



Integrity of white matter microstructure in alcoholics with and without Korsakoff's syndrome Human Brain Mapping Integrity of white matter microstructure in alcoholics with and without Korsakoff's syndrome

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1 **Integrity of white matter microstructure in alcoholics with and without**
2 **Korsakoff’s syndrome**

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Abstract

Alcohol dependence results in two different clinical forms: “uncomplicated” alcoholism (UA) and Korsakoff’s syndrome (KS). Certain brain networks are especially affected in UA and KS: the frontocerebellar circuit (FCC) and the Papez circuit (PC). Our aims were 1) to describe the profile of white matter (WM) microstructure in FCC and PC in the two clinical forms, 2) to identify those UA patients at risk of developing KS using their WM microstructural integrity as a biomarker.

Tract-based spatial statistics and non-parametric voxel-based permutation tests were used to compare DTI data in 7 KS, 20 UA and 14 healthy controls. The two patient groups were also pooled together and compared to controls. k-means classifications were then performed on mean FA values of significant clusters across all subjects for 2 fiber tracts from the FCC (the middle cerebellar peduncle and superior cerebellar peduncle) and 2 tracts from the PC (fornix and cingulum).

We found graded effects of WM microstructural abnormalities in the PC of UA and KS. UA patients classified at risk of developing KS using fiber tracts of the PC also had the lowest scores of episodic memory. That finding suggests that WM microstructure could be used as a biomarker for early detection of UA patients at risk of developing KS.

Keywords: alcoholism, Korsakoff’s syndrome, Fronto-cerebellar circuit, Papez’s circuit, TBSS, classification

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Introduction

The effects of chronic and excessive alcohol consumption on the human brain and cognition result, among others, in two different clinical forms of alcohol-dependence, which differ mainly by the extent of brain damage (Pitel et al. 2012). The more severe clinical form is the Korsakoff’s syndrome (KS, Korsakoff, 1889), which is defined by permanent and debilitating neurological complications that arise from a combination of heavy alcohol consumption and thiamine deficiency. Patients with KS suffer from retrograde (Kopelman. 1989; for review Oscar-Berman. 2012) and anterograde (Fama et al. 2012 for review) amnesia, as well as ataxia (Sullivan et al. 2000), visuospatial deficits (Jacobson et al. 1990) and executive dysfunctions (Oscar-Berman. 2012 for review). Postmortem (Harper and Kril. 1990; Harper, 2009; Mayes et al. 1988; Victor et al. 1971) and neuroimaging studies (Colchester et al. 2001; Krabbendam et al. 2000; Pitel et al. 2009; Sullivan and Marsh, 2003; Sullivan et al. 1999) revealed structural brain abnormalities in KS patients, especially in the thalamus, cingulate cortex, cerebellum, mammillary bodies and white matter tracts of the superior cerebellar vermis (Harper et al. 2003). Studies using magnetic resonance imaging (MRI) have also shown shrinkage of the frontal and parietal cortices (Christie et al. 1988). The impact of the pathology on the hippocampus is still under debate with some studies reporting the region as preserved (Colchester et al. 2001; Squire et al. 1990), while others found it damaged (Sullivan and Marsh, 2003; Visser et al. 1999)

The other clinical form of alcohol-dependence refers to patients often considered as “Uncomplicated Alcoholics” (UA, Pitel et al. 2009, 2012; for review Oscar Berman et al, 2014; Zahr, 2014). Those patients, equally coined as “detoxified alcoholics” (Chanraud et al. 2007 for example), or “non-Korsakoff alcoholics” (Parsons, 1998 for example) are those without ostensible and severe neurological complications or liver dysfunctions (Alexander-

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3 68 Kauffman et al., 2006, Harper, 2007; Harper and Matsumoto, 2005; Matsumoto 2009; for
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5 69 review Oscar-Berman et al, 2014; Zahr, 2014). This clinical form is characterized by its
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7 70 heterogeneity but is known to result in mild-to-moderate cognitive deficits (Parsons and
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9 71 Nixon. 1998; Sullivan et al. 2000) and brain damage (Chanraud et al. 2007; Rosenbloom et al.
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11 72 2003). The neuropsychological profile includes impairment of working memory and
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13 73 executive functions such as planning, organisation, categorisation, flexibility, inhibition, and
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15 74 deduction of rules (Ambrose et al. 2001; Ihara et al. 2000; Noël et al. 2001; Pitel et al. 2007).
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17 75 Episodic memory is also affected in UA with both encoding and retrieval processes being
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19 76 impaired (Noël et al. 2012; Pitel et al. 2007). Neuroimaging investigations revealed gray
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21 77 matter volume losses in the frontal, parietal and medial temporal lobes, the cerebellar cortex,
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23 78 cerebellar vermis, as well as subcortical structures including the thalamus and the caudate
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25 79 nucleus (Chanraud et al. 2007; Pfefferbaum et al. 1992; Shear et al. 1996; Sullivan. 2003;
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27 80 Sullivan et al. 2003). Neuropathological studies reported a disruption of the cytoskeleton and
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29 81 white matter shrinkage especially in the corpus callosum, superior frontal cortex, anterior
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31 82 superior cerebellar vermis and the limbic system (Chanraud et al. 2009; Harris et al. 2008;
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33 83 Pfefferbaum et al. 2006, 2009). While post-mortem examination of the human brain did not
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35 84 indicate demyelination because of the inherent rapid disintegration of cellular membranes
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37 85 following death, animal studies have shown thinning of myelin sheaths (Phillips et al. 1991).
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39 86 Differences in microstructural integrity have also been found in-vivo in diffusion tensor
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41 87 imaging (DTI) studies of alcoholic patients having lower fractional anisotropy (FA) in the
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43 88 genu of the corpus callosum in men and the centrum semiovale in women (Pfefferbaum and
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45 89 Sullivan, 2005). When WM fibre tracts were defined a priori, lower FA values were revealed
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47 90 in the mesencephalic and pontine region, superior longitudinal fasciculus, external capsule,
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49 91 fornix and cingulum (Chanraud et al. 2009; Harris et al. 2008; Pfefferbaum et al. 2006, 2009).
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92 In both UA and KS, two brain networks and associated cognitive functions are
93 predominantly affected: the frontocerebellar circuit (Chanraud et al. 2010) and the Papez
94 circuit (Aggleton. 2012; Parsons. 1998). The frontocerebellar circuit (FCC), identified in non-
95 human primates using viral transneuronal tracing technology (Kelly and Strick, 2003),
96 consists of two distinct, parallel closed-loops within the cortico-thalamo-cerebellar circuitry.
97 The first one underlies executive functions and includes Brodmann areas 9 and 46 of the
98 dorsolateral prefrontal cortex, which receives input from the cerebellar crus I and II through
99 the thalamus, and projects back to the cerebellum through the pons. The second one
100 contributes to motor functions and encompasses the motor cortex, which receives input from
101 lobules IV-VI of the cerebellar vermis through the thalamus and feeds back to the cerebellum
102 via the pons (Chanraud et al. 2010). Diffusion tensor imaging technique and tractography
103 analyses (Mori et al. 2010) have shown that the superior cerebellar peduncle connects the
104 cerebellum to the thalamus, which is then connected to the dorsolateral prefrontal cortex
105 through the anterior limb of the internal capsule and the anterior corona radiata. The feedback
106 loop goes from the dorsolateral prefrontal cortex back to the pons via corticopontine tracts
107 and back to the cerebellum through the middle cerebellar peduncle. The Papez circuit (PC,
108 Aggleton and Brown, 1999; Papez, 1937), involved in episodic memory, includes the
109 hippocampal formation, which connects to the mammillary bodies via the fornix. The
110 thalamus then receives information from the mammillary bodies via the mammilo-thalamic
111 tract. The anterior limb of the internal capsule connects the thalamus to the cingulate gyrus,
112 which is in turn connected back to the hippocampus through the cingulum bundle.

