

# Multivariate patterns of brain structure, brain function and symptoms in schizophrenia

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for the degree of Dr. rer. medic.



Reviewer: Prof. Danilo Bzdok  
Co-reviewer: Prof. Kristin Konrad  
Chair: Prof. Klaus Wilmes

# **The default mode network in schizophrenia, a complex and often inconsistent picture**

# The default mode network in schizophrenia, a complex and often inconsistent picture

**Hyper**connectivity



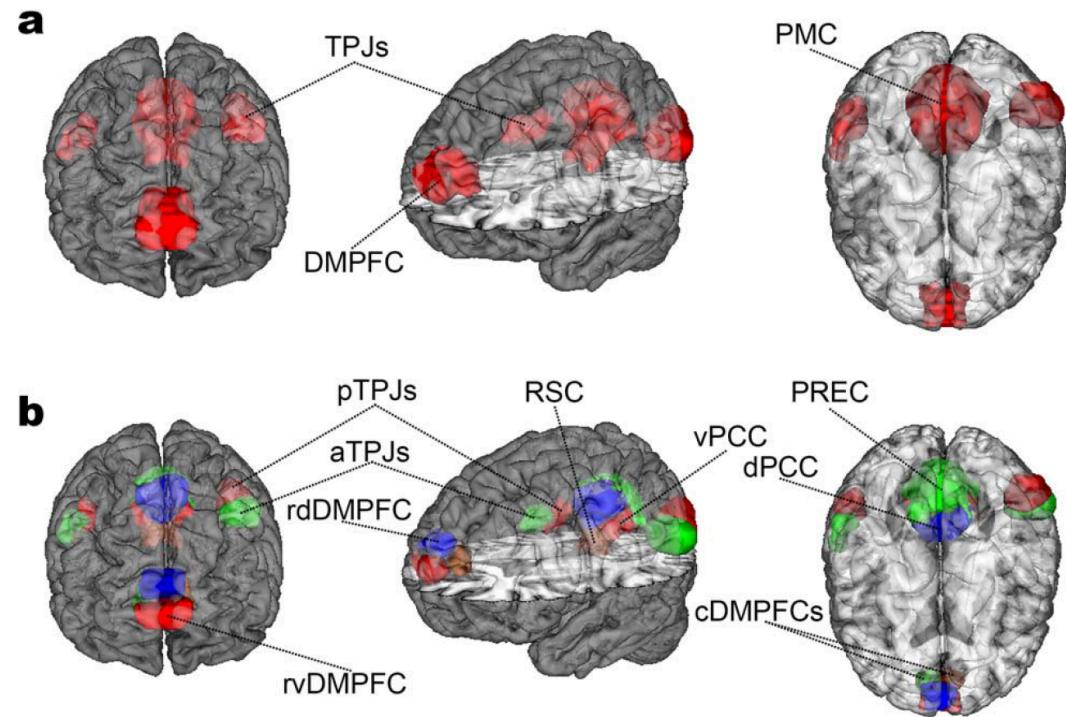
**Hypo**connectivity

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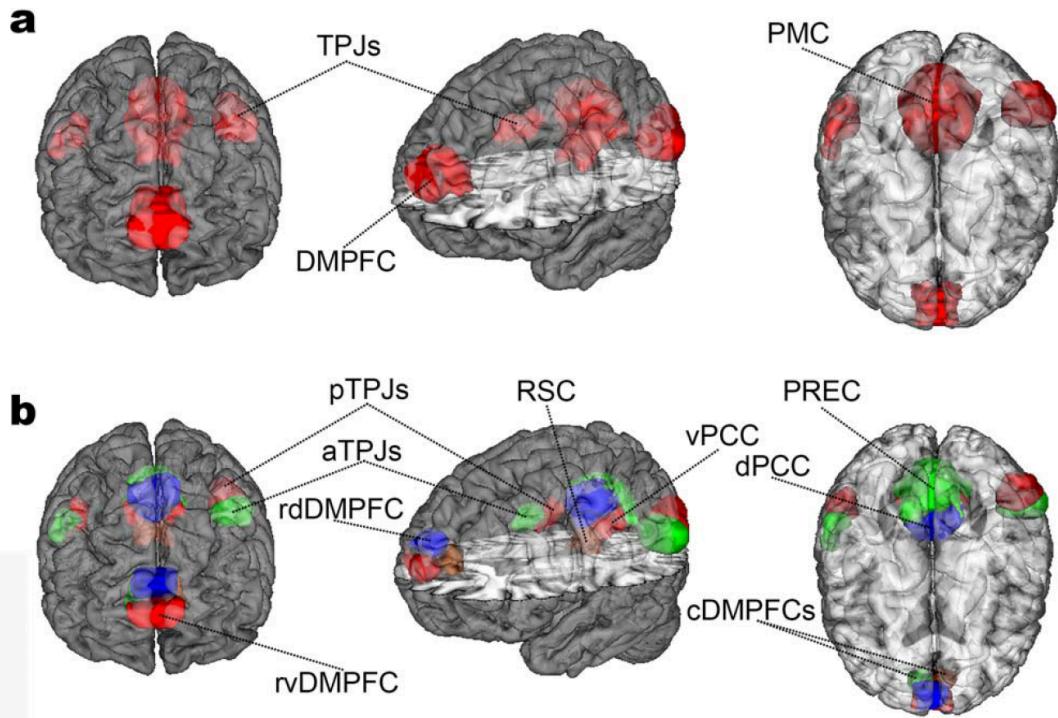
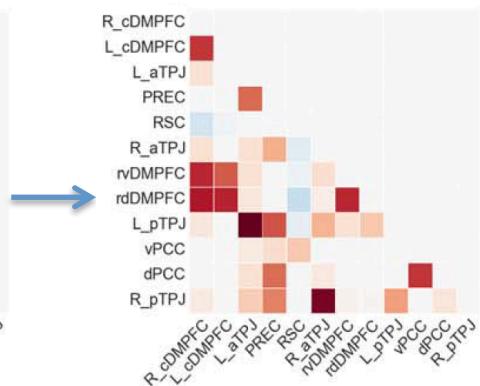
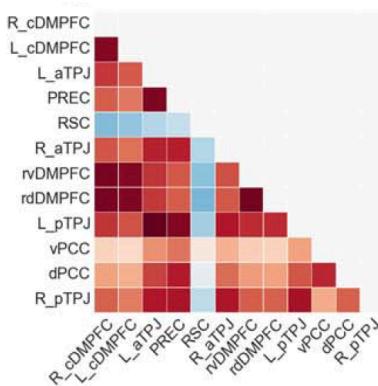


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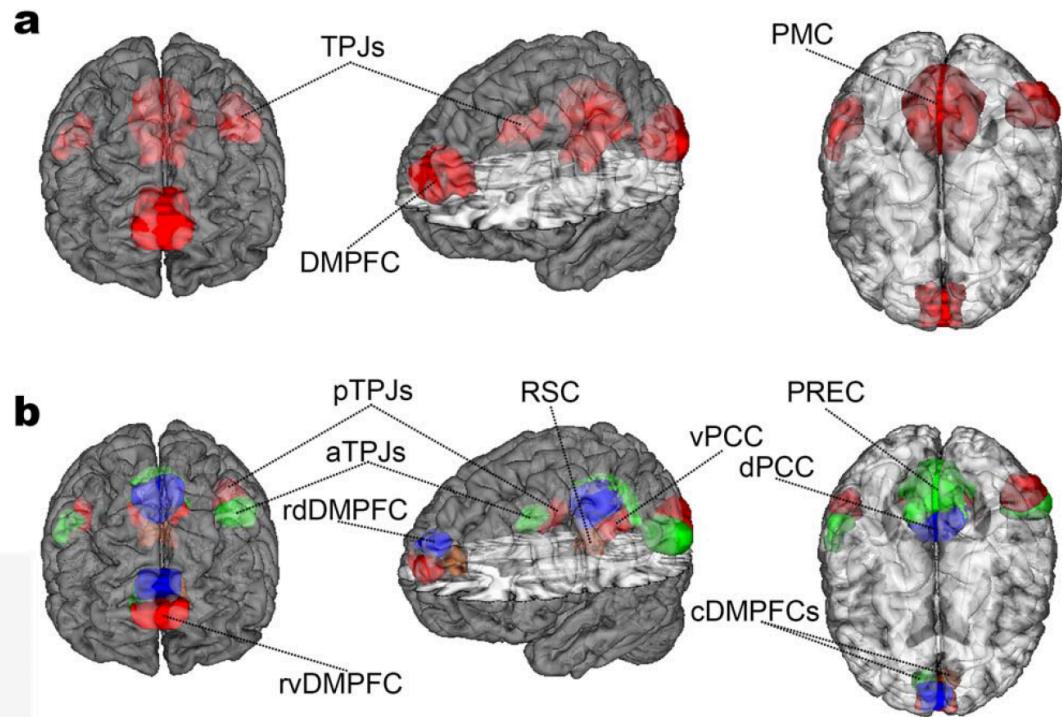
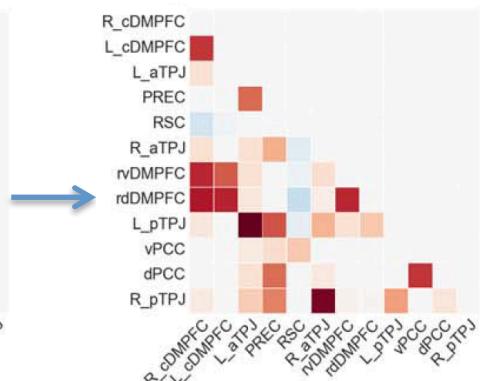
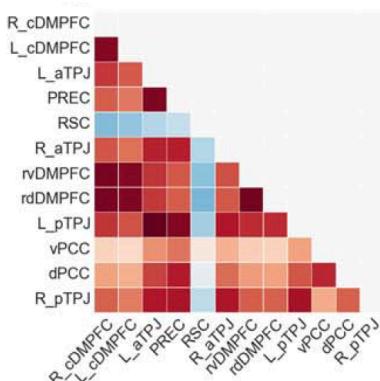


