Transdiagnostic commonalities and differences in resting state functional connectivity of the default mode network in schizophrenia and major depression

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1. Introduction

Impairments of the ability to engage successfully in social interactions are well documented in schizophrenia (SCZ) and major depressive disorder (MDD) (e.g., Billeke and Aboitiz, 2013; Fiszdon et al., 2013; Savla et al., 2012; Schilbach, 2015; Schneider et al., 2012). In SCZ, these impairments of social interaction have been related to disturbances of self-related and other-related reasoning, i.e., social cognition (e.g., Frith and Corcoran, 1996). In particular, SCZ patients are thought to attribute more meaning to their social surroundings than usual, reflected in so-called positive symptoms such as delusions and paranoia (Frith, 2004). Alternatively, alterations of social cognition in SCZ have been described as a “loss of natural evidence” for being in a world intersubjectively shared with others, thereby leading to alienation and social withdrawal, which may culminate in a psychotic crisis, in which lost intersubjective meaning is replaced by a ‘private’ world of delusions (Blankenburg, 1971; Fuchs, 2007; Klosterkotter et al., 2001). The latter changes have been related to the so-called negative symptom dimension of schizophrenia, which is also known to be highly relevant for prognosis and socio-economic outcome (Fulford et al., 2013; Salvatore et al., 2007).
In depressed patients, impairments of social interaction have similarly been related to attributional biases, which become manifest in abnormally increased, self-defeating, introspective thoughts and self-referential concerns (Marchetti et al., 2012). As in SCZ, disturbances of self-perception and self-referential thought can adversely affect interpersonal relations in MDD and make successful participation in social interaction difficult (Fuchs, 2001; Schilbach et al., 2014). Furthermore, it has been recognized that negative interpersonal experiences throughout the life span constitute an important risk factor for the development of depression and have, thus, become a key target of psychotherapeutic interventions (McCullough, 2003). Since social interactions are normally experienced as intrinsically rewarding (Schilbach et al., 2010), unsuccessful or reduced social interactions can further contribute to depressive symptomatology, but are also known to negatively affect the course of SCZ (Aldeniz et al., 2014; Hooker et al., 2014; Lee et al., 2014; Thomas et al., 2014).

Taken together, impairments of social interaction are well documented in both MDD and SCZ and can therefore be considered as a transdiagnostic symptom. The neurobiology that may underlie these transdiagnostic impairments, i.e., symptoms which fall onto a dimension that cuts across different nosological categories, in otherwise highly dissimilar disorders, however, remains poorly understood. In particular, when considering widespread dysconnectivity in both MDD and SCZ (Hamilton et al., 2013; Stephan et al., 2009), it is not clear whether transdiagnostically observed social impairments are subserved by distinct or common patterns of dysconnectivity. This question of similarities and differences in the neurobiological substrates of transdiagnostic social impairments is of particular relevance in light of current efforts of redefining psychiatric nosology in terms of neurobehavioral systems by taking a dimensional approach to the study of the genetic, neural, and behavioral features of mental disorders (Buckholtz and Meyer-Lindenberg, 2012; Cuthbert and Insel, 2013; Morris and Cuthbert, 2012).

Previous neuroimaging evidence indicates that aberrations of intrinsic functional connectivity (FC) in key nodes of the very robust default mode network (DMN) in particular related to social processing (Bastos-Leite et al., 2015; Das et al., 2012; Liston et al., 2014; Meda et al., 2012; Nixon et al., 2014; Schilbach et al., 2014; Yu et al., 2012). The DMN is classically defined as brain regions that show relative neural deactivation when focusing on the external environment and relative activation for internally focused tasks including autobiographic memory retrieval and conceiving the perspectives of others (Buckner et al., 2008). Recently, a large-scale neuroimaging meta-analysis characterized the overlap of the DMN, emotional processing and social-cognitive networks (Schilbach et al., 2012). The spatial convergence was identified in two cortical midline regions, namely the dorsomedial prefrontal cortex (DMPFC) and precuneus including the posterior cingulate cortex (PRC/PCC) representing the anterior and the posterior hubs of the DMN, respectively (Fig. 1).

![Fig. 1. Meta-analytically defined default mode network. Taken from Schilbach et al. (2012), precuneus including posterior cingulate cortex: PRC/PCC MNI: x = −4, y = −54, z 24, dorso-medial prefrontal cortex: DMPFC MNI: x = −2, y 52, z 14.](image-url)
patients and 5.9% were treated with SGA in combination with the two former agents or with reuptake inhibitors only (5.9%, Table 5). It is important to note that systematically different medication for SCZ and MDD should have different within disease group effects on FC. This source of variance should rather make it more difficult to statistically detect similarities in connectivity aberrations over diseases, than representing a major confound to the transdiagnostic analysis. In addition, this more naturalistic setting should also allow better generalization of the FC results to the overall population of patients with depression and schizophrenia.

