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REVIEW

Contributions of Studies on Alcohol Use Disorders to Understanding Cerebellar Function

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Abstract Neuropathological, neuropsychological, and neuroimaging studies of human alcoholism provide evidence for degradation of frontal, pontine, thalamic, and cerebellar brain sites and disturbed associated functions. Current studies using neuroimaging combined with examination of executive functions, traditionally considered the sole purview of the frontal lobes, have identified a role for the cerebellum serving as a compensatory processing adjunct to enable normal performance on challenging tasks tapping executive functions. This overview proposes that disruption of an executive frontocerebellar network is a major contributor to characteristic behaviors of alcoholism that, on the one hand, enable alcohol use disorders, and on the other hand, lead to compensation for dysfunctions in alcoholism traditionally considered frontally-based.

Keywords Cerebellum · Alcohol · Alcoholism · Executive function · Structural imaging · Functional imaging

A salient behavioral characteristic defining alcohol use disorders is the continued use of alcohol despite physiological or psychological problems (http://rethinkingdrinking.niaaa.nih.gov/). Other clinically observed features describing alcoholic behavior include impaired judgment, blunted affect, poor insight, social withdrawal, reduced motivation, distractibility, cognitive rigidity, inattention, and perseveration (Oscar-Berman 2000; Sullivan et al. 2000a). This constellation of higher-order, "executive" dysfunction has classically been ascribed to degradation of frontal lobe integrity (Cummings 1993; Fuster 1999). Application of specialized and detailed neuropsychological tests, however, has demonstrated that individuals with lesions limited to the cerebellum can be impaired in functions previously considered the exclusive purview of the frontal lobes (Schmahmann 1997, 2000).

Brain structural damage in response to chronic alcohol exposure, although widespread (Pfefferbaum et al. 1992; Sullivan et al. 1998), also targets specific brain systems leaving others relatively intact (for review, Chanraud et al. 2010a). The cerebellum (Victor et al. 1959) and prefrontal cortex (Courville 1955; Harper et al. 2003), although spatially disparate, are particularly compromised in the brains of alcoholics. The cerebellum is highly interconnected to the cerebral cortex via feedforward/afferent loops through the pons and feedback/efferent loops through the thalamus. Convergent findings from primate viral tracing studies (Schmahmann and Pandya 2008; Strick et al. 2009), human case studies of patients with cerebellar lesions (Fitzpatrick et al. 2008; Schmahmann and Pandya 2008; Leggio et al. 2009), and human functional imaging studies (Habas et al. 2009; Krienen and Buckner 2009) have revealed the presence of multiple cerebellar-based cortical systems (see Bostan and Strick, Leiner, and Schmahmann this issue).

Dissociable functions of these loops are related to the sites of termination in the cerebral cortex of specific projections from the cerebellum (Kelly and Strick 2003a). Examples of these divergent but parallel loops include the motor and executive loops (Fig. 1): 1) the motor network, involving motor lobules of the cerebellar vermis (e.g., IV, V, VI) and motor cerebral cortices (Biswal et al. 1995)

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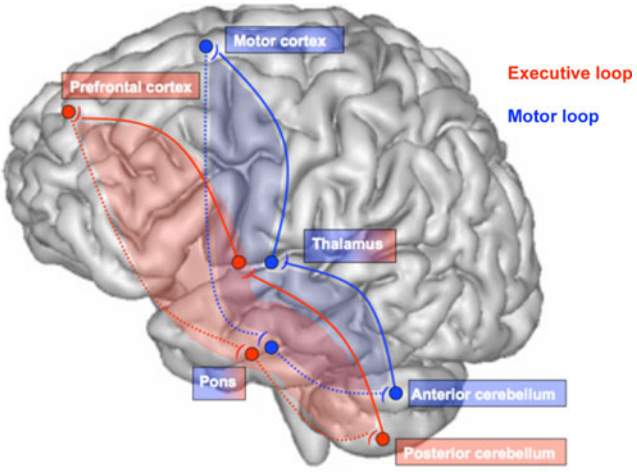


