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In Review

Resting-State Neuroimaging Studies: A New Way of Identifying Differences and Similarities Among the Anxiety Disorders?

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This review examines recent functional neuroimaging research of resting-state regional connectivity between brain regions in anxiety disorders. Studies compiled in the PubMed–National Center for Biotechnology Information database targeting resting-state functional connectivity in anxiety disorders were reviewed. Diagnoses included posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive–compulsive disorder (OCD), panic disorder (PD), and specific phobia (SP). Alterations to network connectivity were demonstrated in PTSD, GAD, SAD, OCD, and PD in several resting-state investigations. Differences from control subjects were primarily observed in the default mode network within PTSD, SAD, and OCD. Alterations within the salience network were observed primarily in PTSD, GAD, and SAD. Alterations in corticostriatal networks were uniquely observed in OCD. Finally, alterations within somatosensory networks were observed in SAD and PD investigations. Resting-state studies involving SPs as a primary diagnosis (with or without comorbidities) were not generated during the literature search. The emerging use of resting-state paradigms may be an effective method for understanding associations between anxiety disorders. Targeted studies of PD and SPs, meta-analyses of the studies conducted to date, and studies of the impact of specific comorbid presentations, are recommended future research directions.

Études de neuroimagerie à l'état de repos : une nouvelle façon d'identifier les différences et les similitudes des troubles anxieux?

Cette revue examine la recherche récente en neuroimagerie fonctionnelle sur la connectivité régionale à l'état de repos entre les régions du cerveau dans les troubles anxieux. Des études de la base de données *PubMed–National Center for Biotechnology* Information portant sur la connectivité fonctionnelle à l'état de repos dans les troubles anxieux ont été examinées. Les diagnostics incluaient notamment le trouble de stress post-traumatique (TSPT), le trouble d'anxiété généralisée (TAG), le trouble d'anxiété sociale (TAS), le trouble obsessionnel-compulsif (TOC), le trouble panique (TP), et la phobie spécifique (PS). Les modifications de la connectivité du réseau ont été démontrées dans les TSPT, TAG, TAS, TOC et TP dans plusieurs investigations à l'état de repos. Les différences par rapport aux sujets témoins ont été surtout observées dans le réseau du mode par défaut dans le TSPT, le TAS, et le TOC. Les modifications du réseau de saillie ont été surtout observées dans le TSPT, le TAG, et le TAS. Les modifications des réseaux corticostriataux ont été observées seulement dans le TOC. Enfin, les modifications des réseaux somatosensoriels ont été observées dans les investigations du TAS et du TP. Les études à l'état de repos impliquant les PS comme diagnostic primaire (avec ou sans comorbidités) n'ont pas été générées durant la recherche de la littérature. L'utilisation naissante des paradigmes de l'état au repos peut se révéler une méthode efficace pour comprendre les associations entre les troubles anxieux. Les études ciblant le TP et la PS, les méta-analyses des études menées jusqu'ici, et les études sur l'effet des présentations comorbides spécifiques sont des orientations de recherche future recommandées.

During the last decade, neuroimaging studies have investigated the neurobiological bases of anxiety disorders in an effort to understand their commonalities and differences. These studies usually involve exposing participants to stimuli with direct diagnostic relevance to their condition. For example, pictures of spiders presented to people with a spider phobia[1] and pictures of angry faces presented to people with a social phobia[2] are common task-driven paradigms used in these research programs. Studies of this sort have shown that hyperactivation of amygdala and insula—activity strongly correlated with fear response—is common to PTSD,[3–7] OCD,[8] SP,[9–12] SAD,[13–15] and PD.[8] These designs presumably maximize sensitivity to detecting responses associated with each specific anxiety disorder diagnosis in comparison with healthy control subjects. However, to date, there has been little effort to understand diagnostic specificity, namely, a direct comparison of different anxiety disorders that reveals their potentially unique neurobiological and diagnostic profile (but see Rauch et al[16] and van den Heuvel et al[17]). As a consequence, post hoc comparisons across diagnoses, such as meta-analyses, are often difficult to conduct. This concern was acknowledged by Etkin and Wager[18] in their voxelwise meta-analysis of functional neuroimaging studies of PTSD, SAD, and SP. In particular, they noted that the heterogeneity of functional paradigms used to study neurobiological responses in different anxiety disorders, as well as the lack of direct comparisons between groups, have generated "results across these studies [that have] often been inconsistent . . ."[18, p 1475] In turn, this may lead to underpowered tests targeting diagnostic specificity.

