Aberrant insular regulation of brain network interactions in schizophrenia

Andrei Manoliu[1,2], Valentin Riedl[2,4], Susanne Neufang[2], Andriy Zherdin[2], Nicholas Myers[2], Mark Mühlau[4], Claus Zimmer[2], Hans Förstl[1], Josef Bäuml[1], Afra M. Wohlschläger[2,4], Christian Sorg[1,2,3]

Department of [1]Psychiatry, [2]Neuroradiology, [3]Nuclear Medicine, [4]Neurology of Klinikum rechts der Isar, Technische Universität München, Germany

1. INTRODUCTION

- **Insula**. In schizophrenia, consistent structural and functional changes have been demonstrated for the insular cortex including aberrant salience and prediction error coding, both representing critical elements of psychosis[1,2].
- **DMN-CEN interactions.** Interactions within and between the default-mode and central-executive network (DMN, CEN) are impaired in schizophrenia[3].
- **Salience Network.** The insula is a critical component of the salience network (SN), an intrinsic connectivity network (ICN) comprising insula, the fronto-insular operculum and dorsal anterior cingulate cortex (dACC). The SN is affected by both impaired structural integrity and functional connectivity in schizophrenia[4,5].
- **SN´s regulatory function for DMN-CEN interactions**. Critical regulatory impact of the SN on DMN-CEN interactions has been shown[6]. Recently, it has been proposed that the SN's key function is its regulatory role in switching between internally oriented self-related (DMN-based) and externally oriented goal-directed (CEN-based) processes[7].

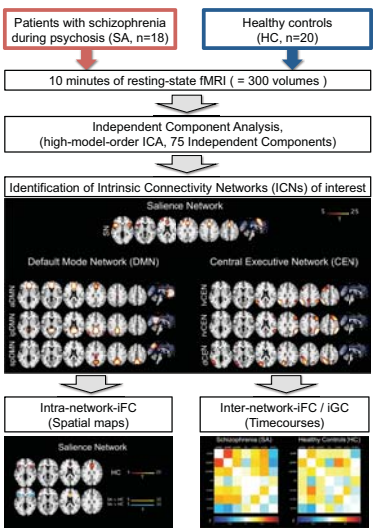
2. QUESTIONS

① Is the insular Salience Network´s regulatory function for the DMN-CEN interactions disrupted in schizophrenia ?

② Are these alterations related to the degree of impaired DMN-CEN interactions and severity of psychosis ?

3. METHODS

Schematic of the analysis pipeline



Participants' demographic and clinical characteristics

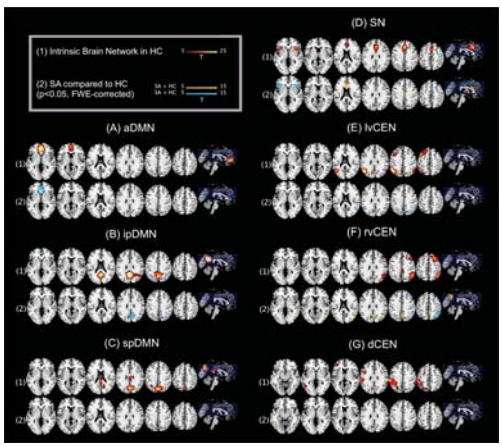
	SA (n=18)	HC (n=20)
Measure	**Mean (SD)**	**Mean (SD)**
Age	35,33 (12,49)	34,00 (13,35)
Sex (m/f)	9 / 9	9 / 11
PANSS		
Total	76,44 (18,45)	30,15 (0,67)
Positive	18,06 (5,74)	7,05 (0,22)
Negative	19,94 (8,11)	7,10 (0,45)
General	37,67 (9,93)	16,05 (0,23)
GAF	41,50 (11,55)	99,75 (1,12)
CPZ	466,72 (440,49)	

Data analysis

- **Selection of networks of interest:** multiple spatial regressions on 75 ICs´ SMs using T-maps of 28 ICNs described by Allen et al[8].
- **Intra-network intrinsic functional connectivity (iFC):** voxel-wise tests on participants´ SMs with age, sex and total gray matter (GM) volumes as covariate-of-no-interest (p<0.05 FWE-corrected).
- **Inter-network intrinsic functional connectivity (iFC)**: ICN TCs were detrended, despiked, filtered using a fifth-order Butterworth low-pass filter with a high frequency cutoff of 0.15Hz, and pairwise correlated by Pearson's correlation. Fisher-transformed correlation coefficients were entered into two-sample-t-tests. (p<0.05, corrected for multiple comparisons)
- **Inter-network-iGC (Granger Causality Analysis):** Pairwise correlation was applied between SN´s TC and all ICNs´ TCs with lag = 1 ($SN_{(i)} \rightarrow ICN_{(i+1)}$ for i=1 to n timepoints). Fisher-transformed correlation coefficients were entered into two-sample-t-tests. (p<0.05).
- **Correlations:** Partial correlations of SN´s right and left AI group difference cluster eigenvariate and z-transformed correlation-coefficients of each pair of network TCs or PANSS scores for hallucination (P3) and delusions (P1), respectively, including age, sex, total GM and CPZ as covariates of no interest.