Fig. 1 The corticocerebellar circuit: two dissociable but associated loops, the motor loop connecting motor cortex, thalamus, and anterior cerebellum and the executive loop connecting prefrontal-pontine-posterior cerebellar sites (see Kelly and Strick 2003b; adapted from Chanraud et al. 2010b)

affecting functions of gait and balance (Sullivan et al. 2006a; Sullivan et al. 2010a); and 2) the executive network, involving the cerebellar neocortex (e.g., lobule VII, lobule VIII, Crus I, and Crus II) and prefrontal cortical sites (e.g., BA9 and 46) contributing to cognitive functions, such as verbal (Desmond et al. 1997, 2003) and spatial (Pfefferbaum et al. 2001) working memory and set shifting (Seeley et al. 2007; see in this issue Marvel and Desmond 2010) (Fig. 2). Such cerebellar-based systems have recently been examined using structure (magnetic resonance imaging (MRI)) / function (working memory tasks) paradigms in alcoholics and controls (Chanraud et al. 2010b). In controls, the best predictors of performance on the spatial working memory task with spatial tracking interference were volumes of the right middle frontal gyrus and right cerebellar Crus I. By contrast, in alcoholics, the best predictors of performance on the spatial working memory task with arithmetic problem solving interference were volumes of the left thalamus and left cerebellar Crus I. These brain structure-function correlations suggest that although the specific regions recruited by the alcoholics and controls were different, performance on the cognitive task by both groups relied on the integrity of cerebellar-based systems.

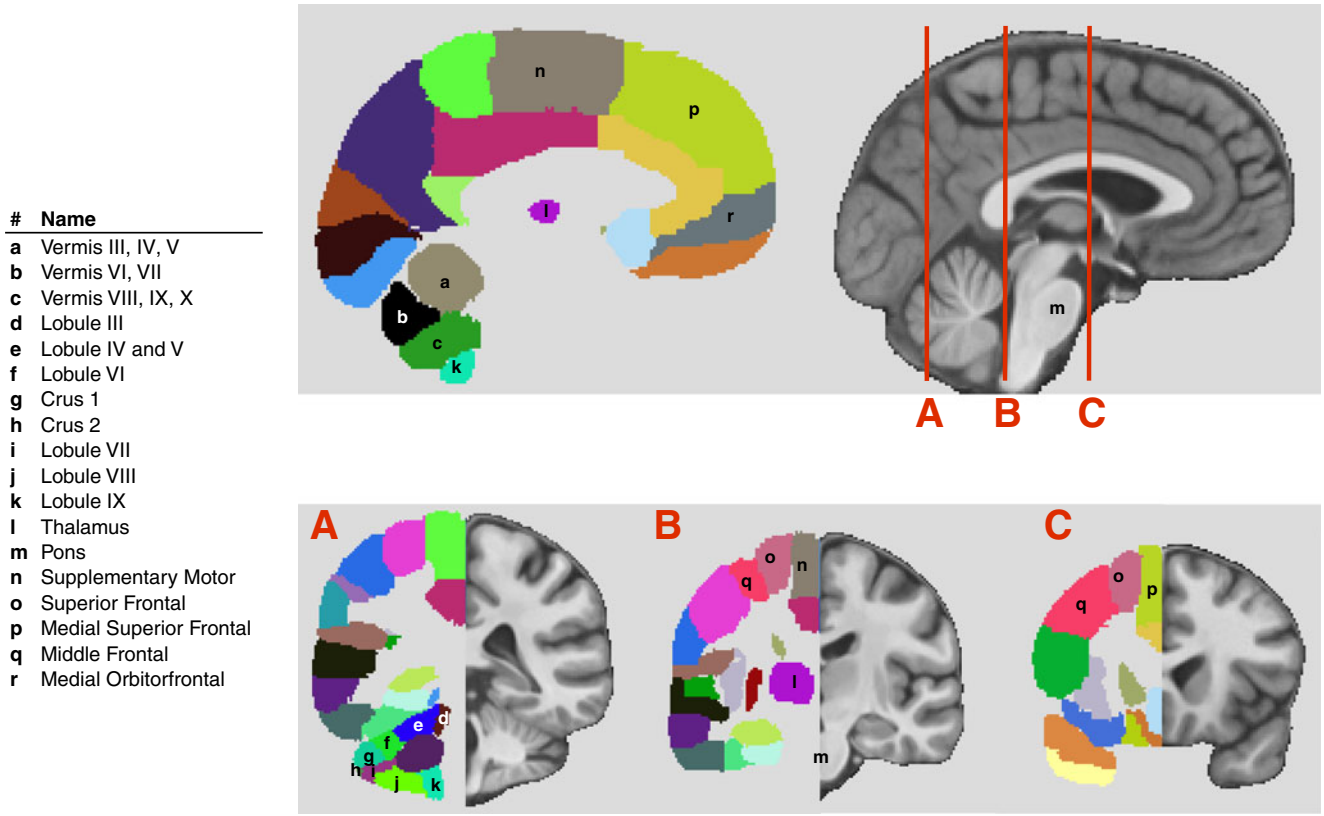
Here, we propose that disruption of the executive frontocerebellar network is a major contributor to characteristic behaviors of alcoholism that, on the one hand, enable alcohol use disorders, and on the other hand, lead to compensation for so-called frontally based dysfunctions in alcoholism. Specifically considered is the possibility that in alcoholism, compromise of the executive loop contributes to dysfunction affecting impulse control (Nixon et al. 2002; Fein et al. 2010), conflict processing (De Rosa et al. 2004), and disinhibition (Hada et al. 2000; Fein and Di Sclafani 2004) that enable maintenance of addictive behavior. On the compensatory side, evidence indicates that recruitment of intact cerebellar loops can compensate for the alcoholic's otherwise impaired performance on tasks requiring, for example, visuospatial or working memory skills (cf., Sullivan and Pfefferbaum 2005).