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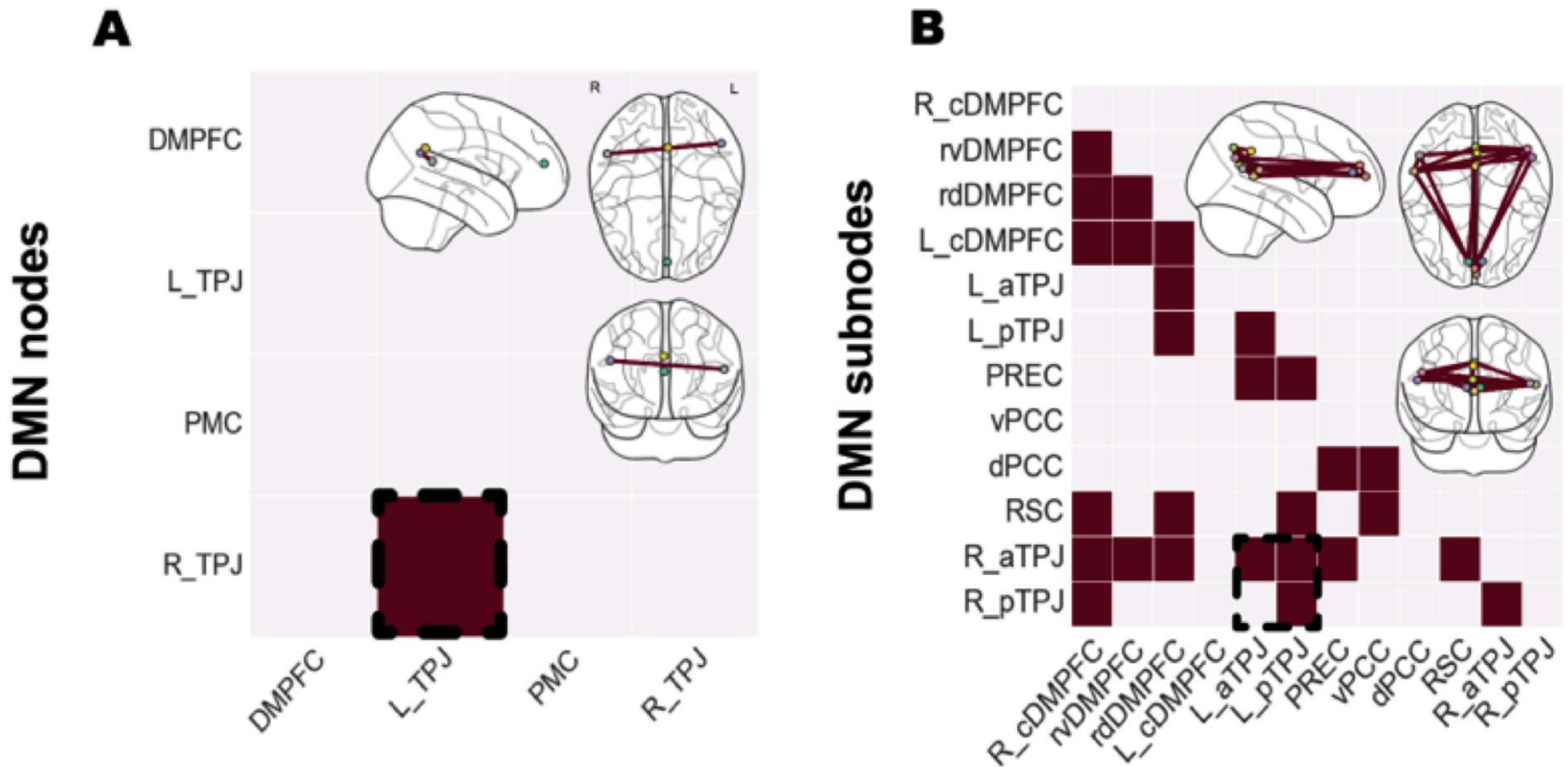


Hypoconnectivity

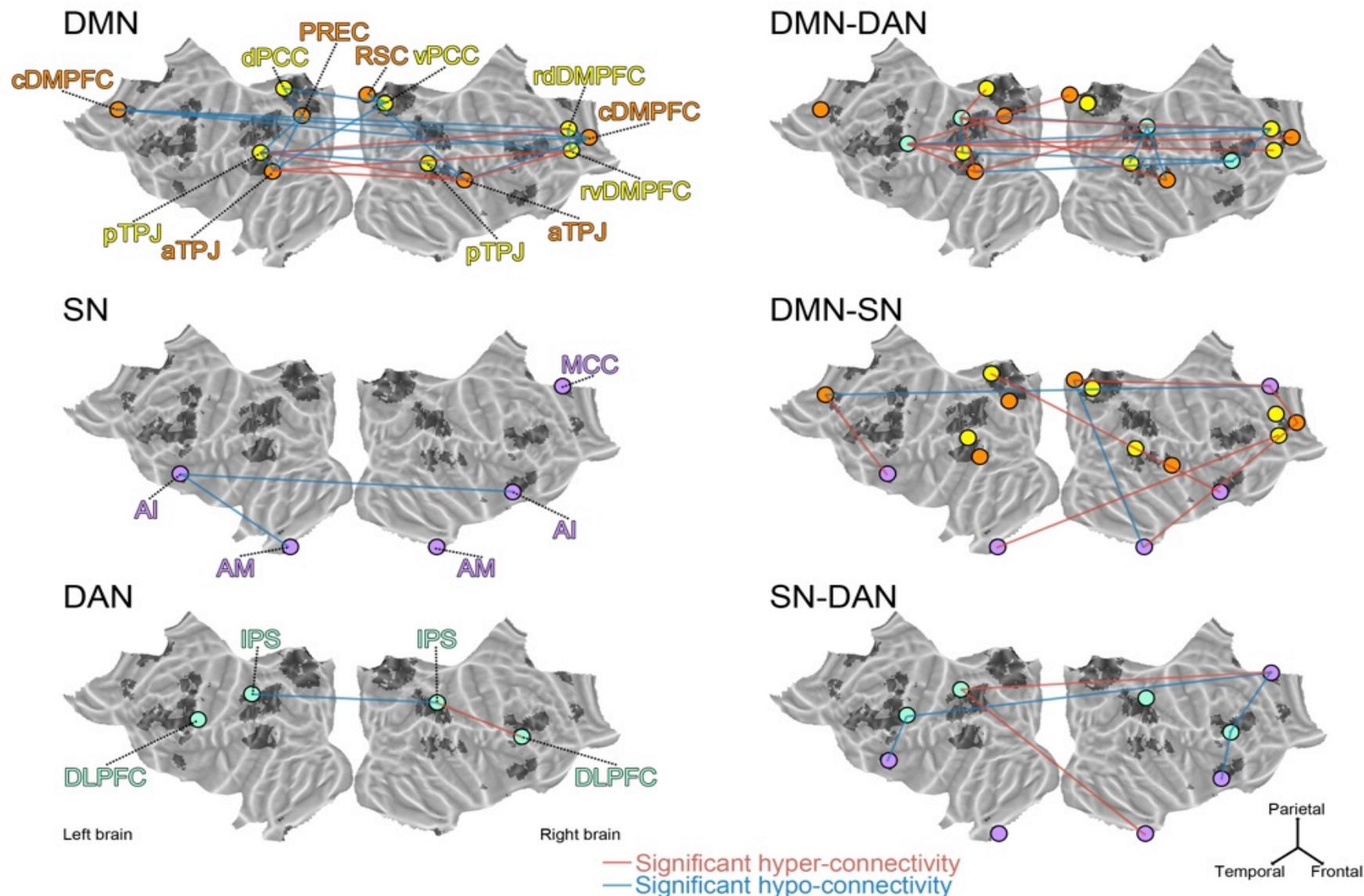


Interoperability

# A more fine-grained approach of the default mode



# Between rather than within network aberrations



# A gold standard for quantifying schizophrenia symptoms

The positive and negative syndrome scale (**PANSS**) for schizophrenia.

SR Kay, A Fiszbein, LA Opler - Schizophrenia bulletin, 1987 - psycnet.apa.org

Abstract The variable results of positive-negative research with schizophrenics underscore the importance of well-characterized, standardized measurement techniques. We report on the development and initial standardization of the Positive and Negative Syndrome Scale ...