113 The PC and the FCC are affected in both clinical forms, but not to the same extent,
114 hence the difference of clinical severity between UA and KS patients. In fact, the comparison
115 between these two clinical forms of alcohol-dependence revealed patterns of differences and
116 similarities in the profiles of cognitive impairments and brain structural deficits.

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3 117 Neuropsychological and neuroimaging studies have shown that impairment of the FCC is
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5 118 generally comparable in both UA and KS, whereas graded effects are observed for the PC
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7 119 (Pitel et al. 2008, 2012). More precisely, it has been shown that while deficits in working
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9 120 memory and executive functions did not differ significantly between UA and KS patients,
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11 121 deficits in episodic memory are more severe in KS patients compared to UA (Butters and
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13 122 Brandt, 1985; Fama et al. 2012; Pitel et al. 2008). Volumetric analyses of gray matter (Harper,
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15 123 2009; Harper et al. 2003; Pitel et al. 2009, 2012; Sullivan and Pfefferbaum, 2009) have also
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17 124 indicated that nodes belonging to the PC including the medial thalami and mammillary bodies
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19 125 were more severely affected in KS compared to UA patients. Similar degrees of shrinkage
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21 126 have been observed in both patient groups in some of the nodes of the FCC including the
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23 127 frontal cortex but not in the pons and cerebellum, for which graded effects were observed
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25 128 (Sullivan and Pfefferbaum, 2008). The few studies that have compared UA and KS patients
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27 129 regarding white matter volumes indicated that the cerebellar white matter (Krill et al. 1997),
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29 130 corpus callosum and thalamic radiations were more severely damaged in KS than in UA
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31 131 (Harper et al. 2003; Pitel et al. 2012).

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37 132 The comparison of neuropsychological functioning between UA and KS patients gave
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39 133 rise to the hypothesis that the effects of chronic alcohol consumption lie along a continuum
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41 134 from mild-to-moderate impairments in UA to severe ones in patients with KS (Butters and
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43 135 Brandt, 1985; Parsons, 1998; Ryback, 1971). The existence of a continuum between these two
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45 136 clinical forms reflects the heterogeneity within the UA group with some patients having
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47 137 preserved results similar to those of healthy controls, while others have severe deficits close to
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49 138 those of KS patients (Pitel et al. 2008). The latter ones are at risk to develop severe alcohol-
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51 139 related neurological complications but they often go undiagnosed (Pitel et al. 2011) and
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53 140 therefore do not receive appropriate treatment. Early identification of these patients would
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55 141 help clinicians in optimising treatment outcome. Clinical, neuropsychological and
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142 macrostructural brain biomarkers of risks for KS have been proposed. Previous studies have
143 suggested that a subgroup of UA patients with episodic memory impairments (Pitel et al.
144 2008) and thalamic shrinkage (Pitel et al. 2012) close to those of KS patients can be
145 identified. This subgroup of patients may even be clinically defined by the presence of signs
146 of Wernicke’s encephalopathy (Pitel et al. 2011). How white matter microstructure can also
147 be used as a biomarker of KS has never been explored. The white matter microstructure and
148 structural connectivity has never been investigated in KS and therefore the integrity of the
149 fibres bundles has never been quantitatively compared between UA and KS. Comparisons of
150 white matter have so far been limited to neuropathological investigations (Harper, 2009) and
151 one voxel-based morphometry (VBM) study of white matter volumes (Pitel et al. 2012).
152 Those studies gave first insights regarding white matter volumes but did not provide a clear
153 picture of the differences in the microstructure of white matter bundles. The latter is better
154 represented by observing the differences in FA values of white matter fibre tracts, obtained
155 through DTI studies, under the assumption that FA is a structural biomarker that depicts white
156 matter disruption involving myelin, cytoskeleton and the axons’ microtubule system
157 (Pfefferbaum et al. 2006). **We should however bear in mind that in absence of sound**
158 **methodological procedures, measurements of FA values could turn out to be artefactual**
159 **instead of reflecting impairments due to factors inherent to alcohol-dependence. One**
160 **example is the ‘correspondence problem’ (Smith et al. 2006) following poor spatial**
161 **normalization. A preserved white matter tract would be observed as impaired if what**
162 **are being effectively measured are FA values in crossing fibres which are inherently**
163 **lower.**

164 The first objective of the present study was therefore to describe the white matter
165 microstructure in UA and KS compared to healthy controls (HC) using a voxel-wise
166 approach. We hypothesize graded effects of compromised white matter integrity in the

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3 167 bundles of the PC ($KS < UA < HC$) but not in those of the FCC ($((KS = UA) < HC)$). Since the UA
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5 168 group is classically heterogeneous, the second objective was to identify UA patients at risk of
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7 169 developing KS through the analysis of white matter integrity across the tracts belonging to the
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9 170 FCC and PC.

171 **Materials and Methods**

172 *Participants*

173 Twenty-seven patients (22 men, 5 women) with alcohol-dependence (DSM IV criteria,
174 American Psychiatric Association. 1994) and 14 healthy subjects (9 men, 5 women) were
175 included in the study. To be included, all participants had to be between 18 and 70 years old,
176 and to have French as their native language. No participant had a comorbid psychiatric
177 disorder (no other axis 1 of the DSM IV as evaluated by MINI 500, American Psychiatric
178 Association 2004), was under psychotropic medication, had a history of serious chronic
179 pathology (diabetes, hepatitis, HIV, endocrinal disorder, as revealed by participants' blood
180 tests), neurological problems (traumatic head injury causing loss of consciousness for >30
181 minutes, epilepsy, stroke, etc.) that might have affected cognitive function. No participant
182 fulfilled the DSM-IV criteria for abuse of another substance over the last 3 months, nor filled
183 the DSM-IV criteria for dependence of another substance (except tobacco). They had not
184 taken any other psychoactive substance for more than 5 times over the last month (except
185 alcohol for the patients) and had not participated in any neuropsychological study or had any
186 neuropsychological evaluation during the previous year. All participants gave their informed
187 consent to the study, which was approved by the local ethics committee. Their demographical
188 details are summarised in Table 1. All patients were recruited for this study while being
189 inpatients at Caen University Hospital. The study was carried out in line with the Declaration
190 of Helsinki (1964).

