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Introduction

# Schizophrenia the disease

## Highly disruptive

# The dysconnectivity hypothesis

Has dominated the past quarter-century of neuroscientific research (Friston 1998).

## 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.

## Not new (1906 Wernike, 1911 Bleuler)

## Considerable evidence amassed in past half-century:

### 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)

## Spans entire spatial scale of brain, from local to global

### Synaptic plasticity

### Local dysconnectivity

### Interneuron development

### fMRI and white matter disruptions

# Large-Scale dysconnectivity

Primary focus of current article

## Most studies are on white matter and static fMRI

### Methods known for longer

### General findings:

#### Reduced global connectivity (FC) (Yu et al. 2015)

#### Specific FC alterations (Damaraju et al. 2014):

##### Reduced connectivity between auditory, sensorimotor, and visual networks

##### increased connectivity to/from subcortical from/to auditory, sensorimotor, and visual networks

###### Conflicting reports

###### Suggests weakened structural connectivity

#### Network analysis suggests reduced network organization across scales (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

## Model-based analyses also suggest reduced connectivity (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)

# Dynamic dysconnectivity

Dynamic imaging methods have had less time in the field than static methods, but are rapidly making up for lost time.

## Static analyses showed that connectivity patterns change due to major changes in brain state, e.g. 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)

## Long known that functional microstates change on order of milliseconds to seconds

### 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)

### Initial capture in fMRI in 2009

### Known to change on timescales of seconds (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).

### May correspond to basic building blocks of human information processing

## Methods of estimation

### Atlas-based FC

### 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

# microstate dynamics in schizophrenia patients

Past analysis has demonstrated microstate dynamics alterations in schizophrenia patients.

## (Damaraju et al. 2014)

### 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 (Damaraju et al. 2014)

#### Increased intra-sensory connection (Damaraju et al. 2014)

### Increased thalamo-sensory low-frequency power

## (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 reported (Damaraju et al. 2014)

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