Alcohol related brain damage. State of the art and a call for action

Daño cerebral relacionado con el alcohol. Situación actual y llamada a la acción

Carlos Soler González*, Mercè Balcells Oliveró*, Antoni Gual Solé*,**.

* Unitat de Conductes Addictives. Servei de Psiquiatria. Institut Clínic de Neurociències. Hospital Clínic Universitari. Barcelona, Spain. ** Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

Concerns about the harmful health effects of alcohol and calls for moderate drinking are found in mankind's earliest written records. Babylonian and Egyptian laws aimed to regulate alcohol consumption, and Homer's *Odysseus* is full of references to the toxic effects of wine. Many Roman writers, like Pliny and Seneca, anticipated modern observations about the effects of alcohol abuse emphasising associations with loss of memory, antisocial behaviour, and early death. Our current ambivalent relationship with alcohol is foreseen by the fact that whereas most Greek philosophers highlighted the virtues of temperance, others were devoted to the Greek God of Wine, Dionysius (Hornblower & Spaworth, 2012).

Alcohol is the world's third largest risk factor for disease burden (WHO, 2011). Much of the burden is due to the persistent effects of alcohol in the central nervous system. It is well established that excessive alcohol use can lead to permanent brain damage. However, there is little consensus on the characteristics of the associated cognitive impairment.

There is also much debate as to whether acquired cognitive impairment is due to a direct neurotoxic effect of alcohol or if it is more attributable to secondary causes like thiamine deficiency. In this context the use of the label "alcohol related brain damage" (ARBD) to group a wide etiologic and clinical range of pathologies seems very appropriate (Ridley, Draper & Withall, 2013). What is clear is that Wernicke's Encephalopathy (WE) is still misdiagnosed and mistreated (Isenberg-Grezda, Kutberg & Nicolson, 2012, Isenberg-Grezda; Chabon & Nicolson, 2014).

There is a need for translational research in this field to connect "bench to bedside" in order to find the best ways to help patients with ARBD. Public health managers should take responsibility of such a relevant issue, as many of these patients are at the boundaries of different medical specialities, with the consequence that their needs are poorly met.

Alcohol-related brain damage. From categories to dimensions

Established, long-term neurocognitive symptoms are frequently reported in alcohol-dependent patients. These have been traditionally divided in two categories (Ridley et al., 2013):

1. Alcoholic Dementia (AD), a term introduced in the early 1970's (Boeke, 1970, Mallinson & Hoffbrand, 1974). There have been several attempts to establish operative diagnostic criteria (Oslin & Cary, 2003). However, the existence of a specific dementia directly related to ethanol toxicity has been debated for a long time (Victor, 1994). The psychopathologic characterisation of AD is inaccurate, although some authors distinguish two different patterns: frontal and sub-cortical.
2. Secondary forms. The most important is the Korsakoff's Syndrome (KS), the continuum of thiamine deficiency-related WE. Classically described as

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Enviar correspondencia a:
Carlos Soler González. Unitat de Conductes Addictives. Servei de Psiquiatria. Institut Clínic de Neurociències. Hospital Clínic Universitari. C/ Villarroel 170, esc. 9 planta 6. 08031, Barcelona, Spain. E-mail: casoler@clinic.ub.es

a combination of diencephalic amnesia, confabulation, false recognisances and space-temporal disorientation, with typically preserved instrumental functions. Other important syndromes would be Marchiafava-Bignami, pellagrous encephalopathy and acquired hepatocerebral degeneration, all of them with a reasonably well-established pathogenesis (Victor, 1994).

However, the picture is not so clear in daily practice. Many factors may act synergistically with ethanol toxicity and its related consequences to cause cognitive deterioration (e.g., brain vascular pathology, traumatic brain injury, psychiatric comorbidity). The classical syndromes rarely appear isolated, but often overlapping, incompletely or atypically.

Human behaviour and cognition are not linear products of independent "brain modules". They emerge from a complex net of variables that often interact in a modulation/moderation way (Bates, Buckman & Nguyen, 2013). Therefore, their alterations might not fit into categorical taxonomies. We now see addiction as a brain disorder caused by intricated interactions between predisposing traits, environmental factors and neural impairments due to sustained drug abuse (Jupp & Dalley, 2014). Due to this complexity, a big knowledge gap still exists. Deep comprehension that leads to solid theoretical models is probably still out of reach.