Healthy subjects for group comparisons did not have a history of neurological or psychiatric disorders and all subjects gave written informed consent to participate in the study as approved by the local ethics committees. The ethics committee at the HHU Düsseldorf also approved consent to participate in the study as approved by the local ethics committee. The latter was conducted in a naturalistic setting to let their mind wander, but not to fall asleep. The latter was confirmed during a post-scan debriefing interview.

Table 1
Scanning parameters across sites.

| Group          | Siemens TrioTim | Siemens TrioTim | Siemens TrioTim | Philips Achieva 3 T | IRM Philips 3 T |
|----------------|-----------------|-----------------|-----------------|-------------------|----------------|
| Aachen         | TR: 2200 ms     | TR: 2000 ms     | TR: 2000 ms     | TR: 609 ms        | TR: 1000 ms     |
| Göttingen      | TE: 30 ms       | TE: 28 ms       | TE: 30 ms       | TE: 32.4 ms       | TE: 9.6 ms      |
| Utrecht        | Number of slices: 36 | Number of slices: 36 | Number of slices: 33 | Number of slices: 40 | Number of slices: 45 |
| Lille          | Slice-thickness: 3.2 mm | Slice-thickness: 3.3 mm | Slice-thickness: 3 mm | Slice-thickness: 3.4 | Slice-thickness: 3.4 |
|                | Gap: 3.84 mm    | Gap: 3.6 mm     | Gap: 0.6 mm     | Flip-angle: 10°    | Flip-angle: 9°   |
|                | Flip-angle: 77° | Flip-angle: 77° | Flip-angle: 70° | Orientation: axial | Orientation: axial |
|                | Orientation: axial | Orientation: axial | Orientation: axial | Orientation: coronal | Orientation: SAG |

In-plane resolution: 3.1 × 30.1 mm²

Major depressive disorder

Table 2
Group characteristics for schizophrenia (SCZ); SD: standard deviation.

| SCZ patients | Healthy controls | Statistical comparison |
|--------------|------------------|------------------------|
| Participants | n = n =          |                        |
| Entire group | 75 82            |                        |
| Aachen       | 13 13            |                        |
| Aachen #2    | 13 13            |                        |
| Utrecht      | 10 10            |                        |
| Göttingen    | 30 35            |                        |
| Lille        | 9 9              |                        |
| Sex          | Male/female      | Male/female            |
| Entire group | 54/23            | 59/23                  |
| Aachen       | 8/5              | 8/5                    |
| Aachen #2    | 11/2             | 12/3                   |
| Utrecht      | 5/5              | 5/5                    |
| Göttingen    | 24/6             | 28/7                   |
| Lille        | 11/3             | 11/3                   |
| Age          | Mean ± SD        | Mean ± SD              |
| Entire group | 33.46 ± 9.61     | 33.79 ± 10.36          |
| Aachen       | 38.54 ± 8.52     | 38.62 ± 10.29          |
| Aachen #2    | 33.38 ± 10.40    | 33.40 ± 11.36          |
| Utrecht      | 32.68 ± 9.29     | 35.90 ± 12.99          |
| Göttingen    | 31.27 ± 9.50     | 32.66 ± 9.64           |
| Lille        | 34.44 ± 9.58     | 30.33 ± 8.26           |

2.3. Resting state fMRI data: imaging & preprocessing

For each subject resting state EPI images were acquired using standard blood-oxygen-level-dependent (BOLD) contrast (gradient-echo EPI pulse sequence). Prior to further processing (using SPM8, www.fil.ion.ucl.ac.uk/spm) the first four images were discarded allowing for magnetic field saturation. The EPI images were corrected for head movement by affine registration in a two-pass procedure realigning EPI volumes to its mean image. The mean EPI image for each subject was spatially normalized to the MNI single subject template using the “unified segmentation” approach (Ashburner and Friston, 2005). The ensuing deformation field was applied to the individual EPI volumes and smoothed with a 5-mm FWHM Gaussian kernel.

