



## Altered T2\* relaxation time of the hippocampus in major depressive disorder: Implications of ultra-high field magnetic resonance imaging

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### ABSTRACT

Previous studies with 1.5 T or 3.0 T magnetic resonance imaging (MRI) have produced mixed results regarding the structural changes of the hippocampus in major depressive disorder (MDD). Subtle region-specific hippocampal tissue changes might be more sensitively detected by measuring the T2\* relaxation time (T2\*-RT) by ultra-high-field (UHF) MRI, as it provides much higher contrast and sensitivity and consequently greater resolution. We assessed the T2\*-RTs of hippocampal sub-regions in 16 MDD patients (9 with recurrent MDD) and 16 control subjects using an UHF 7.0 T MRI system. T2\*-RTs of CA1, CA2, CA3, CA4, and subiculum were calculated for both left and right hippocampus. MDD patients had significantly longer T2\*-RTs in the right CA1 and subiculum than control subjects. Patients with recurrent MDD had significantly longer T2\*-RTs in the right subiculum than those experiencing a first depressive episode, and longer T2\*-RTs in the right CA1, CA3, and subiculum than control subjects. Values for T2\*-RTs of the right CA3 were significantly correlated with illness duration. In conclusion, we report that T2\*-RTs in the right subiculum and CA1 were increased in patients with MDD, especially in cases of recurrent MDD. These findings suggest that region-specific hippocampal damage may be occurring in recurrent depression.

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### 1. Introduction

Numerous studies have reported reduced hippocampal volume in major depressive disorder (MDD). However, this MDD-induced reduction in hippocampal volume has not been consistently demonstrated (Campbell et al., 2004; Eker and Gonul, 2009; McKinnon et al., 2009). The inhomogeneity of depressed subjects has been suggested as one probable reason for the discrepancy. The most prevailing view is that hippocampal reduction can be found mainly in subjects with longer illness duration (Sheline et al., 1999; Colla et al., 2007). In addition, differences in disease severity (Vakili et al., 2000), age of onset (Lloyd et al., 2004; Janssen et al., 2007), experience of stressful events (Gianaros et al., 2007; Vythilingam et al., 2002), antidepressant medication (Sheline et al., 2003), treatment-resistance (Frodl, Meisenzahl, Zetzsche et al., 2004; Frodl T et al., 2008; Kronmuller, Pantel, Kohler et al., 2008), or genotype (Frodl, Meisenzahl, Zill et al., 2004; Taylor et al., 2005) have been suggested to be related to the discrepancy. A recent

review on structural imaging studies of the hippocampus in MDD patients suggested that a smaller hippocampus was prominent in patients of old age or with severe or recurrent episodes (Eker and Gonul, 2009).

Another plausible cause for this controversy may lie in the imaging methods used in prior studies. Measurements of the total hippocampal volume using conventional imaging resolutions had inevitable limitations in detecting subtle hippocampal changes. Moreover, specific hippocampal sub-regions may be predominantly affected by depression, while others may remain relatively intact. To overcome this limitation, some researchers have conducted shape analysis of the hippocampus (Posener et al., 2003; Ballmaier et al., 2008); however, even with this post-processing technique, the hippocampal sub-regions could not be well differentiated in detail using previous imaging resolutions widely available to most clinics.

T2 or T2\* relaxometry may be a more sensitive measure for hippocampal tissue composition compared to volumetric measurements. T2\* relaxation refers to the decay of transverse magnetization caused by a combination of spin–spin relaxation. In addition, it also refers to additional spin dephasing which causes the magnetic field inhomogeneities and the differences in magnetic susceptibility between tissues. T2\* images are commonly used for evaluating the

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water content of tissue.  $T2^*$  relaxation also correlates with iron content (Gelman et al., 1999) or steady-state regional blood volume (Anderson et al., 2005) in the tissue. Therefore,  $T2$  or  $T2^*$  relaxation time ( $T2^*$ -RT) has been shown to correlate with brain tissue damage (Cross et al., 2008) or resting neuronal activity (Teicher et al., 2000; Small et al., 2000).

It has been reported that depressive symptoms were related to hippocampal  $T2$ -RT in whole-brain wise measurements of  $T2$ -RT in sleep apnea patients (Cross et al., 2008). The relationship between depressive symptoms and hippocampal  $T2$ -RT has also been reported in patients with epilepsy (Nees et al., 2001). However, hippocampal  $T2^*$ -RT in depression has not been extensively investigated, mainly due to the limited resolution of 1.5 T and 3.0 T MR imaging.

Recently, ultra-high-field (UHF) MRI systems have become available for in-vivo human research. The UHF MRI such as 7.0 T has the potential of providing substantially better images in resolution and contrast (Li et al., 2006; Duyn et al., 2007; Cho et al., 2009). Especially,  $T2^*$  contrast at UHF has reveal a number of brain structures which were not visible in 1.5 T or 3.0 T MR images (Li et al., 2006; Duyn et al., 2007). The hippocampal boundaries are well-demarcated in UHF  $T2^*$  contrast images clearly-demonstrating hippocampal sub-regions. In addition to the contrast, the iron concentration and the resting oxygen levels can change signal intensity in MR images, especially at high field (Schenck and Zimmerman, 2004). Thus using  $T2^*$  relaxometry with UHF MRI may be more sensitive in the detection of abnormalities compared to  $T2^*$ -weighted image obtained utilizing conventional scanners.