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**2, 3, 4, 5, 6, and also 7 factors**

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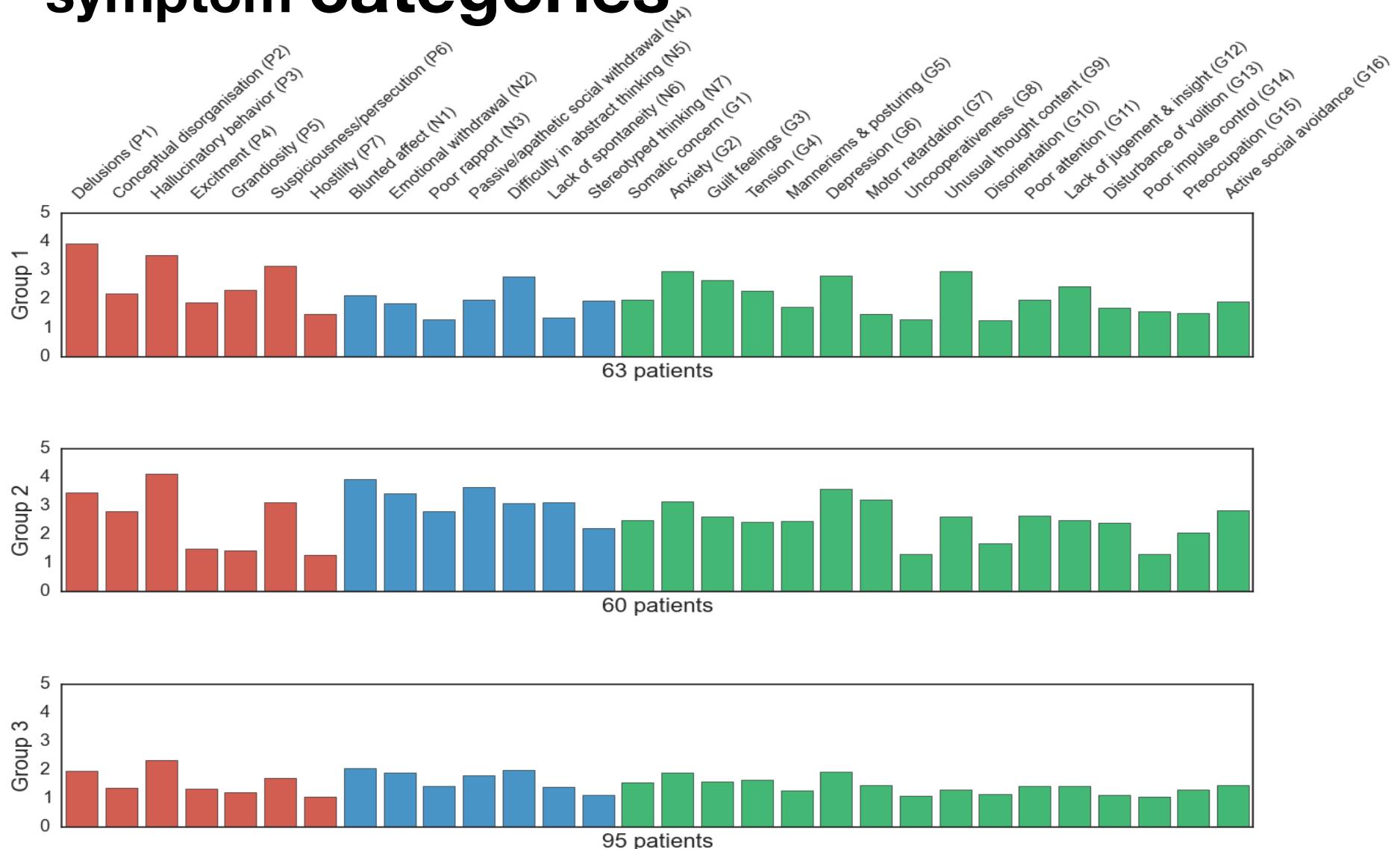
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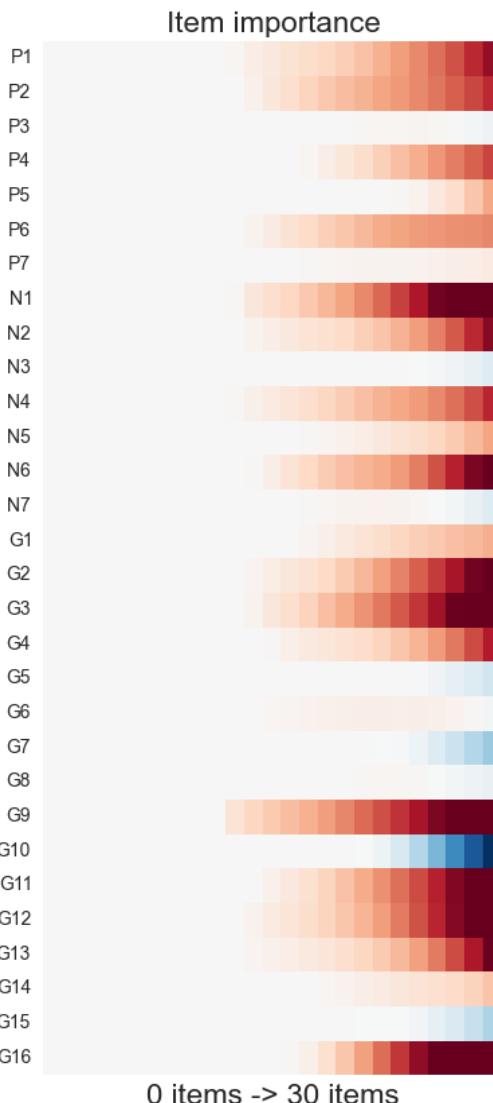
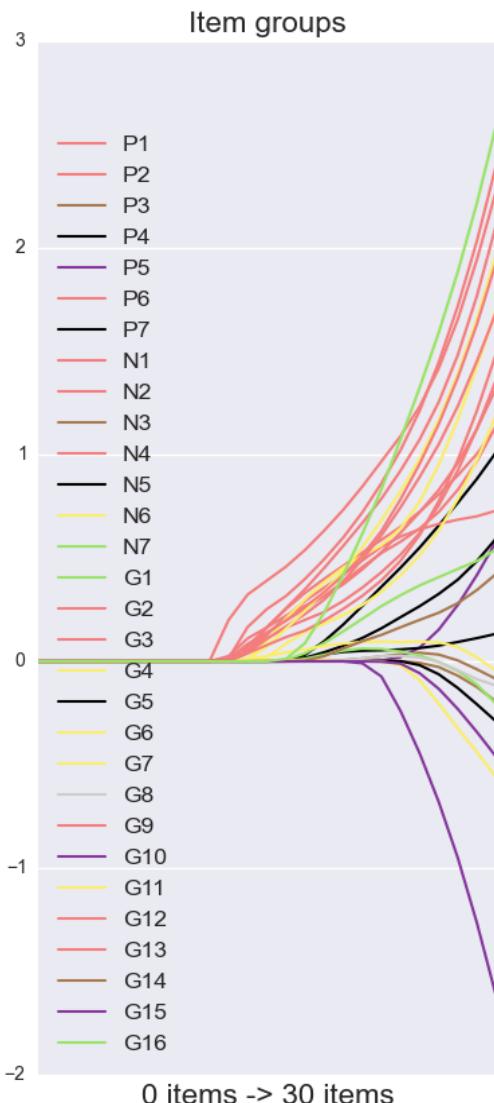
☆ 49 Zitiert von: 15117 Ähnliche Artikel Alle 14 Versionen Web of Science: 10330 ⓘ

2, 3, 4, 5, 6, and also 7 factors

# Emergence of clinically meaningful symptom categories



# Highly predictive subset for making accurate statements about schizophrenia severity



Shades of the DMN in schizophrenia

3/3 Patterns of schizophrenia symptoms

Conclusion

# Take-home message

- DMN proper not convincing to play the main role in schizophrenia
- Deficits **between** (rather than within) the DMN and other multimodal networks