Brain Structures and Systems Affected in Individuals with Alcohol Use Disorders

The following sections review the literature regarding brains of alcoholics from a neuropathological perspective and from the standpoint of results from MRI modalities including structural MRI, diffusion tensor imaging, MR spectroscopy, and functional MRI. The findings presented are not comprehensive but have been selected to indicate compromise of frontocerebellar circuitry and its nodes in alcoholism. For comprehensive reviews of the brain regions targeted by chronic alcoholism and associated neurological deficits, see (cf., Oscar-Berman et al. 1997; Mann et al. 2001; Chanraud et al. 2010a; Sullivan et al. 2010b).

Neuropathology

Classical postmortem neuropathology studies identified damage to nodes of the frontocerebellar circuit in cases of chronic alcoholism. On the gross pathology level, the frontal cortex sustains notable shrinkage, due in part to cell loss, in contrast to the relatively spared motor cortex (Kril and Harper 1989; Harper 1998). Atrophy of the cerebellar vermis has been reported in alcoholics and even more frequently in alcoholics with exceptionally high levels of alcohol consumption (Karhunen et al. 1994) or thiamine deficiency (35–50% Victor et al. 1959). On the cellular level, Purkinje cells (Pentney 1993) and cells in the granular and molecular layers of the cerebellar cortex (Phillips et al. 1987) are particularly affected, especially in alcoholics with a history of thiamine deficiency (Baker et al. 1999). Whether caused by neurotoxic effects of alcohol per se or to secondary events such as dietary deficiencies, excessive alcohol consumption adversely affects the pons (Adams et al. 1959) and thalamus (Kril and Butterworth 1997; Harding et al. 2000). The pons sustains reduction of numbers of serotonergic (Halliday et al. 1993) and noradrenergic neurons (Arango et al. 1994). Although not always forthcoming with in vivo MRI (Shear et al. 1994), neuropathologically, the thalamus has been seen to be abnormally small in alcoholics (Kril and Butterworth 1997) in terms of the size of thalamic nuclei and the number and size of neurons in the thalamic nuclei (Belzunegui et al. 1995; Harding et al. 2000).