Based on prior studies suggesting hippocampal damage in patients with MDD, we hypothesized that  $T2^*$ -RT may be increased in the hippocampus of MDD patients. The aim of the current study was to assess the  $T2^*$ -RT of hippocampal sub-regions in MDD patients using a  $T2^*$  contrast images from UHF 7.0 T MRI. We have also investigated the relationship between the  $T2^*$ -RT of hippocampal sub-regions and the clinical characteristics of MDD.

## 2. Methods and materials

### 2.1. Subjects

Two psychiatrists recruited 16 MDD outpatients (5 men, 11 women,  $45.3 \pm 10.5$  years) from the Department of Psychiatry at Gil Medical Center, Incheon, Republic of Korea. Inclusion criteria were: 1) ages: 20–65 years, and 2) in a current major depressive episode (MDE), as determined by the Structured Clinical Interview for DSM-IV (SCID-IV). Exclusion criteria were: 1) a current or past significant medical illness, 2) current or lifetime Axis I psychiatric disorders other than MDD, as identified by the SCID-IV, 3) MDD with psychotic features or postpartum onset, 4) antisocial or borderline personality disorders based on DSM-IV criteria, and 5) contra-indications to MR scans. Illness duration was defined as the time elapsed from the onset of first MDE. The total time depressed was defined as the sum of the time under MDE.

Sixteen healthy control subjects (4 men, 12 women,  $41.9 \pm 13.0$  years) were recruited through advertisements. The same inclusion criteria were also applied to controls. This study protocol was approved by the Institutional Review Board at Gachon University Gil Medical Center. After a complete description of the study, written informed consent was obtained.

### 2.2. Image acquisition

Experiments were performed using the 7.0 T MRI (Magnetom, Siemens, Erlangen). We used a custom built multi-channel coil which consisted of single dual Helmholtz Tx coil (diameter: 300 mm;

length: 150 mm) with a quadrature field and eight single loop Rx coils (diameter: 220 mm). To cover the upper part of the head, the coil was made in a crown-like shape. For  $T2^*$  calculations, a dual echo flash sequence was used. The parameters used were as follows: TR = 1100 ms, TE = 13.6 and 38.8 ms, FA = 30°, pixel BW = 40 Hz, FOV = 200 × 137.6 mm, matrix size = 576 × 396, thickness = 1.5 mm, number of slices = 20, and NEX = 2. The TA was 10 min 35 s. To reduce scan time, a 3/4 partial k-space acquisition was also used in the phase encoding direction. To set the imaging slices perpendicular to the longest hippocampal axis and to find the anterior and posterior ends of the hippocampus, two low resolution scout scans (sagittal and coronal) were utilized. Imaging slices started from the anterior and posterior ends of the hippocampus. No subjects reported clinically significant side effects during 7.0 T MR scanning.

### 2.3. Image analysis

Pixel by pixel  $T2^*$ -RT was calculated for the hippocampus using first and second echo signals. The pixel maps were calculated for every voxel on the obtained image.

Pixel by pixel  $T2^*$  maps were, then, calculated using the equation given by,

$$T2^* = (TE2 - TE1) / \ln(SI1/SI2) \quad (1)$$

where, TE1 and TE2 are echo times of the first and second echos and SI1 and SI2 are the images obtained with the corresponding echo times, respectively.  $T2^*$ -RTs were calculated from double echo times, as  $T2$ -RTs from double echo times highly correlated with those from multiple echo times even in 1.5 T MRI (Duncan et al., 1996).

The 3D model of hippocampus was constructed from the same data in order to select the coronal slices for the region-of-interest (ROI) placements (Fig. 1). The total volume of both right and left hippocampus consisting of Cornu Ammonis (CA) 1–4, subiculum, and dentate gyrus were also determined using the 3D model. The longest axis of the hippocampal axis and anterior-posterior margin were found using two scout images (in coronal and sagittal). The slice location was set in the perpendicular plane to the longest axis, and the slices covered the anterior and posterior end by adjusting the gap between slices (Fig. 1). Generally, hippocampal sub-regions can be more clearly defined in the hippocampal body rather than in the head or tail. Therefore, the most anterior coronal slice where hippocampal body began to appear clearly was selected for the ROI placements.

$T2^*$ -RT for the ROIs in CA1~4 and subiculum of each side of hippocampus were calculated. As the dentate gyrus difficult to delineate from CA4 even at ultra-high-field (Duvernoy, 2005),  $T2^*$ -RT specifically for the dentate gyrus was not calculated. ROIs were placed manually on the  $T2^*$  images by an experienced investigator, who was blind to the clinical diagnosis or clinical status of the subjects. We selected only one ROI for each sub-regions, as multiple ROIs in a small sub-region could include pixels from other sub-regions. The ROIs containing 21 pixels were placed in each hippocampal sub-regions. The size of each ROI was 21 × 0.35 mm × 0.35 mm.

The positions of each ROI were determined using landmarks described in a previous study with modifications (Mueller et al., 2007)(Fig. 1). ROIs for CA1 were placed on the lateral most part of hippocampus in the selected coronal slice. Four lines were drawn to guide the ROI placements for CA2, CA3, and CA4; 1) a line along the longest axis of the hippocampus, 2) a line parallel to the longest axis on the superior most part of vestigial hippocampal sulcus (vestigial line), 3) a perpendicular line dividing the longest axis by two, and 4) an oblique line in a medial-superior direction with 45°

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