

Prefrontal cortex governs normalcy and psychiatric illness: neuroimaging evidence

Abstract

Objective: We reviewed neuroimaging evidence to determine whether prefrontal cortex is endowed with unique properties that mediate both normalcy and psychiatric illness.

Method: Evidence based upon clinical observations and neuroimaging studies were reviewed.

Results: The cumulative evidence -based upon clinical and neuro imaging evidence- suggest that prefrontal cortex is endowed to mediate normalcy and psychiatric dysfunction. The mediating influence of prefrontal cortex may be independent of molecular and regional brain dysfunction contributory to psychiatric illness.

Conclusion: There seems to be compelling evidence to suggest that prefrontal cortex is endowed to mediate normalcy and psychiatric illness.

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Introduction

Recent studies have offered sound evidence to suggest that prefrontal cortex (PFX) has governing influence in depression, remission and in antidepressant strategies. Studies have also suggested that the mediating influence of prefrontal cortex in depression and remission seem to be independent of molecular and regional brain dysfunctions contributory to depression.¹ A recent study also hypothesized the governing influence of prefrontal cortex based upon biology, phylogeny and clinical observations but did not offer experimental or extensive neuro imaging evidence. Compelling data suggest higher mental functions, executive function, awareness planning and strategic thinking are the domain of Brodman areas 8, 9, 10, 42, 46 or prefrontal cortex. Some evidence has also been offered to suggest the mediating influence of prefrontal cortex in great many psychiatric disorders.² This paper will investigate whether prefrontal cortex governing influence in depression and remission may also be true for other psychiatric disorders supported by neuroimaging studies.

Method

This study will review diverse examples of the governing influence of prefrontal cortex in normalcy and psychiatric illness. Examples of diverse correlations between psychiatric disorders and decline of prefrontal cortex influence will also be shown under the following headings:

- a. Biology
- b. Clinical evidence from depression studies.
- c. Neuroimaging Evidence from depression studies.
- d. Clinical evidence from psychiatric disorders.
- e. Neuroimaging evidence of psychiatric disorders.

Results

Biology supports the governing influence of prefrontal cortex

In general prefrontal cortex seems to be endowed with complex mental functions such as attention concentration of executive function,

self awareness strategic thinking, mastery of impulses, initiative and willpower. It is also true that our ability to initiate and pursue personal goal directed behavior with integration of environmental and internal cues is a major function of prefrontal cortex.³

Hierarchy of influence is observed in nervous system. Furthermore the following observations are consistent with the governing influence of prefrontal cortex.

1. Prefrontal cortex rules motor and sensory cortex.
2. Prefrontal cortex could override functions primarily regulated by other brain regions (remaining awake at night, limiting food intake).
3. Injury to Brodman area 8 is associated with loss of bladder and bowel control (recognition memory nor other memory domains of the temporal cortex and info campus).⁴

Depression and remission are mediated by prefrontal cortex influence

Executive function a domain of prefrontal cortex is compromised in unipolar depression, late life depression and with patients suffering from treatment resistant depression.⁵⁻⁷ Of significance is the observation that executive function improves with remission. Conversely, depressed patients with the greatest decline in executive function are less likely to remit.⁸ Importantly, whereas executive function is compromised in depressed patients neither verbal learning, visuo spatial memory, delayed recall, recognition memory nor other memory domains of the temporal cortex and hippo campus appeared to be so at risk.⁵

Neuroimaging evidence of bidirectional changes in prefrontal cortex glucose metabolism in depression

Neuroimaging evidence reveals a reciprocal relationship between metabolic activities of the prefrontal cortex and the limbic brain in depression and in response to stress.⁹ Decreased metabolism in dorsolateral prefrontal, anterior prefrontal, orbitofrontal and ventral anterior and subgenual cingulate cortex is frequently associated with depression.¹⁰ Decreases in frontal cortical metabolism during depressed mood have also been identified with C glucose PET imaging.¹¹

Remission from depression normalizes hypo-functioning in frontal, prefrontal and orbitofrontal regions while it reduces activity in paralympic, parietal-temporal regions including the amygdala, hippocampus and parahippocampalgyrus.^{9,12} The normalization of limbic cortical circuit abnormalities in the treatment of depression occurs even with the relief from depression due to placebo treatments which increase frontal cortex activity and diminished thalamic activity.¹³

All of these observations along with a recent study suggesting that the therapeutic efficacy of antidepressant strategies may depend less on their presumptive molecular mechanisms of action and more on their ability to restore the predominant metabolic and executive functions of the prefrontal cortex and dampening of excessive subcortical limbic influences support the mediating influence of prefrontal cortex in depression and remission.¹

Almost all psychiatric disorders share symptoms consistent with diminished influence of prefrontal cortex

Great many psychiatric disorders with diverse pathophysiology and origin seem to have clinical symptoms that correspond to the declining influence of prefrontal cortex (Table 1). For instance judgment and reality testing are compromised in schizophrenia, dementia, psychosis and bipolar disorder. Judgment and reality testing are the domain of prefrontal cortex.

