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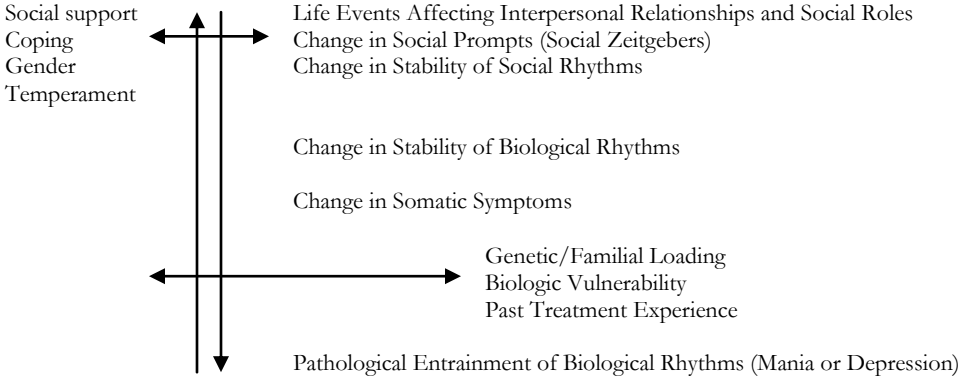
Biology and Genetics of Bipolar Spectrum Disorders

- Biology of bipolar disorder
  - See separate handout on the biology of mood and anxiety for more information in general and also information on the brain effects of medications used to treat mood and anxiety conditions
  - Social Rhythm theory of bipolar disorder (Ellen Frank, PhD)