4. RESULTS

1. Intra-iFC of the SN is disrupted in bilateral anterior insula in psychotic patients.

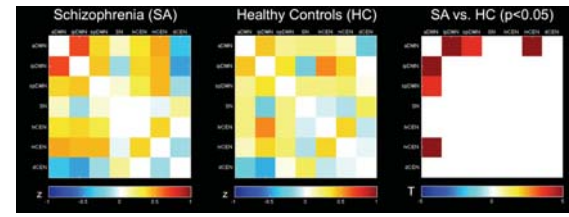


DMN, SN and CEN for HC and corresponding group differences for SA.

- **SN:** SA showed both decreased intra-iFC in bilateral AI and increased iFC in bilateral ACC compared to HC.
- 3 ICNs representing the **DMN**: SA showed decreased intra-iFC in bilateral ACC and bilateral precuneus.
- 3 ICNs representing the **CEN:** SA showed decreased intra-iFC in bilateral inferior parietal lobule and bilateral frontal gyrus and increased intra-iFC in the right angular gyrus and left inferior temporal gyrus.

4. RESULTS (CONTINUED)

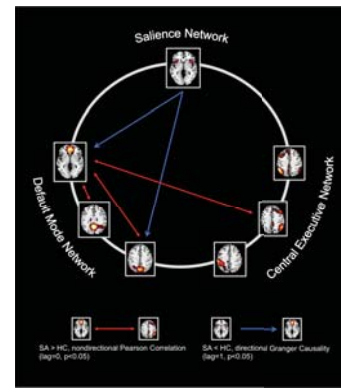
2. Inter-iFC between DMN and CEN was increased in psychotic patients



Inter-network intrinsic functional connectivity (inter-iFC) matrix for SA and HC.

- **Inter-iFC was increased within the DMN in psychotic patients:** SA showed increased inter-iFC between the aDMN and ipDMN as well as between the aDMN and the spDMN.
- **Inter-iFC was increased between DMN and CEN in psychotic patients**: SA showed increased inter-iFC between the aDMN and the rvCEN and a trend to increased inter-iFC between the spDMN and the rvCEN.
- SA did not show altered inter-iFC between the SN and any other ICN.

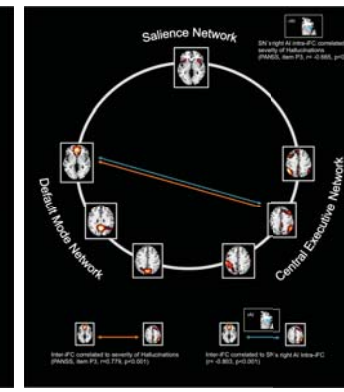
3. SN´s regulatory function for DMN-CEN interactions is altered in psychosis



Between-group differences of both inter-network intrinsic functional connectivity and Granger causality in SA and HC.

- SA showed reduced inter-iGC of the SN on both aDMN and spDMN.
- SA showed a trend to reduced inter-network iGC of the SN on the dCEN (p=0.053).

4. Right anterior insular SN connectivity predicted both DMN-CEN interaction changes and psychosis severity in patients



Partial correlations.

- SN's right AI´s intra-iFC correlated negatively with the inter-iFC between aDMN and rvCEN.
- SN's right AI's intra-iFC correlated negatively with the severity of hallucinations (P3).
- Inter-iFC between aDMN and rvCEN correlated positively with the severity of hallucinations (P3).

5. CONCLUSION

① Impaired anterior insular SN activity is associated with an aberrant regulatory impact on DMN-CEN interactions in patients with schizophrenia

② The degree of these alterations is related to the severity of psychosis.

These findings link changes of insular Salience Network connectivity and both DMN/CEN activity and severity of symptoms via reduced insula network regulation in schizophrenia .

6. REFERENCES

1. Palaniyappan L. (2012), "Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction", Journal of psychiatry & neuroscience, vol. 37, no. 1, pp. 17-27.
2. Craig A.D. (2009), „How do you feel – now? The anterior insula and human awareness", Nature Reviews Neuroscience, vol. 10, no.1, pp. 59-70
3. Hasenkamp W. (2011), „Altered engagement of attention and default networks during target detection in schizophrenia", Schizophrenia Research, vol. 125, no. 2-3, pp. 169-173.
4. Ellison-Wright I. (2008), „The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis", American Journal of Psychiatry, vol. 165, no. 8, pp. 1015-23.
5. White T.P. (2010), "Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia", Schizophrenia Research, vol. 123, no. 2, pp. 105-115
6. Sridharan D. (2008), „A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks", Proceedings of the National Academy of Sciences, vol. 105, no. 34, pp. 12569-74.
7. Menon V. (2011), "Large-scale brain networks and psychopathology: a unifying triple network model", Trends in cognitive sciences, vol. 15, no. 10, pp. 483-506
8. Allen E.A. (2011), "A baseline for the multivariate comparison of resting-state networks", Frontiers in systems neuroscience, vol. 5.

7. ACKNOWLEDGEMENTS

We are grateful to the participants and to the staff of the Department of Psychiatry and Neuroradiology of Klinikum rechts der Isar, Technische Universität München.

8. CONTACT INFORMATION

Andrei Manoliu, M.D.
Ph.D. student, Department of Psychiatry and Department of Neuroradiology,
Klinikum rechts der Isar, Technische Universität München,
Ismaningerstr. 22, 81675 Munich, Germany
Email: a.manoliu@googlemail.com, Phone: +49-89-4140-7666