Could cognitive event-related potentials be used to orient neuropsychological rehabilitation? A perspective paper through the example of alcohol dependence

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Abstract

The prevention of relapse is a main challenge to face with in alcohol dependence. Two major cognitive factors can partially account for alcoholics’ inability to remain abstinent: attentional biases directed towards alcohol-related stimuli that increase the urge to drink, and impaired response inhibition towards these cues that makes it more difficult for alcoholics to resist temptation. A recent study of ours investigated response inhibition in alcohol dependent patients, by means of an event-related potentials (ERP) modified Go/No-Go paradigm, right after a three weeks detoxification cure. Main results of the study are: (1) among 27 recently detoxified patients, 13 relapsed after a three month follow-up period; (2) at a behavioural level, patients displayed more commission errors than healthy matched controls; however, behavioural data did not allow to discriminate between future relapers and non-relappers; and (3) the only parameter discriminating relapers and non-relapers was the No-Go P300 component: future relapers displayed increased amplitudes, suggesting that patients who involve more

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neural resources to perform inhibition will be those of higher risk to relapse. These preliminary data suggest a great clinical potential of the ERP technique in preventing relapse in alcohol dependent patients, as using cognitive ERP may orient an individual patient to an adapted cognitive rehabilitation program.

Keywords: Event-related potentials; Biological marker; Alcoholism; Relapse; Cognitive rehabilitation

1. Introduction

It is estimated that about 27% of the adult European population, 18-65 of age, is or has been affected by at least one mental disorder in the past 12 months (Wittchen & Jacobi, 2005). One main objective of genetic studies is to define vulnerability factors that may help to prevent the development of a mental disease. However, once the disease occurs, the main responsibility of psychiatrists is to render accurate diagnoses that guide medication selection for the severely mentally ill (Basco et al., 2000). A crucial problem in psychiatry, affecting research as well as clinical work, is that, contrary to physicians, applying the scientific method to the investigation of human mental illness reveals to be complicated, as levels of analysis should at least include both mind and brain to explain normal or aberrant behaviors (Epstein, Stern & Silbersweig, 2001). A consequence of this human mind complexity is that, even if psychopathological states may be effectively alleviated by a combination of psychotherapy and drug treatment, the relapse rate is tremendously high in several psychiatric afflictions (Wiborg & Dahl, 1996; Perry, Tarrier, Morriss, McCarthy & Limb, 1999; Robinson et al., 1999). In other words, research is still needed to fill in the gap existing between “illness remission” and “complete recovery” (Andreasen et al., 2005). In the last decades, several orientations have tried to bridge the gap between mind functioning and behavior by promoting the integration across diverse levels of analysis. Neuropsychiatry, through the use of brain imaging techniques, allowed providing a perspective on mental phenomena and their associated brain states, promoting therefore an integrated perspective on both normal and aberrant brain functioning and related behaviors. However, at this stage, a direct link between a specific disease-related symptom phenomenology and a precise abnormal brain activity is still impossible to establish (Epstein et al., 2001). Also, thanks to the discipline of cognitive psychopathology, research suggests that increasing cognitive performance reduces clinical symptoms, boosting the search for ad hoc pharmacologi-
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Neural intervention and efficient cognitive rehabilitation procedure (Kraus & Keefe, 2007). However, despite the considerable research efforts that have been devoted to identify and develop pharmacological agents, results from Randomized Controlled Trial studies are not univocal, and the “real world” cognitive functioning gain provided by these agents seems disappointingly modest (Harvey, 2009).