Clinical Implications

- Our review may lead to an improved understanding of the neurobiological similarities and differences among anxiety disorders.
- Our review may lead to a greater appreciation for disorder-specific clinical therapies for anxiety disorders.

Limitations

- Few studies investigated relations between and among anxiety disorders as currently hypothesized in the literature. This includes disorder-to-disorder comparisons, rather than disorder-to-control comparisons.
- Targeted investigations of PD and SP were not identified in the literature.
- Our review did not employ a quantitative meta-analysis.

One approach to evaluating diagnostic specificity would involve measuring 2 or more anxiety disorder groups as they respond both to diagnostically central and diagnostically peripheral stimuli. For example, people with a spider phobia could be evaluated in their response not only to spider stimuli but also to angry faces. Likewise, people with social phobia could be evaluated not only in their response to angry faces but also to spiders. Although this would be an effective protocol, researchers may have little motivation to conduct such studies in that they are partly designed only to reveal an expected absence of an effect in the unmatched stimulus-by-diagnostic conditions. Moreover, the concern that results will not generalize to other tasks, including even slight modifications to task parameters (for example, for how many seconds a stimulus is presented), remains.

An alternative approach involves examining intrinsic cortical networks underling sensory, motor, and cognitive functions during the resting state (that is, as subjects simply lie awake in the scanner).[19–21] An advantage of this approach includes greater ease of implementation across diagnostic groups. Moreover, several lines of argument suggest that studying resting-state networks may be a useful alternative to task-driven paradigms when involving patients with severe psychiatric conditions.[22] For example, subjects with severe mental illness may find it difficult to maintain response sets for complex or prolonged tasks. The occurrence of symptoms in the scanner, namely, flashbacks or panic attacks, may be interpreted as interfering with task-related activation in subtraction analyses. However, in a resting-state design, these phenomena may contribute useful diagnostic information. Finally, resting-state functional connectivity analyses do not require a priori hypotheses about neural activation as a prerequisite for investigating neural network function.[23,24] Indeed, the study of resting-state network connectivity, for the purposes of diagnosis or prognosis, is already an emerging topic of discussion in neuropsychiatry.[22,25–27]

Abbreviations

ACC	anterior cingulate cortex
ALFF	altered low-frequency fluctuation
BLA	basolateral amygdala
CAPS	Clinically Administered PTSD Scale
CEN	central executive network
CMA	centromedial amygdala
DMN	default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	functional magnetic resonance imaging
GAD	generalized anxiety disorder
IFG	inferior frontal gyrus
MFG	middle frontal gyrus
OCD	obsessive–compulsive disorder
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PD	panic disorder
PFC	prefrontal cortex
PTSD	posttraumatic stress disorder
ROI	region of interest
SAD	social anxiety disorder
SN	salience network
SP	specific phobia

This experimental approach holds that brain activity should be thought of as a predominantly intrinsic and proactive process rather than a reflexive or reactive one.[28,29] The resting brain consumes 20 per cent of the body's energy requirements, yet during task engagement energy consumption does not increase by more than 5 per cent.[30] Fluctuating intrinsic activity observed with fMRI has demonstrated prominent patterns of spatial coherence within known brain systems. To date, at least 7 major brain networks have been reliably identified whose functioning may be affected by various anxiety disorders (reviewed in Raichle[31]). These include the DMN (incorporating the medial temporal lobe, PCC, precuneus, and medial–lateral–inferior parietal cortices), the SN (incorporating the dorsal ACC and insula), the executive control network (incorporating the dorsolateral prefrontal and parietal cortices), the dorsal attention network (incorporating the intraparietal, superiori frontal, and precentral sulci), the auditory network, the visual network, and the sensorimotor network.

