T2-weighted image hyperintensities in major depression: focus on the basal ganglia

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Abstract

A major focus of attention in structural brain-imaging research in major depression is the increased prevalence of T2-weighted image ‘hyperintensities’ (T2-WIH). Our aims in this study were to characterize the distribution and magnetic resonance imaging (MRI) presentation of brain hyperintensities in major depression patients compared to healthy control subjects and to explore the association between the presence of T2-WIH and measures of clinical and cognitive state. Thirty-seven patients suffering from major depression and 27 age- and sex-matched healthy controls underwent brain MRI and were evaluated by the Hamilton Rating Scale for Depression, the Mini Mental State Examination and the Haschinsky Ischaemia Index. T2-WIH (at least one) were found in 26 out of 37 major depression patients and 7 out of 27 controls \( (p=0.0001) \). The number of brain T2-WIH was significantly and positively correlated with age in depressed \( (p=0.001) \) but not in healthy subjects. Mean volume of T2-WIH was significantly greater \( (p=0.004) \) in depressed subjects. In the control group T2-WIH were exclusively located in the supratentorial hemispheral white matter while in the depressed group T2-WIH were also found in basal ganglia, temporal lobe, cerebellum and brainstem. More \( (52\% \text{ vs. } 20\%; p=0.018) \) T2-WIH were demonstrable on T1 in depressed subjects. Depressed patients with T2-WIH in basal ganglia were clearly the most severely depressed and cognitively impaired subjects, and may constitute a clinically distinct subgroup within major depression.

Introduction

Major depressive disorder (MDD) is a severe psychiatric disorder with a lifetime prevalence of approx. 10\%, recurrent periods of morbidity and a significant risk of suicide (Coryell et al., 1992; Klerman and Weissman, 1992). Despite intensive research efforts, a pathophysiological basis for MDD has not been established. Brain-imaging techniques have become extensively used in research on major depression, reporting aberrations in cerebral metabolism (Nobler et al., 1999; Videbech, 2000), blood flow (Bonne et al., 1996) and neuroanatomy (Grasby, 1999; Soares and Mann, 1997; Videbech, 1997). A recent focus of attention in structural brain-imaging research in MDD is the increased prevalence of T2-hyperintensities in the brains of subjects with MDD (Grasby, 1999; Kumar et al., 2000; Soares and Mann, 1997; Videbech, 1997).

The term ‘T2-weighted image hyperintensities’ (T2-WIH) refers to magnetic resonance imaging (MRI) brain findings appearing bright on T2 and proton density (PD) images, also labelled ‘unidentified bright objects (UBOs)’ as well as several additional denominations [white matter hyperintensity (WMH), periventricular hyperintensity (PVH), basal ganglia hyperintensity (BGH)]. Different methods for measuring the presence and evaluating the severity of T2-WIH have been developed (Krishnan, 1993; Scheltens et al., 1993) but an ideal rating scale does not yet exist (Scheltens et al., 1998). T2-WIH are found in healthy individuals, their frequency increasing with age. Thus, they are found in a minority of healthy individuals under 40 (Fazekas, 1989) and in a majority of individuals from the seventh decade onwards, reaching a prevalence of over 90\%
in some large population studies (de Leeuw et al., 2001; Longstreth et al., 1996). T2-WIH are more commonly present and more severe in women, although gender difference does not always reach significance (de Leeuw et al., 2001; Longstreth et al., 1996). High-intensity lesions are an integral part of the medical–vascular complex frequently observed in elderly clinical populations (Kumar et al., 2000). The histopathology of T2-WIH has not yet been definitively determined. In fact, T2-WIH as a radiological finding probably represent more than one aetiology (Boyko et al., 1994; Drayer, 1988). Numerous possible aetiologies such as small brain infarcts (Alexopoulos et al., 1997a; Awad, et al., 1986; Caplan and Schoene, 1978; Greenwald et al., 1998; Krishnan and McDonald, 1995; Roman, 1987; Starkstein and Robinson, 1989), increased water content in perivascular spaces (oedema) (Awad et al., 1986; Grafton et al., 1991; Lenze et al., 1999), loss of axons and myelin (demyelination) (Osborn, 1994b), astrocyte proliferation and deposition of brain toxic materials (Osborn, 1994b) have been suggested. Histopathological examinations of the hyperintense brain areas showed hyalinization of arterioles, arteriolar ectasia, enlarged perivascular spaces, gliosis and/or lacunar infarcts (Awad et al., 1986; Braffman et al., 1988; Chimowitz et al., 1992; George et al., 1986; Grafton et al., 1991; Janota et al., 1989; Kirkpatrick and Hayman, 1987; Lopez et al., 1992; Marshall et al., 1988; Tabaton et al., 1991). Histopathology of T2-WIH is also related to lesion intensity in T1-weighed images. T2-WIH that are also hypointense on T1 may be indicative of infarction, whereas lesions that are isointense on T1-weighted images are suggestive of ischaemic demyelination (Theobald et al., 2000).

