

## SCIENTIFIC COMMENTARY

## Get sober; stay sober

In the decades since alcoholism became widely recognized as a disease (Jellinek, 1960), evidence for alcohol-induced physical damage has accumulated both in quantity and in detail. Prominent amongst the affected organ systems at-risk is the brain, which responds to alcohol in a variety of ways. Free radicals formed during metabolism of alcohol damage the brain. Acetaldehyde, which is generated from ethanol, is highly reactive and toxic. This metabolite cross-links brain enzymes, reducing or eliminating the normal functions of those proteins. Neurotransmitter systems are altered not only through these mechanisms, but by adaptation to the neuromodulatory effects of ethanol itself (Heinz *et al.*, 2003). Furthermore, it is possible to visualize damage to different types of brain cells microscopically (Miguel-Hidalgo and Rajkowska, 2003) and, in particular, changes in the number and size of glia (Miguel-Hidalgo *et al.*, 2002). The alcohol-soaked brain shrinks heterogeneously. The damage involves both white (Rohlfing *et al.*, 2006) and grey matter: one of the most severely affected regions is the frontal cortex (Gazdzinski *et al.*, 2005) which, when damaged, leads to impaired cognitive capacity that may further compromise the individual's judgement and motivation to remain sober. The situation often appears dismal from the view of the patient and the provider of treatment, and patients are often discouraged by the physical and cognitive difficulties of achieving and maintaining sobriety. However, data acquired in recent years provide hope and, when presented appropriately, potentially offer renewed motivation for patients to get sober.

There is anecdotal support that patients are helped by knowing that there have been improvements in their brain volume, neurochemistry and cognition, and that even showing alcoholics the results from a separate, published group of similarly affected individuals can provide motivation. Dieter Meyerhoff and Timothy Durazzo (University of California and the Veterans' Administration at San Francisco, personal communication) report that many of the alcohol-dependent subjects in their studies begin treatment with the belief that 'the damage is done' and are surprised to learn of the significant volumetric and neurochemical recoveries to be achieved after only a few weeks. Several of their study participants have explicitly stated that this information is encouraging and assists in their motivation to stay sober, at least in the short term. Against this background, Andreas Bartsch and colleagues report combined measurements of neurochemicals, brain volumetrics and neurocognitive function in a longitudinal study involving one group of patients in this issue of *Brain* (page 36). Briefly, they use

volumetric measurements, magnetic resonance spectroscopy quantification and neuropsychological testing to show the effects of alcohol abstinence on the brain. A longitudinal design of two time-points is used, with patients studied at zero breath alcohol within a day or two after the beginning of abstinence and again after 7 weeks. The advantage of reporting such a broad spectrum of data in one publication is the ability to integrate the analyses. Although these types of measurement have appeared separately in longitudinal or cross-sectional studies over the past decade, the inclusion of so many metrics within a single study is commendable and adds considerable value to the report. Taken together, the report contributes significantly to the body of knowledge about what happens to the brain with abstinence. Moreover, in addition to advancing alcohol research by relating neurochemistry, brain volume and cognitive improvement, the paper by Bartsch and colleagues may help motivate patients to stay sober. Rigorous studies might now usefully be performed to test the efficacy of this potential motivation using group data and individual patients' own measures of neurological recovery.

The authors use magnetic resonance imaging (MRI) to measure brain volume, and magnetic resonance spectroscopy (MRS) to characterize several neurochemicals. MRS uses the same physical principles as MRI, but the goal is the measurement of chemical concentrations in living brain tissue, without any need for contrast injection or tissue manipulation. The chemicals measured in this study are *N*-acetylaspartate (NAA), total creatine (Cr) and choline along with other trimethylamines (Cho). The multimodal, longitudinal design, with measurements obtained within 1 week of admission and again after 6–7 weeks of sobriety, is especially important given the technology used for the project. MRI and MRS are expensive techniques, and availability of scanner time is often limited, so the number of subjects imposed a practical limitation since the success of this study depends on obtaining all of these measurements in the same subjects.

MRS remains a technique that is used more rarely than other forms of brain imaging. NAA is found primarily in neurons and their processes (Taylor *et al.*, 1994) and is synthesized by a mitochondrial enzyme, *N*-acetylasparyl transferase (Patel and Clark, 1979), which raises the possibility that its production may be related to energy metabolism or brain function. NAA is slowly released or leaks to the extracellular space, although the release is inconsistent with a neurotransmitter function for NAA (Taylor *et al.*, 1994). Astroglia have transporters that import NAA specifically (Sager *et al.*, 1999), and neurons take up very little NAA (Baslow and Resnik, 1997). Aspartoacylase,

which catalyzes the degradation of NAA, is expressed primarily in white matter tracts and oligodendrocytes (Bhakoo *et al.*, 2001), consistent with reports that NAA is associated with myelination and mitochondrial membranes (Burri *et al.*, 1991; D'Adamo and Yatsu, 1966). It is possible that NAA is synthesized in neurons through a process related to cellular energetics, released slowly to the extracellular environment, and degraded to aspartate and acetyl moieties in glia. In alcoholism, concentrations of NAA are reduced, but with sobriety, they increase. Bartsch and colleagues show recovery of NAA, and this is linked directly to improvement in cognitive function.

The signal from total creatine is derived from phosphocreatine and creatine, which are not distinguished from one another *in vivo*. Although their separate quantities depend on the energetics of the brain, the sum is robust even at *post mortem* (Pontén *et al.*, 1973). The total quantity of creatine has been reported to change by 10–15% in some conditions, such as ageing (Pfefferbaum *et al.*, 1999), but the physiological meaning of such changes remains unknown. In most studies of alcoholism, including the work by Bartsch and colleagues, the value of creatine has not been seen to change.

The signal from choline is believed to arise from metabolites related to membrane synthesis or degradation. The amount of choline has been found in several studies to be lower in alcohol-dependent subjects than in healthy control subjects, and to rise with sobriety. In this paper, the authors show that the increase in choline is directly proportional to the recovery of brain volume, and they conclude that the elevation of choline is consistent with remyelination and regrowth of astrocytes.

A strong feature of this work is the choice of value for Total Echo time (TE). This paradigm is not often used in psychiatric studies but is very appropriate for the authors' experimental goals. MRS acquisition protocols are carried out with a series of millisecond-bursts of radiofrequency energy separated by delays, and some of these delays contribute to TE. When small values of TE are used, metabolites such as glutamate and glutamine yield large signals, and this opportunity to study additional neurochemicals sounds appealing. However, they are difficult to quantify individually with standard sequences at today's clinical magnetic field strengths, and the data are contaminated with signals from macromolecules and water, further reducing the accuracy and precision of these measurements. Quantification can be done reliably but is considerably more complicated than with larger values of TE. Bartsch and colleagues used a TE of 135 ms, which eliminates macromolecular contamination and provides accurate and precise results. The authors sacrificed the information concerning glutamate and glutamine, but with their primary hypotheses focused on NAA, the extra complications associated with short TE were avoided.

The novelty and importance of this paper to the field of research on alcoholism lies in the unification of several previously separate lines of investigation. Doctors treating or

studying alcoholism should be made aware that the findings based on cognition, chemistry, and brain volume may provide a motivational tool that offers a broad set of concrete, tangible and rapid benefits of sobriety. Researchers who read this paper might consider other combinations of technologies and clinical observations with respect to patients' ability to reduce drinking or maintain sobriety. Researchers might consider assessing whether such concrete evidence of neurological recovery can be used effectively to motivate patients to stay sober.

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