In recent years, it has repeatedly been shown that head motion is a crucial confounding factor in resting-state analysis leading to spurious connectivity estimates as well as artificial group differences (for review see Power et al., 2015). In order to minimize the influence of motion artifacts on group comparisons, we conducted a matching of within scanner movements between patient and control subgroups. The following three head motion parameters were derived from the individual realignment parameters: i) framewise displacement (FD) represents the volume by volume movements (Van Dijk et al., 2012), ii) root mean squared (RMS) movements indicating variance over
voxels (Satterthwaite et al., 2013) and iii) DVARS as a combination of the former with D referring to temporal derivative of time courses and VARS referring to RMS variance over voxels (Power et al., 2012). In these three parameters, neither patient and control subsamples nor the overall disease cohorts showed group differences (t-tests with p > 0.2) indicating reasonably similar head motion in the scanning process of patients and healthy controls (Tables 6+7). In order to reduce spurious correlations between BOLD time courses through confounds such as physiological noise and motion, variance that could be explained by the following nuisance variables was removed from each voxel’s time series: i) the six motion parameters derived from the image realignment and ii) their first derivative. According to published evaluations, motion regressors entered the model as first and second-order terms resulting in 24 movement regressors (Satterthwaite et al., 2013). In light of evidence suggesting that group comparisons may be distorted by correcting for the global mean signal (Gotts et al., 2013; Saad et al., 2012), no global signal regression was performed. To quantify resting state FC of the meta-analytically de

3. Results

3.1. Within-diagnosis connectivity differences

SCZ patients relative to healthy controls HC showed widespread connectivity reduction of the PRC/PCC to many brain areas including inferior (IPL) and superior parietal lobule (SPL), medial and lateral premotor cortex (PMC), midcingulate cortex (MCC), the Rolandic operculum (OP), superior temporal sulcus (STS) and occipital cortex, fusiform gyrus, primary sensorimotor cortex, cerebellum and the insula (Fig. 2A). For the DMPPC, connectivity reduction in SCZ was found in a similar but less extensive network comprising SPL, IPL, STS, OP, left lateral and medial PMC, MCC, perigenual anterior cingulate cortex (pACC) insula and left postcentral gyrus. The conjunction between FC reduction of the anterior and posterior hubs of the DMN revealed aberrant connectivity of MCC, supplementary motor area (SMA), bilateral SPL, OP and STS, posterior insula and secondary somatosensory cortex (SII). In MDD the PRC/PCC volumes of interest (VOI) for each subject, their time-series were extracted as the first eigenvariate of the gray matter voxels within the VOI. Linear Pearson correlations were computed for both VOIs with all other voxels’ time-series in every subject and correlation coefficients were Fischer’s Z transformed for group comparison. A group-

| Table 4 |
| Schizophrenia | n | SGA | FGA | SGA & FGA | Missing data |
| Aachen (n) | 13 | 12 | - | - | 1 |
| Aachen #2 (n) | 13 | 12 | 1 | - | 0 |
| Göttingen (n) | 30 | 25 | - | 4 | 1 |
| Utrecht (n) | 10 | 3 | 3 | 2 | 2 |
| Lille (n) | 9 | 8 | 1 | - | 0 |
| Overall (%) | 75 | 80% | 6.7% | 8% | 5.3% |

| Table 5 |
| Overview of medication in the major depression cohort (MDD). SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin–norepinephrine reuptake inhibitors; NDRI: norepinephrine–dopamine reuptake inhibitor; TCA: tricyclic antidepressants; SGA: second generation antipsychotics. |
| MDD | n = | SSRI/SDRI/NDRI | SSRI/SDRI/NDRI & TCA | TCA | SSRI/SDRI/NDRI & SGA | SSRI/SDRI/NDRI & TCA & SGA | Other/none |
| Aachen (n) | 30 | 19 | 4 | 1 | 2 | 3 | 1 |
| Munich (n) | 23 | 9 | 8 | 4 | 2 | 9 | - |
| Göttingen (n) | 49 | 24 | 5 | 11 | 2 | 3 | 2/2 |
| Overall (%) | 102 | 51% | 16.7% | 15.7% | 5.9% | 5.9% | 4.9% |
ties), which may point towards common circuit dysconnectivity.

between disorders, both SCZ and MDD are also characterized by clinical insight that in spite of obvious phenomenological differences the DMN (Schilbach et al., 2012). This investigation was based on the FC in SCZ and MDD patients using seed-based resting state analyses of

4. Discussion

4.1. Within-diagnosis functional connectivity differences: Schizophrenia

In line with previous research, our results demonstrate significant alterations of FC of the DMN in SCZ (Bastos-Leite et al., 2015; Fischer et al., 2014; Gong et al., 2014; Guo et al., 2014; Rolland et al., 2015). In particular, the PRC/PCC has been implicated as a ‘hot spot’ for structural as well as FC aberrations in SCZ, which are not only observed across the entire clinical spectrum (Wang et al., 2014), but also appear to be related to relevant genetic variants (Gong et al., 2014). From a cognitive psychology perspective, it has been argued that FC of the PRC/PCC and other parietal areas may be particularly relevant for self-oriented processing and for providing a stable egocentric representation of space (Land, 2014; Lou et al., 2010). Furthermore, it has been argued that this network relevant for self-awareness might be particularly affected in SCZ (Bluhm et al., 2009; Guo et al., 2014).

