Schizophrenia and the lesser brain: Promising new treatment target

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Overview

- 1. Schizophrenia and the theoretical model under investigation
- 2. Supporting evidence for this model
- 3. Multi-method approach to functional studies of motor & cognitive dysmetria in schizophrenia
 - Cerebellar-mediated eye blink conditioning:
 - Behavioral findings
 - Neuroimaging findings
 - Pharmacological studies

Schizophrenia

Diagnostic & Statistical Manual (DSM) Definition

Positive symptoms ("excess" behaviors)

- Psychotic dimension
 - Delusions, Hallucinations
- Disorganization dimension
 - Disorganized thought
 - Loose associations
 - Disorganized speech
 - Neologisms, Perseveration, Clanging, Blocking
 - Inappropriate affect

Negative symptoms ("deficit" behaviors)

- Restricted and flat affect
- Alogia
- Avolition
- Anhedonia

Psychomotor symptoms

- Catatonia
- Neurological soft signs (independent of localized pathological lesion)
 - integrative sensory function; motor coordination; and motor sequencing.
- Lifetime prevalence: ~1%



Eugen Bleuler's model of schizophrenia: "Fragmented Phrene"

"Split mind" (1908)

 "breaking of associative threads" between ideas

Core deficit is a fundamental associative disturbance

"Fragmented Phrene"

"the thousands of associations guiding our thought are interrupted by the disease in an irregular way here and there, sometimes more, sometimes less. The thought processes, as a result become strange and illogical, and the associations find new paths, though they may be irrelevant to the problem at hand" (Bleuler, 1911, p.14)

Theoretical Model Under Study

Schizophrenia is characterized by abnormalities in the temporal coordination of thoughts, perceptions, motor behavior, and emotions (i.e., fragmented phrene

- cognitive dysmetria (Andreasen, 1998).

The examination of temporal processing and related neural substrates may shed light on mechanisms associated with these abnormalities.

Supporting evidence for this model

Cortico-cerebellar loops subserve motor & cognitive functions
Pervasive motor abnormalities in schizophrenia spectrum
Cerebellar findings

Cortico-cerebellar Loops

Ramnani (2006) Nature Reviews Neuroscience:

Theoretical Model of Motor Control:

Theoretical organization of information processing streams that use forward models for motor control. Motor commands directed to systems that control movement are also copied to forward models that mimic input–output relationships exhibited by these systems.

Motor command Efference copy Forward Mimics the Motor dynamic motor system system model to predict its output Error signal Musculo-Forward Mimics the skeletal musculoskeloutput etal system model system to predict its updates output Motor output Predicted models and sensory sensory consequences consequences Corollorv Reafference discharge Error signal Comparator

a Theoretical model

Cortico-cerebellar Loops

Ramnani (2006) Nature Reviews Neuroscience:

Anatomical of Motor Control Model:

b Anatomical correlates



Cortico-cerebellar Loops

Ramnani (2006) Nature Reviews Neuroscience:

Model of Prefrontal Non-motor Control:

Information arising in the prefrontal cortex is copied to the cerebellum in the same way that motor commands are copied from the primary motor cortex to the spinal cord. In this scheme, cerebellar forward models mimic the input–output relationships of prefrontal targets. Forward models might therefore be able to mimic information processing that is intrinsic to the prefrontal cortex. c Cerebellar model of processing in prefrontal targets



What Is The Role of Cerebellum in Cortico-cerebellar Circuits?

Schmahmann & Sherman (1998)

- Cerebellar Cognitive Affective Syndrome
- "a pattern of behavioral abnormalities...that includes impairments of executive function..., often with perseveration, distractibility or inattention; visual-spatial disorganization and impaired visual-spatial memory; personality change with blunting of affect or disinhibited and inappropriate behavior; and difficulties with language"
- Cerebellum modulates neural circuits that link prefrontal, posterior parietal, superior temporal and limbic cortices with the cerebellum.

What Is The Role of Cerebellum in Cortico-cerebellar Circuits?

Schmahmann & Sherman (1998)

Cerebellar Cognitive Affective Syndrome

Andreasen & Pierson (2008)

- Cortico-cerebellar-thalamic-cortical circuit (CCTCC)
- Coordination of cognitive & affective processes

Strick, Dum, & Fiez (2009)

(1) <u>Timing</u>

With a loss of precise timing information and control, motor commands & internal cognitive states may no longer be appropriately selected and sequenced at a fine level.

