the placebo and drug trials was counterbalanced, with the most effective dose level illustrated. Baseline values indicate the mean of the pre-drug treatment measures. Several observations can be made: (1) P3a generally is more sensitive to acute intake and drug effects than P3b, with different patterns obtained for the alcohol, marijuana, and tobacco conditions. (2) Low-use and high-use subjects demonstrated similar ERP patterns, but the groups vary among drug conditions. (3) The low-use and high-use subjects produced similar outcomes for alcohol, with stronger baseline and acute group effect patterns obtained for marijuana and nicotine. Although the origins of these ERP chronic-use effects are unclear, it is reasonable to conclude that P3a and P3b from the three-stimulus distracter task appear differentially sensitive to acute challenge, drug-use level, and drug type. The ERP amplitude variation implies that several mechanisms may be operating. Possible sources of this variability are limned next.

7.1. Alcohol

Alcohol effects on CNS function originally were thought to stem from nonspecific cell membrane lipid fluidity but are now known to influence multiple neurotransmitter systems, with acute and chronic CNS alcohol effects reflecting the wide distribution of its targets (Goldstein, 1984). The reinforcing properties of alcohol are likely regulated by a neural circuit consisting of several brain regions including the prefrontal cortex, nucleus accumbens, and amygdala (Wise, 1996). The neurotransmitter systems glutamate, GABA, NE, serotonin (5-HT), and dopamine affect this neural circuit and are targets of alcohol action. Pharmacological interactions between alcohol and these targets may be responsible for its inhibition of nucleus accumbens outputs to the brain (Koob et al., 1998). Prefrontal activation seems to reduce reward effects, since glutamatergic projections from the prefrontal cortex to limbic structures appear to play a critical role in anticipation and reward-seeking behavior (Carlezon and Wise, 1996; Schultz et al., 1998). However, prefrontal excitatory projections also activate GABAergic nucleus accumbens neurons to oppose alcohol effects. In contrast to its acute effects, chronic alcohol exposure produces neuronal adaptations that reflect tolerance development (Nie et al., 1994).

One of the main mechanisms by which glutamate, the major excitatory CNS neurotransmitter, transduces its signals involves binding to ionotropic receptors (Sucher et al., 1996). N-methyl-D-Aspartate (NMDA) is the receptor with the highest alcohol affinity (Grant and Lovinger, 1995), and acute exposure to low doses of alcohol (5 mM or 20 mg%) inhibits NMDA activity. These inhibitory effects contributes to modulation of the release of several neurotransmitters including dopamine and glutamate (Imperato and Di Chiara, 1986; Moghaddam and Bolinco, 1994). Chronic alcohol administration up-regulates the expression of NMDA receptors, particularly in the cerebral cortex and hippocampus (Gulya et al., 1991). Such NMDA up-regulation during chronic alcohol exposure helps determine alcohol dependence and withdrawal (Hoffman, 1995; Rossetti and Caroni, 1995).

GABA is the major inhibitory neurotransmitter in the CNS. Activation of drugs that potentiate GABA-A receptors (e.g., benzodiazepines and barbiturates) produces sedative–hypnotic effects that resemble those characterized by acute alcohol exposure (Sucher et al., 1996). The GABA-A receptor also is one of a high alcohol affinity target in the brain (Suzdak et al., 1986; Allan and Harris, 1987). The potency of alcohol actions on GABA-A function is dependent on the brain region and their specific subunits where the receptors are expressed (Simson et al., 1991). The acute effects of alcohol on GABA-mediated inhibition of neuronal activity are dependent on other neurotransmitter and second messenger systems. For instance, alcohol potentiation of GABA inhibition of cerebellar Purkinje cell activity only is observed during simultaneous activation of β-adrenergic receptor and protein kinase A (Lin et al., 1993; Freund and Palmer, 1996). The acute and chronic effects of alcohol on GABA-mediated function are different. Animal models have shown that chronic administration of alcohol alters the expression of GABA-A receptor subunits (Montpied et al., 1991). Moreover, in vitro electrophysiological studies have demonstrated tolerance development to alcohol actions on GABA-A function: Acute alcohol loses its ability to potentiate GABA-mediated function in tissue from animals treated chronically with alcohol (Allan and Harris, 1987).