Dysconnectivity of the anterior hub of the DMN, i.e., the DMPFC, has also been previously associated with a familial risk for SCZ and its intrinsic connectivity is known to carry measurable consequences for social functioning (Doddell-Feder et al., 2014). Consistent with these previous findings, our results demonstrate a significant reduction of FC for DMPFC with pACC, MCC, bilateral insula and STS, all of which are regions that are involved in cognitive control and self-monitoring processes and could, therefore, contribute to social abilities (Bernhardt et al., 2014; Meyer et al., 2013). In particular, it has been demonstrated that DMPFC serves an important modulatory role by influencing activity in other brain regions when task requirements make it necessary (Wheelock et al., 2014). Therefore, alterations of DMPFC-based intrinsic connectivity as observed in SCZ patients may adversely affect cognitive processing by disallowing for such modulations to take place (Becerril and Barch, 2013).

4.2. Within-diagnosis functional connectivity differences: Depression

Within the MDD group connectivity reductions of the posterior node of the DMN, i.e., the PRC/PCC, was found to bilateral SPL, which constitutes a striking parallel to the findings in the SCZ group. While alterations of SPL activity at rest are less often described in the literature to be associated with MDD (Liu et al., 2012), the structural connection between bilateral SPL was found to discriminate depressed patients from controls in a classification analysis using diffusion tractography (Korgaonkar et al., 2012). With regard to symptom severity, an increase in PRC/PCC activation was found for depressed patients responding to treatment with fluoxetine (Mayberg et al., 1999) as well as for deep brain stimulation (Lozano et al., 2008).

Reduced connectivity in MDD was also observed for the anterior node of the DMN, as indicated by a significant reduction of DMPFC connectivity with left inferior frontal gyrus. These two regions and their co-activation patterns are known to be relevant for planning, carrying out and responding to actions, in particular when they occur in a social context (Schilbach et al., 2011), which can be disturbed in MDD. Consistently, both regions have also previously been found to show aberrant activation patterns in patients relative to controls for tasks that are typically associated with depressive symptomatology (Seidel et al., 2012).

4.3. Transdiagnostic similarities in functional connectivity alterations

Based on the assumption that phenotypic commonalities could rely on common brain circuit dysfunction (Buckholtz and Meyer-Lindenberg, 2012), we conducted an analysis of transdiagnostic similarities in connectivity alterations across SCZ and MDD patients relative to the respective control groups. This analysis demonstrated a significant reduction of FC between PRC/PCC and bilateral SPL across both patient groups. Interestingly, the interaction of medial and lateral parietal network hubs has been shown to be important for regulating the balance between internally and externally directed attention (Leech et al., 2011). More specifically, the brain regions implicated (PRC/PCC and SPL) have both been associated with top-down control of attention and indirectly with sensorimotor integration and are thus thought to provide a coherent self-representation across space and time (Schedlbauer et al., 2014). While SPL activity change has been linked to spatial shifts of attention (Kelley et al., 2008), precuneus has been linked to non-spatial
shifts of attention (Giesbrecht et al., 2003). Further evidence has demonstrated strong reciprocal relations between activity in these two regions, which have been discussed as contributing to a finely tuned interplay between stimulus-oriented and stimulus-independent cognition (e.g., Dosenbach et al., 2008).

Fittingly, both SCZ and MDD are associated with a dysbalance between internally and externally directed attention and mental state attribution: While patients with MDD are known to attribute internally when making sense of external occurrences and tend to do so in a self-defeating manner, patients with SCZ often use an externalizing bias in the attribution of causation of social events (Janssen et al., 2006). Social difficulties in both disorders could, therefore, be related to such negative self-referential thoughts, distorted attributional biases and the subsequent development of anxiety. Also, patients from both diagnostic groups often withdraw from social contexts, which may lead to a further consolidation of disorder-specific symptomatology. It is tempting to speculate that these social impairments could be related to common dysconnectivity patterns of posterior nodes of DMN that are present in both patient groups, but unfortunately no measures of social behavior were available in our study to directly investigate this putative association.

4.4. Disorder-specific differences in functional connectivity alterations

Finally, we explored disorder-specific differences in FC by testing whether observed connectivity alterations are more pronounced in one patient group than in the other. This analysis revealed a specifically reduced connectivity pattern in SCZ patients for PRC/PCC and DMPFC with the parietal operculum. In general, disruption of the parietal operculum has already been demonstrated in SCZ (Andreou et al., 2015;
tions carried by using the SPM Anatomy toolbox.

