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Neuroimaging of the Wernicke–Korsakoff Syndrome

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Abstract — Aim: Presented is the neuroradiological signature of acute Wernicke's encephalopathy (WE), derived from different types of magnetic resonance imaging (MRI) sequences. WE results from thiamine depletion, and its most typical antecedent is chronic alcohol dependence. Brain regions observed with *in vivo* MRI affected in acute WE include the mammillary bodies, periaqueductal and periventricular gray matter, collicular bodies and thalamus. These affected areas are usually edematous and are best visualized and quantified with MRI sequences that highlight such tissue. Following the acute WE phase and resolution of edema and inflammation of affected brain tissue, WE, if not adequately treated with thiamine repletion, can herald Korsakoff's syndrome (KS), with its symptomatic hallmark of global amnesia, that is, the inability to commit newly encountered (episodic) information to memory for later recall or recognition. **Methods:** Neuropathology of KS detectable with MRI has a different neuroradiological signature from the acute stage and can be observed as tissue shrinkage or atrophy of selective brain structures, including the mammillary bodies and thalamus and ventricular expansion, probably indicative of atrophy of surrounding gray matter nuclei. Quantification of these and additional gray matter structures known to underlie global amnesia reveal substantial bilateral volume deficits in the hippocampus, in addition to the mammillary bodies and thalamus, and modest deficits in the medial septum/diagonal band of Broca. The infratentorium is also affected, exhibiting volume deficits in cerebellar hemispheres, anterior superior vermis and pons, contributing to ataxia of gait and stance. **Results:** Consideration of WKS structural brain changes in the context of the neuropathology of non-WKS alcoholism revealed a graded pattern of volume deficits, from mild in non-WKS alcoholics to moderate or severe in WKS, in the mammillary bodies, hippocampus, thalamus, cerebellum and pons. The development and resolution of brain structures affected in acute, chronic and treated WE was verified in longitudinal MRI study of rats that modeled of the interaction of extensive alcohol consumption and thiamine depletion and repletion. **Conclusions:** Thus, neuroradiological examination with MRI is valuable in the diagnosis of acute WE and enables *in vivo* tracking of the progression of the brain pathology of WE from the acute pathological phase to resolution with thiamine treatment or to progression to KS without treatment. Further, *in vivo* MRI facilitates translational studies to model antecedent conditions contributing to the development, sequelae and treatment of WE.

INTRODUCTION

This report focuses on *in vivo* characterization of the acute and chronic brain lesions associated with Wernicke's encephalopathy (WE) detected with different forms of structural MRI, with particular emphasis on sequences with sensitivity to the edematous lesions marking WE. Although studies of MR spectroscopy (MRS) and functional MRI (fMRI) have been conducted in WE, these modalities are less often available than structural MRI in clinical settings and so have been less useful diagnostically. Further, task-based fMRI would be difficult to impossible to conduct in the acute, confusional phase of WE. Therefore, neither MRS nor fMRI studies are reviewed herein. Because of WE's close relationship with Korsakoff's syndrome (KS), examples of MR images and new quantitative MRI analysis of KS are featured. Also presented is a hypothesis about the etiology of the heterogeneity of neuroradiological and behavioral features of the WE–KS complex.

ACUTE WE: AETIOLOGIES AND CLINICAL SIGNS

Classically, acute thiamine deficiency-associated WE is marked neuropathologically by lesions of periventricular nuclei, hypothalamic nuclei, tectal plate and thalamus, which are caused by thiamine (vitamin B1) deficiency and result in WE's cardinal signs of ophthalmoplegia, nystagmus, ataxia and confusional state (as noted in Victor *et al.*, 1971, 1989). The acute WE condition, when left untreated with thiamine or if treated incompletely or too late, can herald profound, debilitating global amnesia marking KS. Another form of WE, beriberi, is also caused by a thiamine-deficient diet but usually has a more insidious progression; beriberi causes damage to central and peripheral nervous systems, musculature and cardiovascular system (Victor *et al.*, 1989).

Clinically relevant thiamine deficiency (Bender and Schilder, 1933; Jolliffe *et al.*, 1941) and evolving WE can result from conditions that restrict eating, such as orofacial cancers, or limit adequate vitamin absorption, such as gastric bypass surgery, gastric and colon cancer, hyperemesis gravidarum or starvation by choice or associated with sepsis, surgical complications and comma (for review of physiological mechanisms of thiamine deficiency, see Martin *et al.*, 2003; Thomson and Marshall, 2006; Sechi and Serra, 2007). Infarction of the mammillothalamic tracts is another antecedent of WE (Yoneoka *et al.*, 2004). By far the most common cause of thiamine deficiency throughout the world is alcoholism (Thomson, 2000), as described in landmark studies of alcoholic WE–KS (Victor *et al.*, 1971; Jarho, 1973; Harper *et al.*, 1986, 1995). Alcoholics are at special risk for thiamine deficiency because of the poor diet associated with their lifestyle and because chronic alcoholism compromises thiamine absorption from the gastrointestinal tract, impairs thiamine storage and may reduce thiamine phosphorylation, essential for cellular function (Thomson *et al.*, 1987; Todd and Butterworth, 1999; Thomson, 2000; Lieber, 2003; Martin *et al.*, 2003). Severe or insufficiently treated cases may show the enduring memory impairment and ataxia defining KS (Victor *et al.*, 1959; Talland, 1965; Butters and Cermak, 1980; Kopelman, 1995). Although WE does not necessarily evolve into KS if adequately treated (Victor *et al.*, 1971, 1989; Caine *et al.*, 1997; Thomson *et al.*, 2002), it remains controversial whether KS can develop without WE and whether

mild forms of neuropsychological sequelae arise from repeated bouts of thiamine deficiency or inadequate treatment of such episodes.

