Article

Event-Related Potentials in Substance Use Disorders: A Narrative Review Based on Articles from 1984 to 2012

Clinical EEG and Neuroscience
2014, Vol. 45(2) 67–76

DOI: 10.1177/1550059413495533
eeg.sagepub.com
SAGE

Salvatore Campanella[1], Oliver Pogarell[2], and Nash Boutros[3]

Abstract

Mechanisms that mediate the transition from occasional, controlled, drug use to the impaired control that characterizes severe dependence are still a matter of investigation. The etiology of substance use disorders (SUDs) is complex, and in this context of complexity, the concept of "endophenotype," has gained extensive popularity in recent years. The main aim of endophenotypes is to provide a simpler, more proximal target to discover the biological underpinnings of a psychiatric syndrome. In this view, neurocognitive and neurophysiological impairments that suggest functional impairments associated with SUDs have been proposed as possible endophenotypes. Because of its large amplitude and relatively easy elicitation, the most studied of the cognitive brain event-related potentials (ERPs), the P300 component, has been proposed as one possible candidate. However, if a P300 amplitude alteration is a common finding in SUDs, it is also observable in other psychiatric afflictions, suggesting that the associations found may just reflect a common measure of brain dysfunction. On this basis, it has been proposed that a multivariate endophenotype, based on a weighted combination of electrophysiological features, may provide greater diagnostic classification power than any single endophenotype. The rationale for investigating multiple features is to show that combining them provides extra useful information that is not available in the individual features, leading ultimately to a multivariate phenotype.The aim of the present article is to outline the potential usefulness of this kind of "combined electrophysiological procedure" applied to SUDs. We present a review of ERP studies, combining data from people with SUD, family members, and normal control subjects, to verify whether the combination of 4ERPs (P50, MMN, P300, and N400) may produce profiles of cortical anomalies induced by different types of SUD (alcohol vs cocaine vs cannabis vs heroin).

Keywords

ERPs, addiction, substance use disorder, combined endophenotypes

Received December 21, 2012; revised May 17, 2013; accepted June 4, 2013.

Introduction

Despite the widespread availability and prevalence of addictive substances in most societies,[1] only some drug users ultimately become dependent.[2] Mechanisms that mediate the transition from occasional, controlled, drug use to the impaired control that characterizes severe dependence are still a matter of investigation.[3] Over the past several decades, multidisciplinary direct evidence in humans have indicated that SUDs result from a confluence of risk factors related to biology, cognition, learning, personality, genetics, and social environment.[4] Despite presenting very different pharmacological properties, virtually all drugs are acutely rewarding because of their actions on a final common biological pathway, involving the dopaminergic system, and more precisely, the nucleus accumbens in the ventral striatum.[5] Through direct projections, dopaminergic system neurons distribute information about rewarding value of events to brain structures, mainly involving the prefrontal cortex, implicated in cognitive control, a mechanism by which previously rewarded but task- or goal-inappropriate responses are inhibited.[6] In this view, addiction has been characterized in terms of deficient interaction between one system encoding the rewarding properties of an event (acting as a reinforcement learning signal, increasing the incentive salience of a reward), and another, implicated in future-oriented processes and regulating current actions in relation to long-term goal-directed motivations.[7]

The etiology of SUDs is more complex than this, and many other factors have been considered. For instance, in a

[1]Laboratoire de Psychologie Médicaleetd' Addictologie, ULB Neuroscience Institute, CHU Brugmann-Université Libre de Bruxelles, Brussels, Belgium
[2]Department of Psychiatry, Ludwig-Maximilians University of Munich, Munich, Germany
[3]School of Medicine, Wayne State University, Detroit, MI, USA

Corresponding Author:
Salvatore Campanella, The Belgian Fund for Scientific Research, CHU Brugmann, Psychiatry Secretary, 4, Place Vangehuchten, 1020 Brussels, Belgium.
Email: salvatore.campanella@chu-brugmann.be

Full-color figures are available online at http://eeg.sagepub.com

developmental perspective, the finding that individuals who first tried alcohol before age 15 years are approximately 4 times more likely to be alcoholics than people whose first experience with alcohol came at age 20 or later, suggests that the origins of SUDs can be traced to childhood and early adolescence.[8] Also, a personality trait, such as impulsivity, has been suggested to lead to addiction, by contributing to a tendency to act impulsively and seek immediate gratification, without weighing future consequences.[9] Obviously, a multitude of environmental factors have been associated with SUD risk, such as prenatal exposure to alcohol and nicotine, or history of abuse and maltreatment as children.[10] In fact, a meta-analysis of Bergen et al[11] indicates that environmental factors shared by members of a family are relatively influential early in development, with genetic factors later becoming more influential. Many genetic studies in SUD research have aimed to reveal the susceptibility genes underlying the disorder. However, despite well-established evidence that a large part of the variance for the etiology of SUD is explained by genetic factors,[12] the precise nature of the genetic basis of SUD still remains unclear,[13] mainly because of the many intervening variables between genetic transcription and its behavioral consequences on clinical phenotypes.[14] It is in this context of genetic and phenotypic complexity that the concept of "endophenotype" has gained extensive popularity in recent years.[15]

As defined by Gottesman and Gould,[16] an endophenotype should be heritable, be present in patients displaying the pathology, manifest in an individual whether or not illness is active, and be found in unaffected biological relatives of those who have the disorder at a higher rate than in the general population.[13] The main aim of endophenotypes is to provide a simpler, more proximal target to discover the biological underpinnings of a psychiatric syndrome.[17]

However, in current literature, very few putative endophenotypes have been proposed in SUDs. One main reason is surely that, unlike other areas of medicine, the imprecision of categorical psychiatric diagnoses can be a limiting factor in understanding the genetic basis of human behavioral abnormalities.[15] But another important point is linked to the fact that there is not yet standardization of the methods by which candidate endophenotypes should be chosen and applied.[15]

In past years, neurocognitive and neurophysiological impairments that suggest functional impairments associated with SUDs have been proposed as endophenotypes. Because of their high sensitivity, ERPs have the potential to monitor brain electrical activity with a high temporal resolution (on the order of milliseconds). Therefore, it is possible, during a cognitive task, to observe in healthy subjects the different electrophysiological components, representing the different cognitive stages needed to reach a "normal" performance.[18] Conversely, a highly valuable interest in cognitive ERPs is that it is also possible in people presenting cognitive deficits to identify the electrophysiological component(s) representing the onset of a dysfunction, and then to infer the impaired cognitive stages.[18] On this basis, because of its large amplitude and relatively easy elicitation, the most studied of the cognitive ERPs, the P300 component, has been proposed as one possible candidate.[17] However, some investigators have proposed that the utility of a particular endophenotype depends on the specificity it has for a particular disorder.[19] If findings seem to suggest the potential validity of P300 amplitude as an endophenotype in SUDs, similar results have also been displayed in schizophrenia, outlining the necessity to carry out studies in different disorders to find out whether the associations found are "disease-specific" or just reflect a common measure of brain dysfunction.[17] Therefore, it has been suggested that a multivariate endophenotype, based on a weighted combination of electrophysiological features, may provide greater diagnostic classification power than any single endophenotype.[20] With this in mind, Price et al[21] compared and contrasted 4 electrophysiological endophenotypes—mismatch negativity (MMN), P50, P300, and antisaccades—and analyzed their covariance on the basis of a single cohort of schizophrenic patients, family members and controls, tested with all paradigms. Data showed that the use of an electrophysiological battery provided novel information on the characteristics of these features in schizophrenia and family member groups. In particular, it has highlighted the heterogeneity of electrophysiological features within these groups, and how a combination of features could serve to minimize the impact of such heterogeneity.[21]