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Of those 27 patients, 7 (6 men, 1 woman) filled the DSM IV criteria of persisting amnesic disorder (American Psychiatric Association. 1994) and were therefore diagnosed as KS patients. All KS patients had a history of heavy drinking (longer than 20 years), a Mini-Mental State (MMS, Folstein, 1975) score of at least 20, were abstinent for at least 7 days and were diagnosed with severely impaired episodic memory as revealed by a neuropsychological examination. The consequences of their memory impairments were such that none of the KS were able to go back to their previous jobs and all of them lived in sheltered accommodation or were inpatients waiting for a place in an institution. It was difficult to obtain accurate information about their alcohol intake due to their amnesia. The background information for the KS came mainly from family members and medical records. For each KS patient, the selection was made according to a codified procedure in a French officially registered centre for addiction. The case of each patient was examined by a multidisciplinary team made up of specialists in cognitive neuropsychology and behavioural neurology. Clinical and neuroimaging investigations ruled out other possible causes of memory impairments (particularly focal brain damage).

The 20 alcoholic patients without KS were considered as UA patients. They were recruited by clinicians while being inpatients for alcohol-dependence at Caen University Hospital. Although patients were early in abstinence (2.4 ± 3.1 days of sobriety prior to inclusion), none of them presented physical symptoms of alcohol withdrawal as assessed by the Cushman's scale (Cushman et al. 1985) at inclusion. They were interviewed with the Alcohol Use Disorders Identification Test (AUDIT; (Gache et al. 2005)) and a modified version of the semi-structured lifetime drinking history (Pfefferbaum et al. 1988). Measures included the duration of alcohol use (in years), alcohol misuse (in years), alcohol dependence (in years), number of withdrawal and daily alcohol consumption prior to treatment (in units, a standard drink corresponding to a beverage containing 10 g of pure alcohol).

216 The control group (HC) was recruited locally mainly by word of mouth and to match
 217 the demographics of the UA patients. Inclusion criteria were: a minimum MMS score of 26 or
 218 a minimum MATTIS (Mattis, 1976) score of 129, and a maximum Beck Depression Index
 219 (Beck et al. 1961) of 29. The maximum score at the Alcohol Use Disorders Test (AUDIT)
 220 was 6 for women and 7 for men.

221 UA and HC were age- and education-matched ($p=0.723$ and $p=0.76$ respectively). KS
 222 differed from both HC and UA in age, education (years of schooling) and MMSE scores. Age,
 223 education, depression (Beck Depression Inventory, and anxiety scores (State-Trait Anxiety
 224 Inventory (STAI) for adults with two forms Y-A for “state anxiety” and Y-B for “trait
 225 anxiety”) (Spielberger et al. 1983) as well as nicotine dependence level (Fagerstrom Test,
 226 (Heatherton et al. 1991)) are reported in Table 1.

227 All participants underwent a neuropsychological examination assessing intellectual
 228 abilities (Information and Matrix Reasoning subtests of the WAIS III (Wechsler, 2001a)),
 229 global cognitive function (MMSE; Folstein et al. 1975) and episodic memory (the French
 230 version of the Free and Cued Selective Reminding Test FSCRT (Grober and Buschke. 1987;
 231 Van der Linden, 2004). Neuropsychological performances are reported in Table 2.

232 *DTI data acquisition*

233 All participants underwent a DTI sequence on the Philips Achieva 3T MRI scanner
 234 (Netherlands). 70 slices (slice thickness of 2mm, no gap) were acquired axially using a
 235 diffusion weighted imaging spin echo (DWI-SE) sequence (32 directions at $b=1000 \text{ s/mm}^2$,
 236 repetition time = 10000 ms; echo time = 82 ms; flip angle = 90° , field of view = 224×224
 237 mm^2 ; matrix = 112×112 and in-plane resolution of $2 \times 2 \text{ mm}^2$; one no-diffusion weighted
 238 image at $b=0 \text{ s/mm}^2$ was also acquired).

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239 *DTI data processing*

240 The diffusion-weighted images (DWI) for all subjects were first pre-processed to create FA
241 images using the FSL Diffusion Toolbox (FDT) (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>)
242 that is part of FSL 5.0 toolbox for medical image analysis (Smith et al. 2004). The FA images
243 were further processed using Tract Based Spatial Statistics (TBSS) for subsequent voxelwise
244 statistical analysis (Smith et al. 2006). TBSS presents an improvement on classical voxelwise
245 approaches like voxel based morphometry (VBM). More specifically, it first addresses the
246 “correspondence problem” faced by standard registration algorithms where it is difficult to
247 gauge whether the observed differences are indeed due to differences in tissue
248 volumes/density or are artefactual modifications that result from local misalignment. The
249 issue becomes more pertinent in the case of white matter tracts where a higher level of
250 precision is required to ensure that the FA values contained in the voxels come from exactly
251 the same part of WM tract across all subjects. TBSS addresses the problem by tailoring the
252 non-linear registration algorithm to the requirements of the DTI data, followed by projection
253 onto a tract representation that is an alignment invariant (referred to as the mean FA skeleton).
254 Such an approach also removes the need for applying a spatial smoothing for which the
255 choice of the smoothing kernel is deemed to be done in an arbitrary manner, and results
256 known to be highly dependent on the kernel size (Jones et al. 2005). Smoothing increases
257 partial volume effects between tissues such that it is difficult to differentiate between WM
258 differences that are due to the biological mechanism under investigation or an artefactual
259 measurement due to a mixture of tissues.

260 For each subject, the 32 DWI images were first corrected for distortions due to Eddy currents
261 and aligned to the $b=0$ s/mm² image using rigid-body registration for motion correction
262 (Jenkinson et al. 2002). FA images were then created by fitting a tensor model to the diffusion
263 images and were further processed using TBSS. Briefly, all subjects' FA data were aligned

into MNI space using the nonlinear registration tool (FNIRT), which uses a b-spline representation of the registration warp field (Rueckert et al. 1999) resulting in FA maps of matrix size of 182x218x182 and voxel size of 1x1x1 mm³. Next, the mean FA image was calculated and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. Each subject's aligned FA image was threshold at 0.3 to exclude low FA values that could be contaminated with partial volume effects from other non-white-matter tissues and to minimise inter-subject variability. The resulting image is then projected onto the mean skeleton by filling every voxel of the latter with the maximum FA value that lies perpendicular to the skeleton structure. Voxel-based statistics are performed on these 'skeletonised' images.