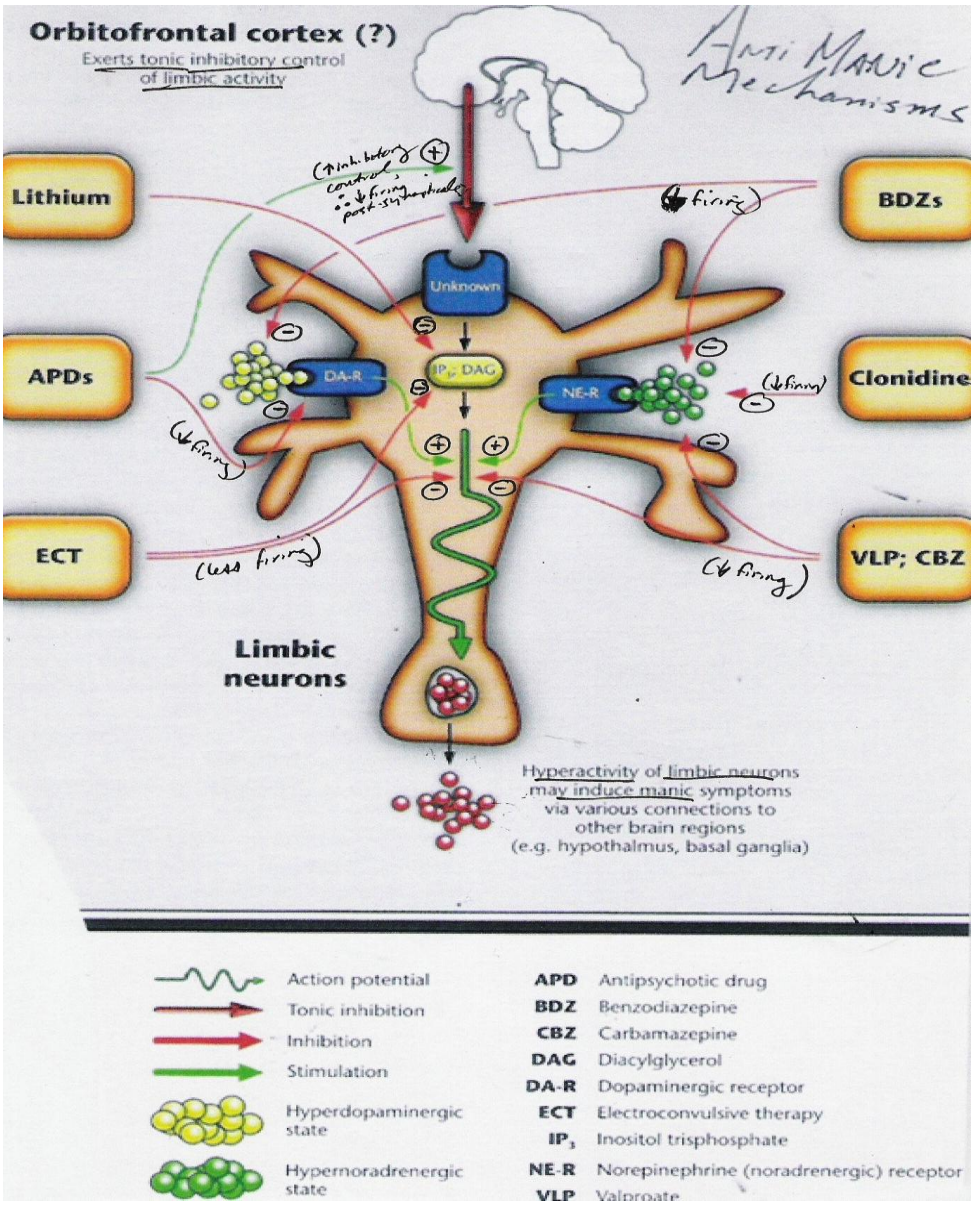


  - Associated with deficits in emotional processing ***and*** impaired neurocognition/executive functioning that persist even in euthymic states
    - General
      - Emotion processing
        - Reduced higher order activity (e.g., dorsolateral prefrontal cortex (DLPFC) in the presence of extreme negative emotions in faces
        - Increased activity in amygdala in the presence of extreme negative emotions in faces
        - Impaired ability to accurately interpret extreme emotions in faces, especially if negative emotions in faces
        - More accurate with more subtle facial expressions, but amygdala still overactive
        - Negative words lead to hyperactivation of amygdala and hypoactivity of prefrontal cortex
        - More sensitive to negative stimuli in fronto-limbic circuitry
        - Emotion processing ciruits
          - Amygdala is the initial emotional processing center for the perception and initial analysis of emotional aspects of stimuli
          - Prefrontal cortex (PFC)regulates the amygdala and the amygdale feeds back on the PFC
          - Visual processing of faces
            - Superior temporal sulcus (STS)—initial analysis of faces
            - Fusiform gyrus—helps in recognition of faces
          - Anterior cingulate cortex (ACC) involved as well
          - Face responsive circuit/visual processing circuit; Affective circuit
            - (STS—V1/V2)—Amygdala—(PFC—ACC)
      - Cognitive impairments, regardless of the presence or absence of ADHD
        - Attachment of emotional valence to tasks for which no processing of emotional information is required
        - Increased ventral-limbic brain activity during purely cognitive-attentional processes, which means that the emotion centers are overactive even in non-emotional tasks
        - Executive functioning and other neurocognitive domains
          - Attention
          - Working memory
          - Vigilance
          - Response inhibition
          - Verbal memory
          - Visual memory
        - Visual processing
        - Visuospatial processing
        - Reading, writing, math
        - Motor skills
      - In sum
        - Overreactive to emotions
        - May not focus, plan, or problem solve effectively when exposed to affectively-laden stimuli
        - Can't focus with excess
    - Hypoactive dorsal-cognitive network (involved in attentional/executive function processing)
      - Dorsolateral prefrontal cortex (DLPFC)
      - Dorsomedial prefrontal cortex
      - Dorsal anterior cingulate cortex
      - Posterior cingulate cortex
    - Hyperactive ventral-limbic network (emotional regulation and socioemotional processing)
      - Ventrolateral prefrontal cortex though hypoactive in impulsive response tasks

- Orbitofrontal cortex (OFC)
- Ventral/subgenual anterior cingulate cortex (vACC)
- Amygdala
- Insula
- Hypothalamus
- Striatum though hypoactive in impulsive response cognitive tasks
- Putamen in cognitive tasks
- Functional link between the two: rostral ACC

- Neuroimaging and other studies demonstrate:
  - Decreased white matter in superior-frontal lobes in adolescents with first episode mania
  - Decreased volume gray matter (with increased size lateral ventricles)
    - Prefrontal cortex
      - Reduced activation associated with mania
      - Decreases in some parts associated with illness duration
      - Subgenual prefrontal cortex
        - decreased volume gray matter is predominantly in the subgenual prefrontal cortex
        - in one study patients with bipolar disorder and patients with recurrent unipolar depression had a 40% reduction in gray matter in the subgenual prefrontal cortex.
        - Glial cell loss is prominent in this area too.
      - Dorsolateral prefrontal cortex (DLPFC)
        - Decreased brain activity which may disinhibit other emotional centers in the brain and may underly the emotional lability of bipolar disorder
        - Decreased gray matter in this area
        - Decreased neurons (esp layer III)
        - Decreased glial cells (esp BA24)
        - Decreased markers of neuronal density in dorsolateral prefrontal cortex (DLPFC) in children and adults
        - Decreased metabolism in depression
        - Decrease CaCMK II, reelin, GAD, GFAP mRNA and protein, MR; increased cortisol
      - Cingulate cortex
        - Increased markers of neuronal density in the anterior cingulate cortex in pediatric bipolar disorder
        - Reduced activation associated with mania; when mania is treated, activation is normalized
        - Reduced metabolism and reduced glutamatergic activity associated with pediatric mania
        - ?Reduced glial function (with subsequent reduced glutamatergic synthesis and release) associated with pediatric mania
        - Tryptophan metabolism and kynurenine metabolic pathways and their interaction abnormal in mania
        - Effective atypical antipsychotic treatment of mania is associated with increased (normalized) glutamatergic activity and/or synthesis
      - Parietal lobe
        - Smaller in pediatric bipolar
      - Temporal lobe
        - Smaller in pediatric bipolar
        - Decreased spatial navigation
    - In some cases, the reduction in gray matter is not the loss of neurons themselves but the loss of synaptic connections (via dendritic spines).
    - When analyzed closely, it appears that the atrophy was mostly in those patients not taking lithium or valproic acid.
    - Reduced frontal lobe asymmetry
    - White matter hyperintensities in cortical and subcortical regions in pediatric bipolar disorder
    - Decreased gray matter seen in the relatives of clients with schizophrenia
  - Amygdala
    - Adults with bipolar disorder demonstrate enlarged amygdala in some studies (may be temporally associated with episodes; may then decrease in size in between episodes)
    - In children, bilateral and left-sided reductions in other studies (by 10%); minimized by treatment of lithium or Depakote (Chang, 2005);
    - Decreased glial cell density
    - Some evidence suggests the amygdala
    - Adults demonstrate increased activation in the left amygdala during mania
    - may enlarge as episodes recur
    - Facial emotion-processing abnormalities are present in youth with bipolar disorder whether or not they are aymptomatic; this likely relates to a trait vulnerability of amygdala
      - Symptomatic or asymptomatic youth perceived facial expression of extreme emotion as moderate or mild
      - Symptomatic patients misperceived subtler facial expressions of emotion
  - Hippocampus
    - 2007: patients with untreated bipolar disorder, compared to patients treated with lithium, demonstrate atrophy in the cornu ammonis 1, the main site of memory processing in the hippocampus; they also demonstrated significantly smaller hippocampi; in 2004, the same group demonstrated increased volume of the left hippocampus in patients treated for bipolar disorder
    - Bilateral decreased volume hippocampus in children and adults
    - Decreased markers of neuronal density/markers
    - Decreased synaptic markers

