Longitudinal brain volume changes in major depressive disorder

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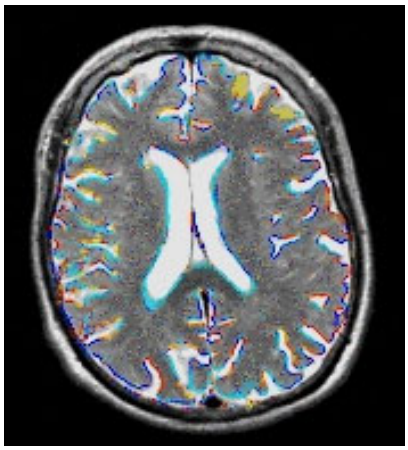
SYNOPSIS: Hippocampal volume loss,[1] focal histological changes[2] and abnormal cellular signalling[3] in major depressive disorder suggest neurodegenerative or neurotoxic processes. To probe for acquired brain pathology, we performed longitudinal assessment (interval 39–93 months) of global brain volume changes in 19 subjects with MDD and no further major comorbidity. Postprocessing was done using the FSL/SIENA software[4]. Annual rates of brain volume loss estimated from T2 (-0.55%) were comparable with T1 (-0.51%). This rate represents the upper range of reported rates of healthy subjects and is considerably smaller than in multiple sclerosis and Alzheimer's disease ruling out a major global neurodegenerative process.

INTRODUCTION: Major depressive disorder (MDD) is one of the leading causes of disability worldwide, yet the underlying neurobiological correlates are still poorly understood. In recent years, neuropathological findings in subregions of the frontal lobe[3] have been reported, and some brain imaging studies revealed hippocampal as well as extrahippocampal volume loss.[1,5] Cross-sectional studies further suggested enhanced volume losses in longer-standing disease suggesting an acquired brain pathology.[5] Hippocampal volume losses in particular were posited to be causally related to elevated stress hormones.[5] Hyperdrive of the hypothalamo-pituitary-adrenal axis is a consistent biological finding in major depressive episodes.[6,7] Elevated glucocorticoids were shown neurotoxic to the dentate gyrus in animal studies,[8] but may cause widespread neurotoxic changes due to the ubiquitous distribution of glucocorticoid receptors within the brain. To investigate whether the reported brain pathology in MDD is indeed acquired over the course of major depression, longitudinal studies are mandatory and feasible due to the noninvasive nature of MRI and recent advances in postprocessing techniques.[4,9-12] Therefore, in a retrospective design, we identified patients with MDD who underwent repeat MR examination for clinical workup (total n>50, interval > 2 years) and report the annual rate of global brain volume changes as estimated by a semiautomated method based on the detection of shifting edge-points[4] on a preliminary subset of 19 patients with a minimal time interval of 39 months.

MATERIAL AND METHODS: 19 patients (age 47.4±13.8 yrs, range 26–74, 10 men, 9 women) with major depression disorder (MDD) according to ICD-10 had undergone repeat MRI after ≥ 3.5 years (62.1±15.4 months, range 39–93 months). Images available were either pairs of high resolution T1 weighted images (T1WI, 11 of 19 subjects; 124 contiguous sagittal slices, resolution 0.9×0.9×[1.0–1.4] mm^3) or pairs of T2-weighted images (T2WI, 17 of 19 subjects; 20–24 axial slices, resolution 0.9×0.9×5 mm^3, 1 mm gap; eventual omission of 1-2 superior frontoparietal slices). In 9 cases, pairs of both modalities were processed for comparison. For estimation of the percentage brain volume change between the two time points the SIENA and brain extraction tool out of the FSL software package were used (Fig.). Before image registration and edge point detection, brain extraction was optimized first by adjusting the BET input parameters to the individual case (T1 only) and, secondly, by manual correction of the brain-only masks. Both steps had previously been shown to reduce false detection of brain-CSF-edge-points, on which further SIENA steps strongly rely. Annual rates of PBVC were estimated for all available image pairs and are reported descriptively. Pearson's correlations coefficient were calculated between the two imaging modalities in 9 cases and between automatically and manually produced brain-only masks (T1 only).



RESULTS: Annual rates of percentage brain volume change were -0.55% (SD 0.45%, range [-1.57; 0.21]) on the basis of T2-weighted images (n=17) and -0.51% (SD 0.57%, range [-1.22; 0.07]) on the basis of T1-weighted images (n=11). Results of both modalities were highly correlated (n=9; r=0.93). The automated and manually refined BET technique produced highly correlated results for pairs of T1WI (r=0.98). Qualitative assessment of intermediate steps showed that in 90% of all automatically extracted cases false edge points with potential prolongation into end results were present, especially in areas of erroneously included dural tissue.

DISCUSSION & CONCLUSIONS: In this first longitudinal study on global brain atrophy in patients with MDD we estimated an annual atrophy rate of just above 0.5% which ranges at the upper end of rates reported for healthy adult subjects of between 0.24% and 0.5%. (13-15) Though comparisons with longitudinal studies are hampered by variable observation intervals, some positioning of this rate in relation to more commonly studied multiple sclerosis (annual rates of about –1.5%, [16]) and Alzheimer's disease (annual rates > 2% [15]) seems warranted. Thus, the observed atrophy rate dose not corroborate gross global atrophic changes suggestive of enhanced neurodegeneration in MDD, but still needs to be replicated in a larger sample.

LITERATURE: [1] Sheline et al. Proc. Natl. Acad. Sci. USA 1996 [2] Rajkowska et al, Biol Psychiatry. 1999 [3] Manji et al. Biol Psychiatry 2000, [4] Smith et al. Neuroimage 2002, [5] Sheline. Biol Psychiatry 2000, [6] Parker. Horm Behav 2003 [7] Holsboer. J Affect Disord 2001 [8] Sapolsky et al. Endocrine Reviews 2000 [9] Smith et al. JCAT 2001 [10] Fox et al. JMRI 1997 [11] Lemieux et al. Medical Image Analysis 1998 [12] Freeborough et al. IEEE Trans Med Imaging 1997 [13] Resnick et al. J Neurosci 2003 [14] Wang et al. MRM 2002, [15] Chan et al., Neurology 2001[16] Ge et al. Radiology 2000.