#	Name
a	Vermis III, IV, V
b	Vermis VI, VII
c	Vermis VIII, IX, X
d	Lobule III
e	Lobule IV and V
f	Lobule VI
g	Crus 1
h	Crus 2
i	Lobule VII
j	Lobule VIII
k	Lobule IX
l	Thalamus
m	Pons
n	Supplementary Motor
o	Superior Frontal
p	Medial Superior Frontal
q	Middle Frontal
r	Medial Orbitorfrontal

Fig. 2 Parcellated regions (left) of the SRI24 brain (Rohlfing et al. 2010) (right). Principal lobules of the cerebellum are parcellated and numbered; several have been identified to subserve dissociable cognitive and motor functions. The cerebrum is also parcellated into regions defined by gyral markings and roughly corresponding to regional structures, many with known functions. Note the distance traversed by frontothalamopontocerebellar circuitry

In addition to volume shrinkage of the major gray matter nodes of the frontocerebellar circuit, neuropathological studies have consistently reported compromised white matter integrity indicating that chronic alcoholism may disrupt the white matter fiber bundles linking the nodes (Harper et al. 1985; De la Monte 1988; Badsberg-Jensen and Pakkenberg 1993). Postmortem analysis has revealed that white matter in the chronic alcoholic brain is subject to volume shrinkage (Harper and Kril 1985; De la Monte 1988), especially in the frontal cortex of alcoholics with Wernicke-Korsakoff syndrome (WKS, Kril and Butterworth 1997). Indeed, in alcoholics with WKS, white matter impairment is negatively correlated with maximum daily alcohol consumption (Kril and Butterworth 1997). The volume of cerebellar white matter is also reduced in alcoholics (Phillips et al. 1987), and loss of vermal white matter is reported in alcoholics with ataxia (Baker et al. 1999). However, there are no obvious microscopic white matter lesions in the cerebral hemispheres of uncomplicated alcoholics, and studies of lipid profiles have revealed only minor alterations (Harper and Kril 1991; Olsson et al. 1996). An increase in the water content of frontal lobe white matter (Harper 1998) suggests that the white matter shrinkage in this brain region may reflect demyelination. Consistent with this interpretation, expression of three genes encoding myelin proteins that are required for the highly ordered and compact structure of myelin and are specifically involved in stabilization and compaction of the myelin sheath was lower in the superior frontal cortex of human alcoholic subjects than controls (Lewohl et al. 2005). According to Harper (2009), neural loss may also result in axonal (Wallerian) degeneration and a permanent reduction in white matter volume (Harper et al. 1988). Thus, the pathophysiology of white matter disruption in alcoholics may involve changes in both myelination and axonal integrity (Harper et al. 2005).

Structural Neuroimaging

Comporting with postmortem findings, computed tomography (CT) and MRI studies reveal brain volume deficits specific to the prefrontal cortex and cerebellum (for reviews Oscar-Berman and Marinkovic 2007; Chanraud et al. 2010a) even in chronic alcohol dependent subjects

without obvious complications from nutritional deficiencies (e.g., thiamine deficiency) or hepatic disorders (Hayakawa and Kumagai 1992; Wang et al. 1993; Shear et al. 1994; Chanraud et al. 2007). MR volumetric studies have also revealed thalamic (but see, Shear et al. 1992; Sullivan 2003; Benegal et al. 2007; Cardenas et al. 2007; Chanraud et al. 2007) and pontine (Sullivan et al. 2010a) volume deficits in alcoholics. The pons is composed of a complex arrangement of nuclei (Schmahmann and Pandya 1989) and extensive white matter fiber systems. The pons can be affected by central pontine myelinolysis (CPM), a complication associated with alcoholism (Victor 1987). CPM, a relatively rare and serious condition that can result in quadriplegia and curtailed longevity (Adams et al. 1959), is neuroradiologically defined on T2- weighted images as a hyperintense, triangular-shaped lesion in the middle of the pons (Kleinschmidt-DeMasters et al. 1997). Even in uncomplicated and asymptomatic alcoholics, prolonged T2 relaxation times indicative of excessive local interstitial fluid can be observed in the pons of older alcoholics, although more regularly in alcoholics with WKS (Sullivan and Pfefferbaum 2001). Also consistent with the neuropathological literature is the MRI observation of white matter volume shrinkage in the cerebellum and pons of alcoholics (Sullivan et al. 1998; Sullivan 2000; Sullivan and Pfefferbaum 2001; Sullivan 2003; Sullivan et al. 2003; Chanraud et al. 2007).