Many cognitive and behavioural disturbances have been shown to precede the onset of alcohol consumption and have been detected in non-affected relatives (Ersche et al., 2012). Some have been pointed out as addiction biomarkers or endophenotypes: working memory, behavioral inhibition (Iacono, Malone & McGue, 2008), error processing (Euser, Evans, Greaves-Lord, Huizink & Franken, 2013), anxiety-impulsivity traits like delayed reward discounting (MacKillop, 2013) and even subjective responses to alcohol (Setiawan et al., 2014). Neuroanatomical correlates of these predisposing factors have been described (Wetherhill et al., 2012; Seigneurie, Guérin Langlois & Limosin, 2013). A dimensional approach provides promising insights on how their interaction could predispose to addiction (Grégoire, Rivalan, Le Moine & Dellu-Hagedorn, 2012). The way these primary "addiction-related" impairments overlap with acquired ARBD warrants further research.

In this sense, fronto-cerebellar connexions are worth to mention. The cerebellum seems to have an important role in cognition and affect regulation. It also seems to be particularly sensitive to thiamine deficiency and alcohol neurotoxicity and is considered one of their initial "targets" (Wijnia & Goossensen, 2010; Fitzpatrick & Crowe, 2013). Moreover, altered fronto-cerebellar connectivity is a candidate amongst addiction biomarkers, as it has been found in alcohol-naïve youngsters with a family history of alcohol use disorders (AUD) (Herting, Fair & Nagel, 2011).

Even at a population level, many authors have defended the need for introducing drinking patterns into alcohol economic studies in order to better reflect alcohol impact over time (Barbosa et al., 2010). It is well known that distinct drinking patterns can cause different brain alterations in the long term. Binge drinking and the number of "heavy drinking occasions" have received much attention (Hunt, 1993, Ward, Lallemand & de Witte, 2009; Maurage et al., 2012), with results suggesting they could be particularly harmful. It is worth to mention that the raise of these patterns in adolescent and young populations, with their vulnerable, developing brains, has called the attention of specialists and authorities.

Epidemiological findings reflect the abovementioned complexity. Several reviews reported a high prevalence of alcohol abuse in patients with dementia (9-22%) and high rates of dementia in alcohol abusers (up to 24%). Variability may be partially explained by differences in sampling, alcohol use quantification and age limits (Ritchie & Villebrun, 2008). The latter is very relevant. In an Australian analysis of hospital admissions of more than 20.000 dementia patients, AD was found in 1,4% of them, but in 22% of dementia patients under 65 (Draper, Karmel, Gibson, Peut & Anderson, 2011). Similarly, rates of around 10% were found in an English epidemiological study of young-onset dementia (less than 65 years) (Harvey, Skelton-Robinson & Rossor, 2003). Such a prevalence in a relatively young population and on an acquired disease calls for proper interventions.

Apart from the most severe forms, a sizeable proportion (50-70%) of persons with AUD display some degree of neurocognitive deficit (Martin, Adinoff, Weingartner, Mukherjee & Eckardt, 1986; Fein, Bachman, Fisher & Davenport, 1990). Literature remains inconclusive with respect to which cognitive domains are more vulnerable. Some authors claim for a more specific affectation and others defend that impairment is diffuse, the latter perhaps with a little more evidence on their side (Stavro, Pelletier & Potvin, 2012). Anyway, most information is from treatment samples, so numbers could change in general population (Fein & Greenstein, 2012). Some recent approaches have studied community samples (Houston et al., 2014) and detected a positive correlation between executive dysfunction and alcohol consumption.

In the light of this complexity, as mentioned before, the term ARBD has been used for quite a long time (Harper & Kril 1984, Butterworth, 1995). Similarly, DSM V (APA, 2013) uses the categories of major and minor "neurocognitive disorder due to substance abuse".

Wernicke-Korsakoff syndrome: unforgivably forgotten

Concern has been raised on the persistent mismanagement of WE (Rinblad, Blomström, Anevret, Palmstierna, 2012; Day & Del Campo, 2013; Oisezagha et al., 2013; Tartara et al., 2013; Soler-González, Balcells-Oliveró, Sánchez-Peñataro & Gual-Solé, 2013; Wijnia & Oudman, 2013).

Against what is usually thought, WE is frequent and often presents atypically (Donnino, Vega, Miller & Walsh, 2007). Post-mortem studies found WE lesions in 2% of the general population, and up to 12% in alcoholics. The classical triad (ophtalmoparesia, ataxia and confusion) appears complete in less than ¼ of the patients and is absent in up to 1/5. This adds to the low clinician's suspicion rate and the lack of sensitive diagnostic tools to favour the accumulation of undetected WE episodes (Isenberg-Grzeda, Kutner & Nicolson, 2012) that contribute substantially to the ARBD burden, including progression to the KS (Thomson, Guerrini & Marshall, 2012). This is shocking, considering that WE is long-known and has a cheap and safe treatment (Thomson, Cook & Guerrini, 2008).