The aim of the present article was to outline the potential usefulness of this kind of "combined electrophysiological procedure" applied to SUDs. We focused on four major cognitive ERPs with established clinical utility in psychiatric populations, MMN, P50, P300, and N400: Each of these ERP components has been well characterized in terms of eliciting stimuli, technical recording methods and quantification, as well as operationally related to the neurocognitive process it reflects.[22] In the present article, we sought to furnish a review of ERP studies comparing and combining data from people with SUD, family members, and normal control subjects, who were assessed on at least one of these 4 electrophysiological features. Indeed, because of the specific neuropharmacological action of different addictive substances (such as alcohol vs cocaine vs heroin vs marijuana), the combined observation of these 4 electrophysiological features *for each type of SUD* may lead to heterogeneous results, indicating the existence of different profiles of cortical anomalies linked to different cognitive disturbances. The rationale for investigating multiple features is to show that the combination of features provides extra useful information that is not available in the individual features, leading ultimately to a multivariate phenotype.[23]

Method

Literature Search Strategy

The search engine PubMed, which comprises more than 22 million citations for biomedical literature from MEDLINE and life science journals, was used to track available articles (http://www.ncbi.nlm.nih.gov/pubmed/). A simple search, performed in December 2012, using the general keywords "ERP and

Table 1. Number of Articles Found on PubMed Web Site by Using Keywords Related to the Cognitive ERP of Interest (P50, MMN, P300, or N400) and the Considered Drug (Alcohol, Cocaine, Cannabis, or Heroin).

	Alcohol	Cocaine	Cannabis or Marijuana	Heroin
P50	40	12	6	1
MMN	19	0	4	0
P300	183	25	20	10
N400	5	1	2	1

Substance Abuse," disclosed the existence of 1416 available articles.

Selection of Studies for Inclusion

Among these 1416 articles, we chose to focus our review on 4 main ERP components (P50, MMN, P300, N400) and 4 main substances (alcohol, cocaine, heroin, cannabis). Excluded articles mainly concerned with researches on other drugs (eg, amphetamines, nicotine) or on addictions without any substance (eg, Internet addiction, gambling), researching drug use in other disorders such as Parkinson or Huntington, researches examining the toxic effects of solvents and organophosphorous compounds, animal studies, and non-English articles. Therefore, to select appropriate articles, each ERP component of interest (P50, MMN, P300, N400) and each substance (alcohol, cocaine, heroin, cannabis [or marijuana]) were successively used in keywords sequence. For example, the keywords sequence: "ERP and P50 and alcohol" was used to tag articles relating to the investigation of the P50 component in alcoholic participants. Similarly, a sequence using "ERP and N400 and cannabis or marijuana" is supposed to tag articles investigating the N400 components in people consuming cannabis (or marijuana). By using such a method, 319 available and appropriate studies, including articles dealing with chronic abuse and/or abstinence and/or family history of SUD, were defined. Table 1 summarizes the number of articles reported by ERP components for each substance. Please note that among these, only articles (n = 128) fully read by the author, but including the most recent reviews and meta-analyses, are cited and reported in the reference section.

Electrophysiological Endophenotypes and SUDs: A Review

The P50 Amplitude and Its Sensory Gating

Sensory gating is an important feature of the normally functioning brain. When not operating correctly, it can contribute to different kinds of psychiatric illnesses by flooding the higher brain functions with useless information.[24] The auditory P50 component is the earliest (around 50 ms) and the smallest in amplitude of the auditory ERPs.[25] When normal controls are confronted by repetitive auditory stimuli, an inhibitory mechanism is activated to block out irrelevant, meaningless or redundant stimuli. The inhibition of responsiveness to the repeated stimuli is neurophysiologically indexed by a reduced P50.[26] The P50 sensory gating effect refers to this amplitude diminution of the P50 to the second stimulus of a pair of identical stimuli presented with a short interstimulus interval.[27] P50 gating is one of the early brain sensory processing stages linked to screening out and filtering mechanisms of redundant incoming information that can be measured, and it reflects a neuronal inhibitory process[28] that has been proposed to represent an endophenotype of schizophrenia, which could ultimately contribute to our understanding of the genetic basis of the illness.[29]

P50 sensory gating is a heritable neurobiological trait that has shown strong potential to serve as an endophenotype for schizophrenia. Several studies have also investigated this ERP component in SUDs. Reduced P50 suppression, suggesting an inhibitory deficit in early preattentive sensory processing, has been observed for acute and long-term exposure to alcohol,[31] cannabis,[32] heroin,[33] and cocaine,[34] and seems to be highly heritable.[31,35] However, apart from this general affliction of P50 amplitude suppression due to acute or long-term substance abuse, some differential effects have also been reported. Cocaine addicts markedly show P50 reduced suppression compared with alcoholics, suggesting that decrement in P50 amplitude differentiates cocaine abuse from alcohol abuse.[36] Moreover, although a reduced P50 suppression is still observable in at least 4 weeks abstinent alcoholics,[37] some amplitude recovery seems to occur with at least 3 weeks of cocaine abstinence.[38]

Mismatch Negativity

Mismatch negativity (also called N2a) is an ERP component, with a peak latency around 150 ms after stimulus onset and a maximal amplitude at frontal scalp locations, which is usually evoked by a physically deviant auditory stimulus that occurs in a series of frequent standard stimuli.[39] This sensory-specific mechanism is related to preconscious detection of stimulus deviation that activates frontal mechanisms associated with conscious discrimination of stimulus deviation and with the orienting response.[40] MMN reflects a change-detection response of the brain elicited even in the absence of attention or behavioural task, which occurs in early sensory stages of the information-processing stream (around 150 msec). However, recent findings also suggest that the transient auditory sensory memory representation underlying the MMN is facilitated by a long-term memory representation of the corresponding stimulus.[41]