**Results of within-diagnosis analyses.** Suprathreshold clusters at a height threshold of \( p = 0.05 \) cluster-level corr. and a cluster-forming threshold of \( p_{	ext{unc}} < 0.001 \). MNI coordinates of principally activated voxels for each cluster are given; assignment to anatomical locations carried by using the SPM Anatomy toolbox.

| Macroanatomical location | x   | y   | z   | k  | T   |
|--------------------------|-----|-----|-----|----|-----|
| [SCZ \( \times \) CON\(\text{REC}\)] Fig. 2A | Superior parietal lobule | 12  | −38 | 48  | 17022 | 6.64 |
| Right fusiform gyrus      | 52  | −50 | −24 | 1185 | 5.32 |
| Left fusiform gyrus       | −50 | 48  | 12  | 500  | 5.00 |
| Left V3                   | −24 | −100| 14  | 336  | 5.05 |
| LeftRolandic operculum    | −58 | 0   | 6   | 219  | 4.79 |
| Left inferior parietal lobule | −38 | −74 | 20  | 200  | 4.53 |
| Left anterior insula      | −32 | 24  | 2   | 137  | 4.83 |
| Right cerebellum          | 32  | −44 | 52  | 136  | 5.07 |
| Left precuneus            | −20 | −48 | 20  | 103  | 5.39 |
| Right precuneus           | 26  | −56 | 16  | 102  | 4.56 |

**Results of transdiagnostic analyses.** Suprathreshold clusters at a height threshold of \( p = 0.05 \) cluster-level corr. and a cluster-forming threshold of \( p_{\text{unc}} < 0.001 \). MNI coordinates of principally activated voxels for each cluster are given; assignment to anatomical locations carried by using the SPM Anatomy toolbox.

| Macroanatomical location | x   | y   | z   | k  | T   |
|--------------------------|-----|-----|-----|----|-----|
| [PAT \( \times \) CON\(\text{REC}\)] | Right superior parietal cortex | 20  | −52 | 64  | 389 | 4.91 |
| Left superior parietal cortex | −16 | −54 | 68  | 291 | 4.83 |
| [SCZ \( \times \) CON] relative to [MDD \( \times \) CON\(\text{REC}\)] | Right Rolandic operculum | 58  | −18 | 18  | 346 | 4.52 |
| Left Rolandic operculum    | −52 | −12 | 14  | 121 | 3.95 |
| [SCZ \( \times \) CON] relative to [MDD \( \times \) CON\(\text{REC}\)] inclusively masked \( p < 0.05 \) | Right Rolandic operculum | 58  | −18 | 18  | 361 | 4.53 |
| Left Rolandic operculum    | −50 | −14 | 14  | 133 | 4.41 |
| Right caudate nucleus      | 8   | 18  | −4  | 110 | 4.75 |
| [SCZ \( \times \) CON] relative to [MDD \( \times \) CON\(\text{REC}\)] | Right Rolandic operculum | 62  | −20 | 22  | 112 | 3.92 |
| Left Rolandic operculum    | −52 | −12 | 14  | 110 | 4.67 |
| [SCZ \( \times \) CON] relative to [MDD \( \times \) CON\(\text{REC}\)] | Right Rolandic operculum | 62  | −20 | 22  | 67  | 3.92 |
| Left Rolandic operculum    | −52 | −12 | 14  | 56  | 3.95 |

Fornito et al., 2011) and is well in line with cognitive functions associated with this structure, such as interoceptive awareness, multisensory integration and body perception (Ebisch et al., 2014; Ionta et al., 2011; Tsakiris, 2010). In light of these findings, connectivity of the parietal operculum may represent a disorder-specific aspect of SCZ that could be linked to alterations of a basic sense of self. Furthermore, it is conceivable that activity alterations of this region feed into or trigger higher-order self-processing disturbances and subsequent misattributions of mental states, which could be related to activity changes of medial parietal or dorso medial prefrontal cortex (Menon et al., 2011; Nekovarova et al., 2014; Rotarska-Jagiela et al., 2010). Taken together, the reduced coupling of OP with the DMN in SCZ may represent an important and disorder-specific pathophysiological mechanism for self-disturbances in SCZ.

Furthermore, disorder-specific connectivity differences in SCZ as compared to MDD were also found for the ventral striatum, which has been strongly linked to reward processing (Weiland et al., 2013). In schizophrenia, ventral striatal activity has furthermore been related to the concept of “aberrant salience”, according to which a deregulated state of activity can lead to “an aberrant assignment of salience to elements of one's experience” and whereby hallucinations “reflect a direct experience of the aberrant salience of internal representations” (Kapur, 2003). Accordingly, clinical studies of visual and auditory hallucinations have demonstrated alterations of ventral striatal connectivity (Rolland et al., 2015). Our findings corroborate these findings by documenting that ventral striatal dysconnectivity is significantly associated with SCZ rather than MDD.