<table>
<thead>
<tr>
<th>Category</th>
<th>Stimulus</th>
<th>Component</th>
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<tbody>
<tr>
<td>Target (0.12)</td>
<td>5.0 cm</td>
<td>P3b (P300)</td>
</tr>
<tr>
<td>Distracter (0.12)</td>
<td>18.0 cm</td>
<td>P3a</td>
</tr>
<tr>
<td>Standard (0.76)</td>
<td>4.5 cm</td>
<td>N1, P2, N2 (sensory potentials)</td>
</tr>
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Category=P3a/P3b stimulus type (probability). Stimulus=physical characteristics and width. Component=potentials produced for specific conditions. Blue circles were presented on a light gray background. The checkerboard was composed of black and white checks approximately 1 cm square.
Alcohol modulates the activity of other neurotransmitter systems, including NE, 5-HT, and dopamine. As outlined above, the LC–NE system has been implicated in P300 generation (Nieuwenhuis et al., 2005), with substantial evidence that the LC–NE system contributes to the sedative effects of alcohol since alcohol exposure reduces basal firing rates and activation of LC neurons (Aston-Jones et al., 1982; Shefner and Tabakoff, 1985). Similar to the pharmacological interactions between alcohol and GABA, the sensitivity of the LC–NE system to alcohol actions is region-dependent (Tabakoff and Hoffman, 1996). Alcohol interactions with the 5-HT3 receptor subtype appear to play an important role in self-administration and in the discriminative stimulus properties of alcohol (Grant and Barrett, 1991; Johnson et al., 2000). However, most reports have focused on the dopamine neurotransmitter system due to its role in the reinforcing properties of alcohol and other drugs of abuse (Koob and Bloom, 1988). Evidence from preclinical studies suggests that alcohol increases the activity of nigral and ventral tegmental

![Fig. 4. Mean distracter-P3a (Cz) and target-P3b (Pz) amplitude from baseline, post-placebo (30 min), and post-drug (30 min) conditions in low-use and high-use male subject groups for independent alcohol (n=16/group), marijuana (n=12/group), and tobacco (n=2/group) drug studies. Table 1 summarizes the stimuli and task conditions.](image-url)
dopamine neurons (Mereu et al., 1984; Brodie et al., 1990), and some alcohol dopaminergic effects are mediated by opioid and nicotinic cholinergic function (Blomqvist et al., 1996; Gonzales and Weiss, 1998).

Fig. 4 (top panel) indicates appreciable CNS acute alcohol effects, but little chronic difference between low-use versus high-use young adults was observed. The suggestion that placebo challenge reduces ERP amplitudes could indicate drug expectancy and test habituation. The acute rewarding effects of ethanol on dopaminergic activity are clear from animal studies, as enhancement of dopamine transmission in the nucleus accumbens increases ethanol-reinforced responding, whereas decreasing transmission decreases ethanol responding (Hill et al., 1998). In addition, genetic history for alcoholism can influence P300 measures (Polich et al., 1994; Begleiter et al., 1998; Polich and Bloom, 1999; Hill et al., 2000; Carlson et al., 2002), but how this factor may interact with acute and chronic alcohol intake is unclear. In sum, alcohol clearly affects P3a and P3b, but the ERP outcome patterns are similar for low-use and high-use young adult drinkers for the visual discrimination task used here.

7.2. Marijuana

Cannabis (marijuana) is the most extensively used illicit drug in the western world (Goldstein and Kalant, 1990). Although behavioral studies indicate that acute marijuana use inhibits attention and memory operations (Miller and Branconnier, 1983; Chait and Pierri, 1992), these results do not provide information on marijuana’s neural effects in terms of where and when such impairment occurs. The long-term neuropsychological effects of marijuana use are debated (Pope et al., 2001; Solowij et al., 2002). Increased marijuana use seems to be related to the distribution of cannabinoid receptors, which includes brain regions engaged in attention processing (Bidaut-Russell et al., 1990; Herkenham et al., 1990; Matsuda et al., 1990). Frequent and heavy use of marijuana may promote cannabinoid buildup in tissue and the brain in the absence of an acute dose (Leirer et al., 1991; Chait and Pierri, 1992; Solowij et al., 1995). Impaired cognitive processing from chronic marijuana use would have serious implications even for quotidian tasks such as driving an automobile, but the behavioral data are equivocal (Pope and Yurgelon-Todd, 1996; Grant et al., 2003). Thus, understanding the implications of acute and long-term use of marijuana is a necessary initial step in assessing how human cognition is affected, especially in terms of how social pressures to legalize marijuana for medicinal uses (Iversen, 2001).