To our knowledge, no previous review of resting-state fMRI studies of the anxiety disorders has been conducted. Therefore, we review and discuss the results of this emerging literature to determine whether resting-state connectivity may be an effective conceptual and experimental framework for investigating the diagnostic specificity between the anxiety disorders.

Methods

We reviewed resting-state studies published and compiled on the PubMed database between January 1, 2009, and January 15, 2013. PTSD was included in our literature search of anxiety disorders as the transition between the DSM-IV-TR and the DSM-5 cut across our search dates. Permutations of "posttraumatic stress disorder," "social anxiety disorder," "obsessive compulsive disorder," "specific phobia," "panic disorder," or "general anxiety disorder," combined with "fMRI," "neuroimaging," "resting state," "amygdala," or "intrinsic networks" were used as search criteria.

Results

Posttraumatic Stress Disorder

An electronic search of PTSD resting-state studies, between 2009 and January 15, 2013, returned 11 investigations.[32–42] These studies primarily examined resting-state connectivity within the DMN, SN, and limbic structures using ROI-based functional analyses. Five studies focused on brain structures that are associated with the DMN and found decreased as well as increased connectivity within different regions of the DMN[33,34,37,38,40] (see also online eTable 1). Moreover, the strength of connectivity within the DMN appeared to correlate with PTSD symptoms, and correlations between DMN connectivity and PTSD symptom severity were generally reported.[33,34,38,40] Two studies reported a negative correlation between DMN connectivity and scores on the CAPS in patients with PTSD or acute posttraumatic stress symptoms.[38,40] In addition, there is some emerging evidence that altered resting-state connectivity between the PCC and the amygdala may be a reliable prognostic indicator of PTSD symptomatology.[34,40] Sripada et al[37] demonstrated an increased coupling between the DMN and SN, suggesting an alteration within the interaction between large-scale brain networks.

Given that there is now substantial evidence that PTSD is associated with altered brain responses in limbic and paralimbic brain areas—namely, the amygdala and insula—in response to emotional (and typically trauma-related) stimuli (reviewed by Sripada et al[37]), investigators have also turned to examining resting-state limbic–SN connectivity. Three studies[35–37] investigated the connectivity of brain areas related to the SN and identified an increased connectivity within those regions. Specifically, PTSD patients showed a greater functional coupling between the left anterior insula as a seed region and each of the left peri-insula–superior temporal gyrus, right hippocampus, and right amygdala,[37] compared with a combined control group consisting of combat and noncombat control subjects. The same investigators[36] also reported greater positive connectivity between the amygdala as a seed region and the right insula in subjects with PTSD, compared with combat control subjects. Altered connectivity within the SN may suggest a change in threat-sensitivity circuits, contributing to the hypervigilance and hyperarousal symptoms often exhibited by people suffering from PTSD.

In addition to examining resting-state functional connectivity of large-scale brain networks in PTSD, one study also explored resting-state functional limbic–cortical connectivity.[41] Results demonstrated an increased functional coupling between the left thalamus seed and left IFG and MFG, as well as with the right precuneus in PTSD, compared with combat control subjects. The investigators also found an increased connectivity in the right thalamus seed and the left IFG, MFG, inferior parietal lobe, as well as with the right IFG in PTSD subjects, compared with combat control subjects. In contrast, combat control subjects showed an increased coupling within the left thalamus seed and the right MFG, as well as an increased functional connectivity in the right thalamus seed and left ACC and right MFG, compared with PTSD subjects.[41] These findings point to a disrupted thalamo–cortical connectivity pattern, which may contribute to the enhanced fear recall and lack of extinction characteristic of PTSD.[41]

