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Setting the stage for understanding alcohol effects in late aging: a special issue including both human and rodent studies

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Abstract

It is widely recognized that people world-wide are living longer than in previous decades, with formidable projections regarding the expansion of elderly age groups in the decades to come. Older individuals are also sustaining higher levels of alcohol consumption later in life, and binge drinking remains a prevalent pastime in a significant proportion of aged individuals. Older people are more sensitive to neurobehavioral effects of alcohol, and as individuals age, the cumulative impact of lifetime alcohol intake begins to emerge. This brief review provides a perspective on the emerging field of how alcohol interacts with the aging brain and sets the stage for understanding the relationship between alcohol and overall brain health. In doing so, we introduce a set of articles collected in this book series (all chapters available on Pubmed) which spans human epidemiology and clinical outcomes, along with a series of neurobehavioral studies in pre-clinical (rodent) models. Because both natural aging as well as alcohol use and abuse include tell-tale signs of neuroinflammation (heightened expression of neuroimmune genes, activation of inflammatory signaling pathways, and signs of glial activation), particular emphasis is placed on the role of neuroinflammation in both aging- and alcohol-related alterations in neurobehavioral function, with special emphasis on the spectrum of cognitive dysfunction ranging from mild cognitive impairment to Alzheimer's-associated brain pathology.

Keywords

Alcohol; ethanol; aging; lifespan; development; neuroimmune; neuroinflammation; Alcohol-related brain damage; Alzheimer's Disease

Introduction

Alcohol Use Disorders (AUD) have long been recognized as a disease state with its roots in developmental processes, with much of the field focused on early developmental periods during which alcohol exposure is most prevalent: prenatal alcohol exposure (PAE), where alcohol exposure occurs surreptitiously through maternal consumption; during early post-natal development via alcohol transmission through milk consumed from the lactating maternal figure; and during adolescence. During adolescence, humans sample their first

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alcoholic drinks, succumb to vast peer pressure to engage in high risk drinking, and—despite significant progress in the past decade, binge drinking remains higher than any other developmental epoch (Spear, 2018). As a result, much of what we know about immediate and long-lasting effects of early alcohol exposure has arisen from a well-developed portfolio of pre-clinical and highly tractable models of early life alcohol exposure for studying neural mechanisms contributing to cognitive, behavioral, affective and motivational effects of early alcohol exposure.

As researchers, we have a natural proclivity toward early developmental studies due to the presumed impact of early life alcohol effects on the overall trajectory of lifespan development. However, substantial gaps exists in the elaboration of (i) early developmental alcohol exposure effects into *life-long* changes in neurobehavioral function; and (ii) how contrasting levels of alcohol consumption across the lifespan contribute to the *cumulative impact* of alcohol on not just mortality rates, but ultimately into *senescence* and *quality of life* in late aging. A critical problem that has been recognized recently is that older adults are engaging in binge drinking and developing AUDs much later in life (Tampi et al., 2015; Han et al, 2019), as well as displaying increased cognitive decline (Grønkjær et al, 2019; Wood et al, 2014). Even in the absence of AUDs, more older adults report drinking alcohol than in the past (Britton & Bell, 2015). Furthermore, it is widely recognized that late aging is associated with substantially increased sensitivity to alcohol, yet very little is known about the neural mechanisms contributing to this increased alcohol sensitivity. Much can be gleaned from human epidemiological studies, and now is the time to commit effort to the development of highly tractable animal models that effectively recapitulate realistic levels of alcohol consumption across the lifespan. With this in mind, the intent of this Book Series is to pull together a succinct set of human and rodent translational studies of alcohol exposure effects across the lifespan to accelerate progress in our understanding of neurobehavioral consequences of alcohol across the lifespan. Our hope is to provide a practical conceptual framework to guide the alcohol research community toward the study of late aging effects, while at the same time inciting broader participation of the aging research community into the alcohol field.

To this end, authors contributing to this special issue were tasked with providing a review of their emerging work in neurobehavioral aspects of aging-alcohol interactions. Some authors elected to provide a more traditional summary and review of the literature, whereas others provide new empirical data that has been prepared with a substantially longer-than-usual *introduction* to more thoroughly frame the literature and general topic area of their work. The importance and timeliness of this Book Series is underscored by the rapidly expanding world-wide population of aging individuals, due in part to people living longer and healthier lives (Ortman et al., 2014). We should also note that several of the contributing authors (Keyes, Nixon, Deak, Matthews) presented variations of their work at the 2019 Research Society on Alcoholism (RSA) meeting held in Minneapolis, MN in a similarly-themed symposium.