The psychoactive component of marijuana is Δ9-tetrahydrocannabinol (THC), the CNS effects of which are mediated by activation of CB1 and CB2 receptors (Matsuda et al., 1990; Munro et al., 1993). Anandamide (arachidonylethanolamide) and 2-DG (2-arachidonoylglycerol) are two endogenous ligands for cannabinoid receptors (Devane et al., 1992; Mechoulam et al., 1995). Both endocannabinoids bind to CB1 and CB2 receptors and produce effects similar to those from THC (Martin et al., 2002). Chronic treatment with THC in rats increases the levels of anandamide in the limbic forebrain region without down-regulation of CB1 receptors (Di Marzo et al., 2000) — effects that appear mediated by a THC-mediated increase of dopamine release (Giuffrida et al., 1999). This possibility implies that the endocannabinoid system plays a role in reward and drug reinforcement by enhancing the effects of dopamine in the nucleus accumbens (Martin et al., 2002).

CB1 receptors are highly expressed in the hippocampus (CA pyramidal neurons, dentate gyrus), basal ganglia (substantia nigra pars reticulata, globus pallidus, caudate putamen), cerebellum, and olfactory bulb (Herkenham et al., 1990). CB1 receptors also are expressed at lower levels in the hypothalamus, brainstem, thalamus, and limbic forebrain. This distribution is consistent with the effects of THC on body temperature, appetite, pain/sensory perception, mood, and reward (Martin et al., 2002). Most of the cells expressing CB1 receptors at high levels are GABAergic interneurons, such as the basket cells in the hippocampus. In the striatum, GABAergic interneurons expressing CB1 receptors play an important role regulating striatal output pathways (Hohmann and Herkenham, 2000).

CB1 mRNA has been detected at low levels in non-GABAergic projecting neurons in the hippocampus, amygdala, and entorhinal cortex, and with the exception of the microglia there is no evidence suggesting expression of CB2 receptors in the CNS (Martin et al., 2002). Activation of CB1 receptors results in presynaptic inhibition of neurotransmitter release (Di Marzo et al., 1998). THC can modulate CNS function by inhibiting glutamate and GABA release or by increasing dopamine release (Martin et al., 2002). THC effects in humans can manifest tolerance as evidenced by cardiovascular, sleep, and autonomic function measures; no tolerance develops on food intake or social behavior or if the doses of THC were too low or infrequent (Jones et al., 1976; Haney et al., 1999).

Although cessation of chronic marijuana exposure is unassociated with severe withdrawal symptoms (Jones, 1983), some individuals appear dependent on marijuana (Martin et al., 2002). These findings could be due to the potency of the marijuana and the period of time used.

Fig. 4 (middle panel) indicates appreciable acute marijuana effects obtained for the low-use but less for the high-use groups. Chronic use also contributes to both P3a and P3b group differences, with overall larger amplitudes obtained for high-use individuals. It is reasonable to suppose that tolerance is contributing to ERP outcomes. However, high-use individuals may be self-selected since large P300 effects for personality variables such as introversion/extroversion or sensation-seeking can contribute to baseline ERP differences between groups (Stenberg et al., 1988; Dittraglia and Polich, 1991; Cahill and Polich, 1992). Whether ERPs could differ for self-selection of marijuana intake amount, at least in young adults, is unclear although the inter-subject P3a and P3b group effect patterns appear distinct and may be related to individual differences in the availability of specific receptor sites.

7.3. Nicotine

Nicotine receptors are distributed widely in the brain including the cortex, hippocampus, and nucleus accumbens.
from dopamine mesolimbic neurons; nicotine regulates dopamine release by modulating the impulse flow to nerve terminals (Wonnacott, 1997; Jones and Benowitz, 2002). Nicotine binds to a wide family of nicotinic cholinergic receptors and increases the release of several neurotransmitters, including dopamine, NE, acetylcholine (ACH), 5-HT, glutamate and GABA (Benowitz, 1999). Nicotinic cholinergic receptors have diverse pharmacological profiles. However, the functional relationships among nicotinic receptor subtypes and regulation of specific neurotransmitter systems are unclear (Wonnacott, 1990).

Nicotinic receptors are composed of α and β subunits, and receptor subtypes consisting of α-4 and β-2 subunits may play an important role in the stimulant and rewarding effects of nicotine (Grottick et al., 2000; Jones and Benowitz, 2002). Studies in knockout mice have demonstrated that the β-2 subunit plays an essential role in dopamine release (Picciotto et al., 1998). In addition, activation of the α-7 nicotinic cholinergic receptor increases the release of glutamate and regulates dopamine function (Jones and Benowitz, 2002). Although the reinforcing properties of nicotine are mediated at least in part by an increase in dopamine neurotransmission, other neurotransmitter systems such as NE and 5-HT also have been implicated (Balfour and Ridley, 2000). The effects of nicotine on 5-HT release are diverse, depending on several factors including the pattern of nicotine exposure and concentration of nicotine (Balfour and Ridley, 2000). Chronic exposure of nicotine produces sensitization to dopamine release in the nucleus accumbens, which is dependent on co-activation of NMDA receptors (Wonnacott, 1997; Jones and Benowitz, 2002). However, chronic nicotine administration also can desensitize nicotinic cholinergic receptors (Wonnacott, 1997). Chronic nicotine treatment in animal models and postmortem human smoker brain studies suggests that nicotine tolerance promotes increases in nicotinic cholinergic receptors (Benwell et al., 1988; Collins et al., 1994; Breese et al., 1997; Court et al., 2000).