The existence of a structural scaffolding for the frontocerebellar circuitry in alcoholism has been supported by correlational analysis. In alcoholics, volume deficits quantified with MRI in the pons co-occur with volume deficits in the white matter of the anterior superior cerebellar vermis and white and gray matter of the cerebellar hemispheres. By contrast, volume deficits in the thalamus co-occur with volume deficits in the gray matter of the posterior inferior vermis, cerebellar hemispheres, and parietal cortex (Sullivan 2003). A lack of correlation between pontine and thalamic volumes suggests their independence in the afferent and efferent loops of the frontocerebellar network.

Diffusion Tensor Imaging

Whereas structural MRI provides measurement of regional tissue expressed as a volume over multiple image slices and voxels, MR diffusion tensor imaging (DTI) provides a qualitative assessment of the microstructure of tissue, typically white matter, within voxels (Basser and Pierpaoli 1996). DTI image acquisition and data analysis are complex, and details of these methods are available in numerous reviews (e.g., Le Bihan 2003; Jones 2010). In short, white matter fiber integrity is commonly measured in terms of fractional anisotropy (FA), which is usually higher in fibers with a homogeneous or linear structure, such as healthy white matter, and bulk mean diffusivity (MD), for which higher values, commonly due to larger presence of mobile water molecules in a tissue sample (Pierpaoli et al. 2001; Pfefferbaum et al. 2003; Pfefferbaum and Sullivan 2003), reflect diminished fiber integrity. MD can be decomposed into two components: axial (longitudinal) diffusivity (λL), which can be altered with disruption of axonal integrity and axonal deletion; and radial (transverse) diffusivity (λT), which increases selectively with decline in myelin integrity (Song et al. 2002; Song et al. 2005; Sun et al. 2006a,b). DTI has been further extended to provide visual depictions of white matter fiber systems (Stieltjes et al. 2001; Xu et al. 2002; Lehericy et al. 2004) and quantification of the integrity of specific fiber tracks (Gerig et al. 2005; Sullivan et al. 2006b).

Studies using DTI have detected untoward effects of alcoholism on the microstructure of white matter. In some cases, DTI has been shown to be more sensitive than conventional volumetric MRI in identifying disordered tissue (Pfefferbaum et al. 2000; Pfefferbaum and Sullivan 2002). One pattern of spared and affected tissue that has emerged over a series of studies using quantitative fiber tracking is that frontal and superior fiber bundles show greater abnormalities than posterior and inferior fiber bundles in alcoholics relative to controls (Pfefferbaum et al. 2009; Pfefferbaum et al. 2010). Using Tract-Based Spatial Statistics (Smith et al. 2006) for DTI analysis, Meyerhoff and colleagues reported lower FA and higher diffusivity, indicative of tissue degradation, in dorsomedial and dorsolateral prefrontal cortical and cerebellar regions (Yeh et al. 2009). Another quantitative fiber tracking study revealed fewer white matter fibers per unit volume running between the midbrain and the pons in alcoholics than controls (Chanraud et al. 2009). Together, these DTI studies indicate a frontal selectivity to white matter damage in the context of widespread microstructural degradation of white matter systems (Pfefferbaum et al. 2006) and initial evidence that white matter tracts of the corticopontine pathway are also compromised. A caveat is the observation from one study showing relative preservation of corticocerebellar fiber systems in alcoholics (Pfefferbaum et al. 2009). Such preservation may be an avenue to enable invoking cerebellar systems in compensatory efforts, as observed in functional imaging studies (cf., Sullivan and Pfefferbaum 2005).

