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New approaches in the treatment of alcohol dependence

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"*Addiction is a brain disease*" was the title of an editorial in the renowned journal "Science" 15 years ago. The author argued that recognising addiction as a disorder of the brain can impact society´s overall health and social policy strategies and help diminish the health and social costs associated with drug abuse and addiction (*Leshner, 1997*). Such a presentation of the complex concept of addiction was revolutionary, as social and psychological aspects were largely considered as the most important, although not the only ones involved.

Some years later, clinicians were able to translate this scientific concept into significant changes in understanding, treating, and improving the outcome of one of the most prevalent addiction forms, i.e. alcohol dependence, which is one of the leading causes of preventable deaths in the EU and seen as a major public health hazard (*Kogoj et al., 2011*). Exciting progress based on such a concept includes:

1. proposing a *motor rehabilitation* (instead of the usual cognitive control to reduce impulsive choices);
2. using *positive environmental conditions* (environmental enrichment) to reduce the intense and urgent desire for alcohol (anti-craving);
3. *starting treatment* to increase the insight into the disease (facilitated by the use of anti-craving medications) rather than expecting a better insight as requirement to begin with treatment; and
4. *acting directly on the brain* with Deep Brain Stimulation (DBS) in severe cases of alcoholism

Motor rehabilitation

As a clinical index of inhibitory control and impulsivity the time required to stop a response that has already been initiated, the **stop-signal reaction time (SSRT)**, is extensively used. Human subjects classified as impulsive are slower to respond to a stop signal. For instance, cocaine users display significantly poorer ability to inhibit their behavioural responses compared to healthy controls (*Fillmore & Rush, 2002*). Active inhibition is a marker of the correct functioning of the cortical networks in the orbitofrontal brain, and decreased function in these networks is associated with higher risk of initiating drug use in early adolescence (*Whelan et al., 2012*). A recent study discovered abnormalities in brain systems linked to controlling behaviour as measured by SSRT in both cocaine-dependent individuals and their biological siblings who had no history of chronic drug abuse (*Ersche et al., 2012*). These results support the idea of an underlying neurobiological phenotype for stimulant drug addiction and indicate that brain abnormalities associated with self-control and inhibition may exist before drug use, increasing the risk for addictive behaviour.

Impaired impulse control is also implicated in the shaping of habitual alcohol use and eventual alcohol dependence, and evidence for altered neural processing during impulse control in alcohol dependence has been provided (*Li et al., 2009; Lawrence et al., 2009*).

Accordingly, a rehabilitation programme trying to increase motor inhibition might be helpful to deal in a different way with the usual cue reactivity related to alcoholism such as being proposed a drink in a group, shopping and seeing bottles, etc. This programme would need to have different proposals, for example click “yes” instead of “no” when a specific signal appears on the screen, and then another message that will ask to stop the expected action although it is already initiated. Training on the computer with neutral signals, and then with signals related to alcohol, would/should cognitively increase the capacity to reduce a motor response.

Environmental enrichment

Environmental conditions can dramatically influence the behavioural and neurochemical effects of drugs of abuse. On the other hand, positive conditions such as environmental enrichment can reduce the reinforcing effects of drugs and may provide protection against the development of drug addiction.

Experimental results demonstrate that environmental enrichment also can eliminate already established addiction-related behaviours, and suggest that environmental stimulation may be a fundamental factor in facilitating abstinence and preventing relapse (*Solinas et al., 2008*). Thus, the protocol of “enriched environment for alcohol withdrawal” during an alcohol detoxification programme is mimicking the stimulation that was found active in eliminating behavioural sensitization to cocaine in rodents. Since it is difficult to guess the exact stimulating features that explain the efficacy of environmental enrichment in rodents, a model was tested with the advantage of gathering many aspects of the initial experiment, namely “**daily cycling in a group on a virtual 3D path**” (see figure 1). Aspects of the enriched environment used in rodents could be characterised as

1. stimulating social interactions (including more than one rodent in each cage),
2. higher motor activity (a specific wheel allows more recreative running), and
3. larger cognitive stimulations (with regularly changed new objects to be discovered).

