Contributions to Understanding the Neuropsychology of Alcoholism: An INS Legacy

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Abstract
Alcohol use disorder (AUD) has been a major cause of family, social, and personal strife for centuries, with current prevalence estimates of 14% for 12-month and 29% lifetime AUD. Neuropsychological testing of selective cognitive, sensory, and motor functions complemented with in vivo brain imaging has enabled tracking the consequences of AUD, which follows a dynamic course of development, maintenance, and recovery or relapse. Controlled studies of alcoholism reviewed herein provide evidence for disruption of selective functions involving executive, visuospatial, mnemonic, emotional, and attentional processes, response inhibition, prosody, and postural stability and brain systems supporting these functions. On a hopeful front, longitudinal study provides convincing evidence for improvement in brain structure and function following sustained sobriety. These discoveries have a strong legacy in the International Neuropsychological Society (INS), starting from its early days when assumptions regarding which brain regions were disrupted relied solely on patterns of functional sparing and impairment deduced from testing. This review is based on the symposium presentation delivered at the 2017 annual North American meeting of the INS in celebration of the 50th anniversary since its institution in 1967. In the spirit of the meeting’s theme, “Binding the Past and Present,” the lecture and this review recognized the past by focusing on early, rigorous neuropsychological studies of alcoholism and their influence on research currently conducted using imaging methods enabling hypothesis testing of brain substrates of observed functional deficits.

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INS LEGACY OF ALCOHOLISM RESEARCH
This review is based on the symposium presentation delivered at the 2017 annual North American meeting of the International Neuropsychological Society (INS) in celebration of the 50th anniversary since its institution in 1967. In the spirit of the meeting’s theme, “Binding the Past and Present,” the lecture and this review recognized the past by focusing on early, rigorous neuropsychological studies of alcoholism and their influence on research currently conducted using imaging methods enabling hypothesis testing of brain substrates of observed functional deficits. Of particular note is the legacy in alcoholism studies of the men honored by two of the five named INS awards and past INS presidents: Nelson Butters and Laird Cermak. An overarching principle taken from their early work is the recognition of alcohol dependence as a medical disorder marked by physiological, functional, and structural brain insult, some of which is at least partly reversible with sobriety. Research themes taken from the past are Butters’ quest for brain structure–function relations and Cermak’s focus on memory processes and memory disorders.

Accordingly, one focus of this review is on studies of short-term, or working, memory as they apply to alcoholism with expansion into current concepts of meta-memory; additional functions will be addressed in pursuit of historical hypotheses regarding broad characterization of alcoholism-related functional impairment and in recognition of current studies of function. The structure of the review follows the talk’s three learning objectives: to recognize that alcoholism disrupts wide-reaching yet selective brain structures and functions; to appreciate that functional brain changes are a form of neuroadaptation; and to learn that sustained sobriety can result in at least partial reversal of brain structural and functional insult associated with excessive, chronic drinking.

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DEFINE ALCOHOL USE DISORDER AND RECOGNIZE THAT ALCOHOL DEPENDENCE DISRUPTS SELECTIVE BRAIN STRUCTURES AND FUNCTIONS

What Is Alcoholism and How Common Is It?
Over the years, problem drinking has been called alcoholism, alcohol abuse, alcohol dependence, and now its formal diagnosis defined with DSM-5 criteria (American Psychiatric Association, 2013) is alcohol use disorder (AUD). Its current conceptualization is as a spectrum disorder, which is a problem pattern of alcohol use leading to clinically significant impairment or distress, manifested by 2 or more of 11 symptoms in a 12-month period. Several symptoms are particularly relevant to neuropsychological considerations because they are also symptoms of frontal lobe impairment: (1) had times when drinking more or longer than intended; (2) wanted a drink so badly to not be able to think of anything else; (3) continued use despite social or interpersonal problems; (4) continued use despite physiological or psychological problems.

There are many diseases and conditions that produce frontal lobe symptoms, including an extensive list of more than a dozen conditions provided in a neurology Web site (http://emedicine.medscape.com/article/1135866-differential). Curiously, alcoholism was excluded despite its higher prevalence than most other entries in the differential diagnoses—indication of how often AUD is overlooked in clinical settings outside of addiction treatment facilities. Indeed, alcoholism remains a major health problem in the world. In the United States, estimates from nearly a generation ago (Arciniegas & Beresford, 2001) indicated that alcoholism occurs in 8–12% of the adult population. Individuals with alcohol-related problems account for 14–20% of admissions to private hospitals, 30–35% of those entering teaching hospitals, and upward of 50% of those treated in Veterans Affairs (VA) medical centers; approximately one-third to half of treatment-seeking alcoholics have detectable cognitive or motor impairments. Estimates from 2015 note that over the previous month, nearly 27% of people in the United States reported binge drinking incidents and 7% reported heavy alcohol consumption; 6.2% had AUD; yet, only 8.3% of adults needing treatment received treatment at a specialized facility (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics).

Why Do Some People Drink Alcohol to Excess?
A fundamental question about alcoholism is why do some people consume alcohol to excess even though it interferes knowingly with their well-being? Alcohol changes the brain. Acute alcohol intoxication reversibly affects brain function, whereas chronic alcohol abuse affects the brain in enduring ways. These effects themselves may contribute to the loss of control. Initially, alcohol is the cause producing the effect of brain structural and functional compromise, and that brain change can itself become the cause to seek alcohol. In this way, alcoholism can become a self-perpetuating disorder, resulting from neuroadaptation (cf., Koob & Le Moal, 2006).