ACUTE WE: NEURORADIOLOGICAL SIGNS

Noninvasive neuroradiological examination of WE dates to the 1970s. Early studies used computed tomography (CT) scanning and revealed ventricular enlargement, especially of the third ventricle (Escobar *et al.*, 1983; McDowell and LeBlanc, 1984; Mensing *et al.*, 1984; Shimamura *et al.*, 1988) but were largely unable to detect edema or focal damage (Gotze *et al.*, 1978; Gallucci *et al.*, 1990). The introduction of MR imaging with its exquisite sensitivity to tissue water content and mobility enabled visualization of acute and chronic radiological signs of neuropathology not visible on CT (Antunez *et al.*, 1998). In some sequences, the MR signal of selective brain structures is hyperintense, indicative of high water content, present in WE because of the edematous nature of the lesions. A direct comparison of CT and MRI in the detection of WE-related neuropathology identified low-density signal abnormalities on CT in the paraventricular regions of thalamus in only 2 of 15 WE patients examined, whereas MRI identified abnormality in this thalamic region in 7 patients of this WE group. Additional affected areas included periaqueductal gray matter in 6 patients and mammillary body shrinkage in 6 WE and 4 of 15 non-WE alcoholic patients. Thus, *in vivo* neuroimaging has been instrumental in revealing WE-like neuropathology in alcoholics who do not present with the obvious signs of WE (Sullivan, 2003; Sullivan and Pfefferbaum, 2005). Overall, although the sensitivity of MRI in detecting WE was only 53%, the specificity was 93% (Antunez *et al.*, 1998). Fig. 1 presents an exemplary comparison of CT and different MRI sequences.

MR techniques used to enhance visualization of edematous lesions were initially based on T2-weighted late-echo sequences, which are acquired after the majority of the tissue signal has decayed but while the signal of unbound water remains robust (for review, see Bigler, 1996). The most obvious neuroradiological sign of acute WE, regardless of etiology, is bilateral hyperintensity on late-echo MRI, generally occurring in gray matter tissue of the mammillary bodies, anterior and medial nuclei of the thalamus, periventricular gray matter, inferior and superior colliculi (e.g. nonalcoholics: Doraiswamy *et al.*, 1994; Chu *et al.*, 2002; Unlu *et al.*, 2006; Zhong *et al.*, 2005) (alcoholics: Schroth *et al.*, 1991) and occasionally cererbellum (Shear *et al.*, 1996; Nicolas *et al.*, 2000; Sullivan *et al.*, 2000; Bae *et al.*, 2001). These observations are consistent with postmortem reports (e.g. Torvik *et al.*, 1982, 1986; Harper and Kril, 1988, 1990; Kril *et al.*, 1997; Baker *et al.*, 1999). The bilateral distribution of the neuropathology may contribute to the severity of the clinical signs and symptoms. Although the pons is not usually implicated in WE, an MR study examining T2 relaxation time, a measure of interstitial fluid reflecting axonal and myelin integrity, provided evidence of excessive fluid in the central pons of patients with alcoholic WKS (Sullivan and Pfefferbaum, 2001). Predictors of prolonged relaxation time in non-KS alcoholics in this study were hematological measures of nutritional status, e.g. macrocytic anemia and cognitive fluency.

The development of the MR fluid-attenuated inversion recovery (FLAIR) sequence provided significant improvement over the conventional T2 approach by incorporating additional T1 contrast mechanisms. An advantage of the FLAIR approach is that it essentially eliminates only signal with T1 characteristics of CSF, including in regions of non-tissue CSF, such as sulci and ventricles, and therefore enhances the conspicuity of the signal in boggy, edematous tissue. Several case studies have published *in vivo* FLAIR images of acute WE (Maeda *et al.*, 1995; Ashikaga *et al.*, 1997). An early study of a woman with hyperemesis gravidarum revealed high signal intensity of the mammillary bodies and hypothalamus; following thiamine treatment, although the high signal intensity resolved, the mammillary bodies shrank (Maeda *et al.*, 1995). A series of six cases of nonalcoholic WE studied with FLAIR revealed hyperintense signal in the tissue around the aqueduct, third ventricle, floor of the fourth ventricle, anterior ventricular caps and medial thalami; follow-up examination noted recovery in the four cases without cortical damage but not in the two cases with such damage (Zhong *et al.*, 2005).

MR diffusion-weighted imaging (DWI), in which signal from freely diffusing water is suppressed, is another MRI method that has proved sensitive to the detection of WE brain pathology. An example of WE lesions with DWI is presented in Fig. 1. Paradoxically, the edematous lesions of WE, which would be expected to have high levels of diffusivity and have their signal suppressed with DWI, are instead hyperintense. This is an example of the 'T2 shine-through effect', in which tissue with long T2 value is bright (Koch and Norris, 2005); thus, the bright signal, rather than representing low diffusivity, reflects the opposite. In addition to the periventricular and thalamic tissue abnormalities typically identified with WE (Halavaara *et al.*, 2003; Unlu *et al.*, 2006), one case study concluded that bright signal on DWI was caused by abnormally low diffusivity in the cerebellum. Even though the diffusivity abnormality in the cerebellum resolved with thiamine repletion, noted at a 3-month follow-up study, associated motor impairment persisted (Lapergue *et al.*, 2006). DWI-increased signal intensity, confirmed as decreased diffusivity with apparent diffusion coefficient (ADC) images, in affected brain regions has been reported in two studies of acute WE (Halavaara *et al.*, 2003; Lapergue *et al.*, 2006). Because interpretation of DWI can be confounded by the T2 shine-through effect, DWI is probably of greatest value when accompanied by ADC imaging for quantitative assessment of the water diffusion. Together, the two techniques provide a method for characterizing the evolution of WE lesions from early edematous high diffusivity through later atrophic low diffusivity.