Statistical analyses

A. Comparison of white matter integrity in HC, UA patients and KS patients in the whole-brain (voxel-based analysis)

Non-parametric permutation tests (Nichols and Holmes, 2002) were performed between HC and UA; HC and KS; and UA and KS groups. Age was included as a covariate to account for between-group differences (KS being older than the two other groups). For each between-group comparison, 5000 permutations were done, and the data corrected for multiple comparisons (FWE, $p < 0.05$) using threshold-free cluster enhancement (TFCE; (Smith and Nichols, 2009)) for cluster-wise correction. This statistical toolbox is implemented within FSL 5.0. (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise>).

B. Identification of UA patients at risk of developing KS

1. Because of the heterogeneity within the UA group, UA and KS patients were pooled together to form a single group of alcohol-dependant patients (UASK). The UASK group

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was then compared to the HC group using non-parametric permutation tests (5000 permutations, FWE $p < 0.05$, TFCE).

2. The John Hopkins University International Consortium for Brain Mapping (JHU-ICBM) DTI-81 WM atlas (Mori *et al.* 2010), implemented as an atlas tool in FSL 5.0 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>), was then used to extract and binarise clusters highlighted in the previous between-group analysis (UASK vs HC). Only the WM fibre tracts that belong to the FCC and PC were used to produce “fibre-cluster masks”. These “fibre-cluster masks” were then employed to extract the mean FA value within each tract belonging to the FCC and PC for each subject. Focus was laid on a couple of fibre tracts only for each circuit. In that respect, the cingulum and the fornix were chosen for the PC and the middle cerebellar peduncle and superior cerebellar peduncle for the FCC. These are the tracts that are believed to offer less variability in terms of specificity to the PC and FCC respectively, having a lower involvement in fibres connecting other parts of the brain or involved in other circuitry.

3. For each fibre tract, a k-means clustering classification was then performed on the mean FA values, with the algorithm constrained to separate the 41 participants into 2 groups. The aim was to find which white matter fibre tract enables the identification of some UA patients classified into the same group as KS patients. A reliable classification would include all HC into one group, and all KS patients into the other group with the heterogeneous UA group fitting into either of these. Those UA who will be sorted within the same group as the KS patients will be deemed as UA_HIGH patients (for high risk of developing KS) while those who will be sorted within the same group as the HC will be labelled UA_LOW patients (for low risk of developing KS). It is hypothesised that a more robust classification will be obtained when using FA values in the fibres of the PC than in

those of the FCC. Comparisons of episodic memory performance among the subsequent subgroups should help in asserting the robustness of the classification step.

4. Between-group comparisons of episodic memory performance:

Episodic memory scores were compared between the groups of HC, UA_LOW, UA_HIGH and KS using non-parametric Mann Whitney U tests. The hypothesis is that the scores on the episodic memory test in UA_LOW patients will differ significantly from the UA_HIGH and KS patients but not from HC. UA_HIGH patients are expected to differ significantly from HC and UA_LOW and KS patients.

Results

A. Comparison of white matter integrity in HC, UA patients and KS patients

(i) *UA versus HC*

Non-parametric permutation tests (FWE, $p < 0.05$) between UA and HC showed lower FA values in fibre tracts spread across the whole brain including the corpus callosum ($T_{\max} = 6.01$; $k = 6258$; $\eta^2 = 0.17$), the anterior limb of the internal capsule ($T_{\max} = 5.86$; $k = 742$; $\eta^2 = 0.10$), the anterior corona radiata ($T_{\max} = 5.52$; $k = 2215$; $\eta^2 = 0.16$), the fornix ($T_{\max} = 5.91$; $k = 560$; $\eta^2 = 0.15$); the cingulum ($T_{\max} = 4.95$; $k = 821$; $\eta^2 = 0.14$); the middle cerebellar peduncle ($T_{\max} = 5.17$; $k = 1320$; $\eta^2 = 0.11$) and the superior cerebellar peduncle ($T_{\max} = 4.92$; $k = 252$; $\eta^2 = 0.15$) as shown in Fig. 1.

Note: Values for effect size (η^2) have been calculated from T-scores resulting from the non-parametric permutation tests.

(ii) *KS versus HC*

The profile of WM structural impairment in KS versus HC was similar to that between UA and HC. FA values were lower in KS than in HC in the same tracts as reported above but with higher T and k values: corpus callosum ($T_{\max} = 10.52$; $k = 7279$; $\eta^2 = 0.26$), anterior corona

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3 335 radiata ($T_{\max} = 7.45$; $k=2936$; $\eta^2=0.31$), anterior limb of the internal capsule ($T_{\max} = 7.00$;
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5 336 $k=1179$; $\eta^2=0.23$); cingulum ($T_{\max} = 6.93$; $k=869$; $\eta^2=0.14$); the fornix ($T_{\max} = 6.60$; $k=693$;
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7 337 $\eta^2=0.31$); the middle cerebellar peduncle ($T_{\max} = 6.30$; $k=1153$; $\eta^2=0.27$) and the superior
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9 338 cerebellar peduncle $T_{\max} = 7.27$; $k=270$; $\eta^2=0.35$).

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13 339 (iii) *UA versus KS*

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15 340 Group differences between UA and KS were found mainly in the corpus callosum ($T_{\max} =$
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17 341 4.93 ; $k=4453$; $\eta^2=0.139$) and anterior corona radiata ($T_{\max} = 4.9$; $k=932$; $\eta^2=0.13$). Other
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19 342 tracts with significant differences were also observed but they either had low T-values or their
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21 343 cluster sizes were small. For example, anterior limb of the internal capsule ($T_{\max} = 3.59$;
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23 344 $k=163$; $\eta^2=0.11$); cingulum ($T_{\max} = 3.61$; $k=103$; $\eta^2=0.14$) and the fornix ($T_{\max} = 3.81$; $k=107$;
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25 345 $\eta^2=0.16$). There were no significant differences in the middle and superior cerebellar
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27 346 peduncles.

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32 347 [FIGURE 1]

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34 348 There was no gender effect in the UA and KS groups across all white matter fibre tracts. In
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36 349 the control group, differences between men and women were significant for the cingulum
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38 350 (Mann-Whitney U test, $p=0.014$). There was no correlation between FA measures and BDI
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40 351 scores or years of education across all tracts for all 3 groups. There was also no correlation
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42 352 between FA measures and the number of detoxifications in the UA group. The same analysis
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44 353 could not be performed for the KS group since it was not possible to obtain complete and
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46 354 accurate information regarding alcohol history for these patients.

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B. Identification of UA patients at risk of developing KS

(i) *Comparison of white matter integrity between HC and UASK*

The comparison between HC and UASK (UA and SK patients pooled together) showed lower FA values in the patients in all the tracts mentioned in the previous results, including the middle cerebellar peduncle ($T_{\max} = 5.14$; $k=1457$; $\eta^2=0.10$); the superior cerebellar peduncle ($T_{\max} = 5.20$; $k=278$; $\eta^2=0.14$); the fornix ($T_{\max} = 7.20$; $k=609$; $\eta^2=0.14$) and the cingulum ($T_{\max} = 5.47$; $k=840$; $\eta^2=0.14$). Fig. 2 shows the white matter tracts of the FCC and PC that are significantly disrupted in the UASK group compared to the HC group.