Brief Precis of Contributions in this Book Series

The series begins with an article by Dr. Katherine Keyes and her collaborators, focusing on alcohol consumption patterns among older adults (Keyes et al., 2020; Chapter 1). Their approach was to harmonize multiple datasets across industrialized nations to develop a more complete portrait of alcohol use patterns in older adults over the last several decades, and the extent to which alcohol use later in life might serve as a risk factor for mental health problems, such as depressive episodes. Their work supports a growing consensus in the literature that excessive alcohol consumption later in life causes substantial harm compared to that observed in younger populations, and that these effects extend to mental (not just physical) health. A major strength of their findings and approach is the intrinsic emphasis on global health burden of excessive alcohol use among older adults. In our opinion, this article nicely frames the breadth of issues to be addressed with future studies focused on how alcohol consumption influences neurobehavioral processes among older adults.

The second article from Drs. Sara Jo Nixon and Ben Lewis (Nixon & Lewis, 2020; Chapter 2) specifically addresses the influence of moderate drinking on neurobehavioral function. While there is little doubt that heavy drinking throughout life compromises many aspects of physical health and neurobehavioral function, the relative influence of low-to- moderate drinking has become somewhat more controversial, as the general public seeks guidance from the scientific community on how much alcohol consumption is too much. In their review, Nixon and Lewis provide a thoughtful and balanced review of studies examining how low-to-moderate levels of alcohol consumption influence three critical health domains: cardiovascular function, Type 2 diabetes, and cognitive function. Importantly, their approach recognizes the scientific necessity of determining alcohol consumption effects not just on neurobehavioral function, but also more broadly on general health conditions associated with late aging. Importantly, their review elaborates their cleverly-designed studies to frame a better understand how sensitivity to alcohol changes in older adults. An important contribution of their work is the demonstration that even though older adults may not display differences in neurobehavioral function at baseline, they often display greater impairments in response to alcohol challenge, suggesting older adults are more sensitive to the disruptive effects of alcohol than young adult comparators.

Interestingly, this basic premise is supported by pre-clinical studies using rodent models, providing the opportunity for the field to dig deeper into the causal mechanisms of alcohol-induced neurobehavioral changes in late aging. The general topic area of the review provided by Dr. Douglas Matthews (Matthews et al., 2020; Chapter 3) summarizes age-related differences in alcohol sensitivity by comparing, in many cases, three lifespan-developmental periods: (i) adolescence, a time when alcohol use and abuse is typically initiated and binge consumption patterns are most prevalent; (ii) young adults, which are typically utilized as the benchmark for “typical” or mature alcohol sensitivity and consumption; and (iii) aged rats, typically ranging from 15-24 months of age. Using a wide array of behavioral testing procedures, the Matthew’s research group has shown that aged rats are more sensitive to alcohol-induced motor impairments, hypnotic effects of alcohol, and disruptions of cognitive function compared to young adults. This review lays a basic behavioral foundation for the field to elaborate studies that will ultimately reveal neural

mechanisms contributing to intrinsic age differences in alcohol sensitivity that are evident in response to acute or subchronic alcohol administration procedures.

In contrast, the review submitted by Dr. Savage's research group (Toledo et al., 2020; Chapter 4) provides a comprehensive review of neural circuits that are compromised by extended periods of severe alcohol use and abuse across protracted periods of time. In reviewing literature from both human alcoholics and rodent models, this review elaborates the critical role of thiamine deficiency in setting the stage for the development of Alcohol-Related Brain Damage (ARBD), an outcome most typically associated with severe alcohol abuse. Although the role of thiamine depletion in severe alcoholics has been recognized for decades and thiamine loading is a mainstay of treatment for acute withdrawal crises (Pruckner et al., 2019), the role of nutritional factors in mitigating the effects of alcohol are especially important given trends toward extreme dieting that severely restrict or expand key nutritional categories to achieve weight loss. Nevertheless, the manuscript does an outstanding job associating changes in forebrain cholinergic neurons with specific cognitive deficits and provides insightful guidance into how the aging brain may be compromised by chronic alcohol use and abuse across the lifespan. Given the role of neuroinflammatory processes in both natural and pathophysiological brain aging, heightened activation of inflammatory signaling is posited as a key culprit in the loss and/or change in phenotype of cholinergic neurons under conditions of both chronic alcohol and thiamine depletion, forming a neuroimmune basis for cognitive dysfunction to emerge in the aging alcoholic brain.