Figures 1 and 2 present FLAIR images of an acute WE case, a 35-year-old man with schizophrenia, found lethargic and confused in his apartment. He had suffered weight loss from inadequate nutrition. Examination revealed failure of horizontal gaze and ataxia of gait; management included daily doses of intravenous thiamine 100 mg. This case is striking because all neuropathological indices are present, and the lesions are bilateral and visible as signal hyperintensities. The structures affected in this case of WE are the mammillary bodies, periventricular gray matter, thalamus, inferior colliculi and fornix.

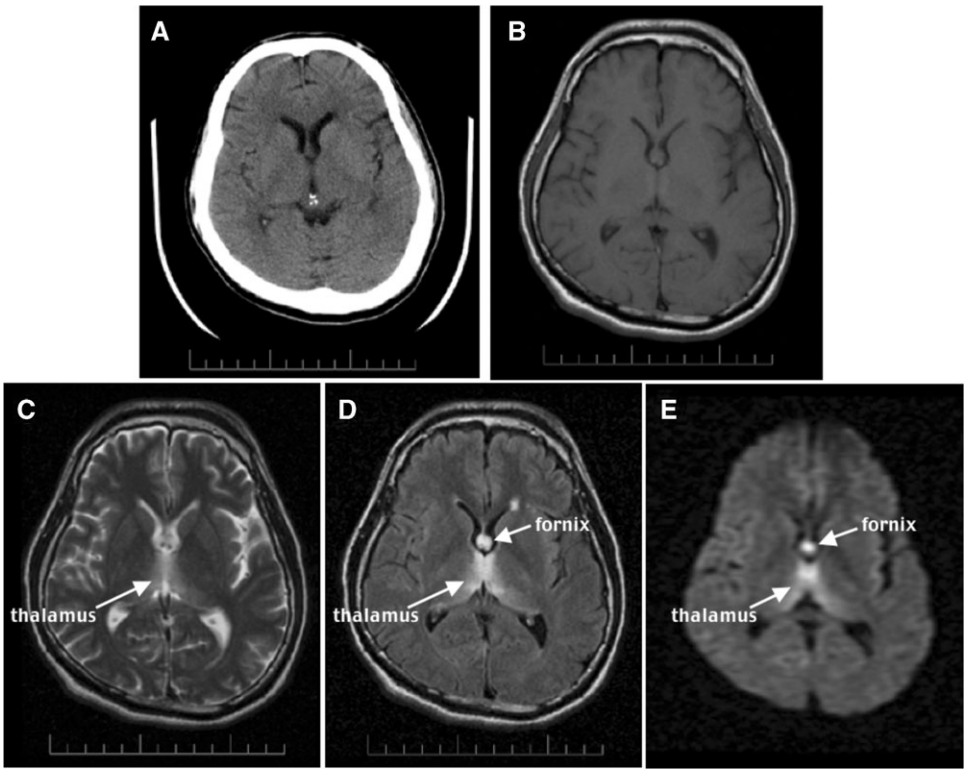

Fig. 1. CT and MR images of an acute 35-year-old man with schizophrenia and acute nutritional deficiency-induced WE. (A) Axial CT at the level of the lateral ventricles. (B–E) Axial MR images at a similar level to the CT. (B) A proton density-weighted image. (C) A T2-weighted late-echo fast spin echo (FSE) image. (D) A fluid-attenuated inversion recovery (FLAIR) image. (E) A diffusion-weighted image (DWI). Note the hyperintensity of the fornix and thalamus, especially in D and E, less so in C, and lack of lesion conspicuity in A and B.

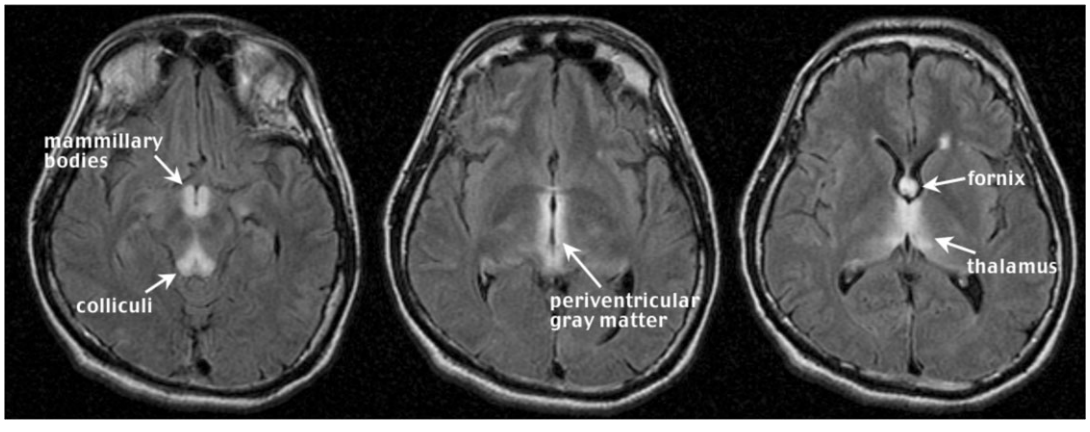

Fig. 2. Three contiguous FLAIR images (5 mm thick with a 2.5 mm skip) of the acute WE case in Fig. 1. Note the hyperintense signal in the mammillary bodies and colliculi (left), periventricular gray matter (middle), and fornix and thalamus (right).