# Take-home message

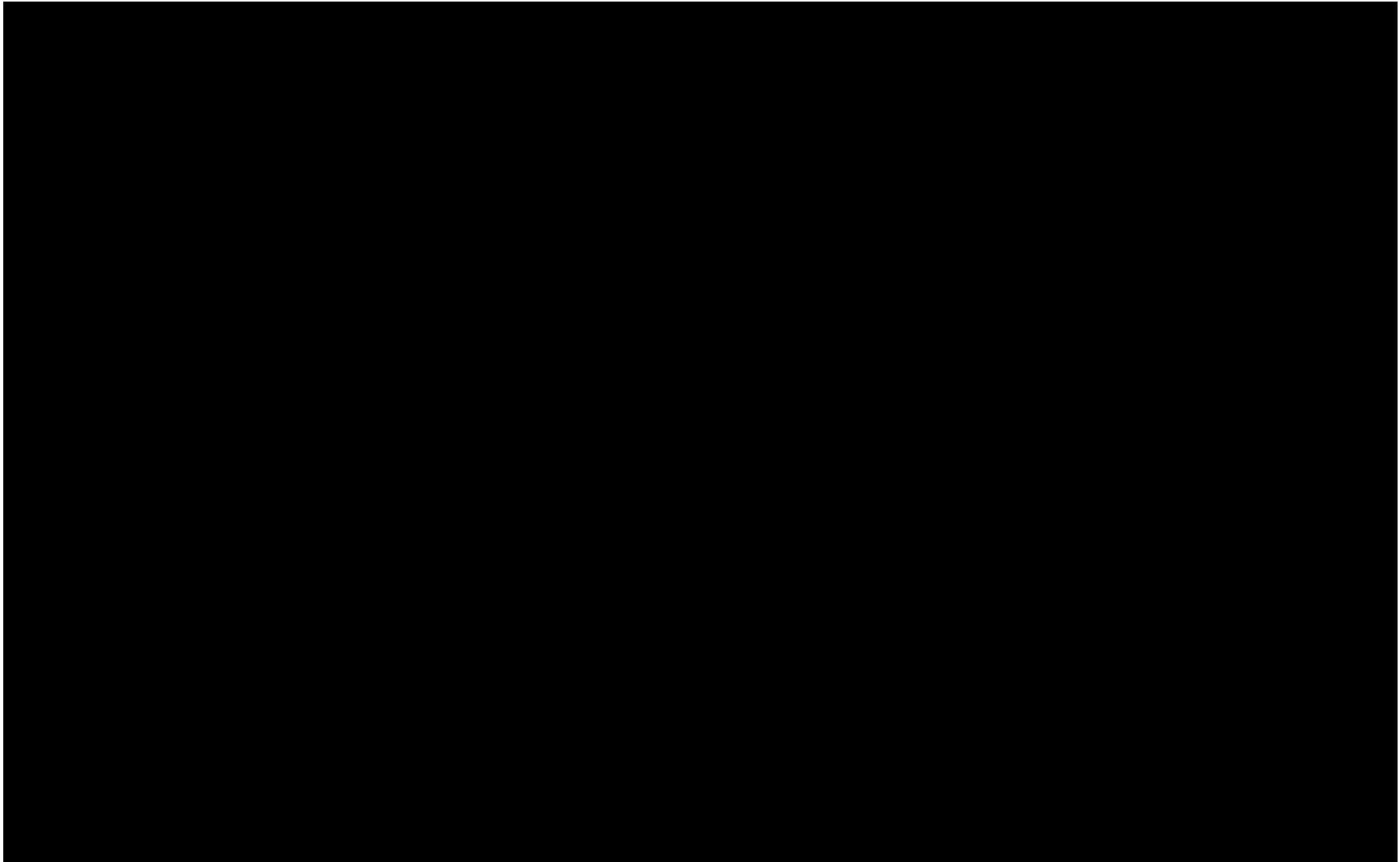
- DMN proper not convincing to play the main role in schizophrenia
- Deficits **between** (rather than within) the DMN and other multimodal networks
- 3 patient groups uncovered presenting distinct symptom profiles
- 11 PANSS items highly effective in detecting severe schizophrenia patients