Aging, however, does not exact its toll on the brain solely through the passage of time. This is underscored by major movements in the aging field to identify longevity-related (or longevity-compromising) genes, as well as genetic studies to better understand the basis of neurodegenerative disease (Slagboom et al., 2018). The manuscript arising from Dr. Clyde Hodge's research group (Hoffman et al., 2020; Chapter 5) exploits a triple transgenic mouse (3xTg-AD) that expresses three human genes associated with Alzheimer's Disease (AD)-like pathology: MAPT (Tau), amyloid beta precursor protein (APP), and presenilin-1 (PSEN-1). The intent of the studies was to determine whether 3xTg-AD mice would be more vulnerable to cognitive deficits associated with chronic alcohol consumption that persist during alcohol abstinence. The studies found evidence of impaired spatial memory, diminished sensori-motor gating, and potentiated conditioned fear in the 3xTg-AD mice after voluntary consumption of a sweetened alcohol solution for 4 months. In addition, several markers of AD-like brain pathology (Aβ upregulation, Tau phosphorylation, etc) were observed, suggesting that chronic alcohol consumption may increase vulnerability to AD-like brain pathology and cognitive deficits in genetically-prone individuals. Although the article does not address aging as a developmental process per se, these findings are among the first to demonstrate increased vulnerability to AD following alcohol exposure in a rodent model, and provide an important foundation for causal, mechanistic studies in the near future. More generally, these studies underscore the utility of transgenic models of aging and AD-like pathology for advancing our understanding of alcohol-aging interactions.

Dynamic changes in neuroimmune function across both early development and late aging are the primary topic of the review by Dr. Terrence Deak's research group (Perkins et al.,

2020; Chapter 6). Specifically, adolescence appears to be a period of *reduced* neuroimmune reactivity to most challenges, including alcohol, with lower ambient and substantially impaired induction of neuroimmune genes during this key developmental period (Doremus-Fitzwater et al., 2015). In contrast, late aging is associated with *heightened* basal inflammation that manifests as both increased basal expression of neuroimmune genes (Gano et al., 2016) and increased number of microglia (Perkins et al., 2018). These natural, age-related fluctuations in neuroinflammation are examined through the lens of social behavior regulation, which shows profound changes across these developmental periods and is highly vulnerable to inflammation. This manuscript also begins discussion of low- versus high-dose alcohol effects on aging-related neuroinflammation, which remains a substantive issue for the alcohol field. This is important because very few studies have examined how alcohol interacts with the normal aging processes, and most studies examining neuroimmune effects of alcohol (regardless of age) appear to require supra-binge levels of alcohol exposure to fully manifest.

The manuscript by Dr. S. Alex Marshall's group (Grifasi et al., 2020; Chapter 7) also begins to address the critical distinction between high- and low-dose alcohol effects on neuroinflammation. This manuscript took a unique approach by comparing microglial density in the CNS using two distinct rodent model systems: in the first experiment, the authors utilized a modified version of the Majchrowicz (1975) model of extreme intoxication in Sprague Dawley rats to examine microglial involvement in alcohol-induced neurodegeneration. Although no differences were apparent in aged rats, this extreme alcohol model significantly changed microglial density and was associated with reduced hippocampal neurogenesis. These findings were contrasted in mice exposed to the Drinking-in-the-Dark (DID) paradigm, a well-established model of binge drinking (Thiele & Navarro, 2014), , for a total of 12 drinking sessions (4 days on, 3 days off, repeated for 3 cycles). Here again, microglial density in the examined regions seemed to show a downward trend, with some emerging evidence of microglial activation. Despite the many differences between the two experiments, together these studies suggest that (a) fluctuations in neuroimmune status and reactivity were clearly evident in both models, and (b) the ability to detect alcohol-aging interactions will require exquisitely sensitive techniques to detect effects that might be rather subtle in any one brain region, but widespread across the CNS.