Larger hyperintensities in central grey matter are considered representative of lacunar infarctions. The MRI characteristics of these infarcts are consistent with T2-WIH. These are small, deep cerebral infarcts in white matter and central grey-matter nuclei (Osborn, 1994a). These infarcts occur due to occlusion of penetrating vessels secondary to atheromata, lipohyalinosis, fibrinoid necrosis, and embolization (Braffman et al., 1988). Histologically the involved tissue is necrotic, surrounded by dense astrocytic gliosis (Osborn, 1994a). These lesions may remain clinically silent for prolonged periods of time. The putamina are the most common sites for lacunar infarctions (Fisher, 1982), possibly because they are situated at a relatively greater distance from the origin of the penetrating arteries responsible for their blood supply (Hughes, 1965). T2-WIH are characteristic of multiple sclerosis (MS) (Bakshi et al., 2000; Berg et al., 2000), where their presence, predominantly in the periventricular white matter, has been attributed to a demyelination processes (Osborn, 1994b).

T2-WIH appear to be more prevalent in the brain of MDD patients compared to healthy controls (Coffey et al., 1989, 1990; Hickie et al., 1997; Rabins et al., 1991; Videbech, 1997; Zubenko et al., 1990). T2-WIH are especially prevalent in elderly MDD patients (Coffey et al., 1990; Greenwald et al., 1998; Guze and Szuba, 1992; Hickie et al., 1997; Rabins et al., 1991; Zubenko et al., 1990). This increased occurrence of T2-WIH, in depressed subjects, in addition to the apparent relationship between vascular disease and high-intensity lesions on MR images, has led investigators to suggest that vascular mechanisms may be pivotally involved in late-life MDD (Alexopolous et al., 1997b; Krishnan et al., 1997). T2-WIH are particularly prevalent in MDD patients with an impaired cognitive state (Emmeier et al., 1997; Videbech, 1997), and total volume of T2-WIH was found to be negatively correlated with performance on neuropsychological testing in bipolar patients (Dupont et al., 1990, 1995b). Lesions localized frontally (Aylward et al., 1994; Dupont et al., 1995a; Krishnan, 1993) and in the basal ganglia (Coffey et al., 1989, 1990; Figiel et al., 1991; O’Brien et al., 1996), are most frequently associated with MDD. Widespread connectivity has been demonstrated between the prefrontal cortex and caudate nuclei from which nerve fibres travel back to the prefrontal cortex through other basal ganglia nuclei (Krishnan, 1993). Lesions in the basal ganglia were particularly prevalent in patients with late-onset depression (Figiel et al., 1991; Rao, 2000; Soares and Mann, 1997; Videbech, 1997). In addition, Simpson et al. (1998) reported that subcortical hyperintensities were increased in patients resistant to antidepressant monotherapy.

The aims of our study were to characterize the distribution and MRI presentation of brain hyperintensities in MDD patients compared to healthy control subjects. We further sought to explore the association between presence and absence of T2-WIH and measures of clinical and cognitive dysfunction.

Methods and materials

Subjects

Thirty-seven patients suffering from MDD (21 women) aged 55 ± 16.3 yr (mean ± S.D.; range 22–83 yr) and 27 healthy controls (14 women) aged 50 ± 11.2 yr (range 24–64 yr) participated in the study. The patients were recruited from our in-patient Department of Psychiatry (n = 17), from our Psychiatry Outpatient Clinic.
T1-weighted (TR = 510, TE = 10), axial and coronal spin–echo T2-weighted (TR = 3000, TE = 80) and axial and coronal spin–echo proton density (PD) weighted (TR = 3000, TE = 20). Images were acquired with a slice thickness of 5 mm and slice spacing of 1 mm. The field of view diameter used was 20 × 25 cm, the acquisition matrix was 180 × 256, within plane resolution was 1.1 × 1.0 mm. No 3D sequences were used. Previously published studies addressing T2-WIH in depression were mostly performed using 1.5 T MRI scanners. However we had a 2 T machine at our disposal. Although the signal-to-noise ratio at 2 T is approximately 30% higher than at 1.5 T, the two systems are essentially equivalent in their sensitivity and specificity for detecting T2-WIH or lesions on T1-weighted images.

