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Relationship between regional brain metabolism, illness severity and age in depressed subjects

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Abstract

We sought to examine the effects of age, depression chronicity, and treatment responsiveness on glucose metabolism in a large well-characterized sample of depressed men and a psychiatrically unaffected control group. The subjects were unmedicated, symptomatic, right-handed males ($n=66$) who met DSM-IV criteria for a major depressive episode in the context of a major depressive disorder (MDD, $n=66$) and never depressed, right-handed, healthy control subjects (HC, $n=24$). Subjects in the MDD group were subsequently classified as responders, or non-responders to a six-week trial of paroxetine monotherapy (20–60 mg). Statistical parametric mapping (SPM) was used to analyze the relationship between age and cerebral glucose metabolism (18-fluorodeoxyglucose positron emission tomography) and the modulation by treatment responsivity and a history of prior depressive episodes. Metabolic activity in the rostral and dorsal anterior cingulate cortex showed a significant negative correlation with age in MDD, but not in HC. Non-response to treatment and previous depressive episodes were associated with a higher degree of age-dependent hypometabolism in the rostral and anterior cingulate cortex. The age-dependent changes documented herein may influence the distinct clinical presentation and treatment response described in older-age depression.

Keywords: Major depressive disorder; Neuroimaging; PET; Glucose metabolism; SPM

1. Introduction

Results from structural and functional neuroimaging studies indicate that mood disorders are associated with regionally-specific changes in brain volume and function (Mayberg, 2003b; Seminowicz et al., 2004; Konarski et al., in press). Mounting evidence suggests that aberrant cortical–limbic circuits subserve affective

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phenomenology. Heterogeneity of patient populations, study designs, and imaging parameters, however, has limited efforts to elucidate a common affective circuit.

The clinical course of major depressive disorder (MDD) is recurrent, often chronic and associated with inter-episodic dysfunction (Kessing et al., 1999). An emerging database indicates that the probability of achieving remission further decreases as a factor of increasing age (Bland et al., 1997; Alexopoulos et al., 2005). Research endeavors which aim to elucidate the biological correlates of syndrome progression in mood disorders have frequently reported changes in distinct limbic regions as a function of episode frequency and/or illness duration (MacQueen et al., 2003; Sheline et al., 2003; Videbech and Ravnkilde, 2004; Campbell et al., 2004).

These observations raise several questions with clinical and patho-etiological translational value. For example, are the structural and functional changes described in multiple-episode depression the consequence of the cumulative depressive symptom burden? A rival hypothesis is that the observed abnormalities may be mediated by other variables (such as aberrant ageing processes). For example, normal ageing processes are associated with global and regional atrophy, changes in brain function (Kessler, 2003), monomine receptor pharmacology (Morgan et al., 1987), and cytoarchitecture (de Magalhaes, 2004), for a thorough review see (Sowell et al., 2003).

The inherent variability in region of interest (ROI) analyses among studies and the lack of ROI validation provide the impetus for a non-biased, fully automated, whole brain analysis of voxel-level metabolic activity (i.e. statistical parametric mapping; SPM) (Friston et al., 1999). Through normalization of macroscopic within-group differences, between-group differences in local tissue composition can be explored without employing unvalidated ROIs.

Herein, we employed SPM to characterize the effects of age on glucose metabolism measured with 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in a large homogenous sample of right-handed men who met DSM-IV defined criteria for MDD. This analysis was augmented by comparison to a similarly-aged group of psychiatrically unaffected right-handed men.

We hypothesized that brain metabolic abnormalities in individuals with major depressive would include age-dependent decreases in metabolism in the prefrontal cortex coupled with age-dependent hyperactivity in subcortical limbic region (Drevets, 2000; Mayberg, 2003a). Moreover, we predicted that this relationship would be more pronounced in subjects with a more severe illness course, arbitrarily defined as non-response to paroxetine monotherapy, or a history of prior depressive episodes.

2. Methods

2.1. Subjects

Sixty-six consecutive unmedicated males (age 20–60 years, mean: 36±11) meeting DSM IV criteria for a major depressive episode in the context of MDD were evaluated and constitute the MDD group. The MDD subjects were enrolled in a six-week clinical trial evaluating the efficacy and tolerability of paroxetine. Clinical diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (SCID-P) and a standard clinical assessment by a senior psychiatrist (SHK) who excluded any potential subjects with clinically detectable evidence of cognitive impairment or vascular depression. Eligible subjects were required to provide written informed consent; the investigation herein was approved by the Research Ethics Board of the Centre for Addiction and Mental Health, University of Toronto.

To assist in the interpretation of age-related differences in metabolism, MDD data were compared to those in a previously published data set of twenty-four right-handed psychiatrically unaffected males (age 21–53 years, mean 35±9), who were included in the healthy control (HC) group (Kennedy et al., 2001). Scans from both groups were acquired with the same PET camera and an identical scanning paradigm.

Table 1
Distribution of depression characteristics by decade (mean±standard deviation)

Group	Illness variable	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years
Depressed subjects (*n*)		14	27	15	9	1
	Depressive symptom severity (HAMD-17)	22.7±2.6	23.0±3.4	23.9±4.0	23.0±2.3	22.0
	Depressive episode number	0.57±0.94	2.15±2.71	2.20±2.68	3.00±2.83	5
	Cumulative time in MDE (weeks)	89.2±77.3	129.3±102.0	208.8±175.0	220.6±121.8	526
Control subjects (*n*)		8	9	5	2	0