Emergent themes

The present book series is by no means a comprehensive review of the field of alcohol and aging, nor was it intended to be. Instead, the intent was to provide a portfolio of human epidemiological and clinical studies in combination with emerging studies in pre-clinical (rodent) models that would illustrate the breadth of approaches possible, and some early intimations of neural mechanisms that might contribute to alcohol-induced, or alcohol-related, brain pathology later in life. From these studies, we can begin to identify emerging themes across studies, identify gaps in the literature, and formulate hypotheses for future work. A few of the common themes are summarized below.

Dose matters.

As one would expect, variation in alcohol consumption or exposure (animal models) varies substantially across both the lifespan, as well as across individuals. At this point, the literature appears to segregate alcohol consumption patterns based on what is considered to be regular, moderate drinking, intermittent binge-like consumption patterns, and heavy alcohol use and abuse that is more emblematic of individuals with Alcohol Use Disorders. This is represented in Figure 1 across the top (blue) box, indicating escalating levels of alcohol consumption/exposure from left to right. For studies in which acute or subacute alcohol effects are being examined, dose response functions are relatively straight forward to conduct and easy to interpret. However, for long-term alcohol studies, there is a strong presumption that what matters is the cumulative alcohol consumption across the lifespan. While cumulative alcohol intake is certainly a key factor in determining overall effects on aging-related parameters, we would be remiss to ignore the powerful influence of episodic differences in alcohol consumption (i.e., 7 drinks on one occasion is not likely to have the same outcome as 7 drinks in a week, despite the weekly intake being identical). Second, the presumption that adverse health consequences of alcohol consumption will be related to alcohol intake by a linear function is highly unlikely, given that low doses of alcohol may in fact produce certain health benefits (eg., Lundgaard et al., 2018). Instead, we should expect lifetime dose response functions may follow distinctly *non*-linear patterns, with the precise function (U-shaped, inverted U, J-shaped or inverted J, as examples) being determined based on sensitivity of the specific neural, behavioral or physiological parameter being examined. Regardless, one over-arching goal for the field should be to establish how normative ranges of alcohol consumption contribute to alcohol-related pathologies across the lifespan, with an eye towards identifying *break-points* in consumption at which disease vulnerability escalates.

A separate but related matter for studies on alcohol and aging pertains to the importance of tending to *pharmacokinetics*. The central issue here is that liver and kidney function do not remain stable across the lifespan, which can significantly change the metabolism and excretion (respectively) for alcohol. For the most part, this is relatively straight forward to address experimentally. Since blood alcohol concentrations (BACs) can be readily measured, momentary changes in BACs can be compared to behavioral effects quite readily in tests of acute alcohol sensitivity. Alternatively, assessment of ethanol metabolites can be used as an aggregate index of ethanol exposure, at least over a recent period of alcohol exposure of up to a few weeks (eg., Bager et al., 2017). The more pernicious pharmacokinetic problem with aging is that aging is associated with substantial changes in both body mass and composition, which can vary dramatically across individual humans and across strains/species in rodents. Indeed, some of the preferred strains of rat (in particular) used in aging studies were selected initially based on their tendency for body weight gain to plateau at an early age. Even in cases where body weight differences between young and old subjects are relatively minimal, we have observed differential BAC curves between young and aged rats that begin to emerge only when doses rise above 1.5 g/kg (through ig intubation; Perkins et al., 2018). What remains unclear, however, is whether the apparent pharmacokinetic differences in young versus aged rats in those studies reflect differential absorption, distribution, metabolism or excretion of alcohol. All are possibilities, especially since aging

in many mammals (including humans) is associated with reduced muscle mass, greater lipid profiles, and heightened total body water. Such effects are even more problematic as lifetime alcohol intake increases, as alcohol-induced liver dysfunction is associated with even greater water retention (i.e., ascites) in the abdominal cavity. We raise these issues here not to dissuade individuals from engaging in alcohol studies in late aging, but instead to highlight the complexity of health issues that might inform (or confound, as the case may be) conclusions on alcohol and aging.

Inflammation matters.