The diminished amplitude/prolonged peak latency observed in SUD patients usually indexes decreased auditory discrimination.[42] This pattern was observed in acute alcohol intoxication,[43-46] in long-term alcohol abusers,[47-50] as well as in opioid dependence[51,52]and long-term heavy use of cannabis.[53] Deficits

in MMN parameters in subjects at high risk for alcoholism could index increased genetic risk for alcoholism. However, at this stage, conflicting results have been obtained. For instance, whereas Rodriguez et al[54] showed no group differences in peak latency, peak amplitude, and mean amplitude of the MMN from a group of young children of alcoholics with a high-density family history of alcoholism and a control group in a dichotic listening task, Zhang et al[55] showed that offspring of alcohol-dependent fathers manifested larger amplitudes of the MMN than low-risk control individuals, suggesting a deficit in inhibition (excessive neural excitation). Also, it should be noted that MMN data suggest some recovery for chronic alcoholism, as no difference in amplitude and latency between a control group and a group of alcoholics displaying a minimum of 6 months of abstinence has been evidenced.[56-58]

The P300

P300 (or P3) is a long-lasting positive component that occurs between 300 and 700 ms after the stimulation onset.[59] The P3 is thought to reflect premotor decisional processes, such as memory updating[60] or cognitive closure[61] and to involve the activation of inhibitory processes over widespread cortical areas.[62] The amplitude of P3 is associated with stimulus probability, stimulus significance, task difficulty, motivation, and vigilance.[63]

Two ERP tasks are usually used to elicit the P300: the "oddball" and the "Go-Nogo" tasks. In the oddball task, 2 different type of stimuli are delivered: rare oddball stimuli and frequent stimuli, and the subject is asked to monitor and identify infrequent "target" stimuli implanted within a series of rapidly presented frequent "standard" stimuli. This response may take the form of a verbal report (silent-counting task) or of an overt signal as typically button pressing. In normal individuals, the P300 occurs following the presentation of the target stimulus. It is a large positive response that is of maximum amplitude over the parietal area with a peak latency of about 300 to 350 ms for auditory and 350 to 450 ms for visual stimuli. The P300 is then produced by brain processes related to attention and memory operations, as it occurs from the initial necessity to increase focal attention during stimulus detection relative to the contents of working memory.[64] An alternative to the oddball task to obtain the P300 is the "Go-NoGo" task, requiring participants to respond to one type of frequent stimulus (Go), but to not to another rare one (NoGo). In the NoGo task, the "NoGo P3" has been identified as one of the markers for response inhibition.[65] Response inhibition involves activation of the executive system of the frontal lobes,[66] and the neural basis for this executive system is believed to be a distributed circuitry that involves the prefrontal areas and anterior cingulated gyrus,[67] the orbitofrontal cortex,[68] the ventral frontal regions,[69] the parietal, dorsal, and ventral prefrontal regions,[70] and the premotor and supplementary motor areas.[71]

More than a hundred articles on P300 amplitude and SUD have been published in the past decade. In alcoholics, a reduced amplitude and a delayed latency of P3 to task-relevant target stimuli has been widely observed, particularly over the parietal regions.[72] This deficit appears in both auditory and visual tasks but is more pronounced in visual tasks.[73,74] Although not as significant as in males, smaller P3 amplitudes have also been observed in female alcoholics.[75] Other studies documented not only low amplitude P3b components to target (Go) stimuli but also reduced frontally distributed P3 amplitudes to NoGo stimuli. These deficits observed in both Go and NoGo conditions suggest that both response activation and response inhibition are dysfunctional in alcoholic individuals.[76,77] Similarly, reduced P3 and NoGo P3 amplitudes have been displayed in cocaine users,[78,79] in heavy cannabis users,[80] as well as in current or even long-term abstinent heroin addicts,[81,82] whereas brothers of heroin-dependent males displayed an intermediate position as compared with matched controls, suggesting a common genetic subtsrate.[83] Interestingly, despite this hypothesized common substrate, it has been shown that buprenorphine treatment (an alternative to methadone for maintenance treatment of opioid dependence, especially for patients with concurrent cocaine dependence or abuse) significantly reversed P3 amplitude decrement after detoxification in cocaine and heroin users, whereas placebo-treated patients continued to show decreased P3 amplitudes.[84] This prompts the question of medical treatments. Some efficacy of medications for alcoholism and opiate addiction has been documented and supports the feasibility of addiction pharmacotherapy. However, with the exception of methadone or buprenorphine maintenance therapy counteracting with the trait effect on P300 amplitudes, the effect sizes of these treatments are small. This emphasized the heterogeneity of addicted people and the need for personalized treatment approaches.[85]

In a multigroup study, Bauer[86] used a visual oddball task to compare P300 amplitude among individuals characterized by histories of cocaine, or cocaine and alcohol, opioid dependence or no previous drug or alcohol dependence, and they found a similar amplitude decrement in all patient groups. In a recent meta-analysis, Euseret al[13] investigated whether P300 amplitude fulfills fundamental criteria to be an endophenotype for SUDs. Results indicated that, even if some conflicting results have been reported, SUDs in general are significantly associated with reduced P300 amplitudes, with a medium effect size of $d = 0.51$, suggesting that P300 amplitude reduction is strongly associated with SUD, and appears in those with the disorder (SUD+) more often than it appears in the general population (SUD−). Interestingly, this effect was strongly moderated by substance use status, as abstinent SUD patients displayed significantly reduced P300 amplitude as compared to current substance users, suggesting that there is no spontaneous recovery of the neurobiological abnormalities associated with detoxification. Some authors have proposed that as the P300 amplitude does not recover with abstinence for at least 32 days,[87] it seems unlikely to be related to drinking behavior, but rather seems genetically influenced,[72] by being present prior to the onset of the disease. This assumption is supported by the metal-analysis by Euser et al,[13] as unaffected individuals with a family history (FH+) of SUD in general (not just for alcoholism) demonstrated significantly smaller P300 amplitudes than individuals without a FH of substance use ($d = 0.28$). Hence, as P300 decrements are strongly associated with SUD, are state-independent and can

be seen at rates above chance in the population in unaffected first-degree biologic relatives of those who have a SUD, P300 amplitude reduction is a useful disease marker and a vulnerability marker for SUD, but the latter only in males.[13,17]

However, if, independently of the kind of substance, SUDs are associated with decreased P3 and NoGo P3 amplitudes, suggesting that higher level attentional, memory, and executive (inhibitory) functions are hypoactive in these patients, it is important to outline that several studies have also disclosed *higher P3 amplitudes* as compared with controls when *drug-related cues* were used (see for instance, for alcohol[88-90]; for heroin[91,92]; for cocaine[93-95]; for heavy cannabis use[96,97]). These data are highly important, as they pointed to 2 main processes associated with addicted behavior: (*a*) an automatic process characterized by an increase in the salience of alcohol-related cues, which tend to "grab the attention" of experienced drug users and (*b*) a lack of executive resources needed to inhibit the salient and dominant response, that is, to consume, because of the neurotoxic effects of repeated drug consumption and/or a state of vulnerability.[98] As such, the imbalance of these 2 systems is believed to play a central role in the emergence and the maintenance of drugs consumption disorders[99] and relapse.[100]