4.5. Limitations

The design of the current study, which draws upon the possibility of data pooling over several measurement sites as well as two psychiatric disorders, includes the following important drawbacks. From a methodological point of view, combining data from multiple sites entails the finding spurious effects due to systematic differences between sample recruitment and the measurement of behavioral and imaging data or solely due to the comparison of different scanners. To minimize the influence of measurement site on group comparisons, one should control for systematic differences in confounding factors like age, gender or within scanner movement between sites. Another approach would be to explicitly modeling measurement site as a variable of no interest, which becomes difficult when dealing with more than two sites, as the actual amount of difference will certainly be unequal between sites. Therefore, and to retain as much variance in the data as possible we applied the former strategy and independently matched groups of patients and controls within every site and disease for age, sex and within scanner movement. As there were no signifi cant differences of these factors within each subsample as well as in the overall cohorts for both diseases, group comparisons should not significantly be driven by site differences. Moreover, due to the data pooling procedure...
implemented in our study with the aim of maximizing sample size, we were not able to collect representative data on the state of social impairments in both patient groups. This fact clearly limits the generalizability of the presented FC decrease as to their specificity for social impairments. Even though, transdiagnostic dysconnectivity between PRC/PCC and SPL could be shown for both MDD and SCZ, its covariation with severity of social impairments in general, as well as with particular disabilities in social behavior, remains to be shown. As resting-state FC is a very indirect measure of these social-cognitive processes, connectivity modeling based on task-based studies would be needed to directly relate the transdiagnostic findings observed in our study to individual clinical symptomatology, attributional styles and real-life social functioning. Furthermore, future research could use connectivity measures to evaluate network dysfunction during the

Fig. 4. Transdiagnostic differences in functional connectivity alterations: A) More pronounced reduction of FC from PRC/PCC and DMPFC with bilateral operculum and B) the ventral striatum in SCZ < CON relative to MDD < CON.
course of illness with the aim of predicting the effects of various treat-
ment options.

5. Conclusions

Taken together, our study provides first-time evidence for common-
alities in transdiagnostic functional connectivity alterations of the DMN
in SCZ and MDD. These findings at the neural level parallel descriptions
of phenotypic commonalities across both disorders, which exist next to
disorder-specific disturbances and have emphasized impairments of
social interaction (for a review see Schilbach, 2015). In light of these
findings, it is tempting to speculate that phenotypic overlap could be re-
lated to common brain circuit dysfunction. Unfortunately, no measures
of social behavior were available in the patient samples here described
to further investigate this possible relationship. In terms of the
neurofunctional alterations present in both disorder groups, previous
research can be taken to suggest that medial and superior parietal cortex
dysconnectivity may lead to a disturbance of the finely tuned and
flexible balance between internally and externally directed attention.
In addition to this, dysconnectivity of the DMN could also be related to
well known differences in attributional style that patients use to
make sense of the environment.

Furthermore, our analysis demonstrates that disorder-specific dif-
ferences also exist as indexed by more strongly reduced coupling of
the parietal operculum with the DMN in SCZ as compared to MDD. In
light of previous research, which has convincingly demonstrated that
the operculum plays an important role in somatosensory integration
and body perception and that SCZ is associated with a disruption of ac-
tivity in this brain region, this finding of opercular dysconnectivity with
the DMN may represent an important and disorder-specific pathophys-
iological mechanism for self-disturbances in SCZ. In particular, one
could speculate that activity alterations of the operculum may trigger
additional self-processing disturbances and could thereby lead to subse-
quent misattributions of mental states.

Disclosures

The authors report no biomedical financial interests or potential con-
fl icts of interest.