Alcohol has a long and sordid history with inflammation, with seemingly paradoxical effects in reducing host defense (Szabo & Saha, 2015) while at the same time promoting symptoms of innate immune activity, including microglial activation and activation of inflammatory signaling pathways (Crews et al., 2017). Like many areas of neuroimmunology, the alcohol-neuroimmune field has witnessed an explosion of new findings pointing toward inflammation as a key culprit in the development of ARBD. Yet, considerable evidence exists showing that relatively low doses of alcohol (i.e., in the range of regular, moderate consumption) produce little detectable effect on neuroimmune processes, suggesting that inflammation is a more substantial concern with supra-binge levels of alcohol exposure or acute thiamine deficiency (Toledo-Nunes et al, 2019). Here again, the developmental timing (Gano et al., 2017; Gano et al., 2019) and schedule of ethanol exposure (Gano et al., 2016) may be key features of alcohol exposure that determine the nature and extent of inflammation observed later in life, rather than simply alcohol load per se.

At the same time, a well-documented consequence of natural aging is heightened inflammation in both body and brain, an effect often referred to as “inflamm-aging” that includes phenotypic changes in microglial activation (Bickford et al., 2017; Stojiljkovic et al., 2019). Such effects are observed in animal models even in cases where the animal has assuredly never been exposed to alcohol. Thus, a critical issue for the field will be to determine how natural aging-related inflammation is influenced by, or interacts with, subsequent alcohol exposure. A few studies have begun to address this interaction through examination of cytokine and chemokine expression (Gano et al., 2016) as well as microglial density and/or activation state, including several manuscripts included here. The general neuroinflammation response to alcohol is represented *symbolically* in Figure 1 (black box), which depicts morphological characteristics of microglia as they become more activated (see Perkins et al., 2020 for a more complete elaboration). It would be a mistake, however, to assert that microglial activation state occurs solely as a function of alcohol exposure, or is the sole indicator of alcohol-related neuroinflammation. Indeed, despite their role as “primary responders” under conditions of neuroinflammation, morphological changes in microglia tend to be lagging indicators of insult relative to induction of neuroimmune genes (see Perkins et al., 2020 for more detailed discussion). Nevertheless, the intent here is to spur interest in neuroimmune consequences across a more comprehensive range of alcohol consumption/exposure conditions so that the relation between alcohol consumption, neuroinflammation, and neurobehavioral aspects of aging (Figure 1, green box) can be established.

Aging matters.

Even typical, healthy aging is associated with altered neurobehavioral function. For instance, late aging in humans suffers a significant transformation in social interaction in which older people tend to interact with fewer social partners, yet their interactions remain deeper and more frequent than younger adults. This narrowing of social circles is thought to reflect a decline in overall social motivational processes which eventually threatens quality of life as bereavement and limited mobility exact their toll later in life (Perkins et al., 2020). The current rises in binge drinking in the elderly are driven by a range of health, social and economic factors that differ as a function of gender (Parikh et al, 2015). Cognitive and motor function also eventually erode over time and ultimately manifest as mild cognitive impairment, motor dysfunction and increased vulnerability to falls, and often times difficulty in emotion regulation. Indeed, the role of alcohol and its associated neuroinflammation in the pathogenesis of Alzheimer's Disease is an ongoing area of research (Skaper, 2012; Venkataraman et al., 2017). Although the factors contributing to these changes are multifaceted, the over-arching goal in geriatric science is to delay the onset of aging-related maladies and to prevent them from manifesting as debilitating, pathological impairments. Thus, vulnerability factors such as excessive alcohol consumption during critical periods of early development as well as the cumulative impact of lifetime alcohol intake likely contribute to accelerated brain aging. Indeed, the fundamental quest in aging research is to establish cellular and systems-level changes that contribute to the transition from normal, healthy function to senescence. While the present volume does not provide conclusive determinations regarding the nature of alcohol's influence or a unified mechanism by which alcohol contributes to brain aging, our hope is that some initial insight offered by this volume might provide a framework for the future.

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**Note that all references highlighted in yellow will need to be updated to ensure authors, year and journal citation information matches the final accepted versions for this book series.