The N400

The label N400 was first reported by Kutas and Hillyard[101] in a comparison of sentence-final words that formed predictable completions and those that were semantically incongruent. Whereas predictable endings elicited a broad positive waveform from 200 to 600 ms, the incongruent words elicited a large negative wave in this latency range.[102] Overall, the data suggest that N400 amplitude is a general index of the difficulty of retrieving semantic stored conceptual knowledge associated with a word. This outcome depends on both the stored representation itself and the retrieval cues provided by the preceding context.[103]

As the presence of N400 is an indicator of semantic comprehension, many studies have applied N400 paradigms to patients with a variety of developmental, neurological, and psychiatric disorders, as, for instance, disorganized speech is a fundamental clinical symptom of schizophrenia.[104] In SUD patients, it has been described that chronic alcoholics,[105-106] alcoholics being abstinent for at least 21 days,[107-108] high-risk offspring of alcoholics,[109] and long-term heavy cannabis users[110] displayed semantic processing deficit indexed by a decreased amplitude and delayed latency of the N400 component. However, opioid addicts only disclosed delayed N400 latencies as compared with controls (while amplitude is spared[111]), and cocaine-dependent individuals showed intact semantic priming effect, as the repetition of related words induced a priming effect on the N400 amplitude similar to the one observed in healthy controls.[112,113]

Discussion

In the present article, our aim was to furnish a review of studies investigating SUDs through the use of 4 main cognitive ERPs. Overall, data reported in this article seem to confirm the idea that the combined use of different ERP components may disclose different effects when SUDs are envisaged, confirming that *different drugs have different sites of action that may lead to different neurocognitive disorders*. This statement emerged from 4 main empirical considerations:

1. Unlike P300 and N400, studies did not find MMN abnormalities in alcoholics who had maintained abstinence for a minimum of 6 months. Moreover, conflicting results have been obtained on a possible link between a genetic risk to develop alcoholism and a disturbed MMN component.[54,55] Therefore, this component appears more as *a state marker* of recent alcohol abuse, and less determined by factors persisting throughout long-term recovery.[113] In this view, MMN appeared as an interesting parameter indexing real abstinence in alcoholics, whereas P50 also has an intermediate position, as studies suggested a partial recovery through abstinence.
2. Unlike P300, P50 appears as a state marker of cocaine addiction, as cocaine addicts reported a normalized P50 suppression after a period of abstinence,[38] whereas this is not the case for P300 alteration. In this view, as for the MMN in alcoholism, the P50 components appear as an interesting parameter indexing real abstinence in cocaine users.
3. Cocaine addicts markedly show P50 reduced suppression compared with alcoholics, suggesting that decrement in P50 amplitude differentiates cocaine abuse from alcohol abuse.[36]
4. The N400 seems to be preserved in cocaine addiction as compared with other substances, suggesting that as compared with alcohol, heroin, and cannabis, cocaine abuse did not affect neural sites related to semantic processing.[112,113] However, only a few studies using N400 are currently available, so that further studies are needed to confirm this point.

In this way, it is important to outline that despite the general term of "addiction," the neurocognitive disorders induced by different drugs are heterogeneous, and should be made precise to enhance our understanding of the pathophysiology of a specific drug and in this way of its treatment. However, even if these data seem highly relevant to understand the pathophysiology related to a specific drug abuse, they are still at this stage preliminary. Indeed, to the best of our knowledge, apart from alcoholism which has been deeply investigated, and apart from the P300 component that has been the most studied ERP component, some important data are still missing, preventing us from disposing of an exhaustive view of what are (*a*) the specific effects of a specific drug consumption after an acute versus a long-term abuse, (*b*) the existence of a recovery after abstinence, and (*c*) the genetic risk, that is, the positive versus negative family history of SUD (see Table 2). In this view, it is currently difficult to make a differential diagnosis for specific SUDs based on this approach, mainly because of the absence of

Table 2. Summary of the Main Findings of Current Studies Having Investigated SUDs Through the Use of Cognitive ERPs, in 3 Specific Situations: Chronic Abuse Versus After a Period of Abstinence Versus Existence of a Genetic Risk (Positive vs Negative Family History [FH]).

	Alcohol			Cocaine			Heroin			Cannabis		
		Abstinence:	Genetic Risk:		Abstinence:	Genetic Risk:		Abstinence:	Genetic Risk:		Abstinence:	Genetic Risk:
ERPs	Chronic	Recovery?	FH?	Chronic	Recovery?	FH?	Chronic	Recovery?	FH?	Chronic	Recovery?	FH?
P50 Suppression	↓	Partial	Positiv	↓↓	Yes	Positive	↓	?	?	↓	?	?
MMN	↓	Yes	Positive	?	?	?	↓	?	?	↓	?	?
P300	↓	No	Positive	↓	No	Positive	↓	No	Positive	↓	No	Positive
N400	↓	No	Positive	OK	?	?	↓, only latency	?	?	↓	?	?

[a]Blueshaded cells outlined the main difference found between SUDs when the P50 sensory gating component is considered. Yellow shaded cells outlined the different effect of alcohol abstinence on these 4 ERP components. Green shaded cells outlined the different effect of cocaine abstinence on these 3 ERP components.Pink shaded cells outlined the main difference found between SUDs when the N400 component is considered. Please note that "?" referred to issues for which empirical data are still not availableat this stage.

empirical data. Indeed, for instance, whereas the finding of MMN as a state marker of alcoholism was based on an available important set of researches, the N400 preserved in cocaine addiction is based on only one study, and clearly deserved further investigation. Nevertheless, available current data are still valuable, as they indicated that different ERP measures reflected various brain functions that may be differently affected by various substances. Therefore, some ERP measures indexing some precise cognitive functions may, for instance, recover through abstinence for some substance, whereas others will cause permanent damage. More data are needed to clarify the situation, and a lot of work remains as further studies should consider various variables, such as "substance-related" variables, that is, quantity/frequency measures or length of use and abstinence, as well as "sample-related variables," such as age, gender, ethnicity of participants.

Conclusions and Future Perspectives

The main aim of the present review was to illustrate how gathering information from different ERPs may help differentiate among different SUD patients. At this stage, a main conclusion seems to emerge: Even if some evidence is already available, there is still a long way to go to obtain a global assessment of what are the precise neurocognitive impairments induced by the acute versus the long-term abuse of a specific drug on the abuser, of what are the genetic risks associated with this consumption for family members, and about the potential reversibility of these deficits after abstinence. As illustrated in Table 3, the main conclusions drawn in this article relied on a limited sample of articles mainly devoted to alcohol-related problems and P300 component, whereas the number of studies investigating genetic risk and/or abstinence effect through the use of MMN, P50, and N400 on other substances is restricted. More precisely, main conclusions currently supported for alcohol were represented by 32 articles, while conclusions currently supported for cocaine, heroin, and cannabis were, respectively, represented by 12, 11, and 7 main articles. Also, the P300 component was the most studied ERP component in SUDs. Indeed, among the 319 available studies, 183 articles focused on alcohol and P300 component, so that "only" 136 articles were devoted to other substances and other ERP components of interest. These "alcohol" and "P300" data were illustrated in the present review by 27 articles, comprising an excellent meta-analysis conducted by Euser et al,[13] whereas 15, 6, and 9 article were, respectively, related to the MMN, P50, and N400 in SUDs.