Brain MRI was evaluated for T2-WIH by a senior radiologist blind to the subjects’ group affiliation (depressed/control). Only hyperintensities appearing in both T2-weighted and PD-weighted images (PDWI) were included. PD was added to avoid Virchow–Robin (VR) space artifacts. VR spaces are cerebrospinal fluid-filled extensions of subarachnoid spaces surrounding small vessels penetrating into the brain. VR spaces will appear hypointense on PDWI while real T2-WIH will appear hyperintense on PDWI. To avoid including artifacts and adding ‘noise’ to our sample, only T2-WIH 2 mm in diameter or larger were included. Although the setting of this minimal threshold was necessary to maintain the validity of our observations, given the importance of ischaemic smaller lesions in elderly depression as reported by Thomas et al. (2002), this constitutes a limitation of our study.

T2-WIH were sought in white matter near the ventricles (i.e. periventricular T2-WIH), in deep white matter of the different cerebral lobes, in the cerebellum and brainstem and in subcortical grey matter (i.e. basal ganglia). Confluent symmetric rim periventricular T2-WIH were not included. These hyperintensities are also called ‘Ependimitis granularis’ and are a normal finding commonly seen along the anterolateral aspects of the frontal horns.

T2-WIH were assessed for size, number and location. In addition we examined which T2-WIH were also hypointense on T1. T2-WIH volume was calculated using simple quantitative methods. Most T2-WIH of the size range found in the current study appear as spheres or ellipsoids. Their volume was calculated according to the formula for calculation of an ellipsoid: \( \frac{4}{3}\pi \times \text{width axis radius} \times \text{length axis radius} \times \text{height axis radius} \). A sphere is a particular case of an ellipsoid where all radii are equal. The volume of irregularly shaped T2-WIH was calculated by summing up the areas of each ROI in every slice in which it appears (5 mm in this study). The latter method is more accurate for large, irregularly shaped T2-WIH, but not for small, sphere- or ellipsoid-shaped T2-WIH (which are the most prevalent in this study and is how most small T2-WIH appear).

Statistical analyses

Demographic, clinical and MRI variable comparisons were made using \( \chi^2 \) analysis for categorical data and Student’s t test and Pearson’s product correlation for continuous variables with normal distribution. Analysis of variance (ANOVA) was used for comparison between more than two grouping variables.
Where statistically significant differences in particular variables existed between groups (e.g. age), such variables were included as covariates in an analysis of covariance (ANCOVA).

**Results**

T2-WIH (at least one) were found in 26 out of 37 MDD patients (68.4%) and 7 out of 27 controls (26.9%) ($\chi^2 = 12.49, p = 0.0001$). The average number of T2-WIH per person was correspondingly different between groups: 3.9±4.27 in the MDD patients and 0.5±1.37 in healthy controls ($t = 3.711, p = 0.004$). Since depressed subjects were (non-significantly) older than controls, we applied analysis of covariance (ANCOVA) with diagnosis as grouping factor and age as covariate. This analysis showed that the mean number of T2-WIH in the depressed group was 5.4±4.1 and in the control group 2.0±2.0 ($t = 2.1, p = 0.05$).

The location of T2-WIH also differed between patients and controls (Table 1). In the control group T2-WIH were exclusively located periventricularly and in supratentorial hemispherical deep white matter, apart from the temporal lobes. In the depressed group, while most T2-WIH were similarly located, T2-WIH were also found in basal ganglia (13 lesions) as well as in the temporal lobe (16 lesions), cerebellum (8 lesions) and brainstem (6 lesions). The mean volume of T2-WIH was also examined. In the depressed patients mean volume of T2-WIH was significantly greater than in controls ($277.08 \pm 878.4 \text{ mm}^3$ vs. $54.7 \pm 57 \text{ mm}^3$; $t = 2.91, p = 0.004$; Student’s $t$ test, unequal variance).