SEQUELAE OF WE: NEURORADIOLOGICAL SIGNS OF ALCOHOLIC WERNICKE–KORSAKOFF SYNDROME

Despite the utility of neuroimaging in diagnosing WE and in identifying the loci and extent of damage, MRI examination often post-dates the acute phase marked by edema and inflammation of affected brain tissue. In this later phase, targeted structures, notably the mammillary bodies, become atrophic (Charness and DeLaPaz, 1987; Sheedy *et al.*, 1999) and assume a different neuroradiological signature from the acute stage. This acute to chronic progression can be tracked with *in vivo* MRI. A gross morphological view of alcoholism-related WKS reveals cortical thinning, sulcal widening and ventriculomegaly (Fig. 3). More detailed examination reveals regional structural

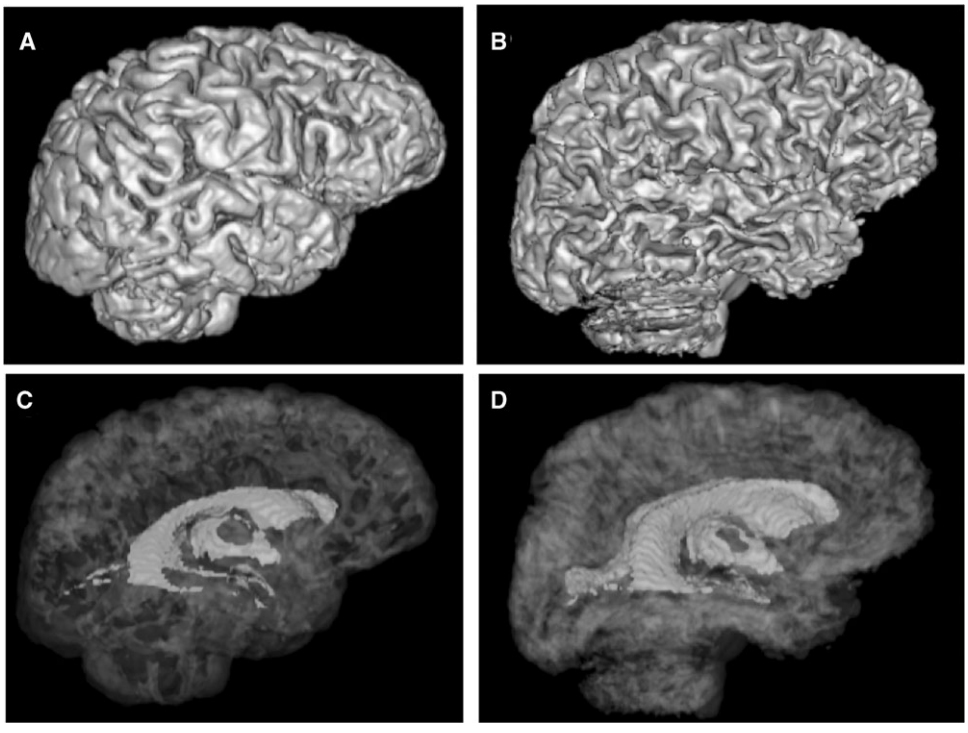

Fig. 3. Surface rendered brains (top) and rendered ventricular system (bottom, green) of a 59-year-old healthy man (A and C) and a 53-year-old man with WKS (B and D). Note the shrinking of the cortical gyri and widening of the sulci (B) and expansion of the ventricles (D) of the WKS compared with the control (A and C).

volume deficits, consistent with postmortem-identified atrophy and prominent in thalamus and mammillary bodies (Fig. 4).

Uncomplicated alcoholism to WKS: a graded effect of brain structural volume deficits

The WKS structural brain changes noted above must be considered in the context of the neuropathology of non-WKS alcoholism. In Fig. 5 we present an examination of the potential compounded effects of chronic alcoholism, WE and KS on brain structure and function in individuals with alcohol-related KS, 'uncomplicated' alcoholism and healthy controls. Selective brain structures were manually identified on MRI to permit volumetric quantification. Description of the MRI sequences used and MRI quantification procedures have been published: volumetric SPGR for mammillary bodies (Sullivan *et al.*, 1999), thalamus (Sullivan *et al.*, 2003, 2004), medial septum/diagonal band (MD/DB) (Sullivan *et al.*, 2005), cerebellum (Sullivan *et al.*, 2000) and pons (Sullivan *et al.*, 2003, 2004); and coronal, dual-echo spin-echo images for the hippocampus (Sullivan *et al.*, 1995). Regional brain volumes were adjusted for normal variation in intracranial volume and age and expressed as standardized *Z*-scores, where the expected mean of the controls was 0 (standard deviation = 1); thus, low scores reflect smaller volumes than would be expected for a particular intracranial volume and age, and the mean *Z*-scores also reflect the effect size. All KS patients had been alcohol dependent, were abstinent from alcohol at examination and met retrospective, chart review criteria for WE (Caine *et al.*, 1997). Neuropsychological tests assessed multiple functional domains, targeting executive functions, declarative and procedural memory, visuospatial abilities and postural stability, and revealed severe to profound deficits in the KS group in memory for new material and gait and balance with sparing of general intelligence, short-term memory and visuoperceptual implicit learning (Fama *et al.*, 2004, 2006; Sullivan *et al.*, 2000). This pattern of functional sparing and impairment is consistent with KS (also see paper in this issue byes Kopelman).