At the end of year 2012, around 1420 articles are available in the scientific literature disclosing ERP modulations in SUDs. Obviously, we are totally aware that, for the clarity of our message, we restrained our analysis on a small part of these available studies (319 of 1416, ie, 22.5%). Indeed, on one hand, we focused our review on 4 main cognitive ERP components (P50 gating, MMN, P300, and N400) that have been extensively investigated in psychiatric disorders.[114-117] Besides the fact that technical details such as task or modality clearly influenced recorded amplitudes and latencies, it should be noted that other ERP components (such as the contingent negative variation[118] or the error-related negativity[119]) as well as other electrophysiological tools than cognitive ERPs (such as resting EEG, oculomotor measures such as smooth pursuit and antisaccade paradigms), or even other brain imaging tools (eg, brain morphometric measures[120]), have clear merits. It could be interesting for other review articles to include these other points of view. On the other hand, we consider addiction based on the consumption of a substance, such as alcohol, cocaine, heroin, or cannabis, but other substances could also have been taken into account (such as,eg, ecstasy[121]). Recent works also showed clear neurocognitive disorders in addiction *without* substance, such as for instance Internet addiction[122] or pathological gambling.[123] Moreover, besides all we have already mentioned, drug abusers can hardly be considered as "pure" drug abuser, as even tobacco and benzodiazepines have been shown to induce neurocognitive disorders.[124,125] This relates to an important social problem, as *polydrug use* is nowadays considered as a peer norm: Indeed, because polysubstance abuse is rampant, increasingly more individuals meeting the criteria for a single

Table 3. List of the Reference Numbers Used in This Article Supporting the Current Main Point-of-View Concerning the Effect of a Specific Substance on a Specific ERP Component for the 3 Main Questions Envisaged in This Article, That Is, Consumption Versus Genetic Risk Versus Recovery After Abstinence.

		Alcohol	Cocaine	Heroin	Cannabis
Acute/long-term consumption	P50	31	34	33	32
	MMN	43-46 (acute); 47-50 (long-term)	/	51, 52	53
	P300	13, 72-77, 86, 88-90	13, 78, 79, 86, 93-95	13, 81, 82, 86, 91, 92	13, 80, 96, 97
	N400	105, 106	112, 113	111	110
Genetic risk	P50	31	/	/	/
	MMN	54, 55	/	/	/
	P300	13, 17, 72	13, 84	13, 83, 84	13
	N400	109	/	/	/
Abstinence	P50	37	38	/	/
	MMN	56-58	/	/	/
	P300	13, 87	13	13	13
	N400	107, 108	/	/	/

SUD also meet the criteria for other substances. For instance, there is clear evidence of widespread tobacco use (62% lifetime prevalence in 1992) and alcohol use (nearly 90%) among high school seniors.[126] Nevertheless, it should be noted that an ethnographic study of the need to smoke cigarettes found that a major reason that adolescents smoke is not because they crave or desire nicotine, but rather because of their perceived need to use cigarettes to manage social situations and maintain their social connections.[126]Polysubstance abuse therefore clearly refers to a complex problem, involving both individual and social parameters. In this view, it is really important to mention that it is currently difficult to separate effects of different substances on ERP components, as for instance inclusion/exclusion criteria often vary across studies, and acute effects of substances are not always excluded through the use of urine toxicology screen and breathanalyzer test. Further studies should clearly take these points into account. Also, drug abusers often displayed psychiatric comorbidity,[127] so that ERP modulations may be associated with the SUD and with a potential underlying personality disorder. For instance, it has been shown that frontal decrements of the P300 in alcohol dependence are correlated with the total number of childhood conduct disorder and adult antisocial personality disorder symptoms.[128]In this way, and at this point, it clearly appears that the generalizability of results may be questioned. Nevertheless, we suggest that, even if preliminary, the reported data have the potential to highlight the pathophysiology of SUDs (and then to improve clinical intervention), and outline the urgent need in further studies to develop multisite guidelines to record a battery of electrophysiological measures that may be compared and used across studies.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

Salvatore Campanella is a research associate funded by the Belgian Fund of Scientific Research (F.R.S.-F.N.R.S.) which in part supported the research, authorship, and/or publication of this article.

References

1. Anderson P. Global use of alcohol, drugs and tobacco. *Drug Alcohol Rev*. 2006;25:489-502.
2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:617-627.
3. Hyman SE. The neurobiology of addiction: implications for voluntary control of behavior. *Am J Bioeth*. 2007;7:8-11.
4. Baker TE, Stockwell T, Barnes G, Holroyd CB. Individual differences in substance dependence: at the intersection of brain, behaviour and cognition. *Addict Biol*. 2010;16:458-466.
5. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freelymoving rats. *Proc Natl Acad Sci U S A*. 1988;85:5274-5278.
6. Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. *Annu Rev Clin Psychol*. 2008;4:325-348.
7. Robinson T, Berridge K. Addiction. *Annu Rev Psychol*. 2003;54:25-53.
8. Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse*. 1997;9:103-110.
9. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci*. 2005;8:1458-1463.
10. Masten AS, Faden VB, Zucker RA, Spear LP. Underage drinking: a developmental perspective. *Pediatrics*. 2008;121(suppl 4):S235-S251.
11. Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young

