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Clinical and medial temporal features in a family with mood disorders

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ABSTRACT

It is debated whether non-affected relatives of patients with affective disorders share a specific brain structure endophenotype. Aim of this work is to explore the medial temporal morphology in affected and non-affected members of a family with mood disorders. Hippocampi and amygdalae were manually traced from the 3D magnetic resonance imaging of five affected family members, 10 non-affected relatives, and 15 unrelated matched controls. Affected and non-affected relatives were characterized by larger left amygdalae (18%, $p = 0.030$), smaller right hippocampus (up to 18%, $p < 0.0005$), and reduced hippocampal asymmetry ($p < 0.001$) than controls. Abnormal, albeit non significant, positive correlations of MTL volumes with age were observed, with the exception of smaller volume of the left hippocampus with advancing age ($r = -0.76$) in the affected relatives. These data add to the evidence that abnormal medial temporal structures may constitute an endophenotype for affective disorders.

The high heritability of mood disorders, and particularly of bipolar disorder [25], reinforces the idea that a genetic contribution could influence some cerebral morphological or functional features, that may constitute an endophenotype for the disease. Endophenotypes are defined as simpler clues to genetic underpinnings than the disease syndrome itself, and may allow to decompose psychiatric diagnoses in more straightforward ways, thus leading to more successful analyses [13]. Different endophenotypes have been proposed for bipolar disorder, based on brain structure, function, or symptom provocation [16]. Among these, a putative morphological endophenotype relates to the system devoted to guarantee a baseline mood in the medial temporal lobe (MTL), including the hippocampus and amygdala. MTL anomalies are frequently detected in mood disorders: adult bipolar patients have larger amygdalae [1,2,7,27] without enlarged hippocampus, whilst smaller, albeit hyperactive, amygdalae are reported in depressed samples [26].

Together with other cerebral features, these MTL abnormalities are considered a putative brain structure endophenotype for affective disorders [16]. A genetic contribution to the abnormal MTL morphology can be hypothesized based on studies on first episode subjects [27] and twin pairs [20].

Aim of this study is to investigate the MTL morphology of affected and non-affected members of a family with unipolar and bipolar depression from magnetic resonance images (MRI).

First degree related outpatients, their non-affected relatives, and unrelated controls were recruited at the IRCCS S. Giovanni di Dio Fatebenefratelli, Brescia, Italy (Fig. 1). Local Ethic Committee approval and written informed consent were obtained.

Cases underwent a clinical psychiatric interview by an experienced psychiatrist and a diagnostic assessment with the Structured Clinical Interview for DSM-IV axis I (SCID-I/P, version 2.0) by an independent rater [9]. Severity of depression was assessed with the 21-item Hamilton Rating Scale for Depression (HAM-D) [15], and bipolar symptoms with the Young Mania Rating Scale [29].

Of the 19 family subjects, 15 (four with unipolar, one with bipolar depression type I, 10 unaffected) had suitable MRI for the study. A healthy and unrelated control was matched by age, sex, education and cognitive status to each subject.

MRI was carried out with a 1.0 T Philips-Gyroscan. High resolution sagittal T1-weighted MRI were acquired with a gradient echo 3D technique (TR = 20 ms, TE = 5 ms, flip angle = 30°, field

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Table 1
Clinical features of the affected and non-affected family members included in this study.

Subject	Age	Onset	Axis I DSM-IV diagnosis	No. of episodes	Status at the time of assessment	Psychotropic medications		Physical diseases	
						Past	Present	Axis III physical comorbidity	Medications
Affected									
II 3	81	50	Bipolar disorder type I	Recurrent	Depressive symptoms	Venlafaxine, lorazepam, alprazolam, trazodone, paroxetine, lithium	Venlaflaxine, lithium carbonate, lamotrigine	Hyperthyroidism (and thyroidectomy at 71 and 76) after the onset of bipolar disorder	Thyroxin, hormonal replacement therapy, nifedipine ramipril
III 2	55	24	Major depressive disorder, generalized anxiety disease, breathing-related sleep disorder sleep apnoea syndrome, coffee abuse	2	Remission	Clomipramine, paroxetine	Zolpidem, lormetazepam, trimipramine	Breast cancer, headache	Naproxene sodium, ibuprofen, tamoxifene
III 6	43	30	Major depressive episode	2	Depressive symptoms	Trimipramine, citalopram, benzodiazepines	Trimipramine		
III 7	43	37	Major depressive disorder	1	Remission	Amitriptyline			Annual therapy with estradiol valerate
II 7	72	28	Seasonal major depressive disorder	4	Incomplete remission	Venlafaxine	Venlafaxine	Hyperthyroidism and Thyroidectomy at 18 and 58	Estrogen replacement therapy
Non-affected									
III 10	31								
III 4	53								
IV 1	24								Estrogen replacement therapy
III 11	45							Hyperthyroidism	Hyperthyroidism therapy
III 13	44					Amphetamine for overweight at 33		Asymptomatic multinodular goiter	
III 15	42							Asymptomatic multinodular goiter	
III 17	34							Asymptomatic multinodular goiter	
II 10	70							Asymptomatic multinodular goiter	
III 19	42							Headache	Pizotifen
II 12	65							Hypercholesterolemia	Cholesterol lowering agents