WE should be diagnosed with broad operational criteria to raise clinical suspicion, and treated as an emergency (Sechi & Serra, 2007). AUD are associated with an impairment of thiamine absorption, storage, transport and utilisation (Thomson et al., 2012). Accordingly, the latest reviews and guidelines recommend treatment with high and frequent doses of parenteral thiamine (up to 500 mg/8h) (Galvin et al.2010; NICE, 2010; Thomson et al., 2012).

Despite this, a recent Cochrane review (Day, Bentham, Callaghan, Kuruvilla & George, 2013) remarked the lack of evidence about optimal thiamine dosage. Only two randomised trials were identified, both with major caveats. Thus, it is mandatory to conduct well-designed trials to determine optimal regimes, also for prophylaxis. Afterwards, clinical guidelines should be properly implemented, as that their mere existence is not enough to change clinician's attitudes (Ward, Murch, Agarwal & Bell, 2009).

Why is neurocognitive evaluation in alcohol use disorders so important? Measuring for change

In alcoholic patients, greater cognitive impairment has been associated with less treatment compliance and fewer days of abstinence (Bates, Pawlak, Tonigan & Buckman, 2006). This redounds in huge socioeconomic costs. Although the interference of cognitive impairment with treatment outcome appears self-evident, this interaction is not simple.

Executive and amnestic problems, including prospective memory, have received particular attention, as they are linked to treatment outcomes and maintenance of abstinence (Le Berre et al., 2010; Fish, Wilson & Manly, 2010, Montgomery, Ashmore & Jansari, 2011; Griffiths et al., 2012; Lyu & Lee, 2012). Despite this, literature remains inconclusive on their extent and clinical relevance. Great individual variability and confounding factors have complicated study designs and replication (Bates, Labouvie & Voelbel, 2002; Hedden et al., 2002).

Most of previous studies focused on the direct effect of cognitive impairment on drinking outcomes, without accounting for other possible ways of influence. Literature about other sources of brain injury suggests that the effects of cognitive impairment are often mediated by some factors and may moderate the influence of others. For instance, cognitive deficits may affect psychosocial outcomes by changing the person's emotional and motivational responses. This is important for AUD treatment, because therapeutic alliance, self-efficacy, readiness to change behaviour, and the use of social support to reinforce treatment goals are key therapeutic processes (Gizewski et al., 2012; Le Berre et al., 2012). Therefore, a mediator-moderator variable distinction in the context of alternative models of brain-behaviour relations may be useful for understanding how cognitive impairment disrupts outcomes in AUD and then for tailoring therapeutic interventions.

Considering its impact, cognitive screening should be generalised and those impaired must be treated. eHealth solutions, which have been suggested to be cost-effective for AUD management (Smit et al., 2011; Stoner & Hendershot, 2012; Brendryen, Johansen, Nesvåg, Kok & Duckert, 2013), could ease the implementation of cognitive testing and rehabilitation.

Neurocognitive evaluation in alcohol use disorders: challenges

There are many good bedside screening tools for cognitive deficits (e.g. MOCA or Addenbrookes') (Copersino et al., 2009; Rojo-Mota, Pedrero-Perez, Ruiz-Sanchez de Leon, Llanero-Luque & Puerta-Garcia, 2013), and there is a great amount of evidence on screening for cognitive impairment in acquired brain damage (stroke, traumatic brain injury, HIV). But there is a shortage of literature about cognitive screening in alcoholism. It is stunning that, despite the growing evidence about ARBD, a significant proportion of alcoholic patients are not systematically screened for cognitive deficits, particularly those with mild and moderate impairments. Several factors may contribute to this situation:

1. The difficulty in distinguishing apparent impairment due to intoxication or withdrawal states from that attributable to more persistent ARBD. Other confounders also challenge the quest for specificity (e.g. psychiatric and somatic comorbidity).
2. The lack of specifically validated screening tests for ARBD. Furthermore, we know from other domains that tests that perform well to screen severe cognitive deficits do not always work for milder conditions. In addition, the results of cognitive tests do not always correlate with everyday functioning, thus failing to provide clinically relevant information.
3. Standard comprehensive neurocognitive tests are high resource-consuming.
4. The shortage of structured services for cognitive rehabilitation.