adulthood: a meta-analysis. *Twin Res Hum Genet*. 2007;10:423-433.
12. Uhl GR. Current status of drug dependence/abuse studies: cellular and molecular mechanisms of drugs of abuse and neurotoxicity. Part 1. Molecular genetics of substance abuse vulnerability: remarkable recent convergence of genome scan results. *Ann N Y Acad Sci*. 2004;1025:1-13.
13. Euser AS, Arends LR, Evans BE, Greaves-Lord K, Huizink AC, Franken IH. The P300 event-related brain potential as a neurobiological endophenotype for substance use disorders: a meta-analytic investigation. *Neurosci Biobehav Rev*. 2012;36:572-603.
14. Frederick JA, Iacono WG. Beyond the DSM: defining endophenotypes for genetic studies of substance abuse. *Curr Psychiatry Rep*. 2006;8:144-150.
15. Bearden CE, Freimer NB. Endophenotypes for psychiatric disorders: ready for primetime? *Trends Genet*. 2006;22:306-313.
16. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160:636-645.
17. Singh SM, Basu D. The P300 event-related potential and its possible role as endophenotype for studying substance use disorders: a review. *Addict Biol*. 2008;14:298-309.
18. Rugg MD, Coles MGH. *Electrophysiology of Mind. Event-Related Brain Potentials and Cognition*. Oxford, UK: Oxford University Press; 1995.
19. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology*. 2004;29:1765-1781.
20. Calkins ME, Iacaono WG. Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. *Am J Med Genet*. 2000;97:72-76.
21. Price GW, Michie PT, Johnston J, et al. A Multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian Family Study of Schizophrenia. *Biol Psychiatry*. 2006;60:1-10.
22. Pfefferbaum A, Roth WT, Ford JM. Event-related potentials in the study of psychiatric disorders. *Arch Gen Psychiatry*. 1995;52:559-563.
23. Iacono WG. Identifying psychophysiological risk for psychopathology: examples from substance abuse and schizophrenia research. *Psychophysiology*. 1998, 35:621-637.
24. Oranje B, van Berckel BNM, Kemner C, van Ree JM, Kahn RS, Verbaten MN. P50 suppression and prepulse inhibition of the startle reflex in humans: a correlational study. *Biol Psychiatry*. 1999;45:883-890.
25. Pratt H, Starr A, Michalewski H, Bleich N, Mittelman N. The auditory P50 component to onset and offset of sound. *Clin Neurophysiol*. 2008;119:376-387.
26. Pogarell O, Mulert C, Hegerl U. Event-related potentials in psychiatry. *Clin EEG Neurosci*. 2007;38:25-34.
27. Adler LE, Pachtman E, Franks RD, Pecevich M, Waldo MC, Freedman R. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry*. 1982;17:639-654.
28. Freedman R, Waldo M, Bickford-Winner P, Nagamoto HT. Elementary neuronal dysfunction in schizophrenia. *Schizophr Res*. 1991;4:233-243.
29. Wickham H, Murray RM. Can biological markers identify endophenotypes predisposing to schizophrenia? *Int Rev Psychiatry*. 1997;9:355-364.
30. Myles-Worsley M, Ord L, Blailes F, Ngiralmau H, Freedman R. P50 sensory gating in adolescents from a Pacific Island isolate with elevated risk for schizophrenia. *Biol Psychiatry*. 2004;55:663-667.
31. Freedman R, Waldo M, Waldo CI III, Wilson JR. Genetic influences on the effects of alcohol on auditory evoked potentials. *Alcohol*. 1987;4:249-253.
32. Patrick G, Struve FA. Reduction of auditory P50 gating response in marihuana users: further supporting data. *Clin Electroencephalogr*. 2000;31:88-93.
33. He S, Yu L, Jia S, Chen Q, Wang D, Hu S. Effects of long-term sustained naltrexone release on the optic center in opioid-dependent patients. *Neural Regen Res*. 2011;6:236-240.
34. Boutros N, Campbell D, Petrakis I, Krystal J, Caporale M, Kosten T. Cocaine use and the mid-latency auditory evoked responses. *Psychiatry Res*. 2000;96:117-126.
35. Anokhin AP. Genetic and environmental influences on sensory gating of mid-latency auditory evoked responses: a twin study. *Schizophr Res*. 2007;89:312-319.
36. Fein G, Biggins C, MacKay S. Cocaine abusers have reduced auditory P50 amplitude and suppression compared to both normal controls and alcoholics. *Biol Psychiatry*. 1996;39:955-965.
37. Marco J, Fuentemilla L, Grau C. Auditory sensory gating deficit in abstinent chronic alcoholics. *Neurosci Lett*. 2005;375:174-177.
38. Boutros N, Gooding D, Sundaresan K, Burroughs S, Johanson CE. Cocaine-dependence and cocaine-induced paranoia and mid-latency auditory evoked responses and sensory gating. *Psychiatry Res*. 2006;145:147-154.
39. Näätänen R. Event-related potentials and automatic information processing. In: Näätänen R, ed. *Attention and Brain Function*. Hillsdale, NJ: Lawrence Erlbaum; 1992:136-200.
40. Kraus N, McGee T, Carrell TD, Sharma A. Neurophysiologic bases of speech discrimination. *Ear Hear*. 1995;16:19-37.
41. Atienza M, Cantero JL. Complex sound processing during human REM sleep by recovering information from long-term memory as revealed by the mismatch negativity (MMN). *Brain Res*. 2001;901:151-160.
42. Näätänen R, Kujala T, Escera C, et al. The mismatch negativity (MMN)—a unique window to disturbed central auditory processing in ageing and different clinical conditions. *Clin Neurophysiol*. 2012;123:424-458.
43. Jaaskelainen IP, Lehtokoski A, Alho K, et al. Low dose of ethanol suppresses mismatch negativity of auditory event-related potentials. *Alcohol Clin Exp Res*. 1995;19:607-610.
44. Jaaskelainen IP, Pekkonen E, Hirvonen J, Sillanaukee P, Naatanen R. Mismatch negativity subcomponents and ethyl alcohol. *Biol Psychol*. 1996;43:13-25.
45. Jaaskelainen IP, Hirvonen J, Kujala T, et al. Effects of naltrexone and ethanol on auditory event-related brain potentials. *Alcohol*. 1998;15:105-111.
46. Jaaskelainen IP, Schroger E, Naatanen R. Electrophysiological indices of acute effects of ethanol on involuntary attention shifting. *Psychopharmacology*. 1999;141:16-21.
47. Realmuto G, Begleiter H, Odencrantz J, Porjesz B. Event-related potential evidence of dysfunction in automatic processing in abstinent alcoholics. *Biol Psychiatry*. 1993;33:594-660.
48. Holguin RS, Corral M, Cadaveira F. Mismatch negativity in young children of alcoholics from high-density families. *Alcohol Clin Exp Res*. 1998;22:1363-1368.
49. Grau C, Polo MD, Yago E, Gual A, Escera C. Auditory sensory memory as indicated by mismatch negativity in chronic alcoholism. *Clin Neurophysiol*. 2001;112:728-731.
50. vanderStelt O, Belger A. Application of electroencephalography to the study of cognitive and brain functions in schizophrenia. *Schizophr Bull*. 2007;33:955-970.
51. Naatanen R. The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its

