

# The effects of alcohol on cognition in the elderly: from protection to neurodegeneration

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## Summary

The effects of chronic alcohol abuse on cognition are well known. Memory and executive functions appear to be the cognitive domains primarily impaired, and prefrontal and frontal damage is reported on neuroimaging studies both at micro- and macrostructural levels. Abstinence can partially reverse these alterations through mechanisms of neuroplasticity. Alcohol acts in a dose-dependent fashion, and a light-to-moderate consumption indeed has protective effects on cardiovascular risk factors and promotes anti-inflammatory and anti-oxidative processes. In the elderly on such a regimen, several epidemiological studies have reported a decreased risk of both coronary and cerebrovascular disease and of dementia. However, because of data heterogeneity and the presence of several confounding variables, further studies are needed to clarify these findings. In addition, the complexity of alcohol neurobiology (interaction of alcohol effects with genetic predisposition and environmental factors) and the occurrence of age-related changes should also be taken into account. As dementia, stroke and cardiovascular disease are the leading causes of mortality in older people in developed countries, a better knowledge of the mechanisms underlying the effects of alcohol intake may be helpful from the perspective not only of medical management but also of social health policy.

*KEY WORDS:* alcohol abuse, cognitive disturbances, dementia, elderly

## Introduction

Alcohol acts on the central nervous system via both direct and indirect effects, frequently a combination of the

two (1-3). Alcohol modifies the fluidity of cell membranes, thus interacting with calcium and chlorine channels and impairing cell functioning. It does not act on a specific receptor, but on several neural networks subserved by different neurotransmitters. The effects appear to be dose-related, since at low dosages alcohol affects monoaminergic transmission and produces disinhibition and euphoria, while at high dosages it exerts known anxiolytic and sedative effects, by increasing GABA activity and inhibiting excitatory amino acids. The main neurotoxic effects appear to be mediated by glutamate, as alcohol blocks N-methyl-D-aspartate (NMDA) receptors, whose chronic inhibition causes increased glutamate release with excitotoxic effects (4-6). Indirect effects are mainly mediated by malnutrition, frequently observed in alcohol abusers, which causes deficiencies in thiamine, nicotinic acid, other B vitamins and folate (7). Thiamine deficiency facilitates excess glutamate release, leading to neuronal damage and therefore enhancing the direct effects of alcohol via an additive or even a synergistic mechanism (1). Presumably through glutamate receptor up-regulation and GABA receptor down-regulation, abrupt abstinence after prolonged or binge drinking can result in tremor, hallucinations (visual, auditory, or tactile), seizures, or delirium tremens, with severely restricted attentiveness, fluctuating levels of alertness, agitation, and autonomic instability (6).

## Effects on cognition

The neurological complications of alcohol abuse encompass different clinical pictures involving cognitive disturbances. The Wernicke-Korsakoff syndrome and Marchiafava-Bignami disease are related to nutritional deficiency, of thiamine in particular. By contrast, "alcoholic dementia", or "alcohol-related dementia", generally occurs in the absence of nutritional deficits or other forms of brain damage as caused, for example, by cerebral trauma and hepatic failure. In these cases, a direct neurotoxic effect of alcohol is presumably implicated, but the reason for this effect has not been established, given that, at equal alcohol intake levels, only some people develop dementia. Diagnostic criteria for alcoholic dementia have been provided in the DSM IV (8). In particular, the presence of prolonged and abnormal alcohol intake and the persistence of the symptoms for more than three weeks after alcohol withdrawal are required for a diagnosis. Mostly, patients develop a gradually progressive multidomain cognitive impairment, while more rarely the dementia is an evolution of the Wernicke-Korsakoff syndrome. However, the morphological substrates are different, given that in alcoholic dementia neuroimaging shows diffuse atrophy, while in Wernicke-Korsakoff syndrome a selective involvement of

the frontal cortex and thalamus and enhancement of mammillary bodies in the acute phase have been reported (9,10).

Besides these peculiar pictures, a cognitive impairment mainly involving memory and executive functions (pre-frontal and frontal damage) can be detected in chronic "uncomplicated" alcoholics (11-14). The degree of the neuropsychological deficits has been related to sex (15), abuse duration, and amount of alcohol intake (13). In addition, the age at onset of abuse appears to be important in the development of future cognitive impairment. Alcoholism also causes changes in brain morphology: enlargement of the ventricular system, in particular of the third ventricle, and cerebellar atrophy are earlier signs, whereas in later stages a shrinkage of frontal and prefrontal regions, related to neuropsychological deficits, has been reported by several authors (10,12,16). Alterations are detectable not only at macrostructural level; indeed, magnetic resonance using diffusion tensor imaging has shown altered connectivity in multiple different fibre systems (17-19). Interestingly, altered fronto-cerebellar connectivity has also been found in alcohol-naïve young subjects with a family history of alcoholism (20). As frontal and cerebellar regions are crucial for executive functioning, the authors suggest that the presence of premorbid derangements in these circuits may increase the risk of developing alcohol abuse in subjects with a family history of alcoholism via altered control processing. Neurochemical changes provoked by alcohol can also be detected, employing MR spectroscopy (21), in otherwise apparently intact brains, i.e. before the expression of structural damage. The tissue changes are more marked in some specific brain areas, i.e. more in the white matter than in the grey matter (12,22,23). These observations support the presence of a selective brain vulnerability to alcohol effects.