MRI indicated graded regional brain volume shrinkage (Fig. 5a and b), where deficits of uncomplicated alcoholics were significant (generally about 0.5 standard deviation deficit) but less severe than those of KS (generally ~1–2 standard deviation deficit) in the mammillary bodies (Shear *et al.*, 1996; Sullivan *et al.*, 1999), thalamus (this report), pons (this report), cerebellar hemispheres and anterior superior vermis (V1 of Fig. 5b) (Sullivan *et al.*, 2000). Contrary to traditional belief and evidence (Squire *et al.*, 1990; Visser *et al.*, 1999; Reed *et al.*, 2003), we observed bilateral deficits in the anterior hippocampus of alcoholics with WKS (Fig. 5a). As an additional neuropathological context, we compared the hippocampal volumes of KS with those of Alzheimer's disease (AD) patients, whose neuroradiological hallmark is severe hippocampal volume loss (Sullivan and Marsh, 2003). We found that the KS group exhibited a deficit in hippocampal volumes bilaterally equivalent to that observed in the patients with AD and more than twice that we previously observed in nonamnesic alcoholic patients (Sullivan *et al.*, 1995). Relations between the amnesia index and hippocampal volumes but not volumes of the mammillary bodies or the temporal cortex, despite tissue deficits in both structures, support the relevance of the hippocampal volume to the amnesia of KS (Sullivan and Marsh, 2003); further, performance on tests requiring historical event naming

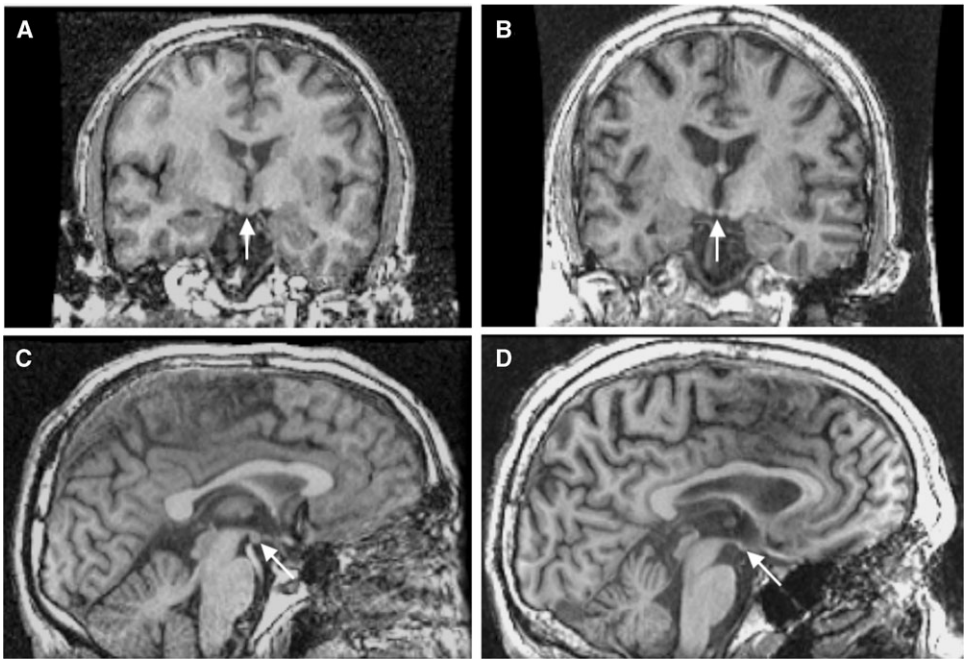

Fig. 4. T1-weighted SPoiled GRadient echo (SPGR) images of the healthy (left panel) and WKS (right panel) men in Fig. 3. Note the shrunken mammillary bodies (arrows) in the WKS (B and D) compared with the control (A and C).

and sequencing (i.e. non-declarative memory) related to frontoparietal white matter volumes (Fama *et al.*, 2004). Volume of the medial septum/diagonal band of Broca was modestly reduced in KS (Fig. 5a), suggesting that volume loss and potential cholinergic compromise due to damage in this nuclear complex may also contribute to the KS amnesic syndrome (cf., Butters and Stuss, 1989; De Rosa and Sullivan, 2003; Sullivan *et al*., 2005).

The graded deficits in regional brain volumes from uncomplicated alcoholics without KS are substantially less than in alcoholics with WE or KS (cf., Blansjaar *et al*., 1992; Charness, 1993, 1999; Sullivan, 2000; Mulholland *et al*., 2005) or even Alzheimer's disease (Charness and DeLaPaz, 1987). This pattern, however, implicates nutritional deficiency as a mechanism of alcoholic regional brain volume shrinkage and ventricular expansion, which can be examined in humans only with naturalistic observational methods.

Factors contributing to brain abnormalities in alcoholic WKS

That brain regions outside of those traditionally associated with thiamine depletion were affected in both uncomplicated and KS alcoholics suggests a role for alcoholism alone or nutritional deficiencies in interaction with continued drinking as mechanisms for the brain abnormalities. Indeed, multiple subclinical bouts of thiamine or other nutritional deficiencies in alcoholism may contribute to the graded effect of brain regional volume deficits and to heterogeneity of presenting signs and neuroradiological profile (cf., Blansjaar and Van Dijk, 1992). Because sustained heavy drinking frequently occurs at the expense of eating (Santolaria *et al.*, 2000), alcoholics prone to intermittent binge drinking are at risk for nutritional depletion. A recent report on the association between alcohol drinking pattern and diet quality in a representative sample of the US population found diet quality was poorest among the highest-quantity–lowest-frequency drinkers and best among the lowest-quantity–higher-frequency drinkers. When alcohol consumption was expressed as average drinks per day, no association with diet was seen (Breslow *et al.*, 2006). A study of recent nutritional intake in a small sample of heavy drinkers found that ∼60% of energy intake came from alcohol and intake of vitamins fell below recommended norms (Manari *et al.*, 2003). Nutritionally based anemia (probably folate deficiency) in alcoholics has been associated with deficits in cortical white matter volume (Pfefferbaum *et al.*, 2004), whereas hematological indices improved with short-term sobriety and nutritional supplementation related to concurrent reduction of ventricular enlargement. Hematocrit and hemoglobin levels at discharge from a 28-day inpatient rehabilitation program discriminated patients who maintained sobriety from those who relapsed over the ensuing months. This finding may reflect the common sense observation that patients who are better fortified physically at the end of treatment will be better equipped for maintaining sobriety.