Neurocognitive rehabilitation: time to act

Is abstinence enough to recover functionality? Many cross-sectional studies have captured some spontaneous cognitive recovery in abstinent alcoholics. A few limited longitudinal designs have compared the same alcohol dependent sample tested twice: early after detoxification and later in treatment or soon after the end of it. Only a few studies have used a longitudinal, prospective design with several assessment points to study within-person changes in cognitive function over time (Bates et al., 2004; Bates, Voelbel, Buckman, Labouvie & Barry, 2005; Bartels et al., 2007). A recent review (Fernandez-Serrano, Perez-Garcia & Verdejo-Garcia, 2011) and a metaanalysis (Stavro, Pelletier & Potvin, 2012) found a similar cognitive performance in multiple domains when comparing 1 month of abstinence versus 1 year, which suggests a stabilisation during the first year of sobriety. Analyses on a longer run revealed less severe cognitive impairment among long-term abstinent patients, which would support previous findings from longitudinal studies (Parsons, 1998; Rourke & Grant, 1999). A strong limitation is the evaluation of long-term abstinent alcoholics, with potential confounding factors like selection bias and differential survivorship rates (Fein & McGillivray, 2007). Effect size estimates could be underestimated, because of relapsing and most severe patients (KS, AD) being excluded from the analyses. Thus, long-term abstinence samples may be overrepresented by former dependent patients that were more cognitively fit at the beginning and therefore, better able to respond to therapy. It could also mean that they are less vulnerable to ARBD.

Neuroimaging has shown some anatomical and functional correlates of spontaneous brain recovery after alcohol cessation (Bartsch et al., 2007; Gazdzinski, Durazzo, Mon, Yeh & Meyerhoff, 2010; Monnig, Tonigan, Yeo, Thoma & McCrady, 2012) and has linked this recovery to several genetic and neurochemical factors, like BDNF (Mon et al., 2013). Despite this, we are still far from depicting at an individual level how the brain recovers from ARBD. More research is warranted, as the prediction of individual recovery trajectories would be useful for developing and tailoring cognitive interventions.

Back to the opening question: within one year, data suggests abstinence *per se* could stop the progression of cognitive impairment. Existing evidence indirectly suggests that this could be a necessary but insufficient condition. Cognitive impairment can affect treatment outcomes and relapse rates are high among alcoholics (Moos & Moos 2006). Moreover, alcoholics who relapse following a prolonged period of abstinence experience a further decline in cognitive function (Loeber et al. 2009; Pitel et al. 2009). Thus, an existing challenge is to help addicted patients to maintain abstinence long enough to benefit from cognitive recovery-potential.

In short, we are facing a harmful loop: heavy alcohol use over time impairs cognition, which affects self-control and can lower the efficacy of standard therapies and subsequently, increases relapsing probability. This should be untangled in two non-excluding ways: researching how to adapt or develop therapies to help cognitively impaired alcoholic patients to control their drinking and also looking for the best cognitive rehabilitation strategies for them (which, in turn, would be expected to impact on treatment outcomes).

Tailoring psychological therapies to the cognitive impaired

Motivational Interviewing (MI) has been adapted for brief interventions in traumatic brain injured patients (Ponsford, Tweedly, Lee & Taffe, 2012) and also for schizophrenic patients with AUD (Carey, Leontieva, Dimmock, Maisto & Batki, 2007). Improving executive function, like working memory, has shown some effectiveness (Houben, Wiers & Jansen, 2011). Attention bias (the automatic distraction towards stimuli related to an addictive substance) modification is also promising, as the attention training techniques are inexpensive, flexible and have shown some effectiveness (Cox, Fadardi, Intriligator & Klinger, 2014). We should also ensure that all who could benefit get pharmacological treatment.

From a global perspective, reduction strategies are getting more attention as an alternative to abstinence as the only therapeutic goal in AUD (Gastfriend, Garbutt, Pettinati & Forman, 2007). Measurement of continuous variables, such as the quantity and frequency of alcohol consumption, has enriched our understanding of alcoholism. In this sense, measurements like heavy drinking days or risk-stratified alcohol consumption are acquiring relevance as treatment outcomes (Falk et al., 2010; Aubin & Daeppen, 2013). A reduction in these has been proven beneficial in many important aspects (Kline-Simon et al., 2013), so it would be interesting to dig in their relationship with cognitive dysfunction and recovery.

Neurocognitive rehabilitation in alcohol use disorders

There is a shortage of evidence about neurocognitive rehabilitation for alcoholic patients (Bates, Buckman & Nguyen, 2013). Three decades ago some reviews associated altered brain function and its significance to the treatment of alcoholism (Parsons et al., 1987). There was evidence for an at least partial recovery of function with cessation or substantial reduction of drinking, and that cognitive rehabilitation could facilitate it.

