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The associations of depression and hypertension with brain volumes: Independent or interactive?

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ABSTRACT

Independent studies on major depressive disorder (MDD) and hypertension, suggest overlapping abnormalities in brain regions associated with emotional and autonomic processing. However, the unique and interactive effects of MDD and hypertension have never been studied in a single sample. Brain volume in these areas may be an explanatory link in the comorbidity between MDD and hypertension. Voxel-based morphometry was used to test for main effects of MDD ($N = 152$) and hypertension ($N = 82$) and their interactions on gray and white matter volumes. Voxel-wise results are reported at $p < .05$ FWE corrected for the spatial extent of the whole brain and a-priori regions of interest (ROIs: hippocampus, anterior cingulate cortex (ACC) and inferior frontal gyrus (IFG)). In addition, analyses on the extracted total volumes of our ROIs were performed. Interactive effects in the mid-cingulate cortex (MCC) ($p_{FWE} = .01$), cerebellum ($p_{FWE} = .01$) and in the ACC total ROI volume ($p = .02$) were found. MDD in the presence, but not in the absence of hypertension was associated with lower volumes in the ACC and MCC, and with a trend towards larger gray matter volume in the cerebellum. No associations with white matter volumes were observed. Results suggest that the combination of MDD and hypertension has a unique effect on brain volumes in areas implicated in the regulation of emotional and autonomic functions. Brain volume in these regulatory areas may be an explanatory link in the comorbidity between hypertension and MDD.

1. Introduction

The incidence of hypertension is increased in depressed patients compared to the general population (Meng et al., 2012). Moreover, both hypertension and depression increase the risk of incident cardiovascular disease (CVD) and accelerate the progression of CVD (Nemeroff and Goldschmidt-Clermont, 2012; Thayer and Lane, 2007). Multiple biological factors have been proposed to play a role in the association between depression and vascular related diseases (de Jonge et al., 2010), including inflammation, hypothalamus–pituitary–adrenal (HPA) axis dysregulation, and autonomic dysfunction, reflected by decreased heart rate variability. Although both depression and hypertension have independently been associated with abnormalities in brain structure and function, regional brain morphology as a shared biological link has rarely been studied.

Depression has been associated with gray matter (GM) volume loss predominantly in prefrontal-limbic networks, such as the anterior cingulate cortex (ACC), hippocampus, and inferior frontal gyrus (IFG) (Arnone et al., 2012; Bora et al., 2012; Du et al., 2012; Lai, 2013), which have been implicated in processing of emotional information (Groenewold et al., 2013). It is not fully clear whether alterations in regional brain volumes are a cause or consequence of depression, or both. Conceivably, pre-existing abnormalities in brain regions involved in emotion processing may render individuals vulnerable to depression. Alternatively, excessive stress during depressive episodes could have damaging effects on the brain. The association between white matter (WM) volumes and depression has been studied less extensively and has resulted in inconsistent findings (Abe et al., 2010; Kim et al., 2008; Steingard et al., 2002).

Like depression, hypertension is also an established risk factor for brain abnormalities such as WM lesions and decreased GM volumes in prefrontal-limbic areas (Beauchet et al., 2013; Gianaros et al., 2006;

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Jennings et al., 2012; Jennings and Zanstra, 2009; Maillard et al., 2012; Raz et al., 2003). In addition to the damaging effects of hypertension on the brain, it has been proposed that alterations in regional brain volume may predispose individuals to develop hypertension and cardiovascular disease, due to reduced regulatory control on blood pressure and heart rate during stressful situations (Jennings and Zanstra, 2009). According to this theory, subclinical hypertension would be associated with similar alterations in brain structure as found in clinical hypertension and CVD. Of interest, GM abnormalities in persons with hypertension are reported in structures that correspond to the 'emotional' areas implicated in depression, i.e. in prefrontal-limbic areas such as the prefrontal cortex, the ACC, and the hippocampus (Beauchet et al., 2013; Gianaros et al., 2006; Gilbert et al., 2010; Jennings and Zanstra, 2009; Maillard et al., 2012; Raz et al., 2003; Woo et al., 2009). In addition to emotion processing, these regions have also been found to play a role in regulating autonomic functions, such as heart rate and blood pressure (Critchley et al., 2011; Gasquoine, 2013; Gianaros et al., 2008; Parvizi et al., 2013; Williamson et al., 2006).

There may be several explanations for this overlap in brain abnormalities, such as a shared vulnerability for depression and hypertension, in which the same brain regions could be involved in multiple (i.e. both emotional and cardiovascular) processes. In addition, stress is a shared risk factor for the development of high blood pressure, CVD, and depression, and could also potentially impact brain volumes (Baune et al., 2012; Brotman et al., 2007; Grippo and Johnson, 2002; Harrison et al., 2013). Furthermore, it has been suggested that depression in the absence and presence of cardiovascular and metabolic conditions has distinctive subtypes, in terms of genetic predisposition (Kendler et al., 2009), time of onset (Alexopoulos et al., 1997), and symptomatology (Ormel and de Jonge, 2011). Possibly, these subtypes may be associated with distinctive brain morphology. Alternatively, the vascular depression hypothesis posits that brain structural abnormalities, such as WM lesions, as a result of vascular pathology may give rise to depressive symptoms (Alexopoulos et al., 1997; Krishnan et al., 2004; Thomas et al., 2002).