[FIGURE 2]

(ii) *Identification of UA at risk to develop KS for each fibre tract*

For all participants, mean FA values were extracted from significant fibre-clusters (see above) for the middle and superior cerebellar peduncles, representing tracts from the FCC and the cingulum and fornix, representing tracts from the PC. A k-means classification was then performed on those tracts. Fig. 3 represents the distribution of the mean FA values for each selected tract identified in the white matter atlas (Mori *et al*, 2010) to be part of the FCC and PC.

With regard to white matter tracts within the PC, the k-means classification conducted on the FA values in the cingulum and fornix showed an expected classification of all HC in one group and all KS patients in another. Some UA patients were classified in the same group as HC and can be therefore considered as UA_LOW, while others were classified in the same group as KS and were thus qualified as UA_HIGH. The same patients were classified as UA_HIGH for both the cingulum and the fornix, except for two of them (one for cingulum and one for fornix). However, these 2 patients were those with the lowest FA values in the

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subsequent UA_LOW class. Comparisons of mean FA values among the 4 subgroups for both the cingulum and the fornix (ANOVA Kruskal-Wallis) have shown that the controls did not differ from the UA_LOW group ($p=1$). KS differed significantly from HC ($p<0.001$) and UA_LOW ($p=0.01$) but not UA_HIGH. UA_HIGH was significantly different from HC ($p<0.001$) and UA_LOW ($p=0.01$).

Regarding the tracts of the FCC, the results of the classification seemed less reliable since each of the two groups identified included a mix of KS patients, UA patients and HC. Moreover, the number and the identity of the UA patients classified as UA_HIGH completely differed between the two tracts of the FCC.

[FIGURE 3]

(iii) Comparison of episodic memory performance in the UA_HIGH and UA_LOW groups

Since a better classification of patients for UA_HIGH and UA_LOW were obtained for the two white matter tracts of the PC as opposed to the FCC, we compared episodic memory performances between the two subgroups of UA identified with the classification analysis conducted on FA values in the fornix and cingulum individually. Non-parametric Mann-Whitney U tests showed that UA_LOW did not differ from HC ($p=0.37$ for the classification using the fornix and $p=0.32$ for the classification using the cingulum). UA_LOW differed from UA_HIGH ($p=0.038$ for the classification using the fornix and $p=0.025$ for the classification using the cingulum). UA_HIGH differed significantly from HC ($p=0.002$ for both fornix and cingulum) and KS ($p=0.001$ for classification with the fornix and $p=0.002$ for classification with the cingulum). The latter was significantly different to all the other 3 subgroups for both classifications ($p<0.001$). These results are illustrated in Fig. 4.

[FIGURE 4]

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3 406 We conducted the same analysis on the performances on matrix reasoning, and forward and
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5 407 backward block spans but found insignificant differences between the UA subgroups for
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7 408 neither the cingulum nor the fornix (data not shown). Hence, the ability to identify UA
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9 409 patients at risk of developing KS seems to be specific to performances in episodic memory
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14 411 Note that we have also tested classification with the corpus callosum but it yielded poor
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16 412 results (data not shown since the corpus callosum is neither part of the FCC, nor the PC).

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20 21 414 **Discussion**

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24 415 The first aim of this study was to describe the profile of microstructural white matter
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26 416 integrity in UA and KS in the whole brain, at a voxel-level, since most of the previous studies
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28 417 had been carried out using a region of interest approach (with anatomical regions defined a
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30 418 priori). In accordance with neuropathological (Harper et al. 2003; Kril et al. 1997) and
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32 419 neuroimaging studies (Chanraud et al. 2010; Pfefferbaum and Sullivan, 2005; Pfefferbaum et
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34 420 al. 2006, 2009), the present TBSS analysis of FA values in UA revealed widespread
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36 421 compromised WM microstructure including notably fibers of the FCC and the PC. Using a
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38 422 stringent statistical threshold (TFCE and FWE, $p < 0.05$), our voxel-based analyses have
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40 423 successfully replicated previous DTI results in fibres defined a priori (Pfefferbaum et al.
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42 424 2009) such as the superior longitudinal fasciculus, external capsule, fornix and cingulum.
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44 425 Moreover, our analyses revealed compromised WM integrity in other fibre tracts such as the
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46 426 internal capsule, cerebral peduncles, corona radiata and thalamic radiations, which has also
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48 427 been reported in a TBSS study comparing alcoholics who have been abstinent for at least 5
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50 428 years with healthy controls (Fortier et al. 2014). Contrary to previous neuropathological
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52 429 (Harper et al. 2003) and neuroimaging studies (Chanraud et al. 2009; Pfefferbaum et al.
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54 430 2009), we also found microstructural abnormalities in the middle and superior cerebellar
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431 peduncles. The use of a voxel based approach may have enabled the observation of the latter
432 finding since a ROI approach, which would average the FA values within a region defined a
433 priori, would not reveal any localized impairments within those fibres. Thus, WM
434 abnormalities in the middle and superior cerebellar peduncles revealed by TBSS suggest that
435 disruption may be more localized than spread-throughout in those fibres.

436 Our study is the first to evaluate white matter microstructural integrity in KS patients.
437 When KS patients were compared to HC, the profile of WM abnormalities was similar to that
438 observed between UA and HC, in agreement with the patterns of GM and WM shrinkage
439 found in a recent VBM study (Pitel et al. 2012). Compromised WM microstructure in the
440 middle and superior cerebellar peduncles is in-line with previous investigations that have
441 shown significant shrinkage of the cerebellar white matter of KS patients (Harper et al. 2003;
442 Kril et al. 1997) and in proteomics studies where changes in the levels of thiamine-dependent
443 enzymes have been observed (Alexander-Kaufman et al. 2006).

444 Previous neuropsychological and neuroimaging (structural and functional) studies
445 have hypothesized that anterograde amnesia in KS patients is essentially due to a
446 disconnection within the PC (Warrington and Weiskrantz, 1982, Nahum et al. 2014). More
447 specifically, findings of abnormalities in diencephalic structures, including the thalamus and
448 mammillary bodies, and cortical structures from the frontal and medial temporal lobes have
449 pushed towards the hypothesis of a disruption between nodes belonging to this neural network
450 (Aupée et al, 2001; Renou et al. 2008; Kim et al. 2009). Our study provides consolidating
451 evidence of white matter disruptions in the PC that is linked to episodic memory deficits and
452 therefore amnesia (Kessels and Kopelman, 2012 for review). Based on the substantial role of
453 the cerebellum in cognitive processes and its connections with cortical areas, damaged FCC
454 has been hypothesized to be involved in working memory and executive dysfunction in KS
455 (Wijnia and Goossenssen, 2010). Our data confirm compromised WM integrity in the

cerebellum and especially disruption of the middle and superior cerebellar peduncles. In summary, cognitive deficits observed in KS patients, including amnesia, stems from a disconnection of neural networks, which can in turn be due to abnormalities in the nodes of the network(s), disruption of white matter tracts linking those nodes, or abnormal synaptic activity between the nodes. While our study confirms the disruption of white matter tracts in specific brain networks, and another study showed an absence of atrophy within connected regions (Nahum et al, 2014), it is still difficult to evaluate the cascade of events (neurotransmission dysfunction – local or global network disruption – cellular damage/atrophy) that effectively governs the pathophysiological mechanism of KS when using a cross-sectional paradigm,. Longitudinal studies are required to concretely establish this mechanism.