In addition to alcohol itself as an agent to promote addiction, some individuals carry a genetic liability for addiction, possibly selective to alcoholism. As noted by Vanyukov and Tarter (Vanyukov & Tarter, 2000), Falconer (1965) introduced the concept of liability in the context of human genetics, indicating a likelihood rather than a determined fate. A discussion of the genetics and family history of alcoholism is beyond the scope of this review; rather, scholarly discourses are presented elsewhere (e.g., Bierut et al., 1998; Edenberg & Foroud, 2014; Schuckit, 1985b; Vanyukov & Tarter, 2000).

Interrogation of Neural Systems with Neuropsychological Testing and Brain Imaging
To identify brain structural and functional deficits in alcoholism and brain–behavior relations, we have taken two approaches. Some studies start with finding brain structural or functional abnormalities using quantitative MR imaging modalities, and then ask what are the functional ramifications of observed regional brain abnormalities. Other studies start with neuropsychological deficits and seek underlying brain abnormalities as underlying mechanisms.

Profile of Functional Sparing and Impairment
To examine neuropsychological functions, we set out to establish the pattern of sparing and impairment in recently detoxified alcoholics using tests known from the lesion literature to have established specificity to detect impairment in selective functions and the potential to localize brain structures underlying impairment. Use of a large battery assessing multiple functions enabled assessment of the diffuse impairment hypothesis of alcoholism characterizing alcoholism-related deficits as non-specific (e.g., Parsons & Leber, 1981). Test scores were expressed as age-corrected Z-scores based on performance by sex-matched controls, where low scores are in the direction of impairment. Use of both verbal and nonverbal tests of executive skills, working memory, declarative memory, and unimanual motor ability enabled assessment of functions of each cerebral hemisphere and a test of the right hemisphere hypothesis of alcoholism, which posited that the right hemisphere and its nonverbal functions are more vulnerable than left hemisphere and its verbal functions to the untoward effects of alcoholism (e.g., Ellis & Oscar-Berman, 1989; Oscar-Berman, 2000; Parsons & Nixon, 1998).

The resulting performance profile was similar to that identified by Victor, Adams, and Collins (Victor, Adams, & Collins, 1989) using the Wechsler-Bellevue Intelligence Scale in their series of patients with alcoholic Korsakoff’s syndrome (KS), who exhibited enduring deficits in working memory, visuospatial ability, and psychomotor speed despite evidence for some recovery in world knowledge, semantic categorical comprehension, and assembly of familiar objects.
Influenced by the work of Parson, Glenn, and Nixon in women (Fabian & Parsons, 1983; Glenn & Parsons, 1992; Nixon, Tivis, Ceballos, Varner, & Rohrbaugh, 2002; Nixon, Tivis, & Parsons, 1995; Parsons & Nixon, 1998), we also sought a profile of impairment in alcoholic women and found that apart from static balance, alcoholic men and women showed similar deficit patterns (Sullivan, Fama, Rosenbloom, & Pfefferbaum, 2002) (Figure 1).

Furthermore, neither the diffuse impairment hypothesis nor the right hemisphere hypothesis of alcoholism-related impairment was supported, conclusions reached decades ago by Tarter (Tarter, 1975) and supported by the observation of similarly impaired verbal and nonverbal skills in two samples of alcoholics (Tivis, Beatty, Nixon, & Parsons, 1995). Nonetheless, nonverbal tests may be more sensitive to enduring deficits (Brandt, Butters, Ryan, & Bayog, 1983; Fein, Bachman, Fisher, & Davenport, 1990) (for review, Oscar-Berman et al., 2014), possibly because they are often more difficult and use less familiar materials than verbal tests. These profiles indicated also where to look in the brain for underlying mechanisms of impairment.

Frontocerebellar Circuity Hypothesis of Alcoholism

The salient deficit in static balance profile indicated in the neuropsychological performance profile of nonamnesic alcoholic men began the search for neural substrates of ataxia, initially tested with the modified Fregly-Graybiel Walk-a-Line Test (Fregly, Graybiel, & Smith, 1972; Sullivan, Rosenbloom, & Pfefferbaum, 2000). Known neuropathological substrates of ataxia led the search to the cerebellar vermis and ultimately evolved into our frontocerebellar circuity hypothesis of alcoholism (Sullivan, 2003; Sullivan & Pfefferbaum, 2005; Zahr, Pfefferbaum, & Sullivan, 2017). Untoward effects of alcoholism on this far-reaching neural circuitry have foundation in speculations of early studies conducted in AUD uncomplicated by concomitant conditions and AUD complicated by dietary deficiencies or organ compromise (Tarter, 1975) and a later positron emission tomography study showing frontocerebellar glucose metabolism deficits in alcoholics with ataxia (Gilman et al., 1990).