The number of periventricular, deep white matter and basal ganglia T2-WIH was similar between hemispheres in both groups. The relative number of frontal and parietal lobe T2-WIH was not higher in depressed patients. There was no significant pattern in volume distribution regarding both laterality and region in both groups. Volume of T2-WIH was similar across hemispheres and regions.

The designation T2-WIH refers to hyperintensities appearing on both T2 and PD. In the current study we additionally determined the number of T2-WIH that could be detected in T1-weighted images as hyperintensities. Within depressed subjects 72 out of the 138 T2-WIH (52.2%) were demonstrated on T1 while in controls only 3 out of the 15 (20%) T2-WIH appeared on T1 ($\chi^2 = 5.6, p = 0.02$). Among lesions in deep grey matter (basal ganglia) and deep white matter in the brainstem and cerebellum (regions in which lesions were found only in depressed subjects), an even higher percentage of T2-WIH were detected on T1-weighted images: 100% of lesions in basal ganglia; 87.5% of lesions in the cerebellum, and 83.3% of lesions in the brainstem. Prevalence of T1-detectable T2-WIH in the temporal lobe was similar to that of other hemispherical regions, although these lesions were present only in depressed subjects.

Subjects with brain T2-WIH were significantly older than those without lesions (Table 2). Within depressed subjects this age difference was a little larger and significant. Within control subjects this difference was smaller and non-significant. Accordingly, the number of brain T2-WIH was significantly and positively correlated with age in depressed ($p = 0.001$) but not in healthy subjects.

We then examined whether depressed subjects with T2-WIH differ in any clinical measures from subjects without these findings. Although at first glance (Table 3) it seemed that such a difference did exist for several measures, once we controlled for age all previously obtained significances dissipated. Given the association between T2-WIH in the basal ganglia and depression, particularly that of the onset of depression (Figiel et al., 1991; Rao, 2000; Soares and Mann, 1997; Videbech, 1997), we defined subjects with T2 lesions in the basal ganglia (7 patients, all depressed, with 13 basal ganglia lesions) as a separate group. These subjects had a significantly higher average number of T2-WIH than subjects with T2-WIH located elsewhere (9.9 vs. 3.8 per subject; $t = 4.26, p = 0.0003$). ANOVA between groups of depressed subjects without T2-WIH ($n = 11$), with T2-WIH located outside basal...
ganglia \( (n = 19) \) and with T2-WIH in basal ganglia was significant for severity of depression \( [F(2,35) = 10.52, p = 0.0003] \) and for gravity of cognitive impairment \( [F(2,35) = 5.73, p = 0.007] \). These differences remained significant after covarying for age (Table 3). Furthermore, in subjects with no T2-WIH and subjects with T2-WIH located outside the basal ganglia, age was highly correlated with age of first depressive episode, cognitive impairment and Haschinsky Ischaemia Index \( (r = 0.72, p = 0.0005; r = -0.45, p = 0.02; r = 0.53, p = 0.003, \) respectively), whereas no significant correlations were observed between age and any of these measures in subjects with T2-WIH in basal ganglia.

### Discussion

Findings from the present study replicate and extend those of previous studies (Coffey et al., 1989, 1990; Videbech, 1997). We have shown more and larger T2-WIH in the brains of depressed patients than in healthy subjects (Kumar et al., 2000; O’Brien et al., 1996). Subjects with T2-WIH were significantly older than subjects without lesions, irrespective of diagnosis (Grasby, 1999). Likewise, a positive correlation was observed between age and number of T2-WIH in all subjects. However, once these analyses were applied separately to depressed and non-depressed subjects, results remained statistically significant only for depressed subjects, although results for healthy controls were in the same direction, at trend level significance. Previous studies (de Leeuw et al., 2001) frequently report statistically significant associations between age and number of T2-WIH in healthy subjects. However, our healthy control sample size was rather small (27 subjects), compared to samples such as the one studied by de Leeuw et al. (2001), comprising 1077 subjects. In addition, we did not record T2-WIH with a diameter of less than 2 mm, that may be prevalent in healthy, relatively young control subjects such as those who took part in our study. These differences between the current and previous studies may account for our results not reaching the expected significance levels.