Cognitive disturbances as well as brain abnormalities in alcoholics, however, can partially recover with abstinence. Several hypotheses have been advanced to explain this phenomenon. The rehydration hypothesis – vasopressin secretion may be suppressed during alcohol intoxication – has not been confirmed, while changes in perfusion have been demonstrated by functional neuroimaging (24). However, recent evidence supports the role of regeneration (increased glial and dendritic growth) after abstinence, suggesting that neuroplasticity is probably the most important mechanism involved in structural and cognitive recovery (12,25,26). By contrast, it is well recognised that abrupt abstinence after regular or binge drinking causes important cognitive disturbances, possibly related to glutamate receptor up-regulation and GABA receptor down-regulation. The occurrence of tremor, visual and auditory hallucinations, and sometimes seizures is frequently encountered in these patients. In the presence of certain factors or comorbidities, this picture may sometimes progress to delirium tremens, a serious condition characterised by fluctuating levels of alertness, intense agitation, and autonomic instability (27).

An interesting question is whether repeated withdrawals can affect cognitive functions. The data from the literature are not univocal in this respect (13,28), since several confounding factors, such as age at drinking onset, abuse and abstinence duration, concomitant use of oth-

er neuroactive substances, previous head traumas and nutritional deficiencies can affect the results. Moreover, withdrawal probably affects only some specific functions. More recent data (29), however, report that repeated withdrawal episodes might be associated with reduced brain plasticity, as suggested by a delayed recovery from inattention and disrupted executive functions.

### Protective effect

The protective effect of light-to-moderate alcohol consumption (no more than two drinks/day) on the cardiovascular system is well known. *In vitro* and *in vivo* studies have indeed demonstrated that alcohol raises blood levels of high-density lipoprotein cholesterol, increases insulin sensitivity, prevents platelet aggregation, increases fibrinolysis, and inhibits thrombin activity (1,30). Moreover, ethanol facilitates anti-inflammatory and anti-oxidative processes, and by acting on cardiovascular risk factors, reduces the risk of coronary and cerebrovascular disease and promotes cytoprotection of glia and neurons. Most of the cardioprotective effects of alcohol can be attributed to flavonoid resveratrol, which, present in red wine, is endowed with anti-oxidant properties. However, cardiovascular protective effects have also been noted for white wine, beer and spirits, thus confirming the beneficial action of alcohol per se (30). Epidemiological studies have confirmed these data (31-33). The protective effects are dose-dependent: heavy drinkers indeed display an increased risk of developing coronary disease or ischaemic/haemorrhagic strokes, while people with light-to-moderate consumption have a reduced risk, which may even be smaller than that of occasional drinkers or those who are abstinent (34). However, the coexistence of Apo-E genotype may modify this association; indeed, in Apo-E 4 positive subjects even moderate alcohol intake may be associated with an increased risk of ischaemic stroke (33).

### Alcohol and dementia

Since ethanol causes cognitive impairment, an important question in elderly people is whether alcohol consumption may facilitate the onset of dementia. The data in the literature, mostly obtained from longitudinal studies, agree in supporting the concept that light-to-moderate drinking has a protective effect (35-47). Similar to what is observed for cardiovascular risk, light drinkers have a lower risk of developing dementia compared to non-alcohol users. In the study by Arntzen et al. (44), performed on over 5000 subjects, moderate consumption of wine (but not of beer or spirits) was associated with better cognitive performance after seven years, while alcohol abstinence was related to lower cognitive performance in women. In subjects with mild cognitive impairment, light-to-moderate drinking may decrease the rate of progression to dementia (39,43,44). By contrast, another study, by Lobo et al. (48), did not support the hypothesis of an alcohol-dependent protective effect against cognitive decline. Moreover, the presence of the Apo-E genotype may represent a worsening factor (37). Alcohol consumption has been also found to lower the age at onset of Alzheimer's disease (AD), particularly in

the presence of heavy smoking, apparently in an additive fashion (49).

Despite the presence of substantial agreement, it should be borne in mind that data are extremely heterogeneous and must therefore be interpreted with caution. Differences in study design, inclusion criteria, outcomes, drinking patterns, types of beverage and follow-up periods may be sources of variability; moreover, possible environmental and genetic factors can further confound the results. Panza et al. (46), while confirming the protective effect of moderate drinking in late life, underline that it is still unclear whether these results reflect selection effects in cohort studies or indicate a protective role of alcohol throughout adulthood or a specific effect of alcohol in late life. Another important point is that in most of the studies the authors do not define the main outcome, i.e. they do not specify against which type of dementia (AD, other neurodegenerative dementias, vascular dementia) alcohol may have a protective role. As far as vascular dementia is concerned, such a role could be explained, at least in part, by the beneficial effects on the cardiovascular system. On the other hand, results from a meta-analysis of 23 studies found protective effects of alcohol against AD, but not vascular dementia (40). For other, non-vascular types of dementia plausible mechanisms may be related to the anti-oxidant and anti-inflammatory effects of ethanol. The results, however, are again inconsistent. Moreover, in contrast to studies on cardiovascular disease, data from the Framingham Study suggest that moderate alcohol consumption is not protective against the physiological, age-related differences in total brain volume, seeming to show, rather, that the more alcohol consumed, the smaller the total brain volume (50).

### Concluding remarks

The mechanisms of alcohol effects on cognition are very complex. In addition to direct and indirect effects, genetic predisposition and environmental factors can differently modulate the clinical manifestations. Moreover, alcohol increases the risk of exposure to potentially harmful causes such as head trauma, hepatic encephalopathy, greater susceptibility to infections, and concomitant abuse of other neuroactive substances. In elderly people, alcohol-drug interactions and age-related physiological changes also have to be taken into account. The role of alcohol on cardioprotection and neuroprotection needs to be further elucidated. This is not a merely speculative problem; as dementia, stroke and cardiovascular disease are the leading causes of mortality in elderly people in developed countries, a better knowledge of the mechanisms underlying potentially beneficial alcohol effects may be helpful not only in the sphere of medical management but also in that of social health policy.

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