Pursuit of a refined characterization of balance instability used a balance platform, which yields a stabilogram and quantifies the kinetics of the sway path that result when trying to stand still under different sensory and motor conditions, that is, with or without sensory or stance aids—eyes closed, no touch, and feet together (Figure 2). With sensorimotor aids, the sway paths of control men and women were significantly shorter than those of alcoholic men and women, despite sobriety. With sensory and stance aids, however, even the sway of the alcoholics of both sexes was quelled (Sullivan, Rose, & Pfefferbaum, 2006a, 2006b). Thus, the force plate approach for detecting stance instability was sensitive enough for its detection in alcoholic women whose impairment was relatively elusive to the roadside-like ataxia testing.

The next step was to seek a relation between sway path length and volume of the cerebellar vermis as a potential brain substrate of the instability in quiet standing. Correlations indicated that the smaller the anterior superior vermis, the longer the sway path. Furthermore, alcoholics who maintained sobriety longer had shorter sway paths. These patterns occurred in non-KS, recovering alcoholic men (Sullivan et al., 2006) and women (Sullivan, Rose, & Pfefferbaum, 2010a, 2010b).

Cross-sectional study cannot address whether static postural instability, or any other functional impairment, in recovering alcoholics was present before the onset of AUD, was exacerbated by AUD, or occurred because of AUD. With respect to balance specifically, early studies of nonalcoholic, adolescent sons of alcoholic fathers found them to have excess upper body sway, possibly related to hyperactivity (Hegedus, Tarter, Hill, Jacob, & Winsten, 1984). Paradoxically, young adult men with familial risk for alcoholism exhibited less body sway under controlled conditions of acute alcohol ingestion than did matched men who did not carry the familial liability (Schuckit, 1985a). Both studies considered static ataxia as a potential biomarker or genetic trait of a predisposition for alcoholism.

Graded Brain Volume Deficits in Limbic Circuitry of Alcoholics

The deficit profile identifying compromised component processes of memory indicated where to look for neural substrates of compromise and led to Papez circuit and the limbic system. In addition, it was essential to define an appropriate diagnostic comparison to gauge the extent of the memory impairment in “uncomplicated” alcoholism. The comparison group comprised alcoholics complicated by KS, which is marked by dense anterograde amnesia, the result of Wernicke’s encephalopathy (WE) and thiamine deficiency.
Alcoholism, Balance, Stability Aids, and Cerebellar Vermis

Fig. 2. Alcoholism, balance, stability aids, and cerebellar vermis. Top left. Woman on the balance platform. Bottom left. Example of balance platform stabilograms for control (top) and alcoholic (bottom) with and without cues. Note the sway path of “wobble” of the alcoholic as he tries to stand still. Bottom right. Structural MRI of the cerebellum (green circle) from a control (top) and alcoholic (bottom). Note the markedly smaller tissue of the cerebellar vermis of the alcoholic. Top right. Relation of vermis size and sway path length. Modified from Sullivan and Pfefferbaum (Human imaging studies of brain circuitry disrupted by alcoholism. In Noronha A, Cui C, Harris RA, Crabbe JC (Eds.). Neurobiology of Alcohol Dependence. Oxford: Elsevier, pp. 131–151, Chapter 8, 2014; Figure 8.1 on page 134); original data in Sullivan et al. (Cerebral Cortex 2006).
This diagnostic comparison is in the research traditions of Boston (e.g., Cermak, Butters, & Goodglass, 1971), Pittsburgh (Tarter, 1975), and Oklahoma (Parsons & Nixon, 1993), where performance by uncomplicated alcoholics could be compared with non-alcoholic controls, who determined healthy norms, whereas alcoholics with KS determined amnesic performance. At the same time, the uncomplicated alcoholics served as a diagnostic comparison to the KS. Working within the context of classical neuropathological studies of alcoholics with KS, which is marked by lesions in the mammillary bodies and thalamus, we used in vivo MRI to ask what patterns of volume deficits define these two groups of alcoholics. These comparisons were the basis for testing whether the two alcoholic groups differed in deficit pattern or, alternatively, in deficit severity.

Accordingly, MRI data were acquired in groups of healthy controls, uncomplicated alcoholics, and alcoholics with KS, who we assumed from neuropathological studies (e.g., Victor et al., 1989) would have regional limbic system volume deficits underlying their global amnesia. It was not clear what to expect in the uncomplicated alcoholics. First, the mammillary bodies showed marked bilateral volume deficits in KS, and KS with dementia had even smaller volumes. Uncomplicated, nonamnesic alcoholics also had bilateral mammillary body volume deficits but to a milder degree, and this occurred in the absence of an amnesic syndrome (Sullivan et al., 1999). Similarly, bilateral hippocampus (Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995), thalamus, pons (Sullivan & Pfefferbaum, 2009), cerebellar hemispheres, and vermis (Sullivan, Deshmukh, Desmond, Lim, & Pfefferbaum, 2000)—substrates of gait, balance, working memory, and components of executive functioning—each showed graded volume deficits from uncomplicated alcoholism to alcoholism complicated by KS relative to healthy controls (Sullivan & Pfefferbaum, 2009) (also see Blansjaar, Vielvoye, van Dijk, & Rijnders, 1992). That all regional volume deficits observed were bilateral provided no evidence for the right hemisphere hypothesis of alcoholism.

Because the hippocampal finding in the KS patients was so controversial (cf., Squire, 1982; Squire, Amaral, & Press, 1990), we challenged it by measuring the extent of their volume deficit against Alzheimer’s disease (AD) patients, with known pathology of medial and lateral temporal cortex. Although the volume deficits of the AD group were greater than those of the KS in the temporal cortex, the alcoholic KS had hippocampal volume deficits equivalent to those of the AD group, thus providing convergent validity to our original findings (Sullivan & Marsh, 2003).