The complexity to treat a mental illness is obvious if we consider, for instance, alcohol dependence. In Europe, costs of brain disorders induced by mental diseases are around 240 billions by year (Andlin-SoBocki & Rehm, 2005). Among these, 57 billions are devoted to drug and alcohol dependence. Alcohol dependence constitutes one of the most serious public health problems, as it is estimated that 3-8% of all global deaths and 4% of global disability-adjusted life-years are attributable to alcohol worldwide (Prince et al., 2007). Although the first step in alcohol dependence treatment is quite straightforward (detoxification cure), the main problem for clinicians concerns the prevention of relapse, as (1) 40-70% of patients just following a psychosocial therapy typically resume alcohol use within 1 year post-treatment (Finney, Hahn & Moos, 1996); and (2) there currently seems to be little convincing evidence of significant cognitive-enhancing benefits for pharmacological agents or, at least, the reported gains are poor or imperceptible on a clinical and functional level (Laroi & Raballo, 2010). In this view, there is a current strong interest in the development of alternatives to psychotherapy and medication (Dobson et al., 2008). In recent years, we have seen the emergence of several intervention strategies aimed at improving psychiatric treatment, such as multisystemic (Henggeler, 1999), cognitive behavioral (Pike, Walsh, Vitousek, Wilson & Bauer, 2003), or mindfulness (Chiesa & Serretti, 2011) therapies. Also, research is still ongoing to determine what type of alcohol dependent individual benefits the most from using either medication (mainly naltrexone or acamprosate). Experiments, designed to test whether variables for matching treatment of a specific alcoholic patient can be defined, are particularly leading-edge. For instance, the PREDICT study is currently testing the existence of clusters (i.e., subgroups of patients) that differentiate so-called “relief drinkers/cravers” showing geno- and endophenotypes associated with glutamatergic dysfunction (preferably responding to acamprosate), and so-called “reward drinkers/cravers” mainly associated with alterations in the dopaminergic and opioidergic system (preferably responding to naltrexone) (Mann et al., 2009). The goal of these “new” interventions is evidently not to discredit existing treatment methods, but to provide a complementary set of tools to be used by clinicians to improve current patient assessment.
With this in mind, we would like to focus in this paper on event-related potentials (ERPs). By allowing the evaluation of the entire information processing stream, they can help pinpoint the specific neurocognitive functions that should be rehabilitated in each patient through specific and individualized cognitive remediation procedures (Campanella, 2013). The current literature suggests that individuals who chronically abuse alcohol exhibit a wide variety of cognitive deficits resulting from cerebral dysfunction that is either directly or indirectly related to their alcohol consumption history (Allen, Goldstein & Seaton, 1997). These cognitive deficits are increasingly being acknowledged as an important feature of alcohol dependence, mainly by triggering relapse (Wiers et al., 2007). The tagged cognitive candidates are attentional biases towards alcohol-related pictures, and altered inhibitory skills. Indeed, dual-process theories suggest there are two main processes associated with drinking behavior: (1) an automatic process characterized by an increase in the salience of alcohol-related cues, which tend to “grab the attention” of experienced drinkers; and (2) a lack of executive resources needed to inhibit the salient and dominant response (i.e., to drink), due to the neurotoxic effects of repeated alcohol consumption and/or a state of vulnerability (Wiers et al., 2007). In other words, alcoholics suffer from deficits in their cognitive control mechanisms of “inhibiting” and “shifting”, and these deficits are exacerbated by cognitive biases for alcohol-related stimuli (Noël et al., 2001). In this view, last years have seen the emergence of promising Cognitive Retraining Procedures (CRP), which showed for instance that decreasing attentional bias towards alcohol by cue exposure may help to regain control over addictive impulses (Schoenmakers, Wiers, Jones, Bruce & Jansen, 2007; Schoenmakers et al., 2010; Fadardi & Cox, 2009). The underlying neural mechanisms of these phenomena have also been gathered through the use of fMRI studies, suggesting that when conditioned substance stimuli are present, they increase dopamine levels in the cortico-striatal circuit, particularly in the anterior cingulate cortex (ACC), amygdala, and nucleus accumbens, which in turn serves to draw the subject’s attention toward the drug-related stimulus (here, alcohol) (Heinz, Beck, Grüsser, Grace & Wrase, 2009; Vollstädt-Klein et al., 2012). The clinical significance of fMRI cue reactivity is well illustrated by findings that cue-induced activations in regions such as the ventral and dorsal striatum, the ACC and adjacent medial prefrontal regions are associated in alcoholic abstinent patients with subsequent relapse risk and drinking outcomes (Braus et al., 2001; Grüsser et al., 2004). Alternatively, interventions might also focus on cognitive control abilities such as response inhibition and working memory, which are important moderators of the predictive relationship between automatic impulses and drinking behavior. Recent research shows
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that training response inhibition changes both evaluations of stimuli that were associated with a stopping response, and increases inhibitory control over these stimuli in heavy social drinkers (Houben, Nederkoorn, Wiers & Janssest, 2011). However, even if the importance of indexing cognitive disturbances begins to be well-established in psychiatric clinical settings (Wiers, Eberl, Rinck, Becker & Lindenmeyert, 2011), the manner with which to efficiently perform cognitive analyses is a matter of debate. This is mainly due to cognition fractionation (e.g., executive function refers to a wide range of cognitive processes [including problem-solving, flexibility, inhibition, planning, and decision-making], and a patient’s performance in one executive function may have little or no predictive value for how the patient will perform in another; Chan, Shum, Touloupolou & Chen, 2008), which means that a global assessment of all cognitive functions may take several hours to perform, and this is incompatible with both psychiatric patients’ statuses and consultation pressures. In this view, cognitive screening needs to identify genuine impairment in as little time as possible, using an easily administered instrument, in an individual patient (Cullen, O’Neill, Evans, Coen & Lawlor, 2007). We propose that cognitive ERPs may help clinicians to reach this goal (Campanella, 2013), and we will present in this paper some preliminary data illustrating how this can be achieved with alcohol dependent patients.