        - Decreased volume seen in the relatives of clients with schizophrenia
        - Decreased cognitive and spatial memory
        - Decreased brain-derived neurotrophic factor (BDNF) correlates with decreased size of the hippocampus as well as bipolar disorder symptom severity; nb: glial-derived neurotrophic factor (GDNF) is increased in episodes of bipolar disorder
    - Thalamus
        - Decreased volume thalamus in children and adults.
    - Basal ganglia
        - Larger bilaterally
        - Increased metabolism
    - Cerebellar vermis
        - Decreased size; decrease correlates with multiple episodes (vs. one episode)
        - Reduced reciprocal pfo-cerebellar function
    - Locus Coeruleus
        - Increased numbers of noradrenergic neurons
        - Increased activity of norepinephrine
        - Increased norepinephrine in CSF in mania
    - Bipolar depression: frontal, prefrontal, and hippocampal hypofunction, amygdala and cerebellar hyperactivity
    - Mania: increased metabolism in anterior cingulate cortex and global cortex and decreased metabolism in bilateral orbitofrontal cortex during mania.
    - Also: insular cortex
    - Hajek, 2005: in unaffected relatives of bipolar patients, first-episode patients, children or adolescents with bipolar disorder, and patients with familial bipolar disorder: abnormalities in striatum volume, left hemisphere white matter, thalamus, anterior cingulate, as well as MRI signal hyperintensities in unaffected relatives of bipolar patients. Subjects in the early stages showed volume changes in the ventricles, white matter, caudate, putamen, amygdala, hippocampus, subgenual prefrontal cortex.
- Bipolar disorder may be associated with too much brain NMDA glutamatergic functioning and/or too little GABAergic functioning.
    - Increased expression of NMDA NR2B subunit gene transcripts and decreased expression of three associated postsynaptic density protein gene transcripts in schizophrenia; these latter transcripts are similarly reduced in bipolar disorder, and one of the three is also reduced in major depression.
    - Post-synaptic density-95 (PSD-95) protein, associated with NMDA receptors, is decreased in the dentate molecular layer of the hippocampus in schizophrenia and bipolar disorder (but not unipolar depression), not associated with medication use. This could then have a deleterious impact on information flow to other hippocampal regions via granule cells and their projecting mossy fibers.
- Signal transduction pathways
    - Elevated levels of G-apha-s protein (→ increased activation AC → increased cAMP production)
    - Elevated PKC activity in mania; Zarate et al, 2007: Tamoxifen, which reduced PKC more than lithium and Depakote do, was effective in treating mania in a RCT, DB trial of 16 patients
    - Blunted beta- and alpha2-responses
    - Blunted growth hormone and prolactin responses



- Genetics
  - Heritability estimates are 64-85%; this means that genetic factors explain about 80% of the risks for bipolar disorder.
  - Patient with bipolar disorder and risk of bipolar disorders or other psychiatric disorders in family tree/family history
    - At least 2/3's of patients with bipolar disorder have a family history of mood disorders
    - If patient has bipolar disorder (per 2003 study), risk in first degree relatives:
      - 6.7% risk (vs. 0.7% in controls), 10.8 fold increased risk of bipolar disorder
      - 15.4% risk (vs. 5.2% in controls), 3.3 fold increased risk of unipolar depression
    - If patient with bipolar I, prevalence in family members is
      - ***4 to 6-fold increased risk***
      - ***3-15.5% with bipolar I***
        - If patient is adolescent:
          - 8.6% of family members of adolescents with bipolar disorder
        - If patient is child:
          - Overall, 7-fold increased risk
          - 28-34% of family members of children with bipolar disorders (versus 6% in ADHD patients) have bipolar I disorder
          - If child has bipolar disorder AND oppositional defiant disorder OR conduct disorder OR antisocial personality, the risk increases to 74.6%
          - If child has bipolar disorder AND ADHD, risk increases to 55.2%
          - If child has bipolar disorder only, the risk decreases to 10.9%
      - 72.2% with depression (isolated)
      - 47.8% with anxiety disorder
      - 46.4% with substance use disorder

