RESEARCH PROPOSAL

GENE EXPRESSION, MECHANISMS OF CEREBRAL LATERALIZATION, AND SHARED CAUSATION OF DIVERSE BRAIN DISORDERS

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OBJECTIVE. Hemispheric lateralization is among the main architectural features of the mammalian brain but its genetic control is not fully understood. We propose that the aberrant expression of the genes controlling cerebral lateralization is central to the causation of several major brain disorders. Traditional taxonomies of neurological and neuropsychiatric disorders are outdated and stymie rather than facilitate the understanding of the basic mechanisms of major diseases. We propose to explore the common underlying causes of two major disorders that have been traditionally approached in an isolated, disconnected way: schizophrenia (Sch) and fronto-temporal dementia (FTD). This will be accomplished through advancing our understanding of the genetic control over hemispheric lateralization in the normal and abnormal brain.

RATIONALE. The rationale for hypothesizing their shared causation and mechanisms lies in many common features including neuroanatomical similarities: in both Sch and FTD prefrontal (especially orbitofrontal) and temporal (especially anterior temporal) cortical regions are particularly implicated, mostly in the left hemisphere.

HYPOTHESES. Cortical development is regulated by a number of genes, some of which are characterized by distinctly asymmetric gradients of expression: left-right and rostro-caudal. We hypothesize that:

1) Hemispheric lateralization is driven by a set of distinct, asymmetrically expressed genes
2) Aberrations of such asymmetrically expressed genes play a role in Sch and FTD, but at different life stages: early in Sch and late in FTD.
3) Such gene sets are the same or overlapping in Sch and FTD.

RESEARCH PLAN.

1) Identify the genes whose normal cortical expression is asymmetric along (a) the left-right gradient in the frontal and temporal regions; and (b) along the rostral-caudal gradient:
    1a) In human neonatal brain tissue
    1b) In human nasal epithelial cells.
    1c) Verifying human genes in mouse models.

2) Identify a sample of FTD patients (N=20) with particularly strong evidence of left-lateralized involvement and frontal-lobe involvement based on radiological (MRI voxel morphometry; MRS), neurocognitive (neurocognitive test battery) and clinical evidence. Examine the expression of genes identified in (1a) and (1b) in their nasal epithelia. Identify a sample of older healthy controls age-matched to the FTD sample (N=20). Examine the expression of genes identified in (1a) and (1b) in their nasal epithelia; and correlate with lateralization patterns based on radiological (MRI voxel morphometry; MRS), and neurocognitive (neurocognitive test battery) evidence. Compare the gene expression in the patient and control groups and identify the aberrant expression patterns.

3) Identify a sample of young Sch patients (N=20) with particularly strong evidence of left-lateralized involvement and frontal-lobe involvement based on radiological (MRI voxel morphometry, MRS), neurocognitive (neuropsychological test battery) and clinical evidence. Examine the expression of genes identified in (1a) and (1b) in their nasal epithelia. Identify a sample of younger healthy controls age-matched to the Sch sample (N=20). Examine the expression of genes identified in (1a) and (1b) in their nasal epithelia; and correlate with lateralization patterns based on radiological (MRI voxel morphometry; MRS), and neurocognitive (neurocognitive test battery) evidence. Compare the gene expression in the patient and control groups and identify the aberrant expression patterns.

4) Compare the aberrant gene expression profiles in Sch and FTD.

5) Compare the lateralized gene expression patterns in young and old normal controls.

POTENTIAL IMPORTANCE.

1) The project will reveal the genetic codes that control left-right hemispheric specialization, which is the major architectural feature of the brain; and how the expression of these genes may change through the lifespan.
2) It will help clarify how the aberration of such control contributes to the causation, mechanisms, and genetic risk factors of certain subtypes of schizophrenia and dementia.
3) Both schizophrenia and dementia are major, high prevalence brain disorders, which have been traditionally approached as unrelated. Approaching them in concert overcomes the prevailing taxonomic boundaries and represents a paradigm shift.
4) By identifying the common cause(s) of these disorders we will help develop novel treatments for both disorders that will also be relevant to aging in general.
5) By identifying common or overlapping causal features of Sch and FTD subtypes, we will contribute to the development of a new taxonomy of neurological/neuropsychiatric disorders.

6) By identifying the genes playing a role in brain diseases at vastly different life stages, we will help shed light on the normal gene expression throughout the lifespan and their relationship to brain aging.