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a powerful noninvasive approach for the identification, visualization, and quantification of specific brain biochemicals (metabolites and neurotransmitters), thus enabling the direct

assessment of the neurochemical status of discrete brain structures. Whereas MRI detects the spatial distribution and tissue density of hydrogen nuclei (^{1}H) in water and fat, MRS measures ^{1}H of typically carbon-containing compounds that are in sufficiently high concentrations to be detected (van der Graaf 2010). A predominant MRS signal in the healthy human brain is N-acetylaspartate (NAA), found almost exclusively in neurons (Urenjak et al. 1993; Petroff et al. 1995) and thus considered a marker of neuronal integrity. Choline-containing (Cho) compounds, including free Cho, phosphocholine, and glycerophosphocholine, are associated with cell membrane synthesis, turnover, and metabolism (Stoll et al. 1995). The signal from total creatine (tCr), often used as a referent for other metabolites, is influenced by the state of high-energy phosphate metabolism (Tedeschi et al. 1995).

Studies of recently detoxified alcoholics (1–6 weeks) show abnormally low levels of NAA, inferred from ratios to tCr or amount of underlying tissue, in frontal white matter (Schweinsburg et al. 2001, 2003; Meyerhoff et al. 2004; Bartsch et al. 2007), frontal gray matter (Jagannathan et al. 1996; Bendszus et al. 2001; Durazzo et al. 2004), thalamus (Jagannathan et al. 1996; Murata et al. 2001), and cerebellum (Jagannathan et al. 1996; Bendszus et al. 2001; Murata et al. 2001; Parks et al. 2002). Likewise, Cho, whether expressed as a ratio to tCr or tissue water, is lower in recently detoxified alcoholics than controls in thalamus (Murata et al. 2001; Durazzo et al. 2004) and cerebellum (Martin et al. 1995; Jagannathan et al. 1996; Bendszus et al., 2001; Murata et al., 2001; Ende et al., 2005; Bartsch et al. 2007). Such changes in the biochemical status of discrete brain regions are reinforced by findings of correlations with performance on various behavioral tasks. For example, low NAA in the cerebellar vermis was related to poor performance on tasks of visuospatial learning and memory (Durazzo et al. 2004). In another study, an increase in NAA/tCr with continued abstinence for approximately one month was related to improved performance on the auditory-verbal-learning test (Bendszus et al. 2001). These selective relations demonstrate the functional impact of metabolites changes in these nodes of the frontocerebellar circuitry.

When metabolites were evaluated as a function of the likelihood of relapse, only patients that relapsed within 3 weeks of detoxification revealed reduced cerebellar NAA concentrations (Parks et al. 2002). Similarly, in individuals that relapsed relative to those that remained abstinent, baseline compared to one-year follow-up levels of NAA and tCr were lower in the dorsolateral prefrontal cortex and cerebellar vermis (Durazzo et al. 2010). These longitudinal MRS studies thus also provide evidence for the role of a dysfunctional frontocerebellar circuit in the maintenance of addiction to alcohol.

Functional neuroimaging

Functional magnetic resonance imaging (fMRI) provides assessment of the utilization of blood oxygen (i.e., the blood oxygen-level dependent [BOLD] effect) measureable during performance of specific cognitive, sensory, or motor tasks. Several fMRI studies reveal that alcoholics activate either a different neural network (Pfefferbaum et al. 2001; Tapert et al. 2001; Tapert et al. 2004) or activate appropriate regions but more widely (Desmond et al. 2003; Parks et al. 2003) to perform behaviorally (e.g., in terms of accuracy or reaction time) on par with controls. For example, self-paced finger-tapping activated frontocerebellar networks in controls (e.g., anterior cingulate, anterior lobe and vermis of the cerebellum) but only the parietal precuneus in alcoholics (Parks et al. 2010). This finding suggests compensatory alterations of frontocerebellar circuits whereby alcoholics must recruit higher ordering planning regions such as the parietal lobe in order to perform equivalently to controls.