        - 38% with mania (isolated);
        - 29% with ADHD
        - 25.5% with suicide attempt
        - 23.7% with conduct disorder
        - 2.1% of family members diagnosed with bipolar II
    - If patient with bipolar II
        - 85.7% with depression (isolated)
        - 50% with anxiety disorder
        - 42.9% with mania or hypomania (isolated)
        - 40.4% of family members diagnosed with bipolar II
        - 37% with ADHD
        - 31% with suicide attempt
        - 25% with substance use disorder
        - 22.4% of family members diagnosed with bipolar I
    - If patient with bipolar NOS—similar
- Twins
    - If one monozygotic twin has bipolar disorder, risk of bipolar spectrum disorders is 70-87%
    - If one dizygotic twin has bipolar disorder, the risk of bipolar spectrum disorders is 35-37%
- There may be common genetic risk factors between bipolar disorder and:
    - recurrent unipolar depression
    - schizophrenia/schizoaffective disorder
    - other psychotic mood disorders
- Adults (Goldstein et al, 2006); prevalence of bipolar disorder greater if:
    - history of youth anxiety disorder
    - history of youth conduct disorder
    - family history of depression
    - family history of alcohol abuse
- Parents with mood disorders and risk of mood disorders in offspring
    - Depression
        - If one parent has a major mood disorder, the children have a 20-25% risk of also being affected
        - If both parents have a major mood disorder and one parent has bipolar disorder, the children have a 50-75% risk of a mood disorder
    - Bipolar disorder
        - Singh, DelBello et al, 2007
            - 11-fold increased risk (78%) of one or more psychiatric diagnoses than youths of parents with no diagnoses (24%)
            - 16% with bipolar I disorder vs. none in youths of parents with no diagnoses
        - Risk of bipolar disorder
            - There is a 5.4-15% risk (4-fold higher than average risk) that a child of that parent will develop bipolar disorder
                - The risk may be as high as 27% (Gershon, 1982)
                - The probability increases to 50% if both parents have bipolar disorder.
                - The risk of bipolar spectrum disorders may be as high as 50% (and 25-70% with some mood disorder; Soutullo, 1999)
        - Lapalme meta-analysis of children of parent(s) with bipolar disorder; risk of psychiatric disorder(s) in the children:
            - Any psychiatric disorder: 52% vs. 29% in children of parents without bipolar disorder
            - Mood disorders: 26.5% vs. 8.3% in children of parents without bipolar disorder
                - Bipolar disorder: 5.4% vs. 0% in children of parents without bipolar disorder
                - Unipolar depressn: 8.5% vs. 7.5% in children of parents without bipolar disorder
            - Non-mood disorder 20.6% vs. 20.4% in children of parents without bipolar disorder
    - Other psychiatric disorders
        - 2.5-fold more likely to have any psychiatric illness
        - 4-fold more likely to have mood disorder
        - 27.6% with behavioral problems
        - 30.4% with attentional problems or formal ADHD
            - Parents with bipolar disorder AND a childhood history of ADHD more likely to have children with bipolar disorder
        - 39% with verbal IQ's 15 points or more greater than performance IQ; this is compared to the norm of ~11-13%
        - Melatonin suppression
        - Larger hippocampal volumes
        - Shaw, 2005 10-year prospective study of prodromal patterns for bipolar disorder in Amish well youth (who have a parent with bipolar disorder) compared to well youth with no parent with bipolar disorder:
            - Anxious/worried
            - Attention poor/distractible in school
            - Easily excited
            - Hyperalert
            - Mood changes/labile
            - Role impairment in school
            - Somatic complaints
            - Stubborn/determined
            - High energy

- Decreased sleep
- Problems with thinking/concentration
- Excessive and loud talking