2. Methods

ERPs, which are derived from electroencephalography, are highly sensitive and have the potential to monitor brain electrical activity with a fine temporal resolution (on the order of milliseconds). Thus, when healthy individuals perform a cognitive task, it is possible to observe the various electrophysiological components representing the cognitive stages utilized to achieve “normal” performance (Rugg & Coles, 1995). Another highly valuable aspect of cognitive ERPs is that they can permit identification/detection of the electrophysiological component(s) consistent with the onset of a dysfunction, allowing the inference of impaired cognitive stages. In other words, by using a well characterized task and analyzing which ERPs show decreased amplitude and/or delayed latency compared to normal values, it is possible to deduce which ERP component is responsible for the cognitive deficit (Rugg & Coles, 1995). This suggests that during illness, various cognitive stages of the information-processing stream may be affected, and that the recorded ERP components may be considered as biological markers.
of the disease, indexing specific pathophysiological mechanisms, that may or may not recover with the illness’ remission (Campanella, 2013). Moreover, similar patterns at the behavioral level (e.g., an altered recognition of emotional facial expressions) can result from different disturbances in cognitive processes from one population to another (for instance, a decreased P100 in social anxiety and a delayed P300 in generalized anxiety disorder; Rossignol, Philippot, Douilliez, Crommelinck & Campanella, 2005; Rossignol et al., 2012). This point has great clinical relevance, because it suggests that a similar pattern of deficit may be attributable to different neurocognitive disturbances, supporting the notion that similar behavioral deficits should be differently rehabilitated. In other words, this suggests that patients who display a similar group of symptoms and belong to a closed psychiatric category might have deficits that originate from different levels of the cognitive process. Also, ERPs are sensitive enough to detect even minor cognitive restrictions, that are still not observable at a behavioral level (e.g., Wilkinson & Halligan, 2004; Maurage, Pesenti, Philippot, Joassin & Campanella, 2009). This suggests that some biological markers of vulnerability may be detected if appropriate procedures were used.

In order to investigate the potential efficiency of ERPs to orient cognitive rehabilitation of psychiatric patients, we investigated whether the No-Go P300 component, a well-known ERP component underlying the inhibition process, could be used as a biological marker to predict relapse in alcohol dependence. To reach this aim, at the end of a three week detoxification cure, and just before being discharged, twenty-seven alcoholic patients performed a variant of the Go/No-Go task (Petit, Kornreich, Noël, Verbanck & Campanella, 2012), in which a frequent Go signal (letter M), and a rare No-Go signal (letter W) were superimposed on three different types of background images: neutral (black background), alcohol-related and non alcohol-related (Figure 1a). The task was paired with an ERP recording, known to be highly sensitive even to minor cognitive restrictions (Rugg & Coles, 1995). Then, three months later, patients were contacted by phone to know whether they resume in alcohol drinking or not. Our main objective was to investigate whether the parameters (amplitude, latency) of the No-Go P300 recorded at the end of the detoxification cure may help to discriminate patients who will relapse or not. All details concerning this study may be found in Petit and colleagues (Petit et al., 2014).
Part A: Go/No-Go task. Participants were confronted with six blocks of 133 stimuli, divided in 93 Go trials (letter M), and 40 No-Go trials (letter W). The letters were superimposed on two non-alcohol-related background pictures (NAC), two alcohol-related background pictures (AC) or a neutral black background (NC) (from Petit et al., 2012). Part B: Individual mean P3d amplitudes in Patients Group. Mean difference wave (Go P300 wave subtracted from the No-Go P300 wave) for each patient derived from the computation of the six electrodes sites (FC1, FC2, Cz, CP1, CP2 and Pz) and the three contexts (A, NAC, NC) collapsed and as a function of their abstinence status at three months follow-up: relapsers are represented in red and non-relapsers are represented in blue (from Petit et al., 2014).
3. Results

