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ScienceDirect
Psychiatry Research: Neuroimaging 163 (2008) 133–142
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

A magnetic resonance imaging study of the entorhinal cortex in treatment-resistant depression

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Received 17 August 2007; received in revised form 14 November 2007; accepted 15 November 2007

Abstract

Despite a growing interest in this area, we continue to lack an understanding of the pathophysiology of depression and of treatment-resistant depression (TRD) in particular. The role of the medial temporal lobe, particularly the hippocampus, has been widely implicated in the aetiology of depression. However, related structures such as the entorhinal cortex have not been systematically examined. This research study aimed to examine possible abnormalities in the volume of the entorhinal cortex (ERC) in TRD patients. A group of 45 TRD patients and 30 healthy age- and sex-matched controls underwent magnetic resonance imaging (MRI). ERC volumes were manually traced from MRI data using ANALYZE software. An analysis of variance was conducted between subject groups and in the sexes separately while controlling for the effects of brain size via intracranial volume (ICV). Results revealed significant reductions in the volume of the left ERC of female patients. Although preliminary, our findings suggest that anatomical abnormalities in the ERC may confer vulnerability to treatment resistance. Confirmatory longitudinal studies are required to determine whether these abnormalities predate the onset of depression or are the result of a more chronic, treatment-resistant course of illness.

Keywords: Psychiatric illness; Imaging; Volumetric analysis

1. Introduction

Despite major advances in technology and pharmacology, depression remains one of the most concerning and debilitating mental disorders worldwide (Murray and Lopez, 1997; Montgomery, 2006). Treatment-resistant depression (TRD) is usually conceptualized as a failure to respond to several courses of adequate antidepressant treatment (O'Reardon and Amsterdam, 2001). TRD patients account for 15–30% of depressed patients undergoing psychiatric treatment and represent over half of the total annual costs associated with treatment of depression (Petersen et al., 2001). With systematic research it would seem possible to identify the set of unique clinical features that are peculiar to those depressed patients who show resistance to treatment (Fagiolini and Kupfer, 2003). Neuroimaging has been primarily used in depression as a means to 'investigate the pathophysiologic mechanisms of the disorder and the physiologic basis of the clinical response to antidepressive treatment'

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doi:10.1016/j.pscychresns.2007.11.005

(Fagiolini and Kupfer, 2003, p. 643). However, due to the heterogeneity of major depressive disorders, inconsistent findings have been reported. The limitations of many magnetic resonance imaging (MRI) studies include differences in subject populations such as selection criteria, demographic characteristics and diagnosis, as well as differences in imaging protocol (Coffey et al., 1993; Beyer and Krishnan, 2002). Focusing specifically on groups such as TRD may be one way to limit this heterogeneity.

Structural neuroimaging studies that have specifically focused on TRD have reported a range of findings, with several authors concluding that in the elderly, pathologic vascular changes along with frontal lobe dysfunction may play important roles in treatment non-response (Baldwin and Simpson, 1997; Simpson et al., 1998; Fagiolini and Kupfer, 2003). In regards to the identification of individual brain regions, studies have identified atrophy in right frontostriatal regions (Shah et al., 2002), reduction in the frontal lobe volumes (Coffey et al., 1993), subcortical gray and white matter hypertensities (Fagiolini and Kupfer, 2003) and temporal lobe atrophy especially in the hippocampus (Shah et al., 1998). Despite the identification of the hippocampus and its common recognition in studies of treatment-resistant populations (Baldwin and Simpson, 1997; Simpson et al., 1998; Fagiolini and Kupfer, 2003), recent research studies have not systematically investigated the potential involvement of related brain regions such as the entorhinal cortex (ERC).

The ERC is of particular interest because of its intimate connections with the hippocampus. The entorhinal cortex is considered to be a critical component of the mesial temporal lobe memory system and represents the major excitatory input to the hippocampus, supplying it with information from the multimodal cortical association areas (Bonhilla et al., 2003; Goncharova et al., 2001). The ERC functions as a multilevel buffer, holding 'real sensory' information while the hippocampus compares it with internal representations to detect 'familiarity' versus 'novelty' (Prasad et al., 2004). It has been proposed that volumetric abnormalities in the ERC could lead to impairments of the cortico-hippocampal circuit, which has been implicated in the aetiology of major depression (Nasrallah et al., 1997; Bernstein et al., 1998). Disruption in the functioning of this circuitry has been implicated in the development of abnormal mood in other disorders where the ERC has been investigated, such as in schizophrenia (Prasad et al., 2004). Also ERC pathology in Alzheimer's disease is well established, with many investigations of ERC atrophy in this disease reporting consistent findings (Laakso et al., 2000). Neurodegeneration begins in the ERC and as Alzheimer's pathology develops, degeneration progresses to the hippocampus and eventually the cortex (Juottonen et al., 1998; Dickerson et al., 2001; Killiany et al., 2002; Du et al., 2004; Xu et al., 2006). O'Brien et al. (1997) found that atrophy of the entorhinal cortex, in particular, had a high sensitivity and specificity to differentiate Alzheimer patients from patients with depression. However, of note, analyses of ERC volumes have not been reported previously in TRD, and there are no prior studies of ERC volumes in non-treatment resistant depression in adult populations, thereby warranting further investigation.

These findings suggest a possible role of ERC atrophy in TRD, and it may be speculated that ERC damage could occur first and be followed by atrophy progressing to the hippocampus with continual chronic, treatment-resistant depressive episodes. Therefore, the main objective of this present study was to examine possible abnormalities in the volume of the ERC in a group of treatment-resistant depressive patients in comparison to healthy age- and sex-matched controls. Based on previous neuroimaging and neuropsychological studies, it was hypothesized that there would be a significant reduction in the volume of the ERC in female TRD patients compared with female controls. It was also hypothesized that there would be a significant reduction in the volume of the ERC in male TRD patients when compared with male controls.

2. Methods

2.1. Subjects

The experimental group comprised 45 patients aged between 18 and 62 years (M=37.53, S.D.=11.33). Sex breakdown in the patient group was as follows: 22 males (M=37.29, S.D.=8.76), among whom 20 were right-handed and two were left-handed, and 23 females (M=37.47, S.D.=12.96), among whom 19 were right-handed and four were left-handed. The patients fulfilled DSM-IV (American Psychiatric Association, 1994) criteria for major depressive disorder and research criteria for treatment resistance. All patients were recruited from the outpatient department of a public mental health service (Alfred Psychiatry, Melbourne) and by referral from a variety of private psychiatrists. Exclusion criteria included a concurrent or previous DSM-IV axis I disorder, current active medical problem and known neurological disease or a contraindication to MRI scanning. The treating psychiatrist and a study psychiatrist assigned a DSM-IV diagnosis to every patient, as confirmed by the Mini International Interview for Neuropsychiatric Disorders