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connectivity in Schizophrenia

# Schizophrenia in general

## Initially described as a brain disorder in 1883 (*dementia praecox*, Kraepelin 1971)

## Severe mental disease: causes extensive social and employment problems

## Symptoms

### include delusion, hallucination, apathy, social withdrawal (Marin 2012)

### Affects range of cognitive domains

#### Memory (He et. al. 2012)

#### Attention

#### Executive function (Heinrichs and Zakzanis 1998)

# dysconnectivity

The core concept is that schizophrenia is the not just a result of focal abnormalities, but that aberrant connectivity is a, perhaps the, primary cause.

## Hypothesizing:

### First posited in 1906 (Wernike) and Bleuler (1911) (Stephan, Baldeweg, and Friston 2006)

### Reinforced in late 1980s, 1990s via neuroimaging studies

### Formalized in 1998 (Friston)

## Evidence:

### Reduced frontotemporal coupling compared to controls during language tasks

### Reduced gamma-band synchrony in sensory processing

### Review articles: see Friston 2005b (Stephan, Baldeweg, and Friston 2006)

# Local Dysconnectivity

The core concept is that schizophrenia is the not just a result of focal abnormalities, but that aberrant connectivity is a, perhaps the, primary cause.

## Role of synaptic plasticity (Stephan *et*. *al*. 2009)

### Unclear if dysconnectivity exists at global, local level, or multiple levels

#### Different subtypes?

### Strong evidence for local disconnectivity & disruption of synaptic plasticity

#### Disruption of NDMA pathways induce schizophrenia-like symptoms

#### Reduced sensory learning well-known in schizophrenia patients

#### Genetic evidence also suggests disruption of NMDA and thus failure in synaptic plasticity regulation

#### May also indicate dysregulated glutamateric prefrontal influence on midbrain and subsequent mistimed dopamine release

### Likely a failure of uncertainty prediction (Stephan *et*. *al*. 2016)

#### NMDA and AMPA: known involvement in prediction error signaling

#### Known physiological aberrations align with hypothesis

#### Kaplan et.al. provide evidence that schizophrenia patients overestimate environmental instability (probability of context alteration)

## Failure of interneuron development (inhibitory population) (Marín 2012)

# Large-Scale

## Disruptions in resting-state patterns of fMRI:

### Graph analysis: Bassett et al., 2012; Liu et al., 2008; Lynall et al., 2010; Yu *et*. *al*. 2011a,b, 2013a,b (Cabral et al. 2012; Yu et al. 2015)

### SZ patients generally display reduced global FC (Yu et al. 2015)

#### reduced connectivity between AUD, SM, VIS networks (Damaraju et al. 2014)

#### Not universal: (Jafri et al. 2008) suggest that less-connected networks form stronger coupling in patients

#### increased connectivity between SC networks (thalamus) and AUD, VIS, SM cortical networks (Damaraju et al. 2014)

##### Also demonstrated in Woodward et al 2012, Anticevic et al 2013

##### Anticevic et al 2013 shows thalamo-prefrontal-cerebellar coupling inversely related to thalamo-sensory-motor coupling

##### Marenco et al 2011 suggests weakened structural thalamo-prefrontal coupling.

### Substantial reduction in local organization of brain networks (Kambeitz et al. 2016)

#### Multiple reduced network metrics:

##### small-worldness: directly relates to

###### PANSS scores

###### cognitive functions: memory, attention, executive function, psychomotor speed

##### clustering

##### local efficiency

#### Related to clinical scores (PANSS) and cognitive performance

#### Severity of psychosis symptoms may relate to network integration & global efficiency

## Models of reduced long-range connectivity produce results similar to schizophrenia patient (Cabral et al. 2012)

### Suggest structural disconnection

### Conflicting results: EC analysis suggests *increased* structural connectivity

## Considerable evidence for shared circuitry with autism spectrum disorder (Rabany et al. 2019)

## Limited work on dynamic FC (Damaraju et al. 2014)

### Need for dynamic studies (Yu et al. 2015):

#### fMRI: Allen et. al. 2014, Hutchison et. al. 2013a

##### Known to change due to large state changes: task demands (Esposito et al., 2006; Fornito et al., 2012a; Fransson, 2006), learning (Bassett et al., 2011), maturation (Uddin et al., 2011), sleep (Horovitz et al., 2008, 2009)

##### Known to change ﻿within time scales of seconds to minutes (Chang and Glover, 2010; Hutchison et al., 2013b; Kang et al., 2011; Kiviniemi et al., 2011; Li et al., 2013, 2014; Sakoglu et al., 2010).

##### ﻿reported brain connectivity states (patterns) reoccurring over time and subjects identified by a k-means clustering algorithm (Allen et al., 2014) and eigenconnectivities, which capture connectivity pairs with similar dynamics identified by principal component analysis (PCA) (Leonardi et al., 2013).

#### Long known in EEG: functional microstates which may correspond to basic building blocks of human information processing have been well-established in EEG data (Mutlu et al., 2012, Hennings et al., 2009; Koenig et al., 2002; Lehmann and Skrandies, 1984; Lehmann et al., 1998; Pascualmarqui et al., 1995)

### Static FC studies lack consistency

#### Show both increased and decreased connectivity

#### Likely due to errors in static connectivity

### Dynamic studies suggest:

#### Hypoconnectivity of sensory regions (Damaraju et al. 2014)

#### Hyperconnectivity between thalamus and sensory regions (Damaraju et al. 2014)

#### Elevation of these differences in specific connectivity states

#### Alteration in patient state transition probabilities

##### Towards states with decreased cortical-subcortical connection and increased intra-sensory connection (Damaraju et al. 2014)

##### Fewer transitions to specific states (Rashid et al. 2014)

#### Increased thalamo-sensory low-frequency power (Damaraju et al. 2014)

### (Yu et al. 2015) (note alternative compression method in this article vs. LEICA)

#### Patients display reduced clustering, connectivity, efficiency in patients

#### Also display reduced variance in these metrics, which suggests that patients are more homogenous than general population.

#### Patients spend less time in stationary connectivity pattern

#### Note: Kiviniemi et. al. 2011 and Ma et. al. 2014 suggest that ICNs vary with time

### Dynamic results resemble those of light sleep ﻿(Larson-Prior et al., 2009; Spoormaker et al., 2010; Boly et al., 2012; Allen et al., 2013).

## Relation to clinical scores

### None (Damaraju et al. 2014)

## Development of functional network connectivity (FNC): see Allen *et*. *al*. 2011

# Need for dynamics

## ﻿suggested that functional connectivity measures stabilize over 5 or more minutes (Van Dijk et al., 2010) and follow anatomical connectivity (Deco et al., 2011).

### Cannot capture dynamics of network changes over time

### Network alterations crucial to process & respond to stimuli ﻿(Hutchison et al., 2013).

## Lack of metrics specific to *dynamic* functional connectivity ﻿(Bassett and Gazzaniga, 2011; Fornito et al., 2013; Telesford et al., 2011) (Yu et al. 2015)

# Methods

## (Damaraju et al. 2014)

### Explanation of spatial ICA: (Jafri et al., 2008), ﻿(Allen et al., 2012)

### MANCOVA: ﻿(Allen et al., 2011)

## Development of functional network connectivity (FNC):

### Abou-Elseoud et al., 2010

### Kiviniemi et al., 2009

### Yu *et*. *al*. 2011a, 2012

### Allen *et*. *al*. 2011

### De Reus and van den Heuvel 2013

### Fornito *et*. *al*. 2013