- Genetics and risk
  - Parents of children with bipolar disorder
    - More than ½ of mothers and more than ½ of fathers of children with bipolar disorder (in one study) suffer from a mood disorder
    - 80% of children with bipolar disorder have one parent who suffers from a mood disorder.
  - First degree relatives of persons with bipolar disorder
    - Increased risk of schizoaffective disorder, recurrent unipolar depression, bipolar disorder, panic disorder, OCD
    - Not at increased risk for schizophrenia and vice versa.
    - Relatives of children with comorbid ADHD and bipolar disorder have a five times greater rate of bipolar disorder than do relatives of children with ADHD only.
    - Youths with psychotic depression have increased familial aggregation of mania with a substantially increased risk (20-40%) of developing bipolar disorder.
  - Youth of parent(s) with bipolar disorder
    - Children of a parent with bipolar disorder have an increased frequency of (Henin, 2005)
      - Behavioral disinhibition (Hirshfeld-Becker, 2006)
      - Mood symptoms/disorders
        - Jones, et al, 2006: 56% with mood symptoms (vs 9% in children with parents without bipolar disorder
        - Depression
        - Mania/bipolar disorder 10% (vs. 1% in general poptulation
      - Disruptive behavior disorders (ADHD, oppositional defiant disorder)
      - Anxiety disorders (separation anxiety, social anxiety disorder)
    - Adolescents of a parent with bipolar disorder
      - Bipolar disorder: 12% at age 12; 33% at age 18
      - Depression: 23% by age 8; 34$ by age 12; 52% by age 18
      - Anxiety
      - Disruptive behavior disorders
      - Co-morbidity
- Potential genes (that may confer some degree of risk)
  - May relate to the genetics of circadian rhythms (e.g., the mutant 'Clock' gene)
  - May relate, in addition to specific chromosomes and genes below, to dysregulation of various neuroprotective and neuroregulatory genes and gene products such as
    - BAG-1
    - bcl-2
    - cAMP
    - PKC
    - CREB (see under lithium)
    - AKT1
    - GRIN2A
    - XBP1
    - GRK3
    - HTR4
    - IMPA2
    - GABRA1
  - May relate to genetics of the glucocorticoid receptor.
  - May relate to mitochondrial dysfunction
    - 10398A polymorphism
    - 3644C mutation
    - FDUFV2
    - May cause altered calcium homeostasis and changes in neuroplasticity
  - Endoplasmic reticulum stress pathway
    - HSPA5 (GRP78/BiP; Kakiuchi, 2005)
  - Risk for bipolar disorder
    - Chromosome 1
      - 1q31-32
      - 1q32-q41—schizophrenia
    - Chromosome 2
      - 2p11-q14—association with mood-incongruent psychotic features in bipolar disorder
      - 2p13-16
    - Chromosome 3
      - 3q25
    - Chromosome 4
      - 4p12-13
      - 4p15
      - 4p16
      - 4q24-q32—bipolar disorder and schizophrenia
      - 4q35
    - Chromsome 5
      - 5p15.3—dopamine transporter gene
      - 5q22-q31—schizophrenia
    - Chromosome 6
      - 6q21-q22—schizophrenia
      - 6p24-p22—schizophrenia

- 6p25
- Chromsome 7
  - 7q34
- Chromosome 8
  - 8p22-p21
    - Schizophrenia
    - Recurrent early onset-depression
  - 8q24.21-qter
    - Additional recent (2007) evidence of linkage to increased risk of psychosis from bipolar disorder associated with pregnancy and delivery
- Chromosome 9
  - 9p-q
  - 9q34.3
    - GRIN1 which codes NMDA receptor subunit 1
    - Dopamine beta-hydroxylase
    - Bipolar disorder and schizophrenia
- Chromosome 10
  - 10q11.21-q22.1
  - 10p12
  - 10p15-p11—schizophrenia
  - 10q24-26
- Chromosome 11
  - 11p13
    - val66 allele gene
      - codes for a variant of brain-derived neurotrophic factor (BDNF)
      - may be a risk factor for pediatric and adult bipolar disorder.
      - illness specific association with performance on Wisconsin Card Sorting test in bipolar disorder (Rybakowski, 2005).
    - tyrosine hydroxylase gene
      - rate-limiting enzyme in catecholamine synthesis
      - associated with bipolar disorder
      - associated with suicidal behavior in bipolar disorder.
      - Van Den Bogaert, 2006:
        - Protective factor for unipolar and bipolar disorder; disruption of this protective factor increases risk for both
    - dopamine 4 receptor gene
  - 11q22.2-22.3—dopamine 2 receptor gene
  - 11q23.1—neural cell adhesion molecule 1 gene (NCAM1); involved in an array of neurodevelopmental processes
- Chromosome 12
  - 12q23-24
    - 12q24—Slynar gene; present in 10% of folks with bipolar disorder
- Chromosome 13
  - 13q
    - serotonin 2a receptor gene
    - 13q13
    - 13q14-q32—schizophrenia
    - 13q21-33—association with mood-incongruent psychotic features in bipolar disorder
    - 13q31-q32—G72/G30 gene locus
- Chromosome 14
  - 14q24.1-q32.12
- Chromosome 15
  - 15q11-q13—GABA-A receptor alpha 5 subunit gene alleles
  - 15q13-q14—schizophrenia; associated with P50 sensory gating abnormality
  - 15q21
  - 15q25-q26—recurrent early-onset major depression
- Chromosome 16
  - 2 genes around marker D16S2619 are involved in GABA neurotransmission
  - 16p13.3
    - GRIN2A promoter gene: NMDA subunit 1 receptor expression; longer alleles contribute to hypoglutamatergic state
    - Additional recent (2007) evidence of linkage to increased risk of psychosis from bipolar disorder associated with pregnancy and delivery
  - 16q22-23, associated with mental retardation, autism, and bipolar disorder
- Chromosome 17
  - 17q11.1-12
    - the human serotonin transporter (5-HTT) gene has been implicated in bipolar disorder and unipolar depression. Associated with suicidal behavior in bipolar disorder. Mutations (with amino acid levels of more than 200 times normal) in families are associated with clinical anticipation (decreasing age of onset and increasing severity with each successive generation) in bipolar disorder. Short allele may carry more risk
  - 17p12—recurrent early onset-depression
  - 17p13.1 implicated in bipolar disorder.
- Chromosome 18
  - 18p11-11.2
  - 18q12.3
  - 18q21-23
  - Also associated with schizophrenia
- Chromosome 20
- Chromosome 21
  - 21q21
    - 21q21

- D21S171, rs1556314, rs 1785467; brain-expressed genes:
  - TRPM2: encodes a calcium channel receptor and deletion of one portion of the gene can cause calcium dysregulation.
  - C21ORF29 (TSPEAR): encodes a peptide associated with epilepsy in the mouse.
- 21q22.13—especially with pediatric onset