magnetic equivalent MMNm(Presidential Address, 1999). *Psychophysiology*. 2001;38:1-21.
52. Kivisaari R, Lehtinen R, Autti T, et al. Impaired pre-attentive auditory processing in opioid dependence with and without benzodiazepine co-dependence revealed by combined magnetoencephalography and electroencephalography. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:1378-1386.
53. Roser P, Della B, Norra C, Uhl I, Brüne M, Juckel G. Auditory mismatch negativity deficits in long-term heavy cannabis users. *Eur Arch Psychiatry Clin Neurosci*. 2010;260:491-498.
54. Rodriguez HS, Corral M, Cadaveira F. Mismatch negativity in young children of alcoholics from high-density families. *Alcohol Clin Exp Res*. 1998;22:1363-1368.
55. Zhang XL, Cohen HL, Porjesz B, Begleiter H. Mismatch negativity in subjects at high risk for alcoholism. *Alcohol Clin Exp Res*. 2001;25:330-337.
56. Kathmann N, Wagner M, Rendtorff N, Engel RR. Delayed peak latency of the mismatch negativity in schizophrenics and alcoholics. *Biol Psychiatry*. 1995;37:754-757.
57. Pekkonen E, Ahveninen J, Jaaskelainen IP, Seppa K, Naatanen R, Sillanaukee P. Selective acceleration of auditory processing in chronic alcoholics. *Alcohol Clin Exp Res*. 1998;22:605-609.
58. Fein G, Whitlow B, Finn P. Mismatch negativity: no difference between controls and abstinent alcoholics. *Alcohol Clin Exp Res*. 2004;28:137-142.
59. Sutton S, Braren M, Zubin J, John ER. Information delivery and the sensory evoked potential. *Science*. 1965;150:1187-1188.
60. Polich J, Herbst KL. P300 as a clinical assay: rationale, evaluation, and findings. *Int J Psychophysiol*. 2000;38:3-19.
61. Verleger R. Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of P3. *Behav Brain Sci*. 1988;11:343-356.
62. Tomberg C, Desmedt JE. Human perceptual processing: inhibition of transient prefrontal-parietal 40 Hz binding at P300 onset documented in non-averaged cognitive brain potentials. *Neurosci Lett*. 1998;255:163-166.
63. Sommer W, Matt J. Awareness of P300-related cognitive processes: a signal detection approach. *Psychophysiology*. 1990;27:575-585.
64. Knight RT. Distributed cortical network for visual attention. *J Cogn Neurosci*. 1997;9:75-91.
65. Smith JL, Johnstone SJ, Barry RJ. Effects of pre-stimulus processing on subsequent events in a warned Go/NoGo paradigm: response preparation, execution and inhibition. *Int J Psychophysiol*. 2006;61:121-133.
66. Kaiser S, Unger J, Kiefer M, Markela J, Mundt C, Weisbrod M. Executive control deficit in depression: event-related potentials in a Go/Nogo task. *Psychiatry Res*. 2003;122:169-184.
67. Posner MI, DiGirolamo GJ. Executive attention: conflict, target detection and cognitive control. In: Parasuraman R, ed. *The Attentive Brain*. Cambridge, MA: MIT Press; 1998:401-423.
68. Fuster JM. *The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe*. 2nd ed. New York, NY: Raven Press; 1989.
69. Brown GG, Kindermann SS, Siegle GJ, Granholm E, Wong EC, Buxton RB. Brain activation and pupil response during covert performance of the Stroop Color Word task. *J Int Neuropsychol Soc*. 1999;5:308-319.
70. Watanabe J, Sugiura M, Sato K, et al. The human prefrontal and parietal association cortices are involved in No-Go performances: an event-related fMRI study. *Neuroimage*. 2002;17:1207-1216.
71. Ullsperger M, von Cramon DY. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage*. 2001;14:1387-1401.
72. Begleiter H, Porjesz B, Bihari, Kissin B. Event related brain potentials in boys at risk for alcoholism. *Science*. 1984;225:1493-1496.
73. Porjesz B, Rangaswamy M, Kamarajan C, Jones KA, Padmanabhapillai A, Begleiter H. The utility of neurophysiological markers in the study of alcoholism. *Clin Neurophysiol*. 2005;116:993-1018.
74. Maurage P, Philippot P, Verbanck P, et al. Is the P300 deficit in alcoholism associated with early visual impairments (P100-N170)? An oddball paradigm. *Clin Neurophysiol*. 2007;118:633-644.
75. Suresh S, Porjesz B, Chorlian DB, et al. Auditory P3 in female alcoholics. *Alcohol Clin Exp Res*. 2003;27:1064-1074.
76. Hada M, Porjesz B, Chorlian DB, Begleiter H, Polich J. Auditory P3a deficits in male subjects at high risk for alcoholism. *Biol Psychiatry*. 2001;49:726-738.
77. Kamarajan C, Porjesz B, Jones K, et al. Alcoholism is a disinhibitory disorder: neurophysiological evidence from a Go/No-Go task. *Biol Psychol*. 2005;69:353-373.
78. Sokhadze E, Stewart C, Hollifield M, Tasman A. Event-related potential study of executive dysfunctions in a speeded reaction task in cocaine addiction. *J Neurother*. 2008;12:185-204.
79. Sokhadze E, Singh S, Stewart C, Hollifield M, El-Baz A, Tasman A. Attentional bias to drug- and stress-related pictorial cues in cocaine addiction comorbid with PTSD. *J Neurother*. 2008;12:205-225.
80. Theunissen EL, Kauert GF, Toennes SW, et al. Neurophysiological functioning of occasional and heavy cannabis users during THC intoxication. *Psychopharmacology*. 2012;220:341-350.
81. Yang B, Yang S, Zhao L, Yin L, Liu X, An S. Event-related potentials in a Go/Nogo task of abnormal response inhibition in heroin addicts. *Sci China C Life Sci*. 2009;52:780-788.
82. Papageorgiou CC, Liappas IA, Ventouras EM, et al. Long-term abstinence syndrome in heroin addicts: indices of P300 alterations associated with a short memory task. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:1109-1115.
83. Singh SM, Basu D, Kohli A, Prabhakar S. Auditory P300 event-related potentials and neurocognitive functions in opioid dependent men and their brothers. *Am J Addict*. 2009;18:198-205.
84. Kouri EM, Lukas SE, Mendelson JH. P300 assessment of opiate and cocaine users: effects of detoxification and buprenorphine treatment. *Biol Psychiatry*. 1996;40:617-628.
85. Heilig M, Goldman D, Berrettini W, O'Brien CP. Pharmacogenetic approaches to the treatment of alcohol addiction. *Nat Rev Neurosci*. 2011;12:670-684.
86. Bauer LO. CNS recovery from cocaine, cocaine and alcohol, or opioid dependence: a P300 study. *Clin Neurophysiol*. 2001;112:1508-1515.
87. Pfefferbaum A, Ford J, White P, Mathalon D. Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcohol Clin Exp Res*. 1991;15:839-850.
88. Herrmann MJ, Weijers HG, Wiesbeck GA, Aranda D, Böning J, Fallgatter AJ. Event-related potentials and cue-reactivity in alcoholism. *Alcohol Clin Exp Res*. 2000;24:1724-1729.
89. Namkoong K, Lee E, Lee CH, Lee BO, An SK. Increased P3 amplitudes induced by alcohol-related pictures in patients with alcohol dependence. *Alcohol Clin Exp Res*. 2004;28:1317-1323.
90. Heinze M, Wölfling K, Grüsser SM. Cue-induced auditory evoked potentials in alcoholism. *Clin Neurophysiol*. 2007;118:856-862.