Fifteen years later, the topic was revisited (Bates et al., 2002). It was reported a substantial progress in the knowledge about the nature and course of alcohol-related cognitive disorders, but a significant lag in the development of effective treatments. Strong scientific data supported this kind of treatment for other types of acquired brain damage (e.g., stroke or traumatic brain injury), but innovations were not being applied in the addictions field. The lack of conceptual models of alcohol-related cognitive disorders as moderators and modulators of treatment outcomes also contributed to the discordance.

The trend seems to have reverted over the past decade, with an increasing research interest that has unveiled some of the relation between cognition and treatment outcomes, and has generated new conceptual models (Wiers et al., 2011; Bates & Buckman, 2013) and intervention programmes (Alfonso, Caracuel, Delgado-Pastor & Verdejo-García, 2011; Houben et al., 2011; Rupp, Kemmler, Kurz, Hinterhuber & Fleischhacker, 2012).

The integration of current knowledge on time-dependent recovery on the neural and cognitive levels is a major challenge for translational research. For instance, when compared to controls in task performance, alcoholic patients have shown spontaneous, compensatory recruitment of additional brain networks like fronto-cerebellar and others (Chanraud, Pitel, Rohlfing, Pfefferbaum & Sullivan, 2010; Chanraud, Pitel, Pfefferbaum & Sullivan, 2011; Parks et al., 2012; Camchong, Stenger & Fein 2012; Chanraud, Pitel, Muller-Ohering, Pfefferbaum & Sullivan, 2013). Some of these compensatory strategies have been linked to the ability to sustain abstinence (Camchong et al., 2013).

Anyhow, work in the cognitive rehabilitation field is still in its early stages. We should keep an eye on other acquired causes of brain damage and on dementia. In these domains, evidence to support the use of cognitive interventions is cumulating (Hopper et al., 2013) with strategies like goal management training and errorless learning (Bertens, Fasotti, Boelen & Kessels, 2013). But replication of results in large clinical trials is needed and there is not enough evidence to decide if the aim should be restoring cognitive function or enhancing compensatory strategies (van Heughten, 2012, Chung, 2013, Kim & Kim, 2014). The latter have been reported successful in TBI or Schizophrenia (Twamley, Vella, Burton, Heaton & Jeste, 2012), so they deserve further study.

More studies with multiple time point assessments are needed to elucidate the length of abstinence necessary to start rehabilitation, and to rule out other factors that can impact on recovery trajectories. This way we will better understand recovery at the individual level, and so use this knowledge for clinical decisions. The question of whether cognitive rehabilitation also improves treatment efficacy should be addressed. In this sense, studies involving active cognitive interventions are needed, accounting for their ecological validity. It would be of great interest to explore a broad range of approaches to cognitive rehabilitation, from training impaired domains to strengthening and developing compensatory strategies. Future research should be carefully designed and consider several questions, like how cognitive rehabilitation would fit into current AUD treatments that have proven success and whether this rehabilitation should be offered universally or only to those patients with some level of impairment. Moreover, only a limited number of studies have evaluated if neurocognitive training can also improve alcohol outcomes in both non-treatment seeking and treatment seeking populations.

Conclusions

Neurocognitive impairment is common in alcohol use disorders and has a deep negative impact. It is the product of complex interactions between predisposing traits, environmental factors and neural impairments due to the heavy use over time. The synergistic effects of multiple insults, from direct ethanol neurotoxicity to thiamine deficiency, lead to a wide range of dysfunctions, much broader than the classical picture, and are often named under the umbrella term "alcohol-related brain damage" to reflect their etiological and clinical heterogeneity.

Cognitive screening in patients with alcohol-use disorders is crucial in order to early identify and manage those who are impaired. But this is a challenging issue, as it is difficult to distinguish the cognitive impact of intoxication/withdrawal from persistent impairment and to separate them from other sources of brain damage. There are many good bedside tools for cognitive screening, but they need specific validation and, perhaps, some fine tuning for their application in AUD patients.

More research is needed to determine the impact of cognitive impairment on treatment outcomes and how best to improve functional ability in this population. Some approaches, like modified MI, compensatory strategies or errorless learning, have been suggested.

Thiamine deficiency is an important and potentially preventable source of ARBD. Alcoholic patients should be systematically screened for WE risk and receive prophylaxis or treatment if necessary. Randomised clinical trials are needed in order to find the optimal dose regimes.

There is large room for improvement, and we think that it is time for action. To overcome this challenge, we should join our resources and skills in order to offer alcoholic patients the most appropriate evaluation and treatment, keeping an eye on its cost/effectiveness. In the XXI century addictions have been defined as brain diseases (Volkow, 2005). Maybe it is time to look also at brain damage more carefully than we have done in the past.

Conflict of interest

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