It has been suggested that hyperintensities appear predominantly in depressed patients in whom the disease begins at an older age (‘late onset depression’) (Hickie et al., 1997; Kumar et al., 2000). However, this concept has been challenged (Ebmeier et al., 1997; Greenwald et al., 1996) and our findings do not support this contention. Although age of first depressive episode was much higher in depressed subjects with T2-WIH, once current age was introduced as a covariate the difference became non-significant. This
indicates an association between patients’ current age and their age at first depressive episode. Indeed, a highly significant correlation was observed between these measures (age and their age at first depressive episode) in all depressed subjects, except for subjects with T2-WIH in basal ganglia, where these measures were completely non-correlated.

Within depressed subjects with T2-WIH we found, as in other studies (Barber et al., 1999; Dupont et al., 1990, 1995a; Ebmeier et al., 1997; Videbech, 1997), that severity of depression (as measured by the HAMD) was positively correlated with the number of T2-WIH. However, once subjects with basal ganglia hyperintensities were removed from the analysis, these correlations were annulled, and severity of depression in the remaining subjects with T2-WIH was exactly the same as in subjects without these lesions (Table 3). Cognitive function was also particularly impaired in depressed subjects with basal ganglia T2-WIH. Consequently, depressed patients with basal ganglia T2-WIH may constitute a phenomenologically and pathophysiologically different subgroup within this heterogeneous disorder.

Brain-imaging studies implicate basal ganglia and other subcortical regions in the regulation of mood and other higher mental functions (Drevets, 2000; Kiosses et al., 2000). Depression is more common and more severe in subjects with corticobasal degeneration than in all other neurological disorders (Cummings and Litan, 2000). Depression in subjects with Parkinson’s and Huntington’s diseases is also accompanied by reduced metabolism and structural lesions in basal ganglia (Robinson et al., 1999). Patients with vascular dementia show a higher basal ganglia lesion score than those with other types of dementia (Barber et al., 1999). Such findings led to the development of a pathophysiological model for depression based on frontotemporal circuit abnormalities (Austin and Mitchell, 1995; Drevets, 2000; Greenwald et al., 1998; Hickie et al., 1997; Krishnan, 1993; O’Brien et al., 1996; Robinson et al., 1999; Soares and Mann, 1997; Starkstein and Robinson, 1989; Swaab et al., 2000). Indeed, most (Husain et al., 1991; Krishnan et al., 1992; Parashos et al., 1998; Rabin et al., 1991), but not all (Lenze and Sheline, 1996) studies have shown basal ganglia volume reduction in depressed subjects. Moreover, positron emission tomography (PET) studies demonstrated lower cerebral blood flow and/or metabolism in caudate nuclei and the basal ganglia in MDD (Baxter et al., 1985; Buchsbaum et al., 1986; Drevets et al., 1992) as well as uncoupling of the glucose metabolism—cerebral blood flow association in the basal ganglia of depressed subjects (Conca et al., 2000).

Depression and apathy characterize patients with T2-WIH lesions in the basal ganglia (Drevets, 2000; Mayberg, 1994; Mendez et al., 1989). These structures are deeply involved in cognitive processing (Austin and Mitchell, 1995). Psychomotor slowing in patients with depression was associated with reduced regional cerebral blood flow responsivity in the basal ganglia (Hickie et al., 1999) and also with dopamine hypofunction in the caudate nucleus (Martinot et al., 2001). In our study subjects with basal ganglia T2-WIH had particularly high scores on two HAMD items: depressed mood (all 7 subjects had a maximum score) and motor retardation (all but 1 of the 7 subjects had a maximum score on this item). These findings are compatible with the above-mentioned manifestations of basal ganglia involvement in depression as well as with the role of basal ganglia in the regulation of movement. Likewise, the significantly lower cognitive performance of this subgroup (Table 3) is in line with the observations reported above. In light of these radiological, cognitive and motor impairments, it would be interesting to follow this subgroup longitudinally, to find out whether other neurodegenerative diseases of the basal ganglia (i.e. Parkinson’s disease) ensue.

T2-WIH located in the basal ganglia may be particularly characteristic of elderly patients with MDD (Coffey et al., 1989, 1990; Figiel et al., 1991; O’Brien et al., 1996). In our study depressed subjects with lesions in the basal ganglia were indeed older than subjects with lesions located elsewhere (Table 1), but this difference did not reach statistical significance, possibly due to the small number of subjects with basal ganglia T2-WIH. Interestingly, notwithstanding the small number of subjects with basal ganglia T2-WIH, a significant inverse correlation was found for subjects in this subgroup between the number of T2-WIH and age at first depressive episode ($r = -0.78$, $p = 0.03$). The number of T2-WIH in this subgroup was unrelated to the subjects’ current age ($r = -0.01$, $p = 0.98$), lending additional credibility to this finding.