Table 1 Diminished metabolic activity in PFX shown by neuroimaging studies²

Diminished Metabolic Activity in Prefrontal Cortex
1. Schizophrenia
2. Depression
3. Depression with diabetes
4. Depression with Parkinson's
5. Depression with Huntington's
6. Depression with stroke
7. Bipolar disorders
8. Addictive disorders
9. Chronic pain
10. Dementia
11. Add
12. OCD
13. GAD
14. Dissociative Disorder

We can also observe that mastery of impulses and urges are mediated by prefrontal cortex and therefore OCD, ADD and addictive disorders could be viewed as disorders with compromised pre-frontal cortex function. Generalized anxiety disorder and chronic pain are associated with diminished executive function and thus serve as examples of prefrontal cortex decline. In general it appears that there is no psychiatric illness without any decline of prefrontal cortex function or influence. Or we can state that any symptom of psychiatric illness is physiologically correlated with diminished influence of prefrontal cortex.

Neuroimaging evidence is consistent with diminished glucose metabolism of PFX in great many psychiatric disorders

Evidence from neuroimaging studies is consistent with metabolic abnormalities in prefrontal cortex or in the top-down connections diminishing its influence in almost all psychiatric disorders (Table 2). Diminished metabolic activity in prefrontal cortex has been shown in schizophrenia,¹⁴⁻¹⁶ depression,^{9,17} in depression associated with

diabetes,¹⁸ depression associated with Parkinson's disease, depression associated with stroke, depression associated with Huntington's disease, bipolar disorder,¹⁹ addictive behavior,²⁰ obsessive-compulsive disorder,²¹ chronic pain.²² Reduced functional connectivity within cortical limbic loop has been shown in obsessive compulsive disorder^{23,24} and depression.^{9,17,25} Sar and colleagues have also shown evidence of hypofunction of orbitofrontal area in dissociative identity disorder.²⁶

Table 2 Neuroimaging and clinical data of diminished PFX influence in psychiatric disorders²

Disorder	NI Evidence of Diminished Glucose Metabolism	Clinical Evidence
ADD	YES	Poor Mastery Over Impulses
GAD	YES	Poor Mastery Over Impulses
OCD	YES	Poor Mastery Over Impulses
Addictions	YES	Poor Mastery Over Impulses
Bipolar disorder	YES	Impaired Judgement
Schizophrenia	YES	Impaired Judgement
Psychosis	YES	Impaired Judgement
Dementia	YES	Impaired Judgement
Depression	YES	Impaired Motivation

Discussion

Neurophysiological, clinical and neuroimaging observations seem to be consistent with the governing influence of prefrontal cortex in normalcy and in psychiatric disorders. It seems that the emergence of psychiatric symptoms do coincide with prefrontal cortex influence falling below a threshold necessary for normal function. This observation may be worthy of emphasis: evidence suggest, diminished prefrontal cortex influence is a prerequisite for psychiatric illness.

It seems reasonable to conceptualize that in the early stages of any molecular brain abnormality symptoms may remain dormant until prefrontal cortex influence is compromised. This may explain why many psychiatric disorders of diverse origin may not emerge until some decline of prefrontal cortex influence.

Diminished prefrontal cortex influence may have diverse profiles:

- i. Decline of prefrontal cortex function (primary)
- ii. Decline of prefrontal cortex function (secondary)
- iii. Functional disconnection between prefrontal cortex and other brain regions.

Decline of prefrontal cortex function (primary)

Any decline of prefrontal cortex function such as attention deficit disorder or dementia may represent an example of decline induced directly by prefrontal cortex abnormalities independent of other disorders.

Decline of prefrontal cortex function (secondary)

Disorders with a primary origin elsewhere in brain such as chronic pain, amygdala dysfunction²⁷ leading to depression or chronic schizophrenia are included in this category.

Functional disconnection between prefrontal cortex and other brain regions

Any disruption of communication between prefrontal cortex and other brain regions would represent diminished influence of prefrontal

cortex. This is consistent with the observations from studies of people with schizophrenia and obsessive-compulsive disorder.^{5,15}

The main limitation of this study is its theoretical model. It is however based upon observations well substantiated by clinical, experimental and neuroimaging evidence.

Conclusion

The reviewed evidence suggests that brain function is sensitively dependent on the mediating influence of prefrontal cortex and any decline of prefrontal cortex influence may be associated with psychiatric symptomatology. In essence for a psychiatric illness to emerge pre-frontal cortex decline is a prerequisite. The governing influence of prefrontal cortex to mediate normalcy and psychiatric illness represents a novel paradigm that may pave the way for new avenues to study brain function.

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Conflicts of interest

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