(2) Sensorimotor imagery

- Representations & processes that would be engaged during actual movement are co-opted to provide internal representations that assist cognition.
- Conceptual knowledge of the world may rest, in part, upon internally driven activation of perceptual and motor representations (embodied cognition) (Barsalou 1999).

(3) Learning machine

- CB supports adaptive plasticity needed for the emergence of skilled behavior.
- CB adaptively modifies internal representations so that the desired goals of cognition can be achieved.





Figure 1. Cortico-cerebellar-thalamic-cortical circuit.

Supporting evidence for this model

Cortico-cerebellar loops subserve motor & cognitive functions

Pervasive motor abnormalities in schizophrenia spectrum

Cerebellar findings

Motor anomalies in SZ

- Neurological soft signs (NSS) are associated with cerebellar abnormalities in schizophrenia (Bersani et al., 2007; Ho et al., 2004; Thomann et al., 2009).
- NSS are increased in individuals with sz (Bombin et al., 2005; Boks et al., 2000; Boks et al., 2004).
 - Retrospective studies (e.g., Walker et al., 1994)
 - Prospective studies (Cannon et al., 1999; Jones et al., 1994; Schiffman et al., 2009)
 - Correlated with symptoms of schizophrenia (e.g., Bombin et al., 2005)

Increases in NSS also found in populations at risk for SZ

- First degree relatives (Fish et al., 1992; Flyckt et al., 2000; Yazici et al., 2002; Compton et al., 2007)
- Individuals with schizotypal personality disorder (SPD) (Walker et al., 1999)
- Individuals with psychometrically identified schizotypy (Kaczorowski et al., 2009)

Motor anomalies in SZ

Cohen's d and CI 95%



Fig. 1. Median effect sizes for each endophenotype are plotted with 95% CI. Outliers (denoted by "o") and extreme cases (denoted by "*") are labeled by author and year. Note: Outliers were included in main effects summarization tables.

Infant motor development (IMD) and adult executive function & gray matter volume Ridler et al. (2006) PNAS

- Prospective study of infant motor development at 1 year of age and executive functions & gray matter volume at 33-35 years
 - Finnish cohort of 11,000: 49 who developed SZ and 93 who did not
- Results:
 - IMD was delayed in children who would later developed SZ.
 - IMD scores were positively correlated with adult executive function scores in nonpsychotic but not SZ subjects
 - In controls, significant positive association between executive function scores and increased gray matter density in the following four regions:
 - (i) bilateral medial premotor cortex and left rostral prefrontal cortex;
 - (ii) right inferior and middle frontal gyri;
 - (iii) bilateral medial cerebellum; and
 - (iv) right posterolateral cerebellum.
 - Some of the gray matter regions associated with adult executive function were anatomically coincident with regions also associated with infant motor development.
 - 50% of the voxels in prefrontal premotor cortex associated with adult executive function were also associated with infant motor development.
 - 48% of the voxels in medial cerebellum associated with executive function were also associated with infant motor development.

Infant motor development (IMD) and adult executive function & gray matter volume Ridler et al. (2006) PNAS

"adult executive test performance apparently depends on anatomical integrity of a set of distributed cortical and cerebellar regions that include some regions also implicated in early development of motor skills."

"adult executive systems emerge developmentally by integration of...prefrontal and lateral cerebellar...regions with a "core" or prototypic, frontal premotor-cerebellar circuit that has previously matured in support of early motor skills."