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References

Aldenzi, C., Tost, H., Meyer-Lindenberg, A., 2014. The neurobiology of social environmen-
tal risk for schizophrenia: an evolving research field. Soc. Psychiatry Psychiatr. Epidemiol. 49, 507–517.
Andreou, C., Nolte, G., Leicht, G., Polomac, N., Hanganu-Opatz, I., Lambert, M., et al., 2015.
Increased resting-state gamma-band connectivity in first-episode schizophrenia. Schizophr. Bull. 41 (4), 930–939. http://dx.doi.org/10.1093/schbul/sbu121.
Ashburner, J., Friston, K., 2005. Unified segmentation. Neuroimage 26, 839–851.
Bastos-Leite, A., Ridgway, G., Silveira, C., Norton, A., Reis, S., Friston, K., 2015. Dysconnectivity within the default mode in first-episode schizophrenia: a stochastic dynamic causal modeling study with functional magnetic resonance imaging. Schizophr. Bull. 41 (1), 144–153. http://dx.doi.org/10.1093/schbul/sbu080.
Becerril, K., Barch, D., 2013. Conflict and error processing in an extended cingulo-
opercular and cerebellar network in schizophrenia. Neuroimage Clin. 3, 470–480.
Bernhardt, B., Valk, S., Sliani, G., Bird, G., Frith, U., Singer, T., 2014. Selective disruption of
socio-cognitive structural brain networks in autism and alexithymia. Cereb. Cortex 24 (12), 3258–3267. http://dx.doi.org/10.1093/cercor/bht182.
Billeke, P., Aboliz, F., 2013. Social cognition in schizophrenia: from social stimuli pro-
cessing to social engagement. Front. Psychiatry 4, 4.
Lee, H., Ku, J., Kim, J., Jang, D., Yoon, K., Kim, S., et al., 2014. Aberrant neural responses to social rejection in patients with schizophrenia. Soc. Neurosci. 1–12.

Lecho, R., Kamourieh, S., Beckmann, C., Sharp, D., 2011. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. J. Neurosci. 31, 3217–3224.

Liston, C., Chen, A., Zebeley, B., Drysdale, A., Gordon, R., Leuchter, B., et al., 2014. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol. Psychiatry 76 (7), 517–526. http://dx.doi.org/10.1016/j.biopsych.2014.01.023.

Liu, C., Ma, X., Wu, X., Li, F., Zhang, Y., Zhou, F., et al., 2012. Resting-state abnormal baseline brain activity in unmixed and bipolar depression. Neurosci. Lett. 516, 202–206.

Loh, H., Luber, B., Stanford, A., Lisanby, S., 2010. Self-specific processing in the default mode network: a single-pulse TMS study. Exp. Brain Res. 207, 27–38.

Lozano, A.M., Mayberg, H.S., Gaccobbe, P., Hamani, C., Craddock, R.C., Kennedy, S.H., 2008. Subcortical cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 64, 461–467.

Marchetti, L., Koster, E., Sonuga-Barke, E., De Raedt, R., 2012. The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. Neuropsychol. Rev. 22, 229–251.

Mayberg, H., Liotti, M., Brannan, S., McGinnis, S., Mahurin, R., Jacebek, P., et al., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J. Psychiatry 156, 675–682.

McCulloough, J.J., 2003. Treatment for chronic depression using Cognitive Behavioral Analysis System of Psychotherapy (CBASP). J. Clin. Psychol. 59, 831–846.

Meda, S., Gili, A., Stevens, M., Lorenzonzi, R., Glahn, D., Calhoun, V., et al., 2012. Differences in resting-state functional magnetic resonance imaging functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives. Biol. Psychiatry 71, 881–889.

Menon, M., Schmitz, T.W., Anderson, A.K., Graff, A., Kostol, M., Mamo, D., et al., 2011. Exploring the neural correlates of delusions of reference. Biol. Psychiatry 70, 1277–1283.

Meyer, M., Masten, C., Ma, Y., Wang, C., Shi, Z., Eisenberger, N., et al., 2013. Empathy for the social suffering of friends and strangers recruits distinct patterns of brain activation. Soc. Cogn. Affect. Neurosci. 8, 446–454.

Morris, S., Cutbert, B., 2012. Research domain criteria: cognitive systems, neural circuits, and dimensions of behavior. Dialogues Clin. Neurosci. 14(4), 29–37.

Nekovarova, T., Fajnerova, I., Horacek, J., Spaniel, F., 2014. Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory. Front. Behav. Neurosci. 8, 171.

Nixon, N., Liddle, P., Nixon, E., Worwood, G., Liotti, M., Palaniyappan, L., 2014. Biological vulnerability to depression: linked structural and functional brain network findings. Br. J. Psychiatry 204, 283–289.

Power, JD., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic errors in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.

Power, JD., Schlaggar, B.L., Petersen, S.E., 2015. Recent progress and outstanding issues in motion correction in resting state fMRI. Neuroimage 105, 538–551.

Rolland, B., Anad, A., Poulet, E., Border, R., Vignaud, A., Batien, R., et al., 2015. Resting-state functional connectivity of the nucleus accumbens in auditory and visual hallucinations in schizophrenia. Schizophr. Bull. 41 (1), 291–299. http://dx.doi.org/10.1093/ schizbp/sbu079.

Rotarska-Jagiela, A., van de Ven, V., Oertel-Knocher, V., Uhlhaas, P.J., Vogeley, K., Linden, D.E., 2010. Resting-state functional network correlates of psychotic symptoms in schizophrenia. Schizophr. Res. 117, 21–30.