Graded Neuropsychological Deficits in Alcoholics

These graded effects led to the next pursuit: Do uncomplicated alcoholics carry an occult history of WE, the precursor of KS (cf., Blansjaar et al., 1992; Tarter & Ryan, 1983)? Are traces of WE signs also related to neuropsychological performance in alcoholics without KS, given that WE is marked by lesions of periventricular nuclei, mammillary bodies, and thalamus, resulting in the cardinal triad of ophthalmoplegia, ataxia, and confusional state and often heralding the profound anterograde memory impairment of KS (Victor et al., 1989). Indeed, Wernicke-Korsakoff’s syndrome (WKS) is definitively known to be the result of thiamine depletion or severe deficiency, which was once a common concomitant of alcoholism (Harper, 1979; Harper et al., 1998).

The question of a nutritional mechanism of memory impairment in alcoholics has a history in the classical book, Alcoholic Korsakoff’s Syndrome: An Information-Processing Approach (Butters & Cermak, 1980), where Butters and Cermak speculated that “Because most chronic alcoholics may eat enough to maintain a sufficient level of thiamine, the short-term verbal memory deficits associated with diencephalic-limbic [dorsomedial nucleus of thalamus and/or mammillary bodies] lesions may be apparent in only a small percentage of chronic alcoholics” (page 158).

Studies of the pathologist Clive Harper reported that the incidence of neuropathological signs of WE observed post-mortem was far higher in so-called uncomplicated alcoholics than recognized in vivo (Harper, 1979). Pursuing these observations, Caine and colleagues devised 4 criteria for chart review of their postmortem cases: evidence for dietary deficiency, oculomotor abnormalities, cerebellar dysfunction, and altered mental state. Cases having two of four of these signs correlated with presence of neuropathological signs of WE (Caine, Halliday, Kril, & Harper, 1997).

A decade later, Pitel et al. (2011) operationalized the Caine et al. criteria for in vivo use in alcoholics and controls; historical interview enumerated missed meals and quantitative examination tested for nystagmus, ataxia, and cognitive compromise determined with the Mattis Dementia Rating Scale (Mattis, 1988). Although no alcoholic presented with any of the three classical WE signs of ophthalmoplegia, ataxia, or delirium, a large proportion of the alcoholic group met one or two criteria, based on Caine et al. (1997) and operationalized by Pitel et al. (2011). In fact, more than half the group met one criterion; 16% met two criteria; and only approximately one quarter of the group were free of these signs (Figure 3).

These alcoholics and controls were also administered a comprehensive neuropsychological test battery. The pattern of functional impairment across the entire group of alcoholics without consideration of Caine criteria indicated mild to moderate deficits in three of the six functional domains examined. Dividing the alcoholics by Caine criteria, however, presented a different picture, where alcoholics meeting no criteria performed at normal levels in all domains, those meeting one criterion showed modest selective compromise, and those meeting two criteria were the most widely affected, being significantly impaired on all 6 domains (Pitel et al., 2011) (Figure 3).

This finding was recently extended with an enlarged group of uncomplicated alcoholics (Fama et al., 2017). Blood samples for thiamine levels obtained in a subset of the initially studied alcoholics revealed that higher thiamine levels were predictive of better memory performance, and that this relation was selective to memory and not to other performance domains. Thus, occult WE may be a factor underlying alcohol-related neuropsychological deficits (cf., Bowden, 1990).
thereby supporting the earlier speculations of Butters and Cermak (1980), Tarter (Tarter, 1975), and later by Oscar-Berman (Oscar-Berman, 2000).

In summary, rather than concluding that the effect of AUD on brain structure is diffuse, these studies support disruption of frontocerebellar and frontolimbic circuitry with wide-reaching networks. Complementing neurocircuitry disruption are constellations of selective functional impairments that include executive functions, attentional processes, response inhibition, episodic memory, prosody, visuospatial abilities, decision-making, and postural stability, yet leaving language, procedural learning, and upper motor skills largely intact.

APPRECIATE THAT ALCOHOLISM-RELATED FUNCTIONAL CHANGES ARE A FORM OF NEUROADAPTATION THAT MAY UNDERLIE DYSFUNCTION, MAKING ALCOHOLISM A SELF-PERPETUATING DISORDER

In keeping with the focus on memory, examples of neuroadaptation and alcohol-related change will be considered through functional neuroimaging studies of working memory. Information stored through working memory processes is held only temporarily for ultimate consolidation into a more permanent form or for manipulation to transform information from one concept to another, and is a mnemonic process commonly impaired in chronic alcoholism (Stavro, Pelletier, & Potvin, 2013). Functional imaging methods can readily be used to interrogate working memory to reveal neural substrates of change, to determine whether alcoholics recruit the same networks as controls to perform a task at control levels, and to examine whether alcoholics have intrinsic functional connectivity similar to controls.