Under normal circumstances, perhaps early motor development "leads" or facilitates cognitive development by constructing the necessary "scaffolding" for cognition (cf. embodied cognition)

Supporting evidence for this model

Cortico-cerebellar loops subserve motor & cognitive functions
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Cerebellar findings

Cerebellar Findings in schizophrenia

- Neuropathology shows anterior vermal abnormalities, including decreased Purkinje cell size & density (Reyes & Gordon, 1981; Tran et al., 1998; Weinberger et al., 1980)
- Decreased cerebellar size is associated with poor longterm outcome (Wassink et al., 1999) and greater cognitive dysfunction (Nopoulos et al., 1999)
- Medication naïve SZ show cerebellar signs, which are associated with poorer premorbid adjustment, more severe negative symptoms, greater cog impairment, & smaller cerebellar tissue volumes (Ho et al., 2004)
- Decreased cerebellar gray matter (Henze et al., 2010; Kasparek et al., 2010; Molina et al., 2010; Rasser et al., 2010)
- Reduced GABA protein expression (GABBR1 & GABBR2) in lateral cerebella (Fatemi et al., 2011)

Cerebellar Findings in schizophrenia

- Working memory dysfunctions correlated with grey matter in both cerebellar hemispheres and vermis. Mental flexibility dysfunctions correlated with reductions in white matter volume in bilateral cerebellum (Segarra et al., 2008)
- Fronto-cerebellar metabolic abnormalities associated with anhedonia and ambivalence (Park et al., 2009)
- Increased connectivity between frontal-parietal & cerebellar regions predicts better cognitive performance in controls & SZ, and patients with improved connectivity have fewer disorganization symptoms (Rapovs et al, 2010)

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Eye blink Conditioning Study: Aim & Hypothesis

To examine the integrity of cerebellar function using a single-cue delayed eye-blink conditioning task

 Sz patients will show decreased acquisition and poor latency timing of CRs.

Neural Circuitry for EBC



Christian & Thompson (2003). Learning and Memory

Neural Circuitry for EBC



Previous Delay EBC Findings in Schizophrenia

- Higher rates of conditioning have been reported in two studies:
 - to a visual cue (Spain, 1966; N=32 Sz)
 - to an auditory cue (Sears et al., 2000; N=15 Sz)
 - However, spontaneous blinks not well accounted for in either study
- Impaired conditioning observed in an auditory cue study:

- Hofer et al. (2001; N=24 Sz)

No differences in auditory delay conditioning:

- Marenco et al. (2003; N=10 Sz)

– Spain (1966)

Subjects

- All DSM-IV SCID evaluated
- -13 unmedicated schiz patients
- 19 medicated schiz outpatients
- 21 GAD psychiatric controls
- 42 Nonpatient controls

Age and sex matched

Eyeblink Conditioning Task

Acquisition - 10 blocks of 10 trials

- 9 paired trials; 1 CS alone
- ITI was 15 +/- 3 seconds



EBC Analysis Parameters





Brown, Kieffaber, Vohs, Carroll, Tracy, Shekhar, O'Donnell, Steinmetz, & Hetrick (2005) Brain & Cognition

Percent CRs Across Blocks: Healthy nonpatients show learning



Percent CRs Across Blocks: Unmedicated Szs show impaired learning



Percent CRs Across Blocks: Medicated Szs also show impaired learning



Percent CRs Across Blocks: GAD pts did not differ from NPs



Percent CRs Across Blocks: Comparison of all groups



Replication of EBC deficit in 62 SZ & 62 matched controls (Bolbercker et al. 2008)



Conditioning correlated with cognitive functioning in Controls but not SZ



Fig. 4. Scatter plots showing the relationships between IQ and conditioning in healthy controls (left) and in schizophrenia (right).

Bolbecker, Mehta, Edwards, Steinmetz, O'Donnell & Hetrick (2009) Sz Research

EBC Deficits Also Observed in Schizotypal Personality Disorder

Response Acquisition Deficit



Forsyth, Bolbecker, Mehta, Klaunig, Steinmetz, O'Donnell & Hetrick (2010) Sz Bulletin

EBC Deficits in 1st-degree Relatives of Individuals with Schizophrenia

Acquisition Deficit



Bolbecker, Mehta, Klaunig, Forsyth, Steinmetz, O'Donnell & Hetrick (in prep.)