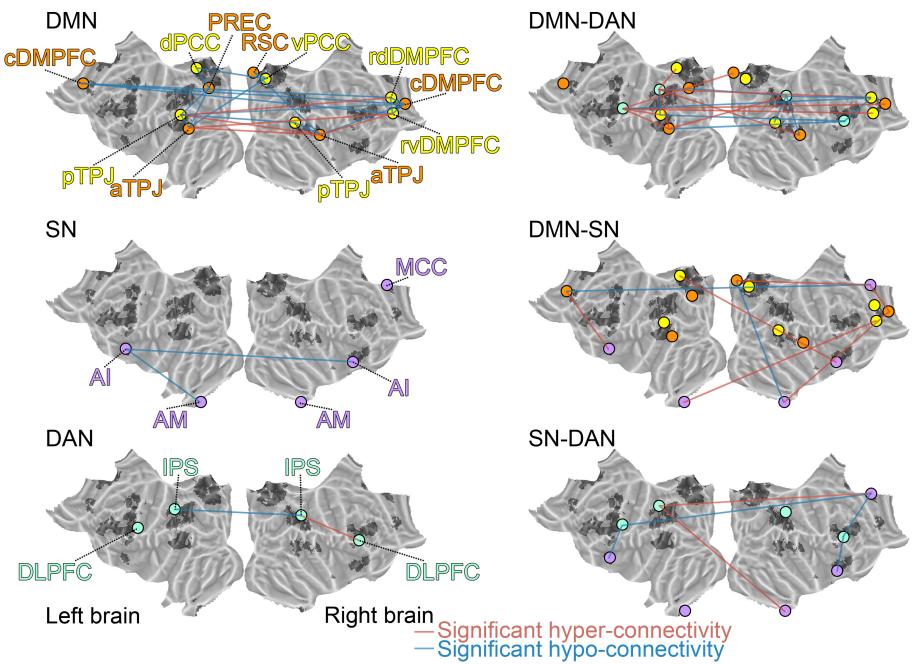
# **Supplementary material**

# **DMN SHADES**

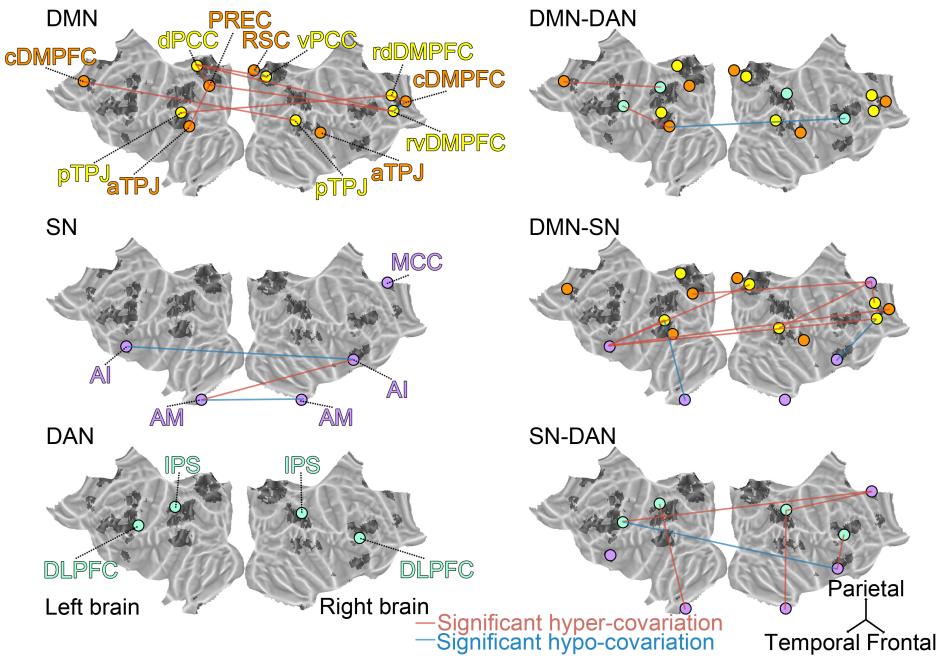
# Flat brain



### A. DYSFUNCTIONAL HYPER- AND HYPO- CONNECTIVITY ACROSS NETWORKS

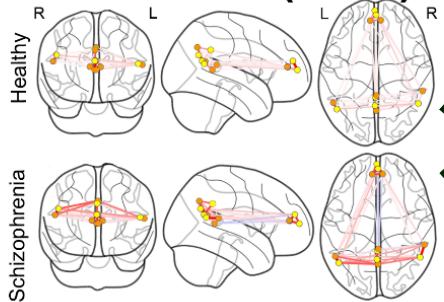


### B. ABERRANT STRUCTURAL HYPER- AND HYPO- COVARIATION ACROSS NETWORKS

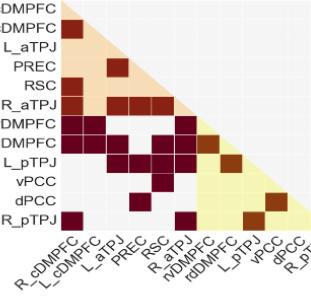


## Brain function (RSFC)

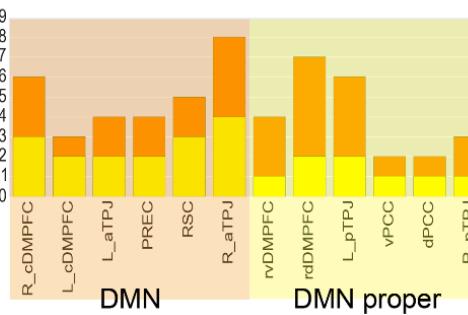
### Intra-network



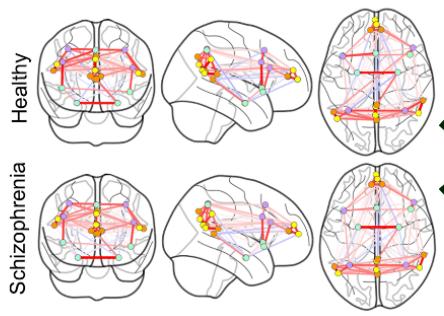
### Group differences



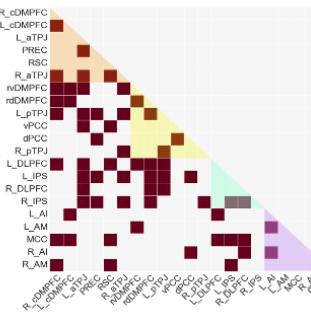
### # aberrations



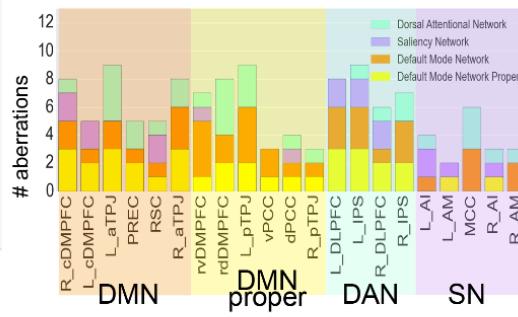
### Across-networks



### Group differences

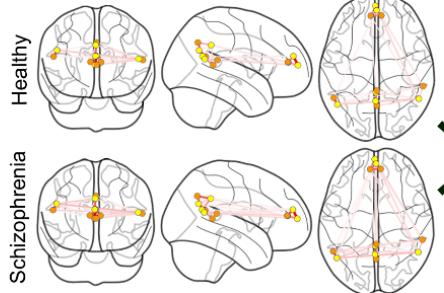


### # aberrations

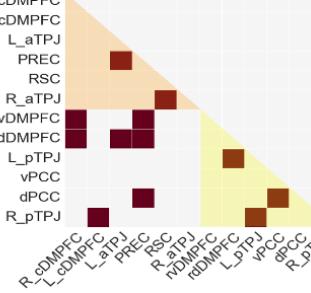


## Brain structure (VBM)

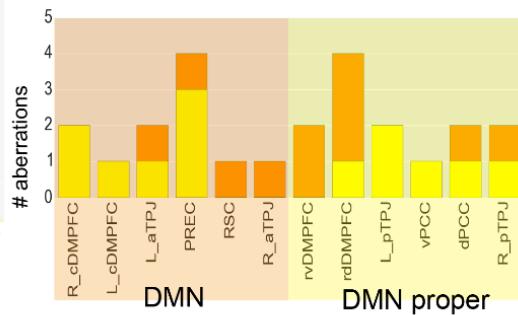
### Intra-network



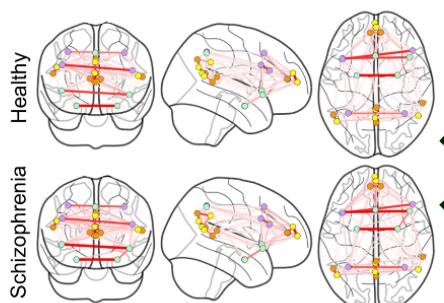
### Group differences



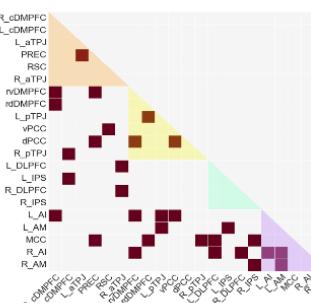
### # aberrations



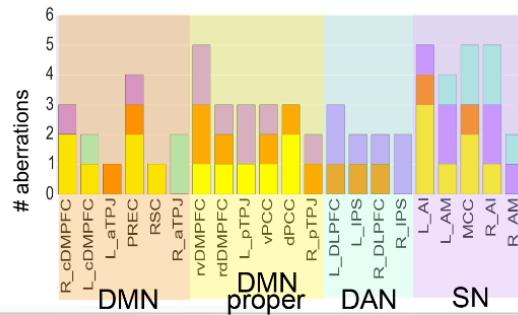
### Across-networks



### Group differences



### # aberrations



# In sum:

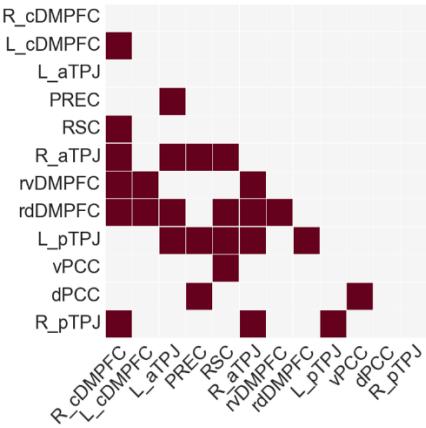
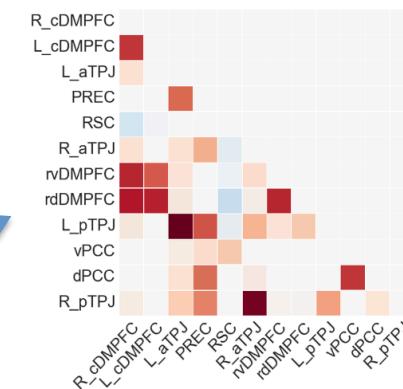
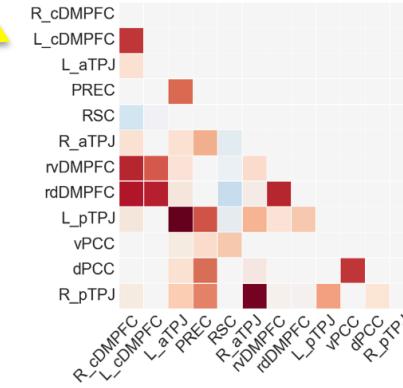
fMRI Sz