- Chromosome 22
  - COMT gene here
    - There is a variant that makes a slow-acting COMT enzyme
    - Having the variant as above and/or missing one allele (each individual is born with two alleles, one from each parent), → excessive dopamine build-up in the prefrontal cortex
  - G protein receptor kinase 3 gene (GRK3) here
  - 22q12
  - 22q13
- Chromosome X
  - Xp22.1
  - Xq24-q27.1
  - Xq28—GABA receptor (GABRA3) dinucleotide polymorphism

- Risk for bipolar disorder AND schizophrenia
  - Chromosome 1
    - linked to bipolar disorder and autosomal dominant medullary cystic kidney disease (Kimmel, 2005)
    - 1q22; Xu, 2005:
      - CAPON (carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase (nNOS)) gene:
        - increased expression of the gene in the dorsolateral prefrontal cortex
        - CAPON, nNOS, and the NMDA receptor are closely related
        - changes in CAPON and nNOS may lead to NMDA receptor hypofunction, postulated to an etiologic mechanism for schizophrenia and bipolar disorder.
    - 1q23.3
      - Regulator of G Protein Signaling 4 (RGS4)
        - downregulated perhaps in compensation for reduced synaptic drive seen in schizophrenia (>90% of postmortem subjects)
        - reduced mRNA in prefrontal, motor, and visual cortices
          - -->decreased acceleration of hydrolysis of GTP to GDP-->increased duration of signaling portion of gene-->prolongation of signaling via the effector cascade
          - in childhood, exuberant number of cortical excitatory synapses could compensate for impaired synaptic efficiency seen in schizophrenia
          - in adolescence, normal or excessive synaptic pruning would reveal the consequences of the synaptic inefficiency and perhaps evoke a downregulation of RGS4 in an attempt to restore pre-pruning levels of G protein coupled receptor signaling
          - early-life environmental insults (such as virus infection or perinatal problems) could lead to permanent dysregulation of the RGS4 levels.
          - reductions in RGS4 expression could reflect allelic variants
    - 1p36: includes gene MTHFR, both the gene and this chromosomal region linked to recurrent depression.
    - 1q42 (close to DISC-1); linked also to schizoaffective disorder
  - Chromosome 6
    - 6p
      - gene for dystrobrevin binding protein (dysbindin), a protein that occurs at the synapse, particularly in the hippocampus and cerebellum—schizophrenia only
    - 6q
      - 6q21—schizophrenia only?
      - 6q—bipolar disorder (McQueen, 2005; in study of 5,179 individuals from 1,067 families)
    - 6p22-24 (maybe bipolar too)
  - Chromosome 8
    - Gene for IMPase (an enzyme inhibited by lithium)
    - 8p21-22/8p12
      - maybe bipolar disorder too
      - makes a protein called neuregulin 1.
      - works via tyrosine kinase receptors
      - exerts key role in neurodevelopmental processes, including neuronal migration and specification, hormonal controls of puberty, regulation of acetylcholine, GABA, and glutamate, and oligodendrocyte development
      - rats with one copy of the gene disabled show the same kinds of electrophysiological deficits as people with schizophrenia show.
  - Chromosome 10
    - 10p14
  - Chromosome 12
    - 12q
      - linkage of mania age of onset
      - 12q24
      - 12q23.3-q24.11: contains gene d-amino acid oxidase which is associated with bipolar disorder and schizophrenia; this region also associated with recurrent depressive disorder.
  - Chromosome 13
    - 13q
      - 13q32 (or 13q33)
        - this gene (which only exists in primates) makes a protein called G72 which may activate d-amino acid oxidase which increases the production of glutamate, a transmitter implicated in schizophrenia
      - 13q34
        - D-amino acid oxidase activator (DAOA)/G30 locus
        - linked to both bipolar disorder and schizophrenia
        - the link to bipolar disorder may be via propensity for psychosis (e.g., persecutory delusions)

