

Genomic studies of mood disorders - the brain as a muscle?

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Abstract

Recent genomic studies showing abnormalities in the fibroblast growth factor system in the postmortem brains of people with major depressive disorder support previous indications of a role for growth factors in mood disorders. Similar molecular pathways, volumetric changes, and the effects of exercise on mood suggest a superficial analogy, and perhaps a deeper relationship, between muscle and brain functioning.

An evolutionary perspective on mood disorders

Mood - the way one feels inside emotionally - is likely to have evolved, broadly speaking, as a sensor and integrator of the environmental availability, or lack of availability, of resources that an organism needs to live, to develop and to propagate its genes. A non-nurturing, hostile environment engenders low mood and depression. This is useful in making the organism conserve existing resources, keep still and stay out of harm's way [1,2]. Conversely, a nurturing, favorable environment engenders high mood and euphoria, making the organism more likely to take advantage of opportunities, to expand and to propagate its genes. The switch from low to high mood becomes loose in bipolar (manic-depressive) illness, and overreacts to minor stimuli in an excessive and persistent fashion that often obscures any correlation with external events that trigger the switch. The incongruence between mood and environment is a hallmark of severe clinical depression or mania. In severe clinical depression (also called major depressive disorder), mood is low even in favorable conditions, whereas in mania, mood is high even in unfavorable conditions. Extremes of mood are often associated with cognitive distortions (psychotic symptoms).

Mood disorders have been studied primarily in humans, although aspects of them can be found in other animals and can be studied in rodent models, for example [3]. They are the result of a complex interaction between genes and the environment, and some people are more susceptible than

others, whether for genetic or other reasons (such as developmental insults or stressors). Little is currently known about the genes involved in susceptibility to mood disorders [4]. Brain-imaging studies have shown that the regions of the brain that are important in mood regulation include the prefrontal cortex and the hippocampus, and depression has been linked with a decrease in volume of these parts of the brain. Depression can be treated with a range of antidepressant drugs, including specific serotonin re-uptake inhibitors (SSRIs such as fluoxetine, one brand name for which is Prozac, sertraline (Zoloft), or paroxetine (Paxil)). A recent study [5] of gene expression in the brains of people with major depression gives some insights into the genes involved in this disorder.

Depression and decreased growth factors

Evans *et al.* [5] used Affymetrix microarrays to study gene-expression patterns in the prefrontal cortex of postmortem human brains, focusing on subjects with depression, bipolar disorder or no psychiatric disorder. They uncovered a down-regulation of members of the fibroblast growth factor (FGF) family and their receptors - with the major factors being FGF1 and FGF2 and the receptors FGFR2 and FGFR3 - in subjects with depression but not in the other brains. A history of antidepressant treatment with SSRIs in the depressed subjects seemed to mitigate this decrease in FGFs and FGF receptors, especially for FGF2, FGFR2 and FGFR3.

The connection between FGFs and depression is particularly interesting in light of the postulated involvement of FGF2 in the cognitive and neurotrophic effects of nicotine [6] and the increased use of cigarettes, possibly as a means of self-medication, in people with depression and schizophrenia [7]. Moreover, recent work in rats has shown that a combination of the SSRI antidepressant fluoxetine and the atypical antipsychotic drug olanzapine, which appear in human studies to be more effective for the treatment of resistant depression in combination than individually, led to increased levels of *FGF2* mRNA in prefrontal cortex, as well as in hippocampus and striatum [8]. Overall, the results of Evans *et al.* [5] are consistent with a body of work *in vitro* and in animal models showing that antidepressant and mood-stabilizer treatments increase the levels of neurotrophic and cell-survival factors in the brain [9-12]. It is of interest that the subjects with bipolar disorder in the study [5] did not show a similar decrease in components of the FGF system to that seen in depressive subjects; this suggests that the decrease might be specific to the depressive state and leaves open the possibility that the opposite may be true - that FGFs may be increased - in more manic states, giving an overall mixed picture in brains from bipolar patients.

As a caveat, Evans *et al.* [5] present data from a relatively small number of subjects; this is typical of the human post-mortem work published so far and is due to the scarcity of good-quality tissue with adequate associated phenotypic information. The first cohort contained 9 depression, 6 bipolar and 7 control subjects; the second contained 4 depressed and 6 control subjects. Generally, given the genetic heterogeneity of human populations and the differences in exposures to environmental factors (including psychotropic drugs) in the lifetimes of different people, work with postmortem human brains needs as high a number of subjects as possible. Careful cross-validation with multiple other independent lines of evidence is also needed, including 'clean' animal model gene-expression data and data on human genetic linkage; my colleagues and I have termed this cross-validation approach 'expanded convergent functional genomics' [3].

A second caveat that should be borne in mind when looking at the work of Evans *et al.* [5] is that it looks predominantly at male postmortem brain samples; also, the samples are often the result of violent death by suicide or accident. One question that needs further study is whether there are differences in the gene-expression patterns and resulting neurobiology of depression between men and women. Clinical epidemiology studies have consistently shown that there is a two-fold higher incidence of depression in women than in men. The phenomenology and environmental triggers of depression and suicidality may be somewhat different in the two sexes - loss of status leading to violent completed suicides in men, and perceived abandonment leading to incomplete attempted suicides by women [1,13,14].