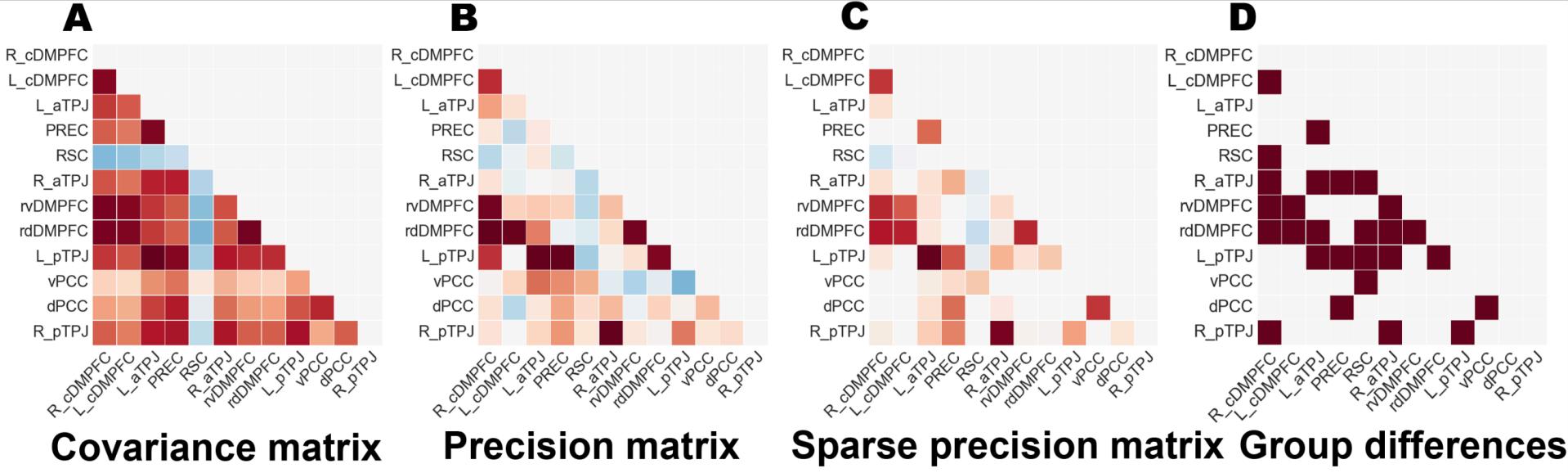
DMN  
(more fine-grained)  
DAN  
SN

n=325

fMRI He

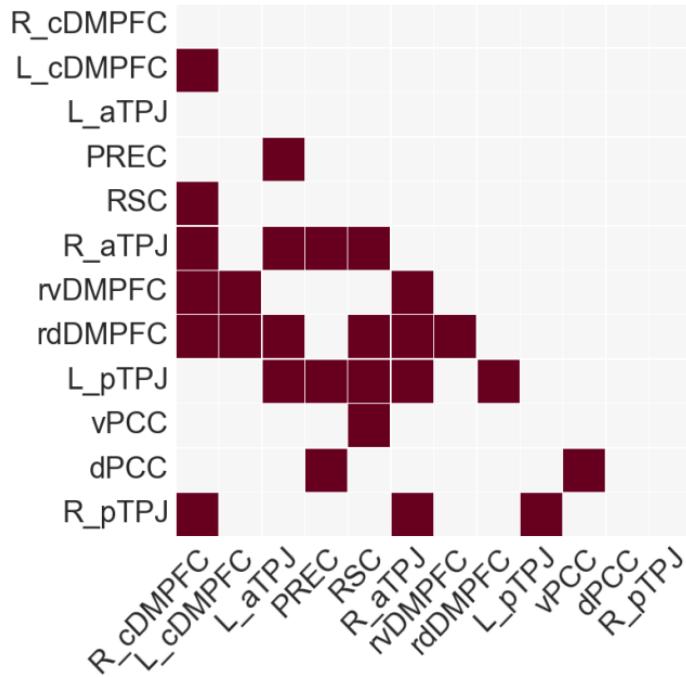
DMN  
(more fine-grained)  
DAN  
SN





# Supplementary information

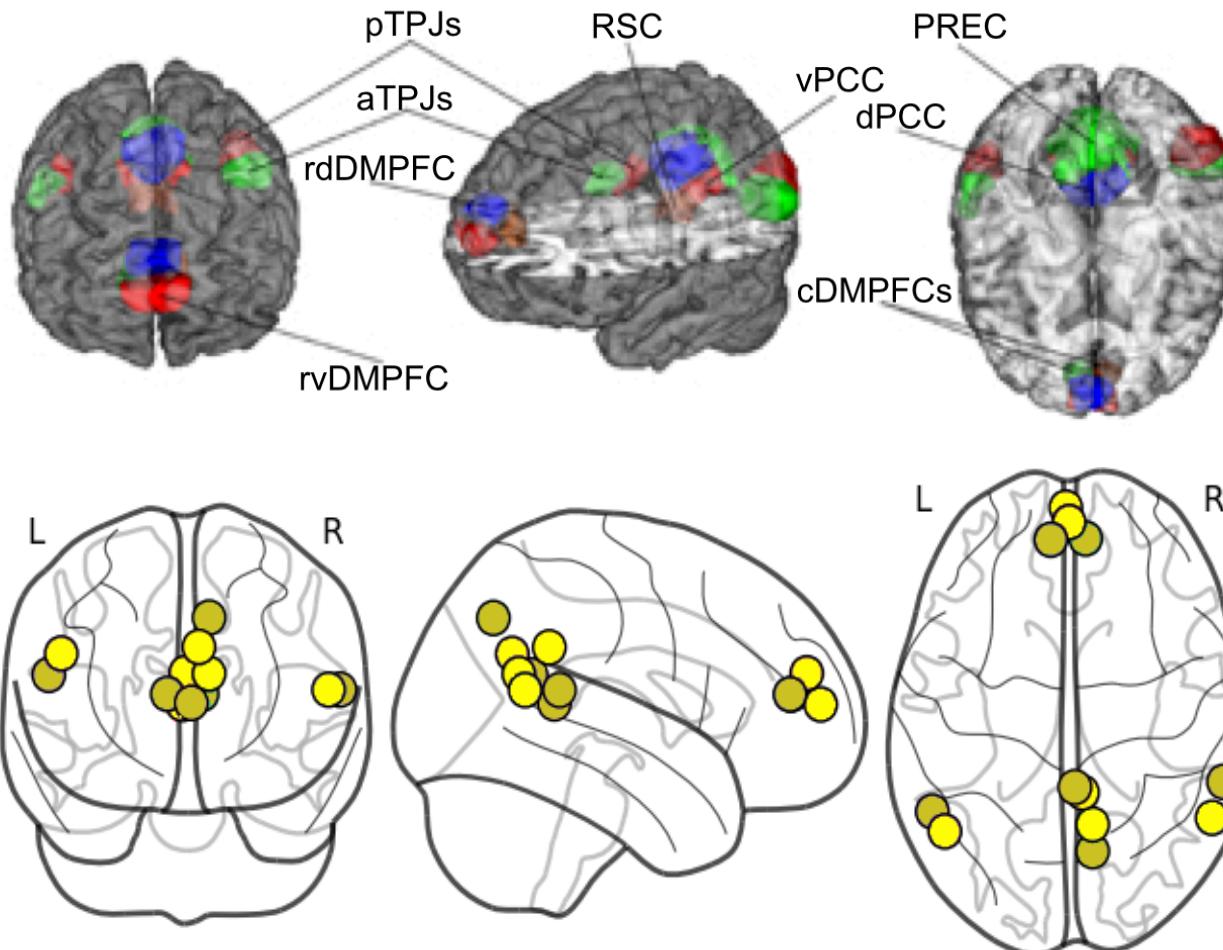
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- **Bootstrap** ( $n=1000$ ) healthy brain data
- **Recompute** sparse inverse covariance estimation for each bootstrap sample
- **Test** for differences between healthy and schizophrenic group ( $p<0.05$ )

Efron and Tibshirani, 1994

# The default mode network proper

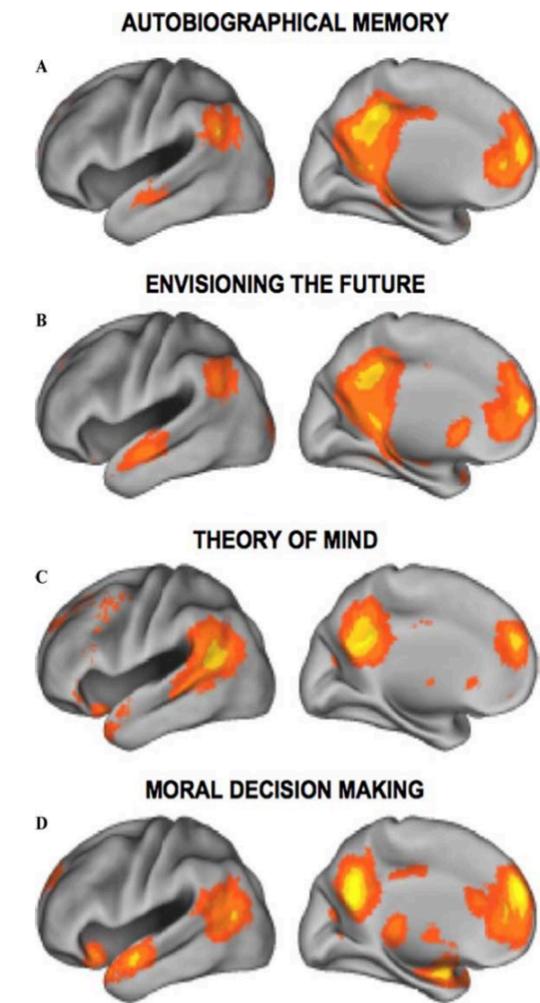
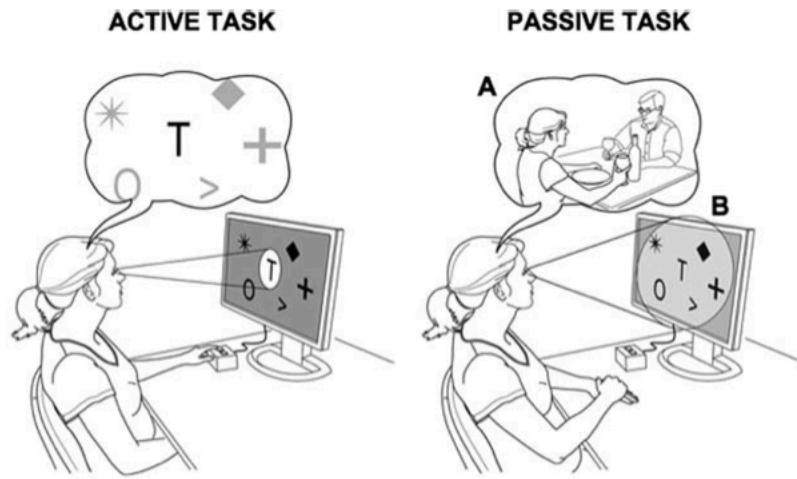


**DMN subregions:** Bzdok et al., 2013; Bzdok et al., 2015; Bzdok et al., 2016b; Eickhoff et al., 2016  
**ROIs Available:** <http://neurovault.org/collections/2216/>.

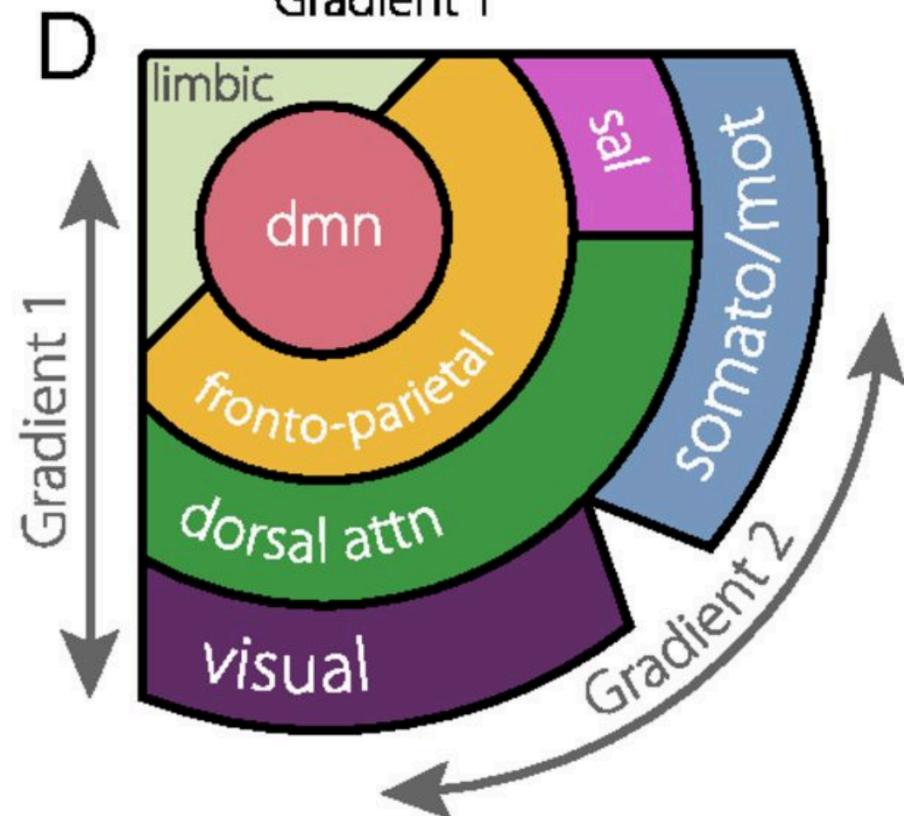
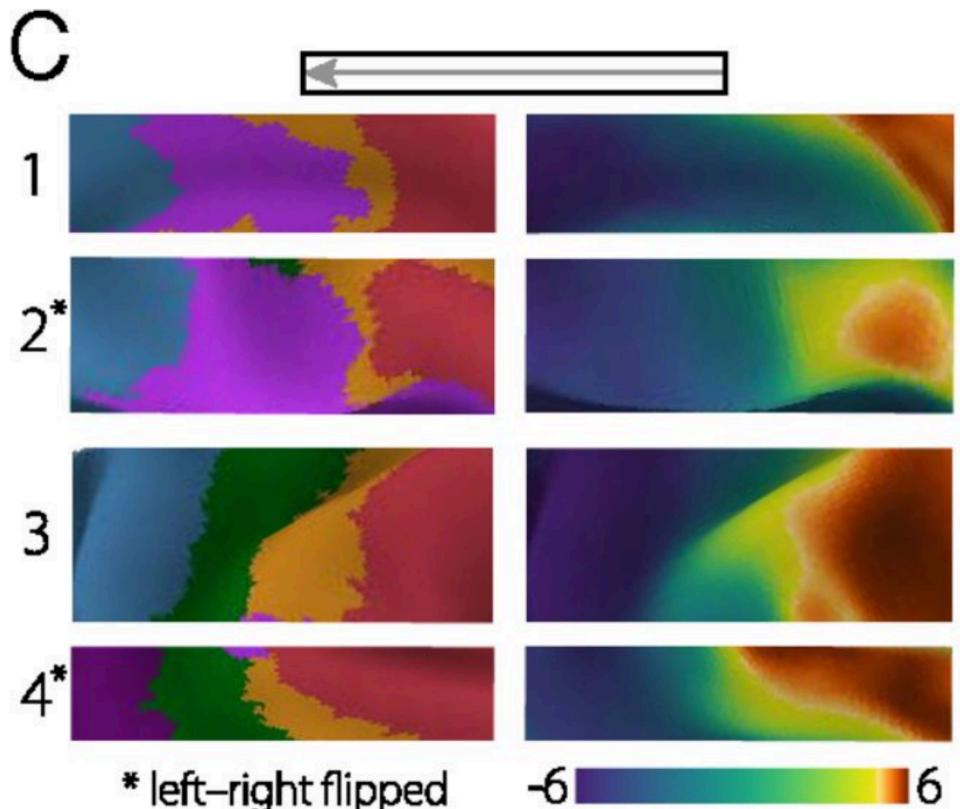
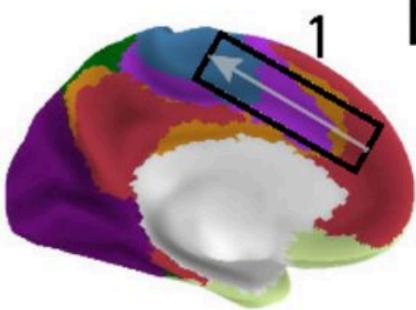
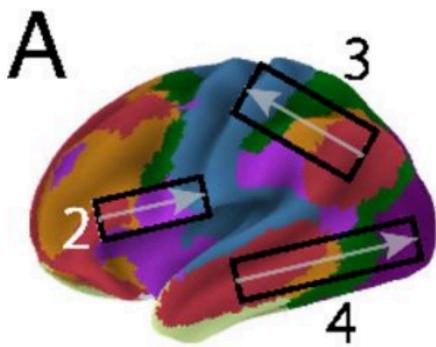
# The Default Mode Network (DMN)

