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Research report

Major depressive episodes over the course of 7 years and hippocampal subfield volumes at 7 tesla MRI: The PREDICT-MR study

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ABSTRACT

Introduction: Smaller hippocampal volumes have been associated with major depressive disorder (MDD). The hippocampus consists of several subfields that may be differentially related to MDD. We investigated the association of occurrence of major depressive episodes (MDEs), assessed five times over seven years, with hippocampal subfield and entorhinal cortex volumes at 7 tesla MRI.

Methods: In this prospective study of randomly selected general practice attendees, MDEs according to DSM-IV-R criteria were assessed at baseline and after 6, 12, 39 and 84 months follow-up. At the last follow-up, a T2 (0.7 mm^3) 7 tesla MRI scan was obtained in 47 participants (60 ± 10 years). The subiculum, cornu ammonis (CA) 1 to 3, dentate gyrus&CA4 and entorhinal cortex volumes were manually segmented according a published protocol.

Results: Of the 47 participants, 13 had one MDE and 5 had multiple MDEs. ANCOVAs, adjusted for age, sex, education and intracranial volume, revealed no significant differences in hippocampal subfield or entorhinal cortex volumes between participants with and without an MDE in the preceding 84 months. Multiple episodes were associated with smaller subiculum volumes (B = −0.03 mL/episode; 95% CI −0.06; −0.003), but not with the other hippocampal subfield volumes, entorhinal cortex, or total hippocampal volume.

Limitations: A limitation of this study is the small sample size which makes replication necessary.

Conclusions: In this exploratory study, we found that an increasing number of major depressive episodes was associated with smaller subiculum volumes in middle-aged and older persons, but not with smaller volumes in other hippocampal subfields or the entorhinal cortex.

1. Introduction

Smaller hippocampal volumes are a common, but not a universal, finding in major depressive disorder (MDD) (Arnone et al., 2012; Du et al., 2012; McKinnon et al., 2009). The hippocampal formation is of importance in MDD for several reasons, as described in a recent review (MacQueen and Frodl 2011): 1) stressful life events are associated with the onset of MDD, but are also thought to be elicited by MDD (Kessler, 1997), and stress is also associated with smaller hippocampal volumes (Sapolsky et al., 1990; Sousa et al., 1999); 2) memory impairments that are dependent on hippocampal functioning, are often observed in MDD (Zakzanis et al., 1998); and 3) the hippocampal formation is part of a network that is often found to be disregulated in MDD (Frodl et al., 2008, 2010).

The hippocampal formation is not a homogeneous structure but consists of anatomically and functionally distinct subfields: the subiculum, cornu ammonis (CA) sections 1–4 and the dentate gyrus (Duvernoy et al., 2005). Tightly connected to the hippocampal formation lies the entorhinal cortex (Duvernoy et al., 2005). Because of their anatomical and functional differences, subfields of the hippocampal formation and the entorhinal cortex are likely to be differentially associated to aging and disease (Small et al., 2011). For instance, a recent review indicated that in MDD the subiculum is mainly reduced (Small et al., 2011), potentially because, according to animal studies, the subiculum has more cortisol binding sites (Reul and de Kloet, 1985) and receives a stronger serotonergic innervation from the raphe nucleus (Muller and Jacobs, 2010) compared to other subfields. Also the subiculum is connected to the basolateral nuclear group of the amygdala (Aggleton, 2000), which is also affected in MDD (Sheline et al., 1998). On the other hand post-mortem studies (Boldrini et al.,

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2009; Stockmeier et al., 2004) and stress research in animals (Sapolsky et al., 1990; Sousa et al., 1999) point to the involvement of CA3 and the dentate gyrus in MDD. However, it should be noted that these studies often did not include the subiculum in their analyses. Investigating whether hippocampal subfield volumes are differentially associated to MDD may provide insight in the neural substrate of MDD.

In recent years, the association between MDD and hippocampal subfield volumes has received increasing attention in MRI studies. The majority of these studies performed surface mapping (Ballmaier et al., 2008; Bearden et al., 2009; Cole et al., 2010; Gold et al., 2014; Posener et al., 2003; Sexton et al., 2012; Tae et al., 2011), a method in which inward deformations of the outer surface of the hippocampal formation are measured and reductions in subfield volumes are derived from these local deformations. Advantages of this method are that it can be performed at standard field strength (1.5 and 3 tesla (T) MRI) and that it is very sensitive to small changes. A limitation of this method is that the dentate gyrus, located within the hippocampal formation, cannot be assessed. Several of these studies reported inward deformations of the subiculum in patients with MDD compared to controls (Ballmaier et al., 2008; Bearden et al., 2009; Cole et al., 2010; Posener et al., 2003; Tae et al., 2011), but surface reductions in other subfields have also been reported (Ballmaier et al., 2008; Bearden et al., 2009; Cole et al., 2010; Tae et al., 2011). Fewer studies measured subfield volumes and/or entorhinal cortex volume (Gerritsen et al., 2011; Gold et al., 2010; Huang et al., 2013; Kook et al., 2012) and these studies reported inconsistent findings. These studies assessed volumes of hippocampal subfields at field strengths ranging from 1.5 to 4.7 T. Recent advances in ultra-high field imaging (e.g. 7 T MRI) have made it possible to visualize the hippocampal formation in great detail in three dimensions, with resolution and signal-to-noise ratio that is superior to lower field strength scanners. Recently, we developed a reliable protocol for the assessment of hippocampal subfield and entorhinal cortex volumes covering most of the longitudinal axis of the hippocampal formation using isotropic 0.7 mm 7 T MRI data (Wisse et al., 2012). In this study we will use this newly developed protocol to investigate the association of occurrence of major depressive episodes (MDEs), assessed five times over seven years, with hippocampal subfield and entorhinal cortex volumes at high field 7 T MRI.