Because alcoholism is a chronic disorder, often spanning decades, the interaction of aging-related involutional brain changes must be considered when interpreting the effects of alcoholism. Cortical gray and white matter may sustain long-term volume shrinkage and even loss (Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1992), especially in the prefrontal cortex (De Bellis *et al.*, 2005) of older alcoholics (Pfefferbaum *et al.*, 1997; Cardenas *et al.*, 2005). Although alcohol-related brain abnormalities are partially reversible with prolonged sobriety (Carlen *et al.*, 1978; Schroth *et al.*, 1988; Pfefferbaum *et al.*, 1995, 1998; Mann *et al.*, 1999; O'Neill *et al.*, 2001; Parks *et al.*, 2002; Gazdzinski *et al.*, 2005), the extent to which

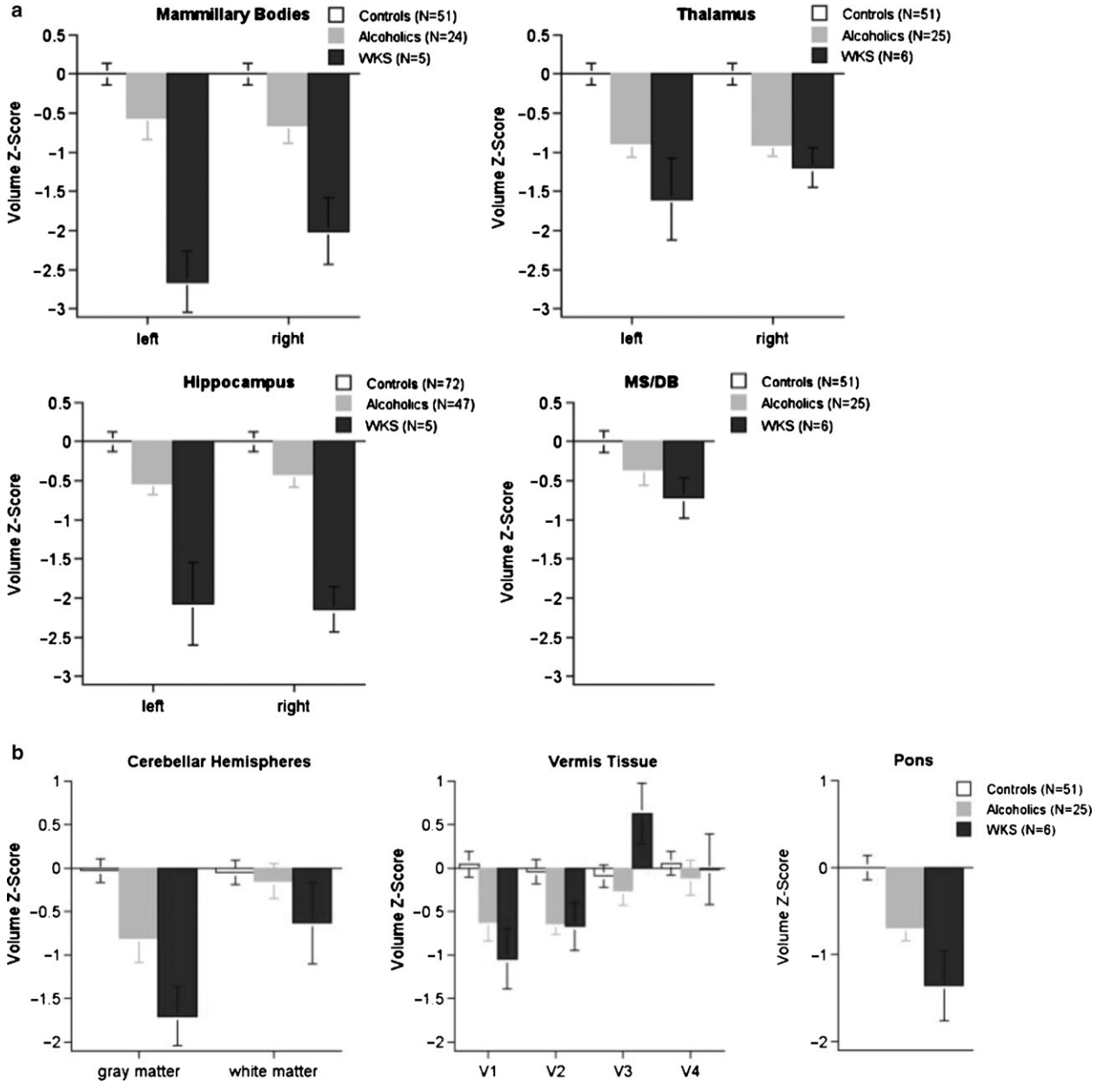

Fig. 5. (**a**) Mean ± SE of volumes of brain structures considered to subserve memory for new information: healthy controls (white), uncomplicated alcoholics (gray) and alcoholic WKS (black). All volumes are expressed as standardized *Z*-scores, adjusted for normal variation in intracranial volume and age. The expected value of the controls is 0 (standard deviation = 1); low values of volume in the alcoholic and WKS groups reflect volume deficits. A graded effect of uncomplicated alcoholism to WKS is present for each of these brain structures but is statistically significant for the mammillary bodies and hippocampus. These four brain structures are considered to contribute to the support of declarative memory, that is, memory for new information; profound impairment in declarative memory is characteristic of WKS. (**b**) Mean ± SE of volumes of brain stem structures. The pons, cerebellar hemispheres and vermis each demonstrate a trend toward a graded effect from uncomplicated alcoholism to WKS.