Functional MRI: BOLD Using Task-Activated Paradigms

The most commonly used noninvasive, functional imaging method, functional MRI (fMRI), is based on a hemodynamic response, the blood oxygen-level dependent response (BOLD), that is typically calculated in task-activated paradigms as a difference in responses between experimental and control conditions (e.g., Glover, 2011). In a seminal task-activated fMRI study, alcoholics and controls performed a 2-back, spatial working memory task while being scanned.
Subjects attempted to remember the location of 0s from trial to trial and to press a key every time a 0 appeared in the same location two trials back. For the comparison task, subjects pressed the response key every time a zero appeared in the center location; therefore, no memory was required. The alcoholics were practiced to perform as well as the controls, which is essential to allow interpretation of group differences in activation patterns should they emerge. After all, if the groups performed differently on the target task, it would be no surprise to see differences in activation patterns.

In this study (Pfefferbaum et al., 2001), while performing the spatial working memory task, controls (top) activated cortical regions of the dorsal stream, typically invoked for spatial processing (where). Bottom left: Alcoholics activated the ventral stream, typically invoked for object naming (what); from Pfefferbaum et al. (2001). Right: Alcoholics activated the frontocerebellar system to maintain verbal material in working memory, whereas controls used only the frontal system to do the task. From Desmond et al. (2003).

fMRI Studies of Working Memory in Nonamnesic Alcoholics

Spatial task
Controls (top) activated the dorsal (where) stream.

Alcoholics (below) activated the ventral (what) stream.

Verbal task
Alcoholics activated the frontocerebellar system to maintain verbal material, whereas controls used only the frontal system to do the task.

Fig. 4. Results from two task-activated fMRI studies. Top left: In a spatial working memory task, controls (top) activated cortical regions of the dorsal stream, typically invoked for spatial processing (where). Bottom left: Alcoholics activated the ventral stream, typically invoked for object naming (what); from Pfefferbaum et al. (2001). Right: Alcoholics activated the frontocerebellar system to maintain verbal material in working memory, whereas controls used only the frontal system to do the task. From Desmond et al. (2003).

In this study (Pfefferbaum et al., 2001), while performing the spatial working memory task, controls activated the dorsal stream traditionally used in spatial processing tasks, whereas alcoholics activated the ventral stream used in object identification tasks (cf., Ungerleider & Mishkin, 1982). In a verbal working memory task, participants were given either six letters or one letter to remember over a 5-s interval and saw a probe letter, to which they responded with a button box key yes if it matched or no if it did not. To perform this simple task, alcoholics activated frontal and cerebellar regions, a task accomplished by controls with only the frontal system (Desmond et al., 2003) (Figure 4).

These were the first of several such studies showing a common theme in alcoholism (e.g., De Rosa & Sullivan, 2003; Tapert et al., 2001), summarized by Oscar-Berman and Marinkovic (2007): that the positive outcome of shift and expansion in functional anatomy can be normal performance but may occur at the price of usurping reserve that reduces processing capacity for conducting multiple tasks simultaneously and efficiently.

fMRI: BOLD Using a Resting-State Paradigm to Identify Intrinsic Functional Networks

These task-activated results led to functional connectivity analysis. Typical task-activated fMRI experiments ask, “What regions respond while engaged in a task?” and use brain activation to identify areas of functional specialization. To understand functional integration, we ask, “What regions respond together?” establishing brain connectivity by identifying brain regions with highly correlated, that is, synchronous, BOLD activity compared with regions that do not show this correlated activity.

Task-free fMRI when done in the so-called “resting state” has revealed intrinsic functional networks, the most prominent being the Default Mode Network (DMN), characterized by a pattern of activation synchrony involving the precuneus or posterior cingulum, parietal cortex, and medial prefrontal cortex (Raichle et al., 2001; Raichle & Snyder, 2007). At rest, alcoholics showed the same pattern of activation synchrony as controls but had less robust synchrony between most nodes of the DMN than controls (Chanraud, Pitel, Pfefferbaum,
& Sullivan, 2011). One exception was for the middle frontal cortex, which had higher activation in the alcoholics than controls.

This finding led to testing whether robustness of resting-state connectivity could predict subsequent performance on a Brown-Peterson distractor task (Brown, 1958; Cermak & Ryback, 1976; Peterson & Peterson, 1959) for spatial working memory with an established frontocerebellar structural substrate (Chanraud, Pitel, & Sullivan, 2010) (Figure 5). Using the middle frontal cortex as the seed region, that is, the point with which BOLD synchrony is tested with every other voxel in the brain, significant functional connectivity emerged with the cerebellum. Critically, higher correlation of this resting functional connectivity between the middle frontal and Crus II of the cerebellum predicted subsequent performance in the alcoholics but not controls (Chanraud et al., 2011). This pattern of group differences in the context of functional connectivity differences between frontal and cerebellar targets fit criteria deeming the activation pattern as consistent with compensation (Chanraud, Pitel, Muller-Oehring, Pfefferbaum, & Sullivan, 2013).