2. Methods

2.1. Participants and design

Participants were included from the PREDICT-MR study, an ancillary study to the PREDICT-NL study (Stegenga et al., 2012a), with the aim to investigate risk factors and consequences of brain changes on MRI in general practice attendees with and without depression. The PREDICT-NL study is the Dutch part of the PredictD study (King et al., 2008), a multicenter prospective cohort study from which a multifactor algorithm was developed to predict risk of onset of MDD in primary care patients in six European countries, including the Netherlands and Chile (Stegenga et al., 2012b). A detailed description of the PredictD and PREDICT-NL cohorts has been published previously (King et al., 2006, 2008; Stegenga et al., 2012b; Stegenga et al., 2013). In brief, in 2003, consecutive adult primary care patients aged 18 years or older were asked to participate while in the waiting room, irrespective of their reasons for consulting their general practitioner. Patients were followed-up after 6 and 12 months. In the Dutch part of PredictD an additional follow-up was conducted after 39 months (Stegenga et al., 2013; Wisse et al., 2012).

Between June 2010 and January 2012 after 84 months, as part of the PREDICT-MR study, eligible participants were invited to the University Medical Center of Utrecht for a 1.5 T and 7 T brain MRI, a diagnostic depression interview, neuropsychological testing, blood sampling, questionnaires and a clinical assessment. Participants were considered eligible for PREDICT-MR if they were not demented or severely ill.

The PredictD, PREDICT-NL, and PREDICT-MR studies were approved by the ethical committee of our institution and all participants gave written informed consent.

2.2. Diagnosis of MDEs

The diagnosis of an MDE was made according to DSM-IV criteria (American Psychiatric Association, 1994; World Health Organization, 1997). A detailed description of the procedures has been published elsewhere (Stegenga et al., 2012a). In brief, trained researchers interviewed all participants using the depression section of the Composite International Diagnostic Interview (CIDI). At baseline, and at the 6- and 12-month follow-up, the diagnosis of an MDE was assessed covering the preceding 6 months. At the 39-month and the 84-month follow-up, diagnosis of an MDE was assessed covering the time interval between the previous and current assessment.

Depressive symptom severity was measured with the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001).

2.3. Image protocol and post-processing steps

Participants were scanned on a 1.5 T MRI whole body scanner (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). For the present study the 1.5 T MRI was used to measure intracranial volume (ICV) with a $4.00 \times 0.90 \times 1.03$ mm dual echo (proton density- and T2 weighted) Turbo Spin Echo (TSE) with a repetition time/echo times 2200/11/100 ms; a flip angle of 90°; a turbo factor 12; an acquisition matrix size of $38 \times 256 \times 168$ and a scan duration of 3:11 min.

The following sequence for hippocampal subfield segmentation was acquired on a 7 T MR whole body scanner (Philips Healthcare, Cleveland, OH, USA) with volume transmit and 16 channel receive coil (Nova Medical, Cleveland, OH USA) (participants included in the study later than May 2011 were scanned with a volume transmit and 32-channel receive head coil (Nova Medical)): a high spatial resolution 0.7 mm (isotropic) three dimensional (3D) T2 weighted TSE (whole brain) with a tissue specific refocusing pulse angle sweep to reduce specific absorption rate (SAR) and to optimize image contrast (Busse et al., 2006); a repetition time of 3158 ms; an echo time of 301 ms (with a contrast equivalent to a TE of 58 ms for brain tissue in spin-echo sequences with full refocusing angles); a flip angle of 120° (to partly compensate inhomogeneity in the RF field); a TSE factor of 182; a field of view of $250 \times 250 \times 190$ mm^3 (FH × AP × RL); an acquisition matrix size of $356 \times 357 \times 272$; the application of 2D SENSE with acceleration factors of 2.0×2.8 (AP × RL) and an imaging duration of 10:15 min per acquisition. The images were interpolated by zero-filling during reconstruction to a nominal spatial resolution of $0.35 \times 0.35 \times 0.35$ mm^3. For outlining of the hippocampal formation, multiplanar reformatting was performed to generate images that were angulated perpendicular to the longitudinal axis, separately for the left and right hippocampal formation with an in-plane resolution of 0.35×0.35 mm^2 and a slice thickness of 0.70 mm.

2.4. Assessment of brain volumes

All segmentations were performed using in-house developed software based on MeVisLab (Kuijf, 2013) (MeVis Medical Solutions AG, Bremen, Germany (Ritter et al., 2011)).

One rater (LEMW), blinded to clinical information, manually segmented ICV acquired at 1.5 T MRI on transversal slices. Every other slice was segmented. The remaining slices were interpolated