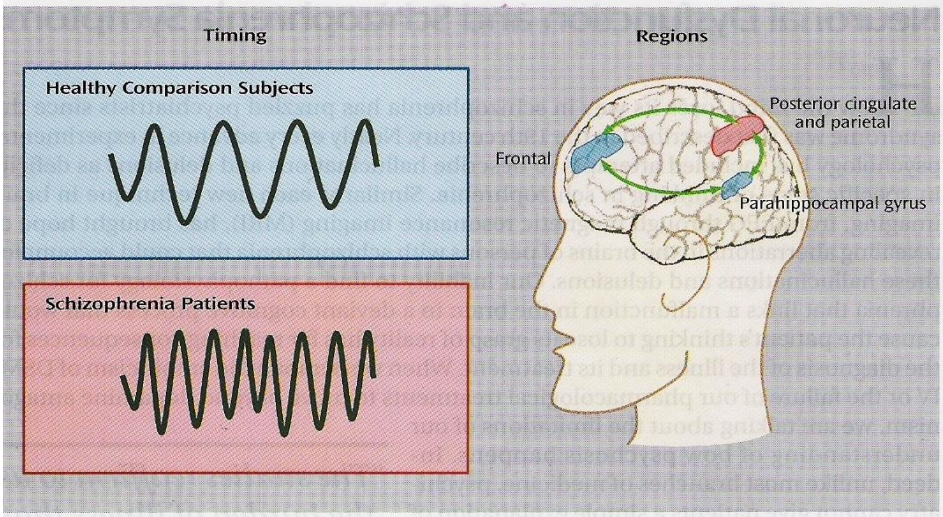
- Chromosome 14
  - 14q
    - linkage of mania age of onset
- Chromosome 15
  - 15q
    - 15q14
    - CHRNA7, associated with psychosis
      - Impact hippocampal information processing (e.g., P50)
    - linkage of mania age of onset
    - associated with recurrent depression.
- Chromosome 18
  - 18p11.2
    - mutations in this chromosome (with amino acid levels of more than 200 times normal) in families are associated with clinical anticipation (decreasing age of onset and increasing severity with each successive generation) in bipolar disorder.
    - McQueen, 2005 (5,179 individuals in 1,067 families): associated with adult onset
  - 18p11.31 (D18S63)
  - 18q12.3 (D18S474)
  - 18q22/18q22.3-qter (D18S1161, D18S70): associated with bipolar disorder
- Chromsome 22
  - This is where the gene for COMT (c-o-methyltransferase, the enzyme that breaks down serotonin, norepinphrine, and dopamine) lies
  - 22q
    - Linkage to psychosis
    - 22q11-13
      - 22q11
        - risk for velocardiofacial syndrome, bipolar disorder, schizophrenia, and schizoaffective disorder
        - 11/15/05, Nature Neuroscience: disruption of the normal interaction between the genes PRODH and COMT contributes directly to the symptoms of schizophrenia by upsetting the balance of glutamate and dopamine.
        - Bassett, 2005: 22.6% of patients with 22q11 deletion syndrome had schizophrenia
      - 22q11-13
        - SYNGR1 gene (Verma, 2005)
          - associated with presynaptic vesicles in neuronal cells
          - Lys99Glu mutation
          - SNP-Ser97Ser
          - Asn ins/del
- GPR88, AD-CYAP1, PAM, GCH
  - former three of which are affected by lithium
  - GPR88 linked to a rat model of mania
  - PACAP (made from the latter three genes) is involved in dopamine activity.
- Glutamate NMDA receptor subunit polymorphism may be associated with bipolar and schizophrenia.
- PSYN
  - genes encoding proteins involved in the machinery of neurotransmitter release
  - reduced expression in schizophrenia
- Glutamic acid decarboxylase, 67 kilodalton isoform (GAD67) gene
  - GAD67 enzyme responsible for synthesis of GABA
  - reduced expression of mRNA seen in prefrontal cortex in schizophrenia
    - 25-30% of prefrontal neurons (but 50% of those neurons that target excitatory pyramidal neurons) in subjects with schizophrenia do not express GAD67
      - might be preferentially reduced in GABAergic inhibitory chandelier neurons targeting excitatory pyramidal neurons of prefrontal cortex (layers 3-5)
      - these chandelier neurons coordinate the firing of pyramidal neurons at gamma frequency oscillations (which is important for working memory)
    - associated with reduction in GABA
    - these neurons are inhibitory so that there is a reduction of inhibition as a consequence
    - GABA-A alpha2 subunits upregulated in the prefrontal pyramidal neurons in subjects with schizophrenia
- GABA membrane transporter (GAT1)
  - responsible for reuptake of GABA
  - reduced mRNA expression in subjects with schizophrenia, especially in chandelier neurons of the middle layers of the prefrontal cortex (which synapse with pyramidal neurons

- Neurophysiological studies
  - Sensory gating (P50)
    - Impairment related to norepinephrine in mania
    - Marijuana adversely affects sensory gating
  - Prepulse inhibition
    - Impairments seen in euthymic bipolar patient and in patients with schizophrenia
  - Leibenluft, 2007: youth with "severe mood dysregulation" (ADHD and severe irritability) have different profiles in P3- and N1-event-related potentials (on EEG) than youth with narrowly defined bipolar disorder
  - N1-P2 augmenting
    - Seen more in bipolar patients than in unipolar
    - Related to risk for suicidal behavior regardless of diagnosis
    - Inversely proportional to serotonergic function
  - P300 after oddball stimulus

- Decreased amplitude seen in bipolar disorder and in schizophrenia
- Decreased amplitude seen in patients with DISC-1 translocation, regardless of diagnosis
- Decreased amplitude and delayed onset associated with anhedonia
- Prolonged latency in bipolar disorder and relatives

- Laterality
  - Loss of right hemisphere dominance in bipolar disorder
  - Impaired interhemispheric switching in bipolar disorder

IGURE 2. Findings From Garrity et al. (p. 450)



IGURE 3. Findings From Ferrarelli et al. (p. 483)