Our direct voxel-based comparison between UA and KS patients showed significant differences mainly in the corpus callosum, which follows previous volumetric studies that has reported further volume loss in the corpus callosum in alcoholic patients with Wernicke's Encephalopathy than those alcoholic patients without (Lee et al., 2005) and the other one between UA and KS (Pitel et al, 2012). The abnormalities in the microstructural integrity of the corpus callosum have also been hypothesized to be due to thiamine deficiency as observed in a study with rats (He et al, 2007).

Contrary to our initial hypotheses, a clear graded effect of deficits in the PC was not observed. This can be attributed to our sample size and to the heterogeneity of the UA group. As neurological complications from UA to KS lie along a continuum (Ryback, 1971), it is difficult to observe a distinct pattern of microstructural degradation between these 2 groups, justifying the need to divide the UA group into sub-groups to better observe their underlying pathological mechanisms. By first combining the UA and KS groups, the statistical power to detect all regions affected in alcohol dependent patients was increased (Monnig et al. 2013),

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481 ensuring that the subsequent classification step did not disregard any white matter tracts that
482 are potential structural biomarkers for identifying alcoholics at risk to develop neurological
483 complications such as KS.

484 The classification step revealed that the use of DTI may be particularly relevant as a
485 structural biomarker towards the early identification of UA patients at risk of developing KS.
486 The early identification is important for clinicians to apply the correct and optimal treatment
487 with the aim of preventing severe, debilitating and irreversible neurological complications.
488 Our analysis provides consolidating evidence of the PC, as opposed to the FCC, being an
489 appropriate neuroanatomical substrate for identifying UA patients that can potentially develop
490 KS (Pitel et al. 2012). The statistical comparisons of the mean FA values between the
491 subgroups of subjects have confirmed the robustness of the classification step. The fact that
492 there is a clear separation between HC and KS as well as consistent classification of the UA
493 subgroups for the cingulum and fornix complements volumetric findings that have shown
494 graded effects in the mammillary bodies, the hippocampus and the thalamus (Sullivan and
495 Pfefferbaum, 2009). In a previous study (Pitel et al. 2012), the volume of the thalamus was
496 found to be comparable between some of the UA patients and the KS ones, reinforcing
497 neuropsychological data that have shown the same trend in episodic memory deficits (Pitel et
498 al. 2008). While the volume of the thalamus was not explored in the present study, we
499 confirm that UA patients classified at risk to develop KS based on WM microstructural
500 abnormalities in the PC had the lowest episodic memory scores. Interestingly, it was also
501 observed that 4 patients out of 10 classified as UA_LOW filled none of Caine’s criteria for
502 Wernicke’s encephalopathy (Caine et al. 1997; Pitel et al. 2011), 4 patients filled one criterion
503 and 2 filled more than 2 criteria. For the UA_HIGH subgroup, 2 patients filled no criterion, 4
504 filled 1 criterion and 4 filled more than 2 criteria. The number of signs of Wernicke’s
505 encephalopathy did not differ between the UA_LOW and UA_HIGH (Chi-squared test, data

not shown). Our refined neuroimaging analyses confirm that a neuropsychological evaluation, especially targeting episodic memory, is highly recommended in clinical settings, where neuroimaging tools are not available, to identify patients at risk of developing KS. Taken together, the analysis of microstructural integrity within the fornix and cingulum, in combination with scores of episodic memory, thalamic volume and signs of Wernicke's encephalopathy, could give a reliable depiction of whether a UA patient is at risk of developing KS. Our study is thus a positive iteration to the heuristic value of the continuity hypothesis (Butters and Brandt, 1985; Parsons, 1998; Pitel et al. 2008; Ryback, 1971). While this inherent heterogeneity in the UA group enabled us to detect alcoholics at risk to develop neurological complications, the currently used average neuropsychological, structural and functional description of a UA group does not reflect the heterogeneity of individual profiles in clinical settings.

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519 **Conclusions and further works**

TBSS has allowed us to describe the profile of white matter integrity at a voxel-level in UA and KS patients. While the chronological position of white matter disruption is still unknown in the cascade of structural and functional events that govern the pathophysiological mechanism underlying the neurotoxicity of alcohol, we have shown the potential of DTI data to identify uncomplicated alcoholics at risk of developing KS. The method paves the way for more in depth analysis of this subgroup in order to better understand the mechanism underlying these two clinical forms. Multi-modal neuroimaging, combined with biological and neuropsychological analyses will enable researchers to explore the characteristics of these clinical forms in terms of detailed microstructure, regional volume, function, enzyme metabolism and cognitive deficits. The specificity of the subgroup of patients at risk to

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530 develop KS is also likely to be confirmed via longitudinal studies in which the progress of the
531 pathology can be monitored and the efficiency of the treatment can be assessed and optimised.
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For Peer Review

Figure legends:

Figure 1 Voxel by voxel comparisons of FA values between HC and UA (top row), HC and KS (middle row) and UA and KS (bottom row) using non-parametric permutation tests (5000 permutations, FWE $p < 0.05$, TFCE for cluster-wise correction). p-value maps are shown as (1-p) images, displayed on a T1-weighted MRI in MNI space.

Figure 2 Voxel by voxel comparisons of FA values between HC and UASK using non-parametric permutation tests (5000 permutations, FWE $p < 0.05$, and TFCE for cluster-wise correction). p-value maps are shown as (1-p) images, displayed on a T1-weighted MRI in MNI space.

Figure 3 Distribution of the mean FA values for the selected white matter tracts within the fronto-cerebellar circuit (mcp = middle cerebellar peduncle, scp = superior cerebellar peduncle) and the Papez circuit (fornix and cing = cingulum). Horizontal black lines represent the separation between the 2 identified clusters.

Figure 4 Episodic memory performance (sum of the 3 free-recalls of FCSRT) in the HC, KS and subgroups UA_LOW and UA_HIGH.

UA_LOW and UA_HIGH have been identified using k-means classification conducted on means FA values of significant fibre-clusters in the fornix and the cingulum bundle.