**Arterial Spin Labeling as a Direct Measure of Cerebral Perfusion**

Another form of noninvasive functional imaging is MR arterial spin labeling (ASL), which measures cerebral perfusion, or cerebral blood flow (CBF), itself rather than the BOLD signal measured with fMRI. Pulsed continuous ASL (PCASL) is a three-dimensional acquisition protocol (Alsop, Makovetskaya, Kumar, Selim, & Schlag, 2005; Detre & Alsop, 1999), which is reliable (Pfefferbaum et al., 2010) and sensitive to change with task demands (Pfefferbaum et al., 2011). Perfusion imaging can determine whether disease-related differences identified with fMRI are caused by impaired microvascular perfusion. To the extent that resting-state paradigms are used for identifying intrinsic functional networks whereas task-activated paradigms are well-suited for identifying nodes and networks, we used PCASL to test whether perfusion imaging could detect and replicate fMRI-identified activation patterns. Accordingly, subjects performed the spatial working memory distractor paradigm to test recall of six spatial locations following a retention interval filled with arithmetic problems (Chanraud, Pitel, & Sullivan, 2010); in other conditions, subjects “rested.”

Like healthy controls, alcoholics showed the DMN pattern in selective regions (medial frontal, temporal, and cingulate cortices, posterior precuneus, and hippocampal/amygdalar complex) with high perfusion in the rest condition, low perfusion in the task condition, and a return to high perfusion in the second rest condition. By contrast, other regions (superior and inferior cerebellum, middle precuneus, parietal, occipital, and calcarine cortices), known to be associated with working memory (Chanraud et al., 2010; Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997; Tapert et al., 2001), showed a task-activated CBF pattern of low-high-low with rest-task-rest conditions. Although both groups showed the DMN pattern in the insula, the level of perfusion was impaired in the alcoholics (Figure 6); yet, in alcoholics, greater task accuracy correlated with higher insular perfusion at rest (Sullivan et al., 2013).

We then used the insula, which is considered the hub of the salience network (Greicius, Krasnow, Reiss, & Menon, 2003; Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008), as a seed for CBF-synchrony analysis. This analysis revealed functional connectivity between the insula and nodes of the salience network (anterior cingulate, medial prefrontal, temporal, and parietal cortices) in the controls but not alcoholics. Functions of the insula may have particular relevance to alcoholism given its role in impulse control, self-regulation, error monitoring, and reward processing. As a principal node of the salience network, the insula enables switching between intrinsic and task networks, notably, the executive control network (Menon & Uddin, 2010). This set of results led to the speculation that low insular CBF impairs connectivity among functional salience network nodes and reduces ability to switch from interoceptive desires, such as cravings (impulsive system), to cognitive control over these desires (executive system). In this way, the insula might be considered an “addiction site.” Later in this review, we will see that the insula plays a role in a critical yet under-studied component of memory function in alcoholics.

Evidence that alcoholism is a self-perpetuating disorder has foundation in observations of AUD-related modification of neurocircuitry affecting, for example, the salience network in its switching capacity to over-ride compulsive urges. Other forms of neureadaptation include shifts and expansions of functional brain regions to accommodate or compensate for AUD-injured sites.

**LEARN THAT SUSTAINED SOBRIETY CAN RESULT IN IMPROVEMENT IN BRAIN STRUCTURE AND FUNCTION, INDICATIVE OF DAMAGE REVERSAL OR COMPENSATORY MECHANISMS THAT CAN BE IDENTIFIED WITH FORMAL NEUROPSYCHOLOGICAL TESTING AND LONGITUDINAL, QUANTITATIVE, STRUCTURAL, AND FUNCTIONAL BRAIN IMAGING**

So far, only deficits related to excess, chronic alcohol consumption have been considered. But, alcoholism follows a dynamic course, with the possibility of brain structural and functional recovery with sustained sobriety, which brings this review to its last section, regarding the potential for recovery of brain structure and function.

**Recovery of Brain Macrostructure**

Remarkably, ventricular expansion, a macrostructural signature of prolonged, chronic, dependent-level alcohol consumption, is reversible, at least in part, with sustained
Spatial Working Memory and Brain Substrates in Nonamnesic Alcoholism

Fig. 5. Spatial working memory and brain substrates in nonamnesic alcoholism. Upper left: Brown-Peterson short-term (working) memory paradigm using three or six spatial or verbal items for recall and a spatial or verbal distractor task or rest conditions. Upper right: Accuracy scores showing poorer performance by the alcoholic than control group, with the greatest performance difference with the largest memory load (six items) with arithmetic interference. Middle: Correlations between better performance on the six-item spatial task with arithmetic distraction condition with larger volumes of the left superior frontal gyrus, thalamus, and Crus I in the alcoholics. Bottom: Atlas locations of the targets for correlations. From Chanraud et al. (2010).
abstinence. This reversal was first detected in vivo with computed tomography (Carlen, Wilkinson, Wortzman, & Holgate, 1984; Carlen, Wortzman, Holgate, Wilkinson, & Rankin, 1978). Serial MRIs of individual cases of recovery reveal brain structural improvement (Rosenbloom & Pfefferbaum, 2008), visible in the lateral ventricles (Figure 7).

A striking example of recovery involved a 41-year-old alcoholic woman, scanned after 2 months of sobriety and then again 1 year later. In addition to ventricular shrinkage, she exhibited resolution of radiological evidence for central pontine myelinolysis, which if left untreated, can be fatal (Lampl & Yazdi, 2002; Sullivan & Pfefferbaum, 2001).