Other work [12] has shown that another growth factor, brain-derived neurotrophic factor (BDNF), is decreased in depression, and it may also be involved in bipolar disorders and schizophrenia, though this is less clear. Interestingly, the work of Evans *et al.* [5] also found that levels of the BDNF receptor *Ntrk2* were significantly decreased in depressed subjects. Other growth factors have been implicated in psychiatric illnesses: nerve growth factor [15], epidermal growth factor [16], and neurotrophin 3 [17]. Decreased levels of growth factors are also associated with decreased brain volume in key areas for psychiatric illness, such as the hippocampus [18,19].

Circumstantial evidence suggests that, conversely, an excess of growth-factor activity might be correlated with mania. *FGFR1* and *IGF1* (insulin-like growth factor 1) were elevated in an animal model of mania [20]. Anabolic steroids, which not only increase muscle mass but also increase the levels of growth factors such as insulin-like growth factor 1 in many parts of the body [21], also have effects similar to (hypo) mania, such as elevation of mood, hypersexuality and promotion of aggression [22,23]. Physical exercise and an enriched environment, both of which can have mood-elevating effects, have been shown in mouse studies to increase proliferation of hippocampal stem cells [24-26], presumably through increased levels and activity of growth factors [27].

Parallels between the regulation of mood and muscle development

FGFs are believed to be important for the differentiation and maturation of many tissues, including muscle. The developmentally regulated expression and distribution of FGFRs, especially *FGFR3*, play a role in muscle maturation [28]. The fact that a molecular signaling system used for muscle and connective-tissue development has been shown to be downregulated in depression raises the intriguing possibility that brain regions involved in mood are regulated in an analogous way to muscle; for instance, that these regions are atrophied in depressed people in the same way that muscle atrophies when it is inactive for long periods. In both brain and muscle, tissue volume and levels of activity seem to correlate with levels of growth factors, and sometimes the same growth factors are involved in both tissues. It is unclear whether depression occurs because of low growth-factor levels in key brain areas or whether the growth-factor levels are low because those brain areas are less active. Both may be true in varying degrees, and the role of environmental stress as a precipitant cannot be overemphasized [29]. Identifying functional polymorphisms in genes of the FGF system in subjects with depression may point to a genetic component, whether inherited or acquired. Regardless of which phenomenon is the cause and which the result, the mood-regulating brain regions appear to shrink the longer the person

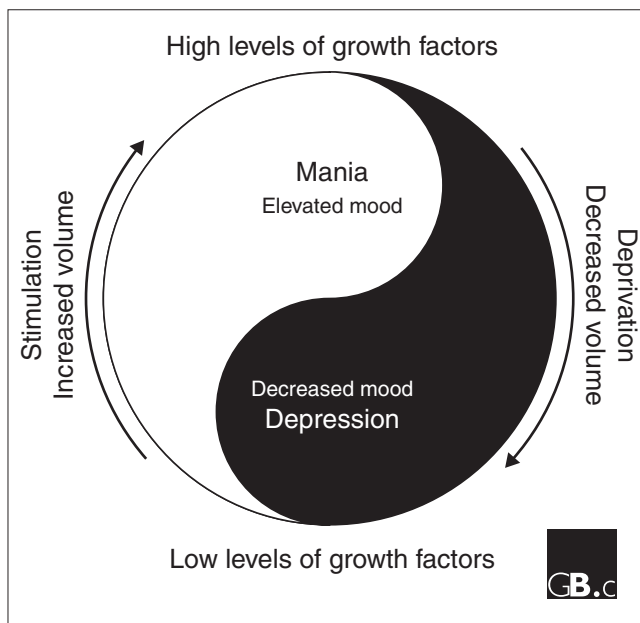


Figure 1

A putative model of the relationship between environmental stimulation, growth factors, and the function of the brain regions involved in mood regulation. The degree of environmental stimulation influences growth-factor levels and brain volume in the brain regions that are involved in mood regulation. In clinical mood disorders, such as bipolar (manic-depressive) illness, there is a loosened connection between environmental reality and internal brain functions underlying mood.

stays in the depressed state [30] - just as muscles shrink when they are unused. Following from the evolutionary perspective outlined above, we can speculate that atrophy of brain regions in depression may be adaptive mechanisms to a chronically deprived and limiting environment, whereas conversely hypertrophy of brain and elevated mood would be adaptive reactions to a supportive and resource-rich environment (Figure 1). The same growth factors may be used in both brain and muscle because evolution is a tinkerer and uses the building blocks that are available.

This analogy has practical implications. The selective short-term use of steroids with anabolic properties might be useful for treating severe depression, albeit as a heroic measure of last resort to jump-start recovery, on a par with electroconvulsive therapy. Moreover, from a more practical standpoint, the analogy suggests that imaging studies that measure the volume of different brain regions [31] could be used for assessing the severity of mood disorders and the response to treatment. Last but not least, what is good for muscle - physical exercise - seems to be good for the brain too [32]. Physical therapy may become a useful supplement to pharmacotherapy and psychotherapy, with a treadmill supplanting the proverbial Freudian couch. The Romans may have had it right with their ideal of *mens sana in corpore sano* (a healthy mind in a healthy body).

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