* : sig different from HC; § : sig different from UA_LOW; ¥ : sig different from UA_HIGH

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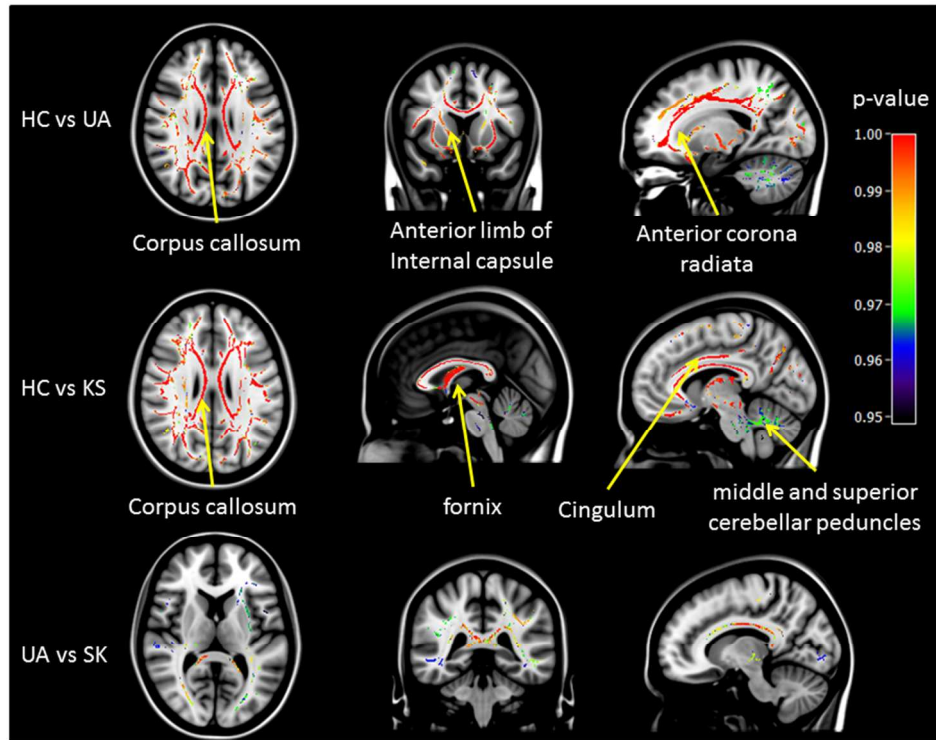
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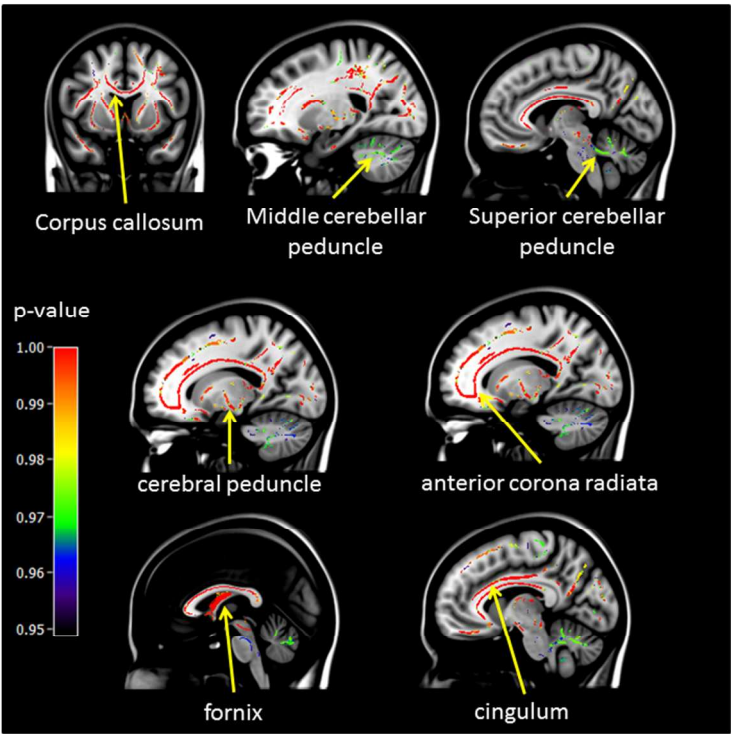
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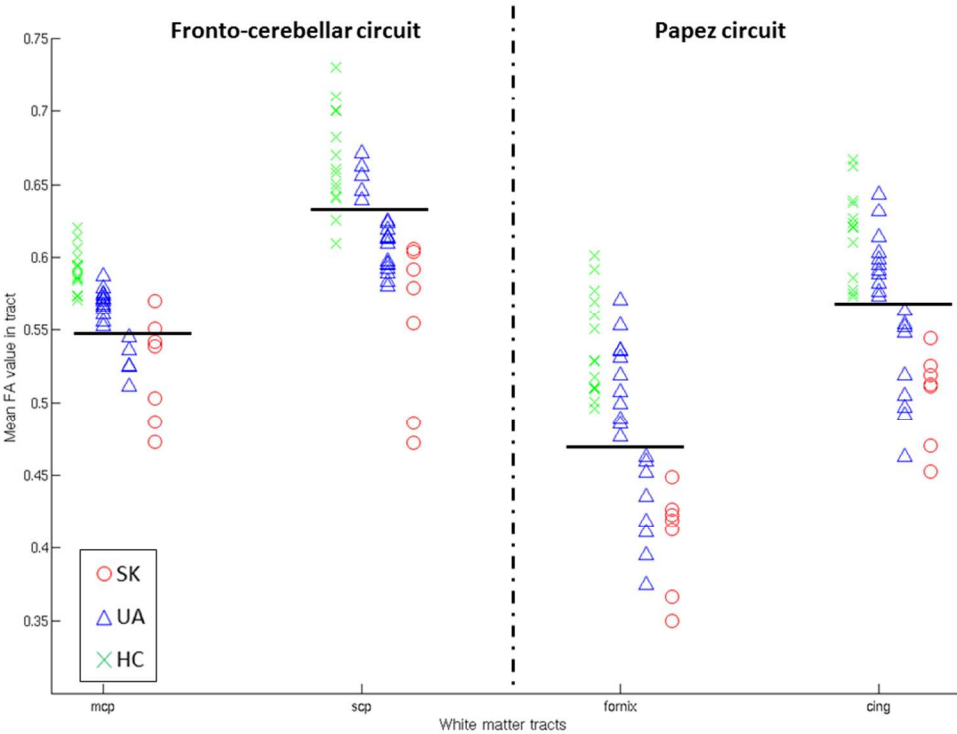


Voxel by voxel comparisons of FA values between HC and UA (top row), HC and KS (middle row) and UA and KS (bottom row) using non-parametric permutation tests (5000 permutations, FWE $p < 0.05$, TFCE for cluster-wise correction). p-value maps are shown as (1-p) images, displayed on a T1-weighted MRI in MNI space.