Our major aim in that study (Petit et al., 2014) was to complement findings on inhibitory neural processes with neural correlates obtained through ERPs in order to assess whether these could predict relapse during a three month follow-up period. Results showed that when alcoholics correctly inhibited a response, patients required more neural resources than controls, as shown by increased No-Go P300 amplitudes. Larger P300 amplitudes are commonly interpreted as indicators that increased cognitive resources are being recruited for inhibition (e.g., Pfefferbaum, Ford, Weller & Kopell, 1985; Albert, Lopez-Martín & Carretié, 2010). The larger No-Go P300 amplitude in patients may hence attest to the need for additional neural resources recruitment required to correctly perform the task. More interestingly, we also established a link between this No-Go P300 increase in patients (N = 27) and relapse. Indeed, after the three months follow-up period, we performed a comparison of relapers (n = 13) and non-relapers (n = 14) that revealed that, at a behavioral level, both groups had similar error rates. However, the No-Go P300 generated by relapers were significantly higher than those produced by non-relapers. In other words, at the end of the detoxification cure, patients who will relapse are those who needed to activate more cognitive resources during the inhibition process to perform correct response inhibitions. These results are illustrated in Figure 1b.

4. Discussion

Overall, the main results of Petit and colleagues (2014) are: (1) among 27 recently detoxified patients, 13 relapsed after the three month follow-up period; (2) at a behavioural level, patients displayed more commission errors than healthy matched controls; however, behavioural data did not allow to discriminate between future relapers and non-relapers; and (3) the only parameter discriminating relapers and non-relapers is the No-Go P300 component: future relapers displayed increased amplitudes in response to correctly inhibited trials, suggesting that patients who involve more neural resources to perform inhibition will be those of higher risk to relapse.

These data, if clearly preliminary, mainly due to small sample size, suggest a great clinical potential of the ERPs technique in preventing relapse in alcohol dependent patients, as enhanced No-Go P300 amplitude could be a reliable biological indicator of an altered inhibitory process. In this view, at a clinical level, last years have seen the emergence of CRP, which showed for
instance that decreasing attentional bias towards alcohol, through training, may help to regain control over addictive impulses (e.g., Schoenmakers et al., 2010), or that training response inhibition changes evaluation of stimuli, associated with a stopping response, and increases inhibitory control over these stimuli in heavy social drinkers (e.g., Houben et al., 2011). Therefore, as some cognitive alterations (behaviourally latent) may only be seen through the use of appropriate neuroimaging procedures, and because a complete cognitive screening is too time-consuming in daily psychiatric practice, ERPs may be used in order to investigate cognitive functions at a neural level in order to highlight in an individual patient which cognitive process(es) should be rehabilitated through CRP (Campanella, 2013).

The originality of this view is to deal with two main problems of nowadays’ clinical practice. The first concerns the DSM approach used by psychiatrists to classify alcoholism. Indeed, by this way, all alcoholics are classified into one category, yet each person is different and singular. Second, the majority of ERP-based studies investigating alcoholics compare them with matched controls using grand-averaged data, whereas, to be efficient, today’s clinical practice need more individual and “personalized” medicine. Hence, in order to be able to recommend an appropriate, individualized intervention for alcoholic patients displaying specific clinical symptoms and cognitive disturbances, we propose a procedure based on two main phases. The first phase focuses on the need to decide, quickly and using a simple task, whether a patient presents a genuine cognitive impairment. In this view, an ERP screening could be performed to indicate the likelihood of genuine cognitive impairment, which can be inferred through the comparison of the patient’s results with reference controls. Thus, a borderline score or a very impaired score (along with supporting history) might lead the psychiatrist to order, in a second phase, a more specialized assessment of cognition (i.e., by neuropsychologists), and thus thoroughly identify which cognitive domain(s) to rehabilitate. Obviously, this would require a significant collaboration between psychiatry departments, clinical neurophysiology laboratories, and neuropsychological rehabilitation centers.

To sum up, at the fundamental level, this project addresses a gap in the current ERP research: indeed, the main part of ERP studies use grand-averaged data. However, in daily clinical practice, we need individual data to move to a kind of “personalized medicine”. A first aim of further studies will then be to gather guidelines for important ERP components known to index main cognitive functions involved in alcohol relapse. To the best of our knowledge, there is still not any normative data for these components that could assist the investigators who use ERPs in clinical research. At the clinical level, this project proposes an ERP-based screening method for alco-
hol dependent individuals that could be a valuable tool to a daily clinical practice as it helps to detect specific cognitive disturbances in each singular patient. This method could allow further to plan and adapt a suitable rehabilitation strategy that targets patient’s individual needs and therefore acts on a likelihood of relapse. Future findings should be of interest to researchers and clinicians working on aspect of chronic alcoholism, wanting to improve their assessment and treatment, especially regarding long-term prevention of relapse. Finally, it is important to note that if this procedure provided encouraging results, it can be easily adapted to other forms of addictions, as also to others forms of psychiatric diseases.

References

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