KS can recover is controversial. Incomplete recovery of affected neural structures and systems are candidate substrates for the enduring cognitive and motor impairments defining alcoholic WE and KS as well as 'uncomplicated' alcoholism. Whether thiamine deficiency is a necessary or sufficient cause of alcoholism-related brain volume and neuropsychological deficits remains a question in humans but is amenable to a systematic study in animals. Conversely, whether alcoholics who, while continuing to drink, achieve good physical condition with exercise and maintain adequate nutrition can escape or at least reduce the neurological throes of alcoholism remains a consideration.

ANIMAL MODEL OF WE: NEURORADIOLOGICAL CONFIRMATION OF ACUTE AND CHRONIC PHASES

Animal models of the brain lesions marking the thiamine deficiency syndrome have typically revealed subsets of the lesions noted in humans [reviewed by Witt (1985),

Martin *et al.* (2003)), involving the thalamus, superior and inferior colliculi, and hypothalamic nuclei. Because dietary deficiency alone requires a month or longer to deplete thiamine stores, a standard approach to shorten experimental time is administration of the thiamine antagonist, pyrithiamine (Langlais, 1995). Studies using pyrithiamine-induced thiamine deficiency (Langlais and Savage, 1995; Langlais and Zhang, 1997; Savage *et al.*, 1999; Pitkin and Savage, 2001, 2004) have demonstrated characteristic neuropathology and behavioral deficits in animal models. For example, significant shrinkage of the corpus callosum was induced several months after only a single bout of pyrithiamine-induced thiamine deficiency (Langlais and Savage, 1995). Ultrastructural studies show splitting of myelin sheaths and swelling of periaxonal spaces within the cerebral cortex of pyrithiamine-treated rats (Takahashi *et al.*, 1988). Some have demonstrated an enhancement of thiamine deficiency pathology by alcohol (Zimitat *et al.*, 1990; He *et al.*, 2007), and others have shown that the thiamine deficiency does not need to be complete to have untoward effects (Pires *et al.*, 2001; Bruce *et al.*, 2003).

Neuroimaging with MR methods provides the means for repeated, longitudinal *in vivo* high-resolution surveys of the whole brain and its structures that can be analyzed with a variety of approaches, including longitudinal examinations before and after treatment. The earliest neuroimaging experiments using rodent models of thiamine deficiency to produce WE were conducted at 1.5T (Pentney *et al.*, 1993) and reported volume enlargement of lateral ventricles followed by normalization with a thiamine-enriched diet (Acara *et al.*, 1995). Glucose administration to thiamine-deficient rats produced the untoward effect of blood-brain barrier impairment, observed with contrast-enhanced T1-weighted MR images (Zelaya *et al.*, 1995). Using T2-weighted MR imaging to emphasize the tissue free-water concentration, hyperintensities in the hippocampus as well as in the thalamus, hypothalamus and collicular bodies were visible and exacerbated by glucose infusion; some lesions noted as hyperintensities endured for a month (Jordan *et al.*, 1998).

Neuropathological and MRI studies of pyrithiamine-induced thiamine deficiency yield inconsistent results with regard to the timing of lesion development and resolution. Langlais and colleagues report white matter and cortical lesions without mammillothalamic involvement at the time of ataxia and righting reflex impairment, with mammillothalamic lesions emerging only after seizure development (Langlais and Zhang, 1997). Nixon and colleagues (Jordan *et al.*, 1998) describe MRI evidence of mammillothalamic and hippocampal involvement at the time of ataxia and righting reflex impairment. The contradiction may reside in differential sensitivity of the two methods. It may be that the histopathology was insensitive to the initial edematous mammillothalamic process, whereas the T2-weighted structural MRI was insensitive to the white matter pathology. Implementation of MR diffusion tensor imaging for the assessment of regional white matter microstructural integrity in combination with high resolution MRI for macrostructural measurement in longitudinal study may serve to resolve inconsistent *in vivo* and postmortem results.

We conducted a longitudinal MRI study of thiamine deficiency in alcohol-preferring rats (Pfefferbaum *et al.*, 2007). Half the sample had voluntarily consumed large amounts of alcohol prior to thiamine manipulation, and the other half had never been exposed to alcohol ('water' control), but both groups had had free access to rat chow, which was adequately enriched with thiamine and other required vitamins and minerals (Pfefferbaum *et al.*, 2006; Sullivan *et al.*, 2006). Following the alcohol exposure arm of the experiment, both samples of rats were given a thiamine-depleted diet for 14 days, and all received daily intraperitoneal injections of either thiamine or pyrithiamine, resulting in a four-group design depending on historical exposure to alcohol and current exposure to pyrithiamine: alcohol + pyrithiamine, alcohol + thiamine, water + pyrithiamine and water + thiamine. Serial MRI examinations identified significant ventricular enlargement and increase in signal intensities in thalamus, inferior colliculi and mammillary nuclei of pyrithiamine-treated rats compared with thiamine-treated rats from baseline to 18 days after thiamine repletion (Fig. 6). Comparison of MR results from 18 to 35 days revealed significant normalization in thalamus and inferior colliculi, but neither in the mammillary nuclei nor in ventricles (Fig. 6). Postmortem