Despite the suggested overlap of brain abnormalities in depression and hypertension, volumetric brain differences associated with hypertension and depression have never been studied simultaneously. The current study investigated whether hypertension and depression share regional volumetric alterations in a whole brain voxel-wise comparison, and in specific regions of interest (ROIs): the hippocampus, inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC). The comorbidity of MDD and hypertension has never been taken into account in previous MRI research. As comorbid depression is associated with accelerated CVD progression (Nemeroff and Goldschmidt-Clermont, 2012), comorbid depression and hypertension may have more advanced vascular pathology, potentially leading to more pronounced volumetric brain alterations. Alternatively, comorbid depression and hypertension may be a vulnerable subgroup characterized by distinctive brain morphology. Therefore, the effects of hypertension and MDD may not be independent, but rather interactive.

2. Materials and methods

2.1. Participants

For this study we used data from the Netherlands Study of Depression and Anxiety (NESDA), a multicenter longitudinal cohort study. This study was approved by the ethical review board of each participating center and all of the participants signed informed consent before inclusion. The design has been described in detail elsewhere (Penninx et al., 2008). Out of 2981 NESDA respondents, 301 native Dutch-speaking participants aged between 18–57 years were asked to participate in the NESDA neuroimaging study if they met the following inclusion criteria: the DSM-IV criteria for a diagnosis of MDD and/or anxiety disorder (panic disorder, social anxiety disorder, generalized anxiety disorder) in the past 6 months, or no life-time DSM-IV diagnosis (except for life-time alcohol and/or drug dependency or abuse) (control group).

The exclusion criteria were: 1) the presence of axis-I lifetime disorders other than MDD or anxiety disorder; 2) use of psychotropic medication other than SSRIs or infrequent benzodiazepine use (i.e. equivalent to 2 × 10 mg oxazepam; 3 times a week, or use within 48 h prior to scanning); 3) presence of major internal and/or neurological disorders (e.g. type 1 diabetes, CVA/TIA); 4) systolic blood pressure >180 mm Hg and/or diastolic blood pressure > 120 mm Hg (because this can affect the brain's hemodynamics and thereby potentially confound functional MRI measurements, which was also part of the NESDA neuroimaging scan-protocol); 5) dependency or recent abuse (past year) of alcohol and/or drugs; 6) use of beta-blockers that may affect the brain's hemodynamics (Carvedilol, Oxprenolol, Pindolol, Bisoprolol, and Nebivolol); 7) general MRI contra-indications.

In total, 301 participants underwent MRI in one of three participating centers, i.e. Leiden University Medical Center (LUMC), Academic Medical Center Amsterdam (AMC) and University Medical Center Groningen (UMCG). Data from patients with CVD (self-reported diagnosis of coronary disease, cardiac arrhythmia, angina, heart failure, or myocardial infarction) was excluded ($N = 6$), because in this study we specifically examined hypertension. In addition, data from 10 participants was excluded because of poor image quality. Therefore the final sample consisted of 285 participants.

2.2. Hypertension

To assess hypertension, systolic and diastolic blood pressure was measured during supine rest on the right arm, using an OMRON M4 IntelliSense digital blood pressure monitor (HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois, USA). The participants were classified as hypertensive when one of the following conditions was met: 1) they reported to have hypertension or to receive medication for hypertension, or 2) when the average of two consecutive baseline measures (at intervals of at least 1 min) for blood pressure exceeded a systolic value of 140 mm Hg, or 3) when blood pressure exceeded a diastolic value of 90 mm Hg, which are commonly used thresholds for hypertension (Pickering et al., 2005). For interpretation purposes, we used hypertension as a categorical measure, as descriptive variables and brain volumes can then be compared across groups. Moreover, we were specifically interested in a clinically relevant measure, that also included currently normotensive participants with treated hypertension. Furthermore, we chose to incorporate systolic and diastolic blood pressure in one measure, as these were highly correlated in the current sample ($r = .75$).

2.3. Depressive disorder

All participants were interviewed with the Composite International Diagnostic Interview (CIDI) version 2.1 to establish the presence of depressive and anxiety disorders according to the Diagnostic and Statistical manual of Mental disorders fourth edition (DSM-IV) (Kessler and Ustun, 2004), administered by trained interviewers. In the current study analyses were focused on Major Depressive Disorder (half-year recency), while anxiety (Social Anxiety Disorder, Panic Disorder with or without Agoraphobia, and/or Generalized Anxiety Disorder; half year recency) was accounted for by including it as a covariate.

2.4. Other variables

Information about baseline characteristics was obtained from interviews, clinical measurements, and questionnaires. Age, sex, years of education, presence of type 2 diabetes, and medication use were determined during an interview. Measures of weight and length were used to calculate body mass index and Doppler measures of blood pressure of the arm and ankle were used to calculate ankle-brachial index (ABI), a