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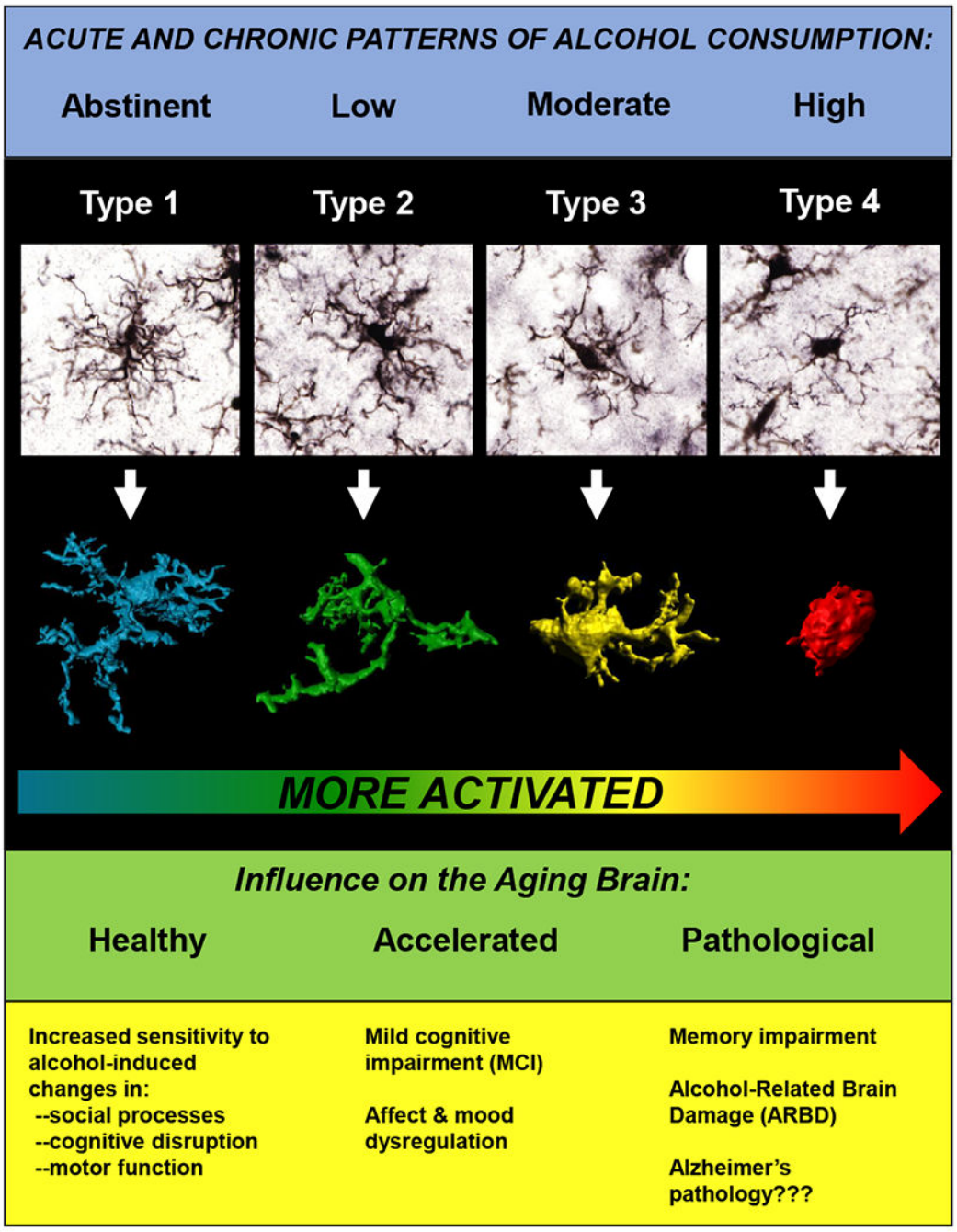

Figure 1. Interactions among alcohol, inflammation and the aging brain.

Cumulative lifetime consumption of alcohol (alcohol load) is likely to be an important contributor to overall brain health as one ages (blue box at top, depicting escalating levels of alcohol consumption from left to right). However, the individual patterns of drinking (regular, moderate drinking versus binge drinking, for example) must be considered as well. Signs of neuroinflammation tend to increase as a result of natural aging, an effect that is likely exacerbated by escalating use or abuse of alcohol. Images of iba1-labeled microglia (black box, top) display the transition of microglia from a quiescent state (Type 1, far left)

toward fully activated, ameboid shape (Type 4, far right), with 3D-reconstruction of cells with surface smoothing shown immediately below. Although microglial activation is one tell-tale sign of heightened inflammation, it is by no means the most sensitive or sole determinant of brain inflammation. Thus, display of microglial activation here is meant to represent symbolically the escalation of neuroinflammation associated with severe alcohol use and abuse (shown on top) and the escalation of brain inflammation due to natural aging. Together, alcohol use and aging are likely to accelerate brain aging (green box) and contribute to the development of neurobehavioral deficits that eventually achieve a pathological state (yellow box).