Cerebellar volume and EBC variables are associated in SZ

Edwards, Newman, Bismark, Skosnik, O'Donnell, Shekhar, Steinmetz, & Hetrick (2008) Psych Res: Neuro

Anterior cerebellum volume correlates with conditioning variables in schizophrenia

Smaller anterior lobules are associated with abnormally short CR latencies

Smaller anterior lobules are associated with larger UR amplitudes

Edwards, Newman, Bismark, Skosnik, O'Donnell, Shekhar, Steinmetz, & Hetrick (2008) Psych Res: Neuro

Effects of secretin on EBC in SZ suggest neural mechanism of dysfunction

- Double-blind, placebo controlled
- 27 medically stable schizophrenia subjects were randomized:
 - 15 received synthetic secretin (20 ug/kg subcutaneously)
 - 12 received placebo

Bolbecker, Hetrick, Johannesen, O'Donnell, Steinmetz, & Shekhar (2009) American J of Psychiatry

- Secretin is released from strongly activated Purkinje neurons (Yung et al., 2001; 2006).
- It acts as a retrograde messenger by binding to presynaptic secretin receptors on basket cell terminals.
- In doing so, it facilitates the inhibition that the basket cells provide on the Purkinje neurons.
- When the Purkinje cells are more inhibited, their inhibition of the interpositus nucleus is released, thus allowing the interpositus to fire and generate a conditioned eyeblink.

Effects of secretin on EBC in SZ suggest neural mechanism of dysfunction

% CRs: Session Averages with Gender as a Covariate

Bolbecker, Hetrick, Johannesen, O'Donnell, Steinmetz, & Shekhar (2009) American J of Psychiatry

Animal developmental preparations implicating cerebellum

- Mouse Prenatal Immune Challenge: Human Influenza Virus
 - Shi, 2003; Winter et al., 2008; Fatemi & Folsom, 2011 (review)
 - Decreased CB volume; Alterations in CB gene expression; reduced 5-HT levels in CB
- Rat 24 hour Maternal Deprivation on Post-natal Day 9
 - Ellenbroek, 1998; López-Gallardo et al., 2008; Llorente et al., 2008; Suárez et al., 2008
 - Neuronal degeneration and glial alterations in cerebellar cortex (males)

Rat Neonatal Immune Challenge: Borna Disease Virus

- Solbrig, 2000; Pletnikov et al, 2002; Hans, 2004; Pletnikov et al., 2000; Eisenman et al., 1999; Lancaster et al., 2007
- loss of cerebellar Purkinje neurons; increased norepinephrine and 5-HT levels in cortex and cerebellum (post-pubertal)

Rodent Prenatal Immune Challenge: Poly I:C (deliv. timing varies)

- Shi et al., 2003; Meyer et al., 2005; 2006, 2008a, 2008b; Ozawa et al., 2006; Zuckerman and Weiner, 2003, 2005; Zuckerman et al., 2003; Smith et al., 2007; Makinodan et al., 2008; Shi et al., 2009
- reduced density of cerebellar Purkinje cells
- 1-hr/day Neonatal Maternal Separation during days 2-14 in Rats
 - Wilber et al., 2007; Wilber et al., 2011
 - Resulted in increased glucocorticoid receptor staining in the adult cerebellar posterior interpositus nuclei AND impaired eyeblink conditioning; This effect is reversed by GR antagonist administration (mifepristone) in the adult rats.

Neurodevelopmental model of SZ

Effects of Maternal Separation

Maternal Separation Is Stressful

Neonatal Maternal Separation Impairs Adult Eyeblink Conditioning

Neonatal Separation Increased Mean Glucocorticoid Receptor Staining in the Adult Posterior Interpositus

Glucocorticoid receptor blockade in the posterior interpositus nucleus reverses maternal separation-induced deficits in adult eyeblink conditioning

Summary

- Both unmedicated and medicated patients with schizophrenia showed deficits in the acquisition of the conditioned eye-blink response (CR), which is consistent with cerebellar dysfunction.
- In healthy controls, but not patients, associative learning was correlated with cognitive function.
- EBC deficits in at-risk groups (SPDs & 1st-degree relatives) suggest that cerebellar abnormalities may be biological markers of disease risk.
- Volumetric and neurochemical abnormalities of the cerebellum may underlie functional deficits in schizophrenia.
- In SZ, a neurochemical abnormality may exist in cerebellum that may be a suitable target for intervention.

Conclusions

- Temporal processing dysfunctions may be a fundamental characteristic of schizophrenia.
- They may underlie the pronounced perceptual, cognitive, and affective disorganization which is characteristic of the disorder.
- Cerebellar dysfunction may be mechanisms by which Bleuler's "fragmented phrene" arises.

Thank you!