In our study three depressed patients and no controls had T2-WIH in the cerebellum. All three also had lesions in basal ganglia. The cerebellum has extensive neuroanatomical links to the limbic system (thalamus, hypothalamus, hippocampus, etc.). PET studies have indicated that the functions of the cerebellum are not limited to motor applications, but that this structure is also involved in linguistic and cognitive functions (Dolan et al., 1992; Videbech, 1997). In a MRI study Shah et al. (1992) found significantly smaller brainstem, cerebellar vermis and medulla in MDD patients compared to controls.
Presence of T2-WIH in patients with major depression is considered indicative of cerebrovascular compromise (Alexopoulos et al., 1997a; Drevets, 2000; Grasby, 1999; Krishnan and McDonald, 1995; Rao, 2000; Robinson et al., 1999; Starkstein and Robinson, 1989). However, increased prevalence of T2-WIH in depression is not fully explained by the accumulation of known cardiovascular risk factors (Altshuler et al., 1995; Coffey et al., 1989; Krishnan, 1993; O’Brien et al., 1996). A possible mechanism responsible for the high prevalence of lacunar infarcts in depressed patients could be increased platelet activation (Lenze et al., 1999). Depressed subjects have been shown to have greater baseline platelet activation and responsiveness than healthy controls (Musselman et al., 1996). Serotonin (5-HT) secretion by platelets produces aggregation and there is substantial literature indicating disturbed 5-HT function in platelets as well as the central nervous system of depressed subjects (Owens and Nemeroff, 1994). Increases in platelet 5-HT-2A receptors have been demonstrated in depression (Biegon et al., 1990). Depressed patients may thus be more susceptible to atherosclerosis, thrombosis and vasoconstriction.

Significantly more T2-WIH (52.2%) were demonstrated as hypointense regions on T1-weighted images in depressed patients than in controls (20%). Among lesions situated in deep grey matter, brainstem and cerebellum, found only in depressed subjects, an even higher percentage (80–100%) of T2-WIH were hypointense on T1-weighted images. It has been suggested that T1 visibility is dependent upon lesion size. In our sample, T2-WIH were significantly larger in depressed patients than in controls. This may explain the greater prevalence of T1-visible lesions in depressed patients. However, we did not find a difference in T2-WIH between the sizes of T1-visible and T1-invisible lesions, among depressed patients and normal controls alike. This suggests that there should be an additional reason to account for the increased prevalence in T1 visibility of T2-WIH in depressed patients. In cerebral microvasculopathy, T2-WIH that are also hypointense on T1-weighted images are indicative of infarction, whereas T2-WIH that are isointense on T1-weighted images are suggestive of ischaemic demyelination (Theobald et al., 2000). Hypointense areas on T1 have been called ‘black holes’. Histopathologically, they have been associated with severe brain tissue destruction, including axonal loss (van Walderveen et al., 1998). These black holes have also been shown to correlate better than lesions appearing on T2 alone with the degree of disability and in patients suffering from MS (Barkhof et al., 1998).

T2-WIH are characteristic of MS, where their presence, predominantly in deep white matter, has been attributed to demyelination processes (Osborn, 1994b). MS is also characterized by a high prevalence of affective, mainly depressive, disorders (Bakshi et al., 2000; Berg et al., 2000). Particular T2-WIH lesion load was observed in temporal lobes of subjects with MS and major depression, which significantly and positively correlated with measures of depression severity (Berg et al., 2000). In our study temporal lobe lesions were observed only in depressed subjects. Are T2-WIH in MS specifically associated with depression? In light of the above, it is conceivable that the presence of depression in MS may be related to the proportion of T2-WIH that are detectable as hypointense lesions in T1-weighted images. This contention may be examined in future studies.

In conclusion, we have shown that T2-WIH in depressed subjects are larger, differently located, more often detectable on T1-weighted images and more closely associated with age than T2-WIH in healthy subjects. The presence of T2-WIH in the basal ganglia of depressed subjects may delineate patients with a more severe manifestation of the disorder or a distinct subtype.

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