A study employing the Sternberg verbal working memory task reported similar levels of performance with respect to reaction time and accuracy in alcoholic and nonalcoholic subjects. In these same subjects, however, activations were greater in alcoholics than in controls in the left prefrontal cortex and the right superior cerebellum (Desmond et al. 2003). Another study revealed that the processing of redundant targets relative to a single target was associated with a significant BOLD response in bilateral extrastriate cortices in controls. By contrast, although alcoholics activated only the left extrastriate cortex, they also showed significant BOLD responses in the thalamus, pallidum, and left cerebellum (Schulte et al. 2010). These fMRI studies provide evidence for the role of the cerebellum in augmenting performance and compensating for the functional deficits attributable to frontal cortical disruption in alcoholics.

Brain Structure/Function Relationships in Alcohol use Disorders

Quantitative studies of brain structure and motor function have revealed the traditionally accepted relationship between postural instability and small volume of the anterior superior cerebellar vermis in alcoholics (Sullivan et al. 2000b), infratentorial tissue volumes (Sullivan et al. 2010a), and postural sway (Sullivan et al. 2006a). Components of sway may be the consequence of damage to other nodes in the frontocerebellar circuit. For example, using posturography and balance platform testing, truncal tremor was observed at two frequencies (3–5 & 5–7 Hz) in alcoholic men (Sullivan et al. 2006a); the tremor at 5–7 Hz could indicate direct damage to the thalamus (Guehl et al. 2003).

In addition to these motor-based relations with the condition of the cerebellum and pons, other analyses have reported correlations between frontally-based cognitive impairment that can be related to compromised cerebellar or pontine structures and even of the white matter connecting the various nodes of the circuitry. Indeed, the volumes of selective regions of the cerebellum have been shown to be better predictors than frontal lobe volumes of executive and visuospatial deficits in alcoholics (Sullivan 2003). Also in alcoholics, the volume of the pons and a white matter region in the midbrain common to both afferent corticocerebellar and efferent cerebellocortical fibers correlated with performance on neuropsychological tests including fluency, letter-number sequencing, trail-making B, Stroop interference, and the Wisconsin Card Sorting test (Chanraud et al. 2007). The number of fibers per volume coursing between the midbrain and pons correlated with performance on Part B of the Trail Making Test, which assesses visual search, working memory, and cognitive flexibility (Chanraud et al. 2009). Alcoholics clinically asymptomatic for pontine signs of CPM reveal significant correlations between poorer verbal and nonverbal fluency production (tests long considered sensitive to lesions of lateral frontal cortex, Lezak 1995; Kolb and Whishaw 1996) and longer pontine relaxation times (Sullivan and Pfefferbaum 2001). Regarding anatomical connectivity, it is possible that the relationships between fluency output and pontine relaxivity arise from compromise of frontal connections to central pontine sites (Schmahmann and Pandya 1997).

Conclusion

This overview proposes the guiding hypothesis that disruption of frontocerebellar circuitry is one of the principal neural mechanisms underlying behavioral deficits in both uncomplicated alcoholism and alcoholics with neurological complications such as WKS (cf., Wijnia and Goossensen 2010). Compromise of the gray matter nodes of this circuit or disruption of the white matter tracts connecting the nodes may adversely influence remote regions within that circuit, resulting in characteristic alcoholism-related cognitive and motor deficits. This network, even when partially compromised, may be invoked by alcoholics for compensation in the performance of challenging cognitive procedures. The cerebellum, therefore, exerts substantial primary and modulatory influence on behavior with its long-reaching loops to frontal sites. Even modest alterations within this frontocerebellar circuitry in alcoholics have the potential to contribute to vulnerability for relapse by virtue of executive function impairment. Involvement of frontocerebellar circuitry in compensatory activity may also be a source of maintenance of addictive behavior, given the roles of the cerebellum (Grafman et al. 1992; Doyon et al. 1997; Hubert et al. 2009) and basal ganglia (Heindel et al. 1989; Pascual-Leone et al. 1993; Witt et al. 2002) in implicit and procedural learning (see this issue Bostan and Strick 2010). By its nature, implicit learning is accomplished with little to no conscious awareness and therefore can skirt the purview of therapy and contribute to denial (cf., Le Berre et al. 2010), the first "step" alcoholics must overcome to reduce harmful drinking levels (Wilson 2001).

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