Figure 1
Environmental enrichment for the treatment of alcohol dependence:
Patients biking on a virtual 3D path, in a group, during the withdrawal process

On behalf of a research programme, four bikes, four computers and associated software systems were bought that allow cycling with precise monitoring of all physical parameters on different virtual paths (tour of Majorque Island, etc.). The slope on the screen was influencing an engine (see red arrow) acting on the rear wheel of the bike, facilitating or reducing the speed of the wheel. Turning right or left (see green arrow) should be adequate to avoid (virtually) falling down.

A preliminary study in 12 patients (groups of at least 2 patients to enhance "solidarity" between patients) showed that biking five times one hour per day including initial warming up as well as cooling down and stretching at the end of each session is not only feasible, but also meets high expectations for patients. However, biking for one hour represents an important physical effort for usually non-sportive, and sometimes unhealthy, patients. Physical exams were required for all patients in order to check cardiologist contra-indications. During this initial period of feasibility, a "passport" was made to help the patient assessing each session according to the intensity of physical exercise, frequency of social contacts, alcohol consumption during the follow-up, etc.

Reducing harmful alcohol consumption (anti-craving)

A large series of studies are currently devoted to the concept of reducing harmful alcohol consumption as a treatment target instead of lifetime abstinence, which was usually proposed before and, for example, represents a pillar of the association of the Anonymous Alcoholics (3A). With medications that reduce craving even in alcohol abusers, it is now possible to treat in the first place and then expect the patient to develop better insight and high motivation to achieve abstinence, rather than the other way around.

This new approach is not only based on the development of novel pharmacological treatments, but also on the discovery of a rather old medication initially proposed for muscle pain, baclofen (*Soyka & Rösner, 2010*). High dosages of baclofen were found to have an impressive effect to reduce relapses in severe alcohol dependent patients (*Addolorato et al., 2007*), but these stimulating findings were not confirmed by other randomized controlled trials. However, baclofen is associated with important benefit according to clinical expertise (although not systematic), and a lot of physicians are using this treatment in patients with alcohol dependence. It is important to consider that, although this type of treatment seems very effective on impulsivity and craving, it has a very low impact on compulsivity and behaviour. Therefore, coaching the treatment benefit is still a major obligation.

Deep Brain Stimulation (DBS)

Lastly, Deep Brain Stimulation (DBS), a surgical treatment involving the implantation of a medical device in the brain, represents an interesting strategy for the treatment of severe cases of alcoholism. DBS sends electrical impulses to specific parts of the brain and directly changes brain activity in a controlled manner; its effects are reversible. Until recently, it was not even possible to propose DBS as an intervention for a behaviour disorder such as addiction. However, DBS was indeed used on a very limited number of cases, with positive outcomes.

Given the devastating effects of severe addiction, with a direct impact on life expectancy, together with the excellent knowledge of the reward circuits in the brain involved in addiction, DBS might be promising in certain cases of alcoholism. The example of Obsessive Compulsive Disorder (OCD) might be a benchmark, since DBS is proposed in this disorder with specific severity criteria, which could be easily transposed to addictive diseases.

Conclusion

Alcohol and drug dependence are among the most frequent mental disorders in the European Union (EU), with a 12-month-prevalence of more than 4% (*Wittchen et al., 2011*). Alcohol dependence is one of the leading causes of preventable deaths in the EU and seen as a major public health hazard (*Kogoj et al., 2011*).

Given the substantial mortality and morbidity rates associated with alcoholism, intervention at the earliest possible stage is essential.

Supported by modern treatment with anti-craving medication, starting treatment to increase the insight into the disease, rather than expecting the patient to develop better insight before initiating treatment, represents a promising approach.

Based on expanding neurobiological knowledge, intriguing research is under way to use brain findings to develop innovative treatments including not only novel pharmacological interventions but also non-pharmacological treatment strategies such as motor rehabilitation, environmental enrichment, and Deep Brain Stimulation (DBS).

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