Buckner et al.: The Brain's Default Network

- Increased activation during wakeful rest, a.k.a. task negative periods
- Consume the vast majority of brain's required energy
- A range of task negative processes: introspection, daydreaming, and memory recall



Whitfield-Gabrielly et al., 2012  
Buckner et al., 2013



# DMN *proper* not convincing to play the main role in schizophrenia

---

## Right anterior TPJ most affected subregion in RSFC

- Externally focused evaluation of sensory input as well as maintenance of perception-action cycles associated with the SN  
(Mars et al., 2012; Bzdok et al., 2013b; Glasser et al., 2015; Humphreys and Ralph, 2015; Bzdok et al., 2016b)
- False subjective beliefs (delusion), perceiving unreal stimuli (hallucinations), awkward sensations (paresthesia), concentration difficulties, disorganized speech and motor movement.

## Precuneus most affected subregion in VBM

- Visuomotor processes (attentional shifting, reaching movements, and hand-eye coordination).  
(Mesulam, 1981; Stephan et al., 1995; Margulies et al., 2009).
- Loss of train of thought, impairments in executive function, working memory, and memory retrieval, as well as psychogenic motor abnormalities (catatonia).

**Both are similarly believed to govern context-dependent reorganization of large-scale networks**

(Downar et al., 2000; Cavanna and Trimble, 2006; Bzdok et al., 2013b; Seghier, 2013).

# Discrepancies between volumetric and functional aberration patterns in schizophrenia.

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- No strong evidence for analogous patterns:  
aRTPJ and DAN-DMN in RSFC  
PREC and SN-DMN in VBM
- Suggest **heterogeneous changes** in cortex architecture that **do not map in a simple way** to patterns of neural communication
- **Similarities: some areas almost intact in brain structure and function:**  
Right posterior TPJ, the ventral and dorsal PCC, as well as the left caudal DMPFC = **DMN proper**
- **DMN-SN:** longer-term compensatory mechanism due to impaired executive function in patients with schizophrenia.
- **DMN-DAN:** multifaceted dysbalance in allocating attentional resources to internal thought and emotion

**Supplementary Table 1: Demographic information on participants**

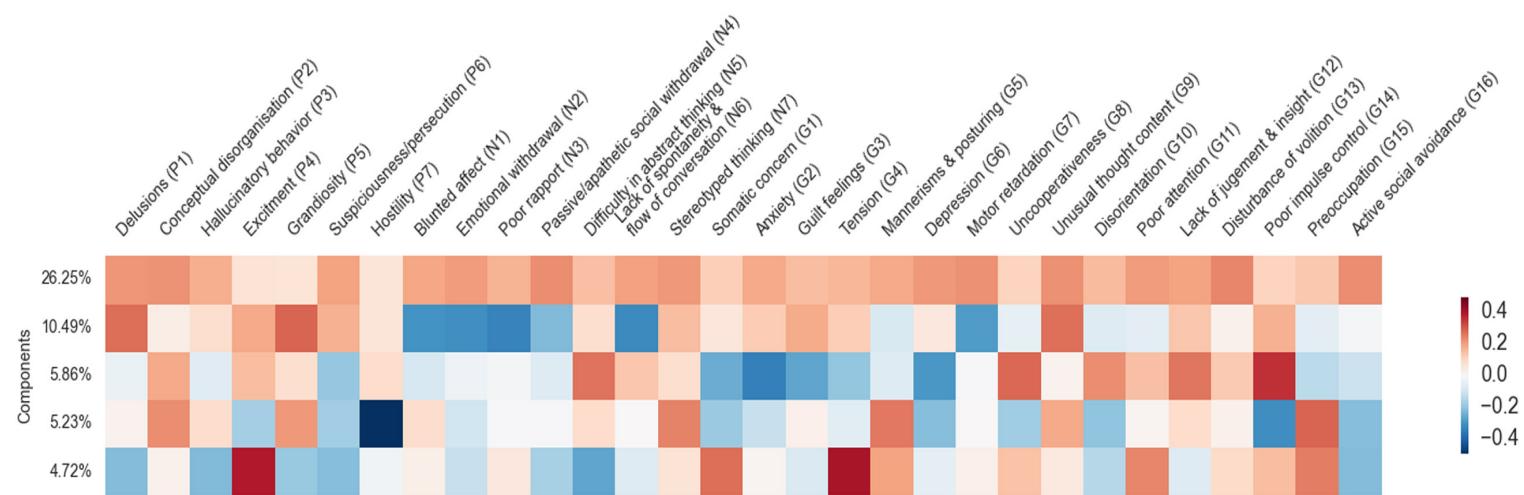
Site	Group	Age	Age Difference (p value)	Female	Male	n	N
Groningen	HC	31.6		13	19	32	
Groningen	SZ	33.6	0.476	13	19	32	64
Göttingen	HC	31.9		7	22	29	
Göttingen	SZ	32.0	0.978	6	27	33	62
Aachen	HC	33.2		3	10	13	
Aachen	SZ	35.1	0.682	3	11	14	27
Lille	HC	29.0		5	11	16	
Lille	SZ	33.3	0.048	6	9	15	31
COBRE	HC	35.8		23	50	73	
COBRE	SZ	38.2	0.270	13	55	68	141
<b>Σ</b>	HC	<b>33.4</b>		<b>51</b>	<b>112</b>	<b>163</b>	
	SZ	<b>35.3</b>	<b>0.491</b>	<b>41</b>	<b>121</b>	<b>162</b>	<b>325</b>