91. Franken IH, Stam CJ, Hendriks VM, van den Brink W. Neurophysiological evidence for abnormal cognitive processing of drug cues in heroin dependence. *Psychopharmacology*. 2003;170:205-212.
92. Lubman DI, Allen NB, Peters LA, Deakin JF. Electrophysiological evidence that drug cues have greater salience than other affective stimuli in opiate addiction. *J Psychopharmacol*. 2008;22:836-842.
93. Franken IH, Hulstijn KP, Stam CJ, Hendriks VM, van den Brink W. Two new neurophysiological indices of cocaine craving: evoked brain potentials and cue moderated startle reflex. *J Psychopharmacol*. 2004;18:544-552.
94. van de Laar MC, Licht R, Franken IH, Hendriks VM. Event-related potentials indicate motivational relevance of cocaine cues in abstinent cocaine addicts. *Psychopharmacology*. 2004;177:121-129.
95. Dunning JP, Parvaz MA, Hajcak G, et al. Motivated attention to cocaine and emotional cues in abstinent and current cocaine users—an ERP study. *Eur J Neurosci*. 2011;33:1716-1723.
96. Wölfling K, Flor H, Grüsser SM. Psychophysiological responses to drug-associated stimuli in chronic heavy cannabis use. *Eur J Neurosci*. 2008;27:976-983.
97. Nickerson LD, Ravichandran C, Lundahl LH, et al. Cue reactivity in cannabis-dependent adolescents. *Psychol Addict Behav*. 2011;25:168-173.
98. Stacy AW, Wiers RW. Implicit cognition and addiction: a tool for explaining paradoxical behavior. *Annu Rev Clin Psychol*. 2010;6:551-575.
99. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002;159:1642-1652.
100. Robbins TW, Everitt BJ. Drug addiction: bad habits add up. *Nature*. 1999;398:567-570.
101. Kutas M, Hillyard SA. Reading senseless sentences: brain potentials reflect semantic incongruity. *Science*. 1980;207:203-205.
102. Duncan CC, Barry RJ, Connolly JF, et al. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clin Neurophysiol*. 2009;120:1883-1908.
103. Kutas M, Van Petten C, Kluender R. Psycholinguistics electrified II: 1995-2005. In: Traxler M, Gernsbacher MA, eds. *Handbook of Psycholinguistics*. 2nd ed. New York, NY: Elsevier; 2006:659-724.
104. Kuperberg GR, Sitnikova T, Goff D, Holcomb PJ. Making sense of sentences in schizophrenia: electrophysiological evidence for abnormal interactions between semantic and syntactic processing. *J Abnorm Psychol*. 2006;115:251-265.
105. Ji J, Porjesz B, Beglieter T. Event-related potential index of semantic mnemonic dysfunction in abstinent alcoholics. *Biol Psychiatry*. 1999;45:494-507.
106. Porjesz B, Begleiter H, Wang K, et al. Linkage and linkage disequilibrium mapping of ERP and EEG phenotypes. *Biol Psychol*. 2002;61:229-248.
107. Nixon SJ, Tivis R, Ceballos N, Varner JL, Rohrbaugh J. Neurophysiological efficiency in male and female alcoholics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:919-927.
108. Roopesh BN, Rangaswamy M, Kamarajan C, Chorlian DB, Pandey AK, Porjesz B. Reduced resource optimization in male alcoholics: N400 in a lexical decision paradigm. *Alcohol Clin Exp Res*. 2010;34:1905-1914.
109. Roopesh BN, Rangaswamy M, Kamarajan C, et al. Priming deficiency in male subjects at risk for alcoholism: the N4 during a lexical decision task. *Alcohol Clin Exp Res*. 2009;33:2027-2036.
110. Kiang M, Christensen BK, Streiner DL, Roy C, Patriciu I, Zipursky RB. Association of abnormal semantic processing with delusion-like ideation in frequent cannabis users: an electrophysiological study. *Psychopharmacology*. 2013;225:95-104.
111. He S, Yu L, Chen Q, Wang D, Hu S, Jia S. Effect of long-term sustained release naltrexone on semantic recognition of opioid addicts. *J Clin Rehabil Tissue Eng Res*. 2009;13:1573-1576.
112. Jasiukaitis P, Fein G. Intact visual word priming in cocaine dependent subjects with and without cognitive deficit. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23:1019-1036.
113. Ceballos NA, Houston RJ, Smith ND, Bauer LO, Taylor RE. N400 as an index of semantic expectancies: differential effects of alcohol and cocaine dependence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:936-943.
114. Patterson JV, Hetrick WP, Boutros NN, et al. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Res*. 2008;158:226-247.
115. Oades RD, Dittmann-Balcar A, Zerbin D, Grzella I. Impaired attention-dependent augmentation of MMN in nonparanoidvs paranoid schizophrenic patients: a comparison with obsessive-compulsive disorder and healthy subjects. *Biol Psychiatry*. 1997;41:1196-1210.
116. Salisbury DF, Shenton ME, McCarley RW. P300 topography differs in schizophrenia and manic psychosis. *Biol Psychiatry*. 1999;45:98-106.
117. Kiehl KA, Laurens KR, Bates AT, Liddle PF. Psychopathy and semantic processing: an examination of the N400. *Pers Indiv Diff*. 2006;40:293-304.
118. Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AL. Contingent negative variation: an electric sign of sensorimotor association and expectancy in the human brain. *Nature*. 1964;203:380-384.
119. Olvet DM, Hajcak G. The error-related negativity (ERN) and psychopathology: toward an endophenotype. *Clin Psychol Rev*. 2008;28:1343-1354.
120. Prasad KM, Keshavan MS. Structural cerebral variations as useful endophenotypes in schizophrenia: do they help construct "extended endophenotypes"? *Schizophr Bull*. 2008;34:774-790.
121. Burgess AP, Venables L, Jones H, Edwards R, Parrott AC. Event related potential (ERP) evidence for selective impairment of verbal recollection in abstinent recreational methylenedioxymethamphetamine ("Ecstasy")/polydrug users. *Psychopharmacology*. 2011;216:545-556.
122. Dong G, Zhou H, Zhao X. Impulse inhibition in people with Internet addiction disorder: electrophysiological evidence from a Go/NoGo study. *Neurosci Lett*. 2010;485:138-142.
123. Oberg SA, Christie GJ, Tata MS. Problem gamblers exhibit reward hypersensitivity in medial frontal cortex during gambling. *Neuropsychologia*. 2011;49:3768-3775.
124. Guney F, Genc BO, Kutlu R, Ilhan BC. Auditory P300 event-related potential in tobacco smokers. *J Clin Neurosci*. 2009;16:1311-1315.
125. Tan KR, Brown M, Labouèbe G, et al. Neural bases for addictive properties of benzodiazepines. *Nature*. 2010;463:769-774.
126. Johnson JL, Bottorff JL, Moffat B, Ratner PA, Shoveller JA, Lovato CY. Tobacco dependence: adolescents' perspectives on the need to smoke. *Soc Sci Med*. 2003;56:1481-1492.
127. Armstrong TD, Costello EJ. Community studies on adolescent substance use, abuse, or dependence. *J Consult Clin Psychol*. 2002;70:1224-1239.
128. Costa L, Bauer L, Kuperman S, et al. Frontal P300 decrements, alcohol dependence, and antisocial personality disorder. *Biol Psychiatry*. 2000;47:1064-1071.