Saat, Z., Gott, S., Murphy, K., Chen, G., Jo, H., Martin, A., et al., 2012. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect. 2, 25–32.

Salvatoro, G., Dimaggio, G., Lysaker, P., 2007. An intersubjective perspective on negative symptoms of schizophrenia: implications of simulation theory. Cogn. Neuropsychiatry 12, 144–164.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Rufapak, K., Loughead, J., Calkins, M.E., et al., 2013. An improved framework for confound regression and filtering for control of motion artifact in the pre-processing of resting-state functional connectivity data. Neuroimage 64, 240–256.

Savla, G.N., Twamley, E.W., Delis, D.C., Roesch, S.C., Jeste, D.V., Palmer, B.W., 2012. Dimensions of executive functioning in schizophrenia and their relationship with processing speed. Schizophr. Bull. 38, 760–768.

Schedlauker, A.M., Copara, M.S., Watrous, A.J., Ekstrom, A.D., 2014. Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. Sci. Rep. 4, 6431.

Schilbach, L., 2015. Toward a second-person neuropsychiatry. Philos. Trans. R. Soc. B http://dx.doi.org/10.1098/rstb.2015.0081.

Schilbach, L., Wilms, M., Eichhoff, S., Romanzetti, S., Tepest, R., Bente, G., et al., 2010. Minds made for sharing: initiating joint attention recruits reward-related neurocircuitry. J. Cogn. Neurosci. 22, 2702–2715.

Schilbach, L., Eichhoff, S., Cieslik, E., Shah, N., Fink, G., Vogeley, K., 2011. Eyes on me: an fMRI study of the effects of social gaze on action control. Soc. Cogn. Affect. Neurosci. 6, 395–403.

Schilbach, L., Bzdok, D., Timmermanns, B., Fox, P., Laird, A., Vogeley, K., et al., 2012. Introspective minds: using ALE meta-analyses to study commonalities in the neural correlates of emotional processing, social & unconstrained cognition. PLoS One 7, e30920.

Schilbach, L., Muller, V., Hoffstaedter, F., Close, M., Goya-Maldonado, R., Graber, G., et al., 2014. Meta-analytically informed network analysis of resting state fMRI reveals hyperconnectivity in an introspective socio-affective network in depression. PLoS One 9, e84973.

Schneider, D., Regenbogen, C., Kellermann, T., Finkelmeier, A., Kohn, N., Derntl, B., et al., 2012. Empathic behavioral and physiological responses to dynamic stimuli in depression. Psychiatr. Res. 200, 294–305.

Seidel, E., Satterthwaite, T., Eichhoff, S., Schneider, F., Gur, R., Wolf, D., et al., 2012. Neural correlates of depressive realism—an fMRI study on causal attribution in depression. J. Affect. Disord. 138, 268–276.

Shannon, B.J., Buckner, R.L., 2004. Functional-anatomic correlates of memory retrieval that suggest nontraditional processing roles for multiple distinct regions within posterior parietal cortex. J. Neurosci. 24, 10084–10092.

Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Disconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr. Bull. 35, 509–527.

Thomas, J., Riba, D., Phillips, L., 2014. Ruminating, depressive symptoms and awareness of illness in schizophrenia. Behav. Cogn. Psychother. 42, 143–155.

Tsakiris, M., 2010. My body in the brain: a neurocognitive model of body-ownership. Neropsychologia 48, 703–712.

Van Dijk, K.R., Sabuncu, M.R., Buckner, R.L., 2012. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 59, 431–438.

Wang, X., Xia, M., Lai, Y., Dai, Z., Cao, Q., Cheng, Z., et al., 2014. Disrupted resting-state functional connectivity in minimally treated chronic schizophrenia. Schizophr. Res. 156, 150–156.

Weiland, B., Welsh, R., Yau, W., Zucker, R., Zubieta, J., Heitzeg, M., 2013. Accumbens functional connectivity during reward mediates sensation-seeking and alcohol use in high-risk youth. Drug Alcohol Depend. 128, 130–139.

Wheelock, M., Sreenivasan, K., Wood, K., Ver Hoof, L., Deshpande, G., Knight, D., 2014. Threat-related learning relies on distinct dorsal prefrontal cortex network connectivity. Neuroimage 102 (Pt 2), 904–912. http://dx.doi.org/10.1016/j.neuroimage.2014.08.005.

Yu, Q., Allen, E., Sui, J., Arbabihriri, M., Pearson, G., Calhoun, V., 2012. Brain connectivity networks in schizophrenia underlying resting state functional magnetic resonance imaging. Curr. Top. Med. Chem. 12, 2415–2425.