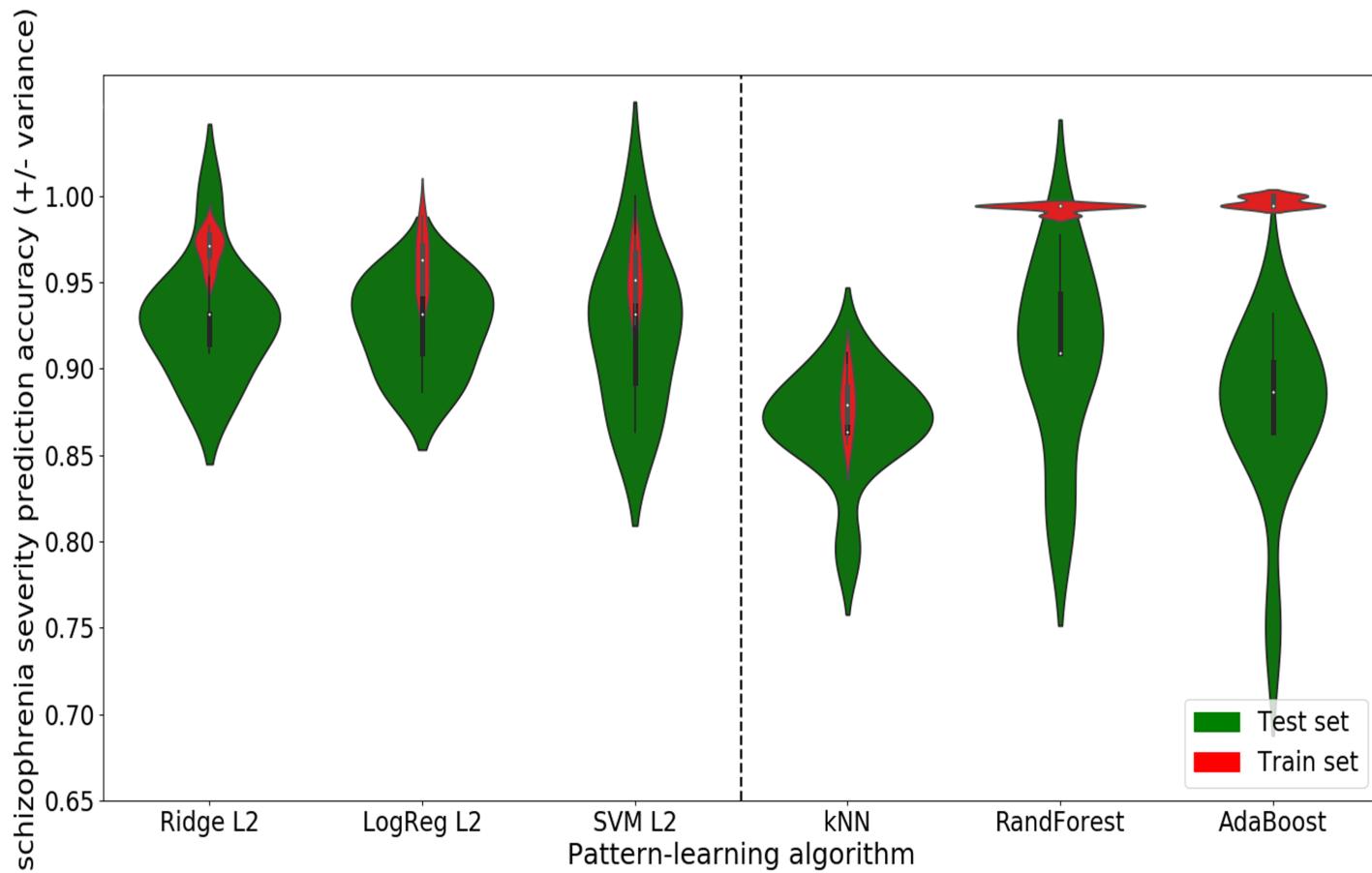
**Supplementary Table 2: Information on MRI scanning sites**

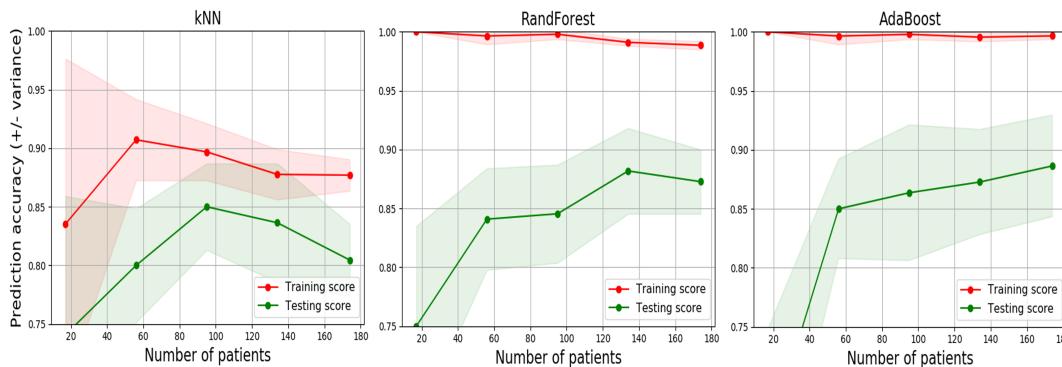
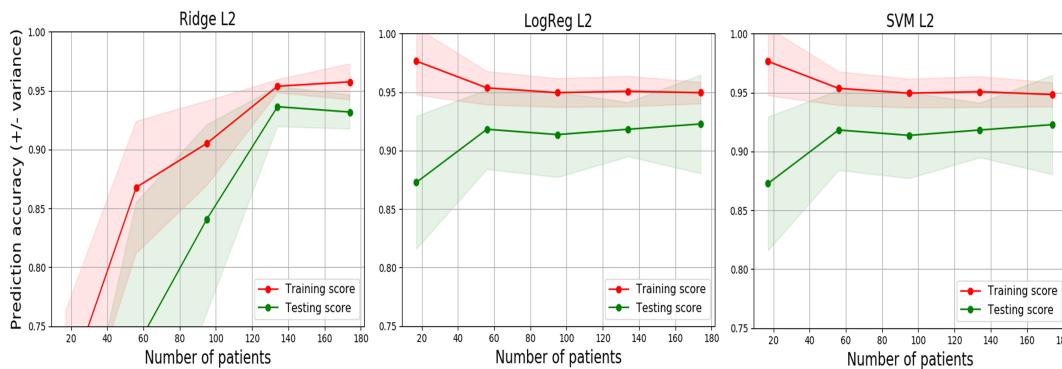
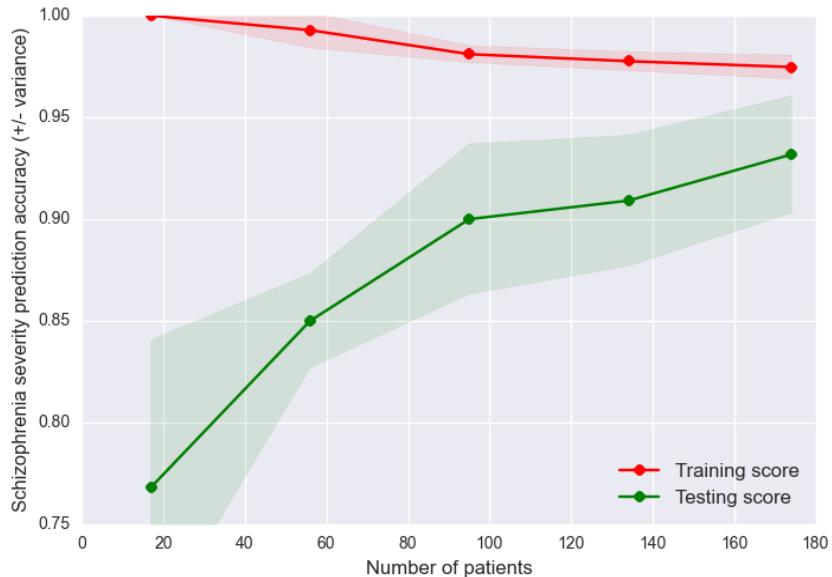
Place	Aachen	Gröningen	Göttigen	Lille	COBRE
Scanner	Siemens 3T TrioTim	Philips Achieva 3 T	Siemens TrioTim	Philips Achieva 3T	Siemens 3T TrioTim
TR (ms)	2000	2400	2000	1000	2000
TE (ms)	28	28	30	9,6	29
Number of slices	34	43	33	45	32
Slice- thickness (mm)	3,3	3	3	3,4	3,5
Gap (mm)	3,6	n.a	0,6	n.a	1
Flip-angle	77	85	70	9	
Voxel-size (mm <sup>3</sup> )	n.a	n.a	n.a	3,219 x 3,219 x 3,4 mm	3 x 3 x 4mm <sup>3</sup>
Orientation	Axial	Axial	Axial	Sagittal	Axial
In-plane resolution (mm <sup>2</sup> )	3,6 x 3,6	3,44 x 3,44	3 x 3	n.a	3,75 x 3,75
Cross hair	Yes	No, eyes closed	Yes	No, eyes closed	Yes

# **Supplementary material**

# **PANSS**







**Supplementary table 1:**

Sites	# patients	# male	# female	Age	Age	Age onset	Age onset
				(M)	(Std)	(M)	(Std)
Aachen	28	20	8	36,57	9,79	27,68	8,61
Groningen	32	19	13	32,97	11,19	25,78	9,27
Utrecht	23	13	10	35,46	9,78	25,28	6,08
Goetingen	36	29	7	32,06	9,81	25,61	8,16
Tuebingen	9	4	5	32,11	9,37	23	0
Lille	18	11	7	33,89	7,65	22,89	2,59
Cobre	72	58	14	38,17	13,89	23,61	5,95
<b>TOTAL</b>	<b>218</b>	<b>154</b>	<b>64</b>	<b>35,3</b>	<b>11,42</b>	<b>24,83</b>	<b>5,06</b>

## Patient Information

## **Personal notes**

## P1. Delusions

Beli  
in tl P

## P2. Conceptual disorganization

Di  
ci

### **P3. Hallucinatory behavior**

1 A B

2 M 1

### **N1. Blunted affect**

Dim

N  
La

### **N2. Emotional withdrawal**

Lack of interest in, involvement with, and affective commitment to life's events. Basis for rating: reports of functioning from primary care workers or family and observation of interpersonal behavior during the course of interview.

1 Absent - Definition does not apply

**2 Minimal** - Questionable pathology; may be at the upper extreme of normal limits

**3 Mild** - Usually lacks initiative and occasionally may show deficient interest in surrounding events.

**4 Moderate** - Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.

**5 Moderate severe** - Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.