In addition to single case studies, an ever-increasing number of longitudinal MRI studies on groups of alcoholics report significant changes in regional brain volumes (e.g., Cardenas, Studholme, Gazdzinski, Durazzo, & Meyerhoff, 2007; Rohlffing, Sullivan, & Pfefferbaum, 2006; Shear, Jernigan, & Butters, 1994; Wang et al., 2016; Yeh, Gazdzinski, Durazzo, Sjostrand, & Meyerhoff, 2007). An early study imaged alcoholics approximately a week after detoxification and again approximately 3 weeks later, at the end of a 28-day VA inpatient treatment regime with enforced abstinence. Controls, scanned over the same interval, showed no change in regional brain volumes, whereas the abstaining alcoholics showed improvement, enlargement of frontal cortical volume and shrinkage of cortical sulci and lateral ventricles (Figure 7).

Follow-up of this cohort after discharge revealed that approximately half relapsed and half maintained abstinence. The abstainers showed further improvement, whereas relapsers showed further shrinkage of white matter and expansion of the third ventricle (Pfefferbaum et al., 1995). Further follow-up indicated that the more relapers had drunk over the 5-year interval, the greater their volume loss of cortical gray matter (Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998) (Figure 7). These results have now been replicated with higher-resolution imaging of regional brain macrostructure (e.g., Segobin et al., 2014) and imaging protocols focused on white matter microstructure (e.g., Pfefferbaum et al., 2014).

**Recovery of Component Processes of Memory Functions with Alcohol Abstinence**

For decades, systematic studies of short-term, or working, memory have revealed significant improvement with sustained sobriety in uncomplicated alcoholics but not in KS alcoholics (Cermak & Ryback, 1976). Our early study of abstinent, non-KS alcoholics showed greater improvement in nonverbal immediate and short-term memory than did relapers (Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000). Improvements in visuospatial ability also noted in the abstainers could have contributed to spatial memory improvements (Figure 7). Critically, improvements in memory correlated with shrinkage of the third ventricle volume, suggesting a neural substrate for recovery (Rosenbloom, Pfefferbaum, & Sullivan, 2004; Sullivan, Rosenbloom, Lim, et al., 2000).

These findings echo both earlier and more recent controlled studies of memory recovery with short-term or sustained sobriety showing a range of recovery, from little to extensive, after short-term (e.g., 1 week) to long-term (e.g., 1 year or more) sustained abstinence from alcohol (e.g., Bartels et al., 2007; Bates, Voelbel, Buckman, Labouvie, & Barry, 2005; Bell, Vissicchio, & Weinstein, 2016; Butters & Cermak, 1980; Fabian & Parsons, 1983; Fein, Torres, Price, & Di Scalfani, 2006; Glenn, Parsons, & Sinha, 1994;
Leber, Jenkins, & Parsons, 1981; Mann, Gunther, Stetter, & Ackermann, 1999; Pitel et al., 2009; Rosenbloom et al., 2004; Rourke & Grant, 1999; Yohman, Parsons, & Leber, 1985) (for reviews, see Oscar-Berman et al., 2014; Pitel, Eustache, & Beaunieux, 2014). Remaining to be established are parameters of recovery, including length of sobriety, age at alcoholism initiation, age at testing, style of drinking, concomitant nutritional deficiencies and non-alcohol drug use, sex, physiological, ethnic, and genetic characteristics of alcoholics (Stavro et al., 2013).

Meaning of Neuroadaptation to the Recovering Alcoholic

How does the alcoholic perceive the fact that brain structure and function change for the worse with chronic drinking and then improve with abstinence? Longitudinal MRI and neuropsychological studies of recovery and relapse can provide insights into this process. Leber, Jenkins, & Parsons (1981), for example, noted that alcoholics who remained abstinent 3 to 12 months after discharge showed further improvement in brain volume changes, whereas relapsers showed worsening.

**Fig. 7.** Longitudinal MRI and neuropsychological studies of recovery and relapse. Top blue box: MRI volume data of alcoholics approximately 1-week post-detoxification and then again after 28 days of enforced abstinence in an inpatient VA treatment facility. The alcoholics showed volume gains with abstinence despite no volume change in the controls. Middle red box: Alcoholics who remained abstinent 3 to 12 months after discharge showed further improvement in brain volume changes, whereas relapsers showed worsening; from Pfefferbaum et al. (1995). Bottom red box: Neuropsychological testing conducted at the 3- to 12-month follow-up revealed improved performance in both groups, suggesting practice effects, which were greater in the abstainers than relapers; from Sullivan et al. (2000).
that they change again with sobriety? How aware is the alcoholic of his or her impairment? There can be significant mismatches between the subjective view of one’s performance and the objective measurement of actual performance. This phenomenon can be operationalized using a metamemory paradigm, which may inform us about the extent to which alcoholics are aware of their deficits.

Work of a predecessor of INS provides insight regarding functional recovery after head injury. Kurt Goldstein, a German neurologist and psychiatrist who fled Germany in the 1930s, went to NY and then Boston, where he studied and treated veterans who had sustained head injuries in The Great War (Goldstein, 1942). His work on visual agnosia together with his initial interest in philosophy likely set the stage for his interest in brain–mind relations. A primary principle proffered was that brain injury affects the organism as a whole, rendering the individual forever different from the pre-injury state (Goldstein, 1995). Thus, recovery can never be complete.