Nicotine’s ability to act as a positive reinforcing stimulus has been demonstrated to be the core of tobacco addiction, with sensory input such as the taste, smell, and irritation that smoke produces important stimuli for smokers (Rose et al., 1985). In rat studies, these conditioned behavioral responses have been traced to the mesolimbic dopamine system that mediates various sources of reinforcement (Watkins et al., 2000), and administration of mecamylamine changes behavioral responses related to nicotine use in rats, monkeys, and humans (Pickworth et al., 1988). Most ERP studies of tobacco smoking have focused on the acute rather than chronic effects of smoking. In general, P300 amplitude generally increases and latency decreases immediately after smoking (Houlihan et al., 1996, 2002; Knott et al., 1995a), although these effects appear relative to information processing task difficulty (Knott et al., 1995b; Pritchard and Robinson, 1998; Ilan and Polich, 1999, 2001; Domino, 2003) and amount smoked as well as nicotine level (Kodama et al., 1996; Lindgren et al., 1999). The recent availability of de-nicotinized cigarettes should help to delineate this area, as previous studies typically employed non-smoking control subjects, “sham” smoking (pretending to inhale an unlit cigarette), or only pre-compared to post-smoking conditions in smokers. Variability of subject populations, stimulus/task parameters, and smoking history also contribute to ERP outcomes (Anokhin et al., 2000; Haarer and Polich, 2000; Polich and Ochoa, 2004). Use-group variation may be related to individual mesolimbic dopamine system differences for nicotine as a positive reinforcer (Rose et al., 1985; Stolerman and Shoaib, 1991; Watkins et al., 2000).

Fig. 4 (lower panel) indicates that the increases in P3a amplitude for smoking tobacco relative to the placebo is pronounced, with similar but weaker effects obtained for P3b amplitude. Moreover, P3a and P3b amplitude were affected in a similar fashion across use-groups. This outcome pattern implies a more specific activation of nicotinic receptors in both frontal and hippocampal cortical areas than observed for alcohol and marijuana. Tobacco smoking amount and smoking history effects on P300 measures suggest that ERP generation is influenced by the chronic presence of nicotine. Taken together with the acute effects outlined above, it is reasonable to suppose that nicotine intake may substantially alter the neuropharmacological brain mechanisms that contribute to P300 generation.

7.4. Summary and conclusion

This review suggests that P3a and P3b amplitude changes from different drugs stem from distinct neuropsychological and neurotransmitter systems. Acute intake appears to alter the P3a and P3b in a fashion specific to the particular drug assessed, whereas chronic intake can produce smaller amplitudes for low-use compared to high-use subjects. Given that frontal/attention P3a and temporal–parietal/memory P3b origins are associated with dopaminergic and NE activity, individual differences for acute and chronic drug intake could reflect individual transmitter responsiveness. The dual-transmitter hypothesis implies that ERP variation is related to how alcohol, marijuana, and tobacco use alters differential neurotransmitter levels within and between individuals. These alterations could determine P3a and P3b patterns that can be used to quantify individual variation to treatment interventions.

Despite the intriguing nature of the empirical portrait, it is not yet possible to complete the theoretical painting. Neuropharmacological studies in humans are famously difficult to execute, with stimulus/task considerations (cue reactivity, performance variation, response difficulty), neurobiological variables (circuitry, dose level, gender effects), and administrative challenges (pre-test deprivation, retest reliability, task fatigue) all possible influences on assessment outcomes. However, characterizing the underlying neurochemical foundations of ERPs will further the understanding of their neurophysiological generation and have appreciable clinical import. The present review is an initial attempt towards the goal of developing a more comprehensive neuropharmacology for P300.

Acknowledgements

This work was supported by RO1-DA018262, RO1-DA11737, RO1-DA08363, and 3 P50 AA06420. The second author was supported by the Clark Fellowship in Neurophysiology from...
Scripps Clinic. We thank Quetzal A. Class and Brian A. Lopez for their superlative assistance and perceptive comments.

References


Houlihan, M., Stelmack, R., Campbell, K., 1998. Intelligence and the effects of perceptual processing demands, task difficulty, and processing speed on P300, reaction time, and movement time. Intelligence 26, 9–25.