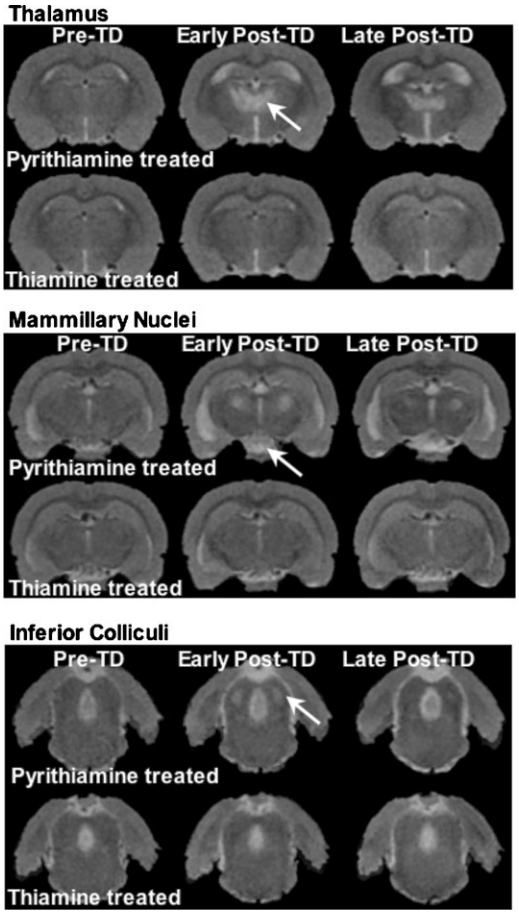

Fig. 6. Left: T2-weighted late-echo fast spin echo (FSE) images of a thiamine-deficient (TD) WE model in rats. Animals were treated with pyrithiamine (top images of each panel) or thiamine supplementation (bottom images of each panel). Images on the left of each panel are pre-treatment (pre-TD); images in the middle are early post-treatment (post-TD); and images on the right are late post-treatment (late post-TD) after thiamine repletion. Early post-TD, hyperintense lesions are prominent in the thiamine-deficient (pyrithiamine-treated) rats in the thalamus, mammillary nuclei and inferior colliculi. Late post-TD after thiamine repletion, the thalamus showed some recovery, the mammillary nuclei remained affected and the inferior colliculi showed complete recovery.

examination of white matter with electron microscopy of these rats revealed increased density of small diameter fibers in the corpus callosum and compromised myelin (He *et al.*, 2007). Whether the structural abnormalities noted in the corpus callosum and hippocampus require combined alcohol exposure and thiamine depletion remains incompletely answered.

Our longitudinal *in vivo* experiment coupled with postmortem examination provides neuroradiological and histological confirmation of the cause, progression and resolve of thiamine deficiency through an animal model of WE. These experiments also support an alcohol–thiamine deficiency interaction, which suggests an added risk of WE in individuals with alcohol dependence. The enduring macrostructural abnormalities involving critical nodes of the Papez circuit carry liabilities for the development of amnesia (Talland, 1968; Zola-Morgan and Squire, 1993; Eichenbaum and Cohen, 2001) and incomplete recovery from other cognitive and motor functions subserved by the affected neural systems.

CONCLUSIONS: IMPLICATIONS FOR PROGNOSIS AND NEUROPATHOLOGICAL LIABILITY

The confusional state marking the presentation of WE can impede accurate diagnosis. Incoherence of thought and communication in cases of alcohol intoxication and protracted withdrawal can further mask the seriousness of acute WE. MRI has been shown to improve and expedite accurate diagnosis, and therefore adequate treatment of WE (Sechi and Serra, 2007). As further noted by Sechi and Serra (2007), '. . .MRI is currently considered the most valuable method to confirm a diagnosis of Wernicke's encephalopathy. MRI has a sensitivity of only 53%, but its high specificity of 93% means that it can be used to rule out the disorder'.

Not all neurological or neuroradiological signs are necessarily present in all WE cases, and the severity of the signs is likely related to the degree of the underlying pathology. This speculation was supported in a retrospective study of 25 WE–KS patients, whose clinical outcome was more favorable with fewer radiological signs detected at onset (Varnet *et al.*, 2002). The bilateral distribution of pathology typically observed probably also contributes to the severity of the signs and symptoms at all stages of encephalopathy. Because only about a third of WE cases exhibit all three signs of the classical triad (Harper, 1983; Zuccoli *et al.*, 2007), diagnosis needs supplementation with more reliable information than signs and symptoms alone. Chart review can help determine whether a symptomatic patient has had bouts of WE (e.g. Caine *et al.*, 1997). MR imaging has also become an indispensable diagnostic tool for encephalopathy, especially in light of the reversibility of the otherwise devastating cognitive and motor features of untreated WE. MRI is sensitive to detection of WE-related or -induced lesions in brain regions classically identified with this encephalopathy—mammillary bodies, periaqueductal gray matter, thalamus and colliculi—but, as noted by Victor (Victor, 1990), can also be helpful in diagnosis and prognosis in cases with atypical symptomatic or neuroradiological presentation, which can include involvement of pons, cerebellum and hippocampus.

The most common antecedent of WE is chronic alcoholism. A possible consequence of clinical or subclinical thiamine deficiency in alcoholism may contribute to the considerable variability in the extent of alcoholism-related brain abnormalities reported, with some individuals having massive brain shrinkage and others little observed effect. Possible explanations for this variability include individual differences in susceptibility, alcohol use pattern (quantity, frequency, duration) and nutrition. Non-treatment-seeking alcoholics tend to have less brain pathology than those seeking treatment (Fein and Landman, 2005) and may represent individuals with lesser predisposing susceptibility or better nutrition when drinking. Subclinical bouts of thiamine deficiency in alcoholism may, therefore, account for the graded effect from uncomplicated alcoholism to KS we noted (also see Blansjaar *et al.*, 1992; Jauhar and Montaldi, 2000). Indeed, the incidence of undetected WE-associated lesions among alcoholics at autopsy suggests greater influence of nutritional deficiency (especially thiamine) than generally appreciated clinically (Victor *et al.*, 1989; Harper and Butterworth, 1997; Thomson, 2000; Harper, 2006), and the neuroradiological traces of WE may linger in the brains of 'uncomplicated' alcoholics yet remain a liability for interaction with other neurodegenerative conditions and the ineluctable regression of brain tissue integrity with aging.

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