This concept is consistent with that of Oscar-Berman and Marinkovich (Oscar-Berman & Marinkovic, 2007) in noting that achieving normal performance in one function can occur at the expense of other functions (cf., Sullivan & Tapert, 2013). This concept cast a long shadow on cognitive rehabilitation efforts and has been eschewed by those who believe that recovery means a return to a premorbid state. Goldstein posited that, as for compensation, there is no such thing. Rather, a head injured patient might undergo restitution and recuperation, achieving “new normal” where health “is restored if a relation between preserved and disturbed performances is reached (page 331)” (Goldstein, 1995). But such adaptation could result in a brain-injured patient’s adapting to the deficit state and rejecting change. This subjective bias would need to be overcome to embrace change through resolving the mismatch between the subjective and objective conditions.

The Goldstein idea is much like that of the First Principle of Neuropsychological Rehabilitation put forth by Prigatano (1999), stating that, “The clinician must begin with patient’s subjective or phenomenological experience to reduce their frustration and confusion in order to engage them in the rehabilitation” (page 3). This conception is even consistent with Step I of Alcoholics Anonymous (Wilson, 1939, 2014), which states, “We admit we were powerless over alcohol.” What we might conclude today, however, is to admit requires accurate assessment of the problem, and to fail at this can be mistaken as denial rather than as a cognitive impairment itself.

**Feeling-of-Knowing: A Test of Metamemory**

Relevant to addressing these queries is metamemory, which is an umbrella mnemonic function that refers to personal knowledge about one’s own ability to remember or recall information (Flavell, 1971). Metamemory draws on cognitive processes to monitor and control memory and can be examined by testing prospectively predictions about how well one might perform a memory test and by testing retrospectively one’s confidence of actual recall or recognition performance (Le Berre et al., 2010, 2016). Assessment of both the prospective and retrospective memory components is achieved with the feeling-of-knowing (FOK) paradigm (Hart, 1965). In short, subjects learn unrelated word pairs, then after a delay judge whether they think they would be able to recall the second word of the pair later on (prospective memory), and finally do a four-choice recognition task and make retrospective confidence judgments (RCJ) about their actual performance on the recognition task (for review of the method, Le Berre & Sullivan, 2016).

In calculating the agreement between predictions of future recognition performance and actual recognition performance, the alcoholics overestimated their recognition ability despite being accurate in their estimation of how they performed (Le Berre et al., 2016, 2010). Structural MRI with parcellation to identify brain substrates of FOK and RCJ performance in the alcoholics revealed a double dissociation, where FOK accuracy was selectively related to insular volume but not to frontolimbic volumes, whereas retrospective confidence accuracy was selectively related to frontolimbic structural volumes but not to insular volumes (Le Berre et al., 2016) (Figure 8). Task-activated fMRI revealed that in the metamemory vs. control task contrast greater activation occurred in the right superior frontal cortex in the alcoholics than controls but that better episodic memory performance and greater FOK accuracy correlated with lower activation in the right superior frontal cortex, a node of the default mode network, in the controls but not alcoholics. Within the alcoholics, greater FOK accuracy correlated with greater activation in the right insula, a correlation not observed in the controls (Le Berre et al., 2017).

**Anosognosia or Denial?**

In summary, internationally based evidence (Le Berre et al., 2016, 2010) was forthcoming for a functional dissociation and mismatch between subjective metamemory processes, with impaired prospective memory showing overestimation of potential mnemonic abilities, and spared retrospective assessment, indicating awareness of actual abilities. Furthermore, evidence for neural substrates of the metamemory impairment from structural MRI data revealed a double dissociation, where poorer prospective memory correlated selectively with smaller insular cortical volumes, whereas better retrospective memory correlated selectively with larger frontolimbic structures. Extending support for a role of the insula in metamemory were fMRI data, which revealed that better performance related to greater insular activation in alcoholics.

Thus, faulty FOK performance by alcoholics is marked by an over-estimation of prospective memory abilities presenting a mismatch between subjective experience and objective abilities, possibly related to the alterations in brain systems invoked to do the best one can. This pattern is consistent with a mild anosognosia (for discussion and review, see Le Berre & Sullivan, 2016), which initially described the inability of a stroke patient to recognize the loss of limb function, with the subjective experience that the limb remains
attached (Babinski, 1914). Agnosognosia has also been characterized by the phrase, “You don’t know that you don’t know.” Taken together, these results provide initial support for neuropsychological and neural mechanisms involving insular cortical structure and function of unawareness, perhaps misinterpreted as the psychological defense mechanism of denial rather than as an actual functional impairment, possibly anosognosia, in addiction (cf., Sullivan, 2012).

It is now objectively established with controlled, longitudinal study that brain structure and cognitive and motor functioning can improve with sustained sobriety. Remaining unknown, however, are the mechanisms and means of neural recovery and whether recovery can ever be complete. The latter requires knowledge about pre-AUD neurostructural and neurobehavioral conditions, which can be determined only with prospective study.

CONCLUSION

Brain structural and functional changes occur in alcoholism. Our INS forefathers’ rigorous experimental work and keen observations initiated and enriched our understanding of
alcoholism with its sometimes elusive, constellation of impairments. That legacy work has enjoyed verification with replication and extension through neuroimaging technologies unavailable in those early days, and now enabling legacy hypotheses to be tested in vivo. Among the myriad brain structure–function hypotheses now testable concern identification of and distinction between mechanisms of compensatory vs. recovery of functions with sustained sobriety and retraining efforts.

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INS legacy in alcoholism research