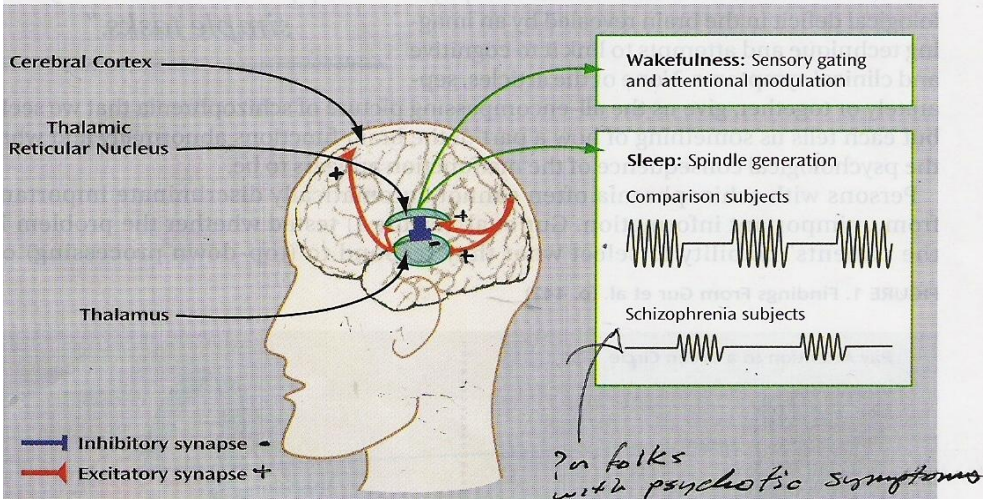


FIGURE 4. Findings From Ford et al. (p. 458)

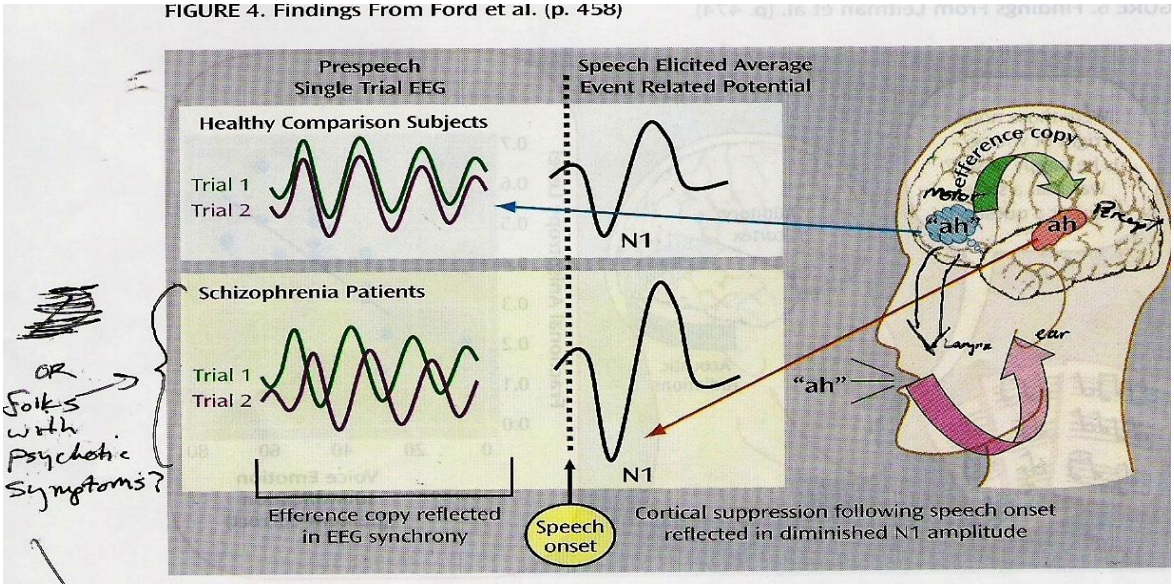
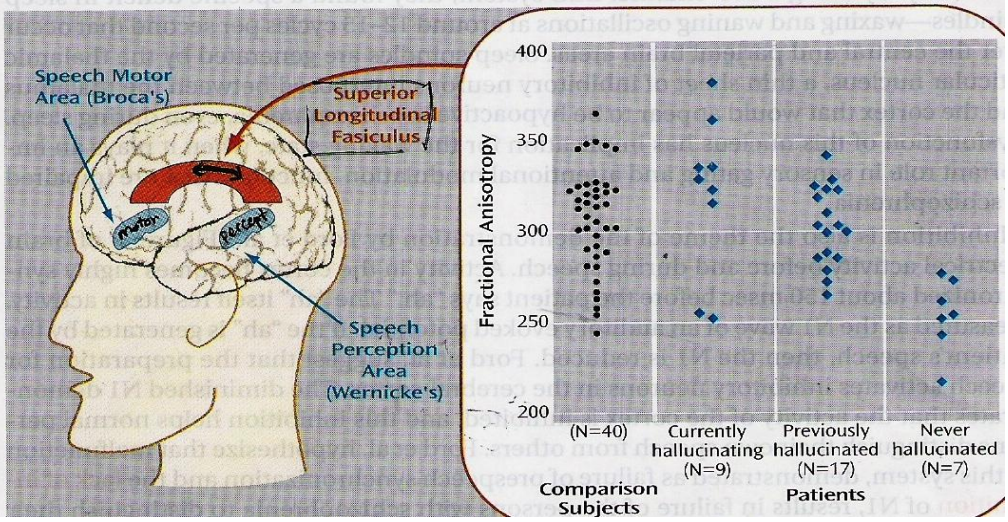


FIGURE 5. Findings From Shergill et al. (p. 467)



- Other
  - Patients with bipolar disorder have a prevalence of cardiovascular risk factors about twice that of the general population