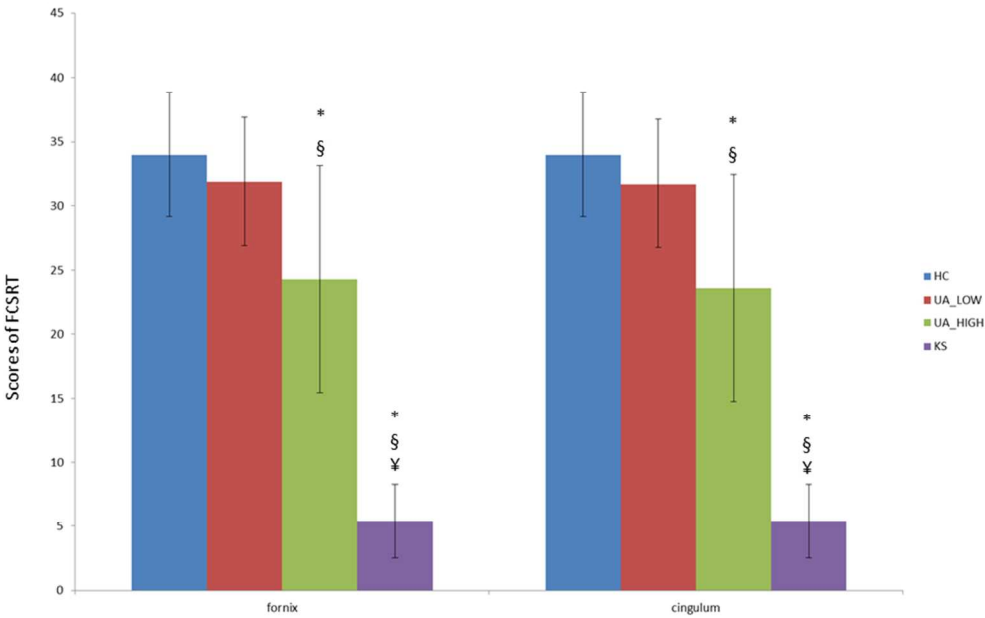
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Voxel by voxel comparisons of FA values between HC and UASK using non-parametric permutation tests (5000 permutations, FWE $p < 0.05$, and TFCE for cluster-wise correction). p-value maps are shown as (1-p) images, displayed on a T1-weighted MRI in MNI space. 254x190mm (96 x 96 DPI)



Distribution of the mean FA values for the selected white matter tracts within the fronto-cerebellar circuit (mcp = middle cerebellar peduncle, scp = superior cerebellar peduncle) and the Papez circuit (fornix and cing = cingulum). Horizontal black lines represent the separation between the 2 identified clusters.
254x190mm (96 x 96 DPI)



Episodic memory performance (sum of the 3 free-recalls of FCSRT) in the HC,KS and subgroups UA_LOW and UA_HIGH.

UA_LOW and UA_HIGH have been identified using k-means classification conducted on means FA values of significant fibre-clusters in the fornix and the cingulum bundle.

* : sig different from HC; § : sig different from UA_LOW; ¥ : sig different from UA_HIGH

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Table 1: Demographical, clinical and neuropsychological description of the alcoholics with and without Korsakoff's syndrome and control participants

Variable	HC (n=14)	UA (n=20)	KS (n=7)	Between-group comparisons [*]
Age (years)	45.4±6.9 [31 - 55]	45.2±8.1 [34 - 63]	55.3±7.8 [44 - 67]	HC = UA; HC < KS UA < KS
Education (years)	11.5±2.5 [7-15]	11.9±1.7 [9-15]	9.4±2.8 [6-15]	HC = UA; HC = KS UA < KS
Alcohol Use Disorders Test (AUDIT)	3.2±1.4 [0 - 5]	29.2±7.5 [9 - 39]	16.6±14.0 [1 - 37]	HC < UA; HC < KS UA < KS
Beck Depression Index (BDI)	3.6±3.2 [0 - 9]	13.2±7.5 [2 - 27]	9.0±10.0 [0 - 29]	HC < UA; HC = KS UA = KS
Mini Mental State (MMS) (/30)	28.4±1.1 [27 - 30]	27.4±2.2 [21 - 30]	22.3±3.3 [18 - 27]	HC = UA; HC < KS UA < KS
MATTIS Total score	141±2.0 [136 - 144]	136± 6.7 [119 - 143]	114±12.3 [95-132]	HC < UA ; HC < KS UA < KS
STAI ^a A	27.2±7.2 [20 - 47]	31.6±11.0 [20 - 59]	33.4±6.4 [25 - 42]	HC = UA; HC = KS UA = KS
STAI ^a B	33.4±7.0 [23 - 47]	44.4±12.3 [28 - 66]	42.0±11.1 [26 - 56]	HC < UA; HC = KS UA = KS
Fagerstrom ^b	0.7±1.8 [0-6]	4.8±3.6 [0 - 14]	N/A	HC<UA
Abstinence before inclusion (days)	N/A	2.4±3.1 [1 - 13]	53.7±29.4 [1 - 100]	UA<SK
Alcohol Use (years)	N/A	29.6±9.3 [18 - 51]	NR	NA
Alcohol misuse (years)	N/A	18.3±8.7 [2 - 30]	NR	NA
Alcohol dependence (years)	N/A	9.5±6.7 [1 - 26]	NR	NA
Number of previous detoxifications	N/A	3.3±2.6 [0 - 11]	NR	NA

HC = Healthy Controls; UA = Uncomplicated Alcoholics; KS = Alcoholics with Korsakoff's Syndrome

NR = data not reported since it was not possible to obtain complete and accurate information regarding alcohol history in all KS patients.

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Mean ± standard deviation and range [minimum – maximum] are reported.

* : Mann-Whitney U tests $p<0.05$

a : State-Trait Anxiety Inventory for adults , Y-A for “state anxiety” and Y-B for “trait anxiety” (Spielberger et al. 1983)

b : Fagerstrom (Heatherton et al. 1991)

For Peer Review

Table 2: Neuropsychological description of the alcoholics with and without Korsakoff's syndrome and controls

Cognitive functions	Tasks	HC	UA	KS	Tests*
Intellectual abilities (WAIS III subtests) ¹	Information	9.1 ± 3.0	6.04 ± 3.0	5.2 ± 3.1	HC>UA>KS
	Matrix reasoning	10.4 ± 2.2	7.71 ± 2.26	5.0 ± 4.4	HC>UA>KS
Episodic memory	FSCRT sum of 3 free recalls	34.0 ± 4.9	28.5 ± 7.8	5.4 ± 2.9	HC>UA>KS
Working memory (MEM-III subtests) ¹	Forward visuospatial span	8.5 ± 2.3	5.8 ± 1.5	5.1 ± 0.7	HC>UA>KS
	Backward visuospatial span	8.7 ± 2.5	5.3 ± 1.3	3.9 ± 0.7	HC>UA; HC>KS

HC = Healthy Controls; UA = Un complicated Alcoholics; KS = Alcoholics with Korsakoff's

Syndrome

(Mean ± standard deviation) and range [minimum – maximum] are reported.

* : Mann-Whitney U tests $p < 0.05$

¹ Standard scores

¥ : comparison with KS not done as no data available

WAIS III Wechsler Adults Intelligence Scale

FSCRT: Free and Cued Selective Reminding Test