Finally, in a novel study performed by Bing et al,[32] cortical thickness and ALFF of neuronal regions commonly implicated in previous imaging studies—namely, the medial PFC, ACC, and superior temporal gyrus—were correlated with PTSD diagnosis. Imaging results indicated a decrease in cortical thickness of key brain regions in PTSD, including the medial PFC, the ACC, and superior temporal gyrus. Moreover, ALFF in the medial PFC and ACC was increased in subjects with PTSD. Interestingly, another investigation also found an increase in ALFF values within the right

medial frontal gyrus and MFG in PTSD, compared with traumatized control subjects. This suggests an increased functional coupling within those regions.[42] Linear regression of cortical thickness and medial PFC ALFF revealed a positive correlation with PTSD symptoms.[32] Indeed, Bing et al[32] concluded that structural integrity of the medial PFC, which may influence its functional connectivity with other networks, may contribute to PTSD progression.

Generalized Anxiety Disorder

An electronic search of GAD resting-state studies, between 2009 and 2013, returned a single investigation.[43] Etkin et al[43] found alterations within limbic–cortical network connectivity. Increased coupling between the BLA and both sensory and medial prefrontal regions, as well as increased functional connectivity between the CMA and cerebellum, thalamus, and midbrain, were identified. In contrast, within subregions of the amygdala, decreased functional connectivity was observed. Moreover, Etkin et al[43] revealed an increased coupling between regions of the CEN, and both the BLA and the CMA. Conversely, functional connectivity between regions associated with the SN, and both the BLA and the CMA, was decreased. Given that, to our knowledge, there is currently only one publication about resting-state functional connectivity in patients with GAD, further research is needed to elucidate potential alterations within large-scale brain networks.

Social Anxiety Disorder

An electronic search of SAD resting-state studies, between 2009 and 2013, returned 8 investigations.[44–51] These studies primarily examined resting-state functional connectivity using ROI-based designs.

Three investigations focused on brain regions associated with the DMN and found mixed results.[47–49] Liao et al[47] found an increased functional coupling within the DMN in patients with SAD, compared with healthy control subjects. Pannekoek et al[48] showed no differences within the DMN in SAD patients, compared with healthy control subjects. In contrast, Qiu et al[49] demonstrated decreased coupling between the bilateral angular gyri, left medial PFC, right dorsolateral PFC, inferior parietal gyrus, and ACC in SAD, compared with healthy control subjects.

Three studies also examined functional connectivity within the SN and found inconsistent results.[48,50,51] Prater et al[50] reported decreased functional connectivity between the amygdala and the rostral ACC in patients with SAD, compared with healthy control subjects. In addition, Liao et al[51] found decreased functional coupling of the insula within the salience network in patients with SAD, compared with healthy control subjects. The same investigators also found increased functional coupling in other regions of the SN, including the dorsal anterior cingulate and mid-cingulate gyrus, in SAD. Consistent with the findings of Liao et al,[51] Pannekoek et al[48] demonstrated increased connectivity in the bilateral dorsal ACC seed and left precuneus and left lateral occipital cortex in patients with SAD, compared with healthy control subjects. Contrary to Prater et al,[50] they also found an increased functional coupling within the right amygdala seed and the left middle temporal gyrus, left supramarginal gyrus, and left lateral occipital gyrus. As several investigations have provided conflicting results regarding the functional coupling of SN subregions, future research is needed to distinguish which of these subregions show increased or decreased coupling with the broader SN in patients with SAD.

Studies examining connectivity within the CEN in SAD showed more consistent findings.[47,49,51] Two studies exhibited decreased functional coupling within the CEN in patients with SAD.[47,49] Additionally, Liao et al[51] found a decreased functional coupling within the left superior frontal gyrus in patients with SAD, compared with healthy control subjects. This finding was negatively correlated with symptom severity. Interestingly, the functional connectivity between areas associated with the CEN and the bilateral angular gyri seemed to be decreased in patients with SAD. As the bilateral angular gyri are known components of the DMN, these findings may be suggestive of a disequilibrium between large-scale brain networks.[49]

Investigators have also turned their attention to resting-state amygdala connectivity in SAD, as amygdala activation has been strongly associated with fear response.[44,46] Hahn et al[44] revealed a decreased connectivity between the left amygdala and the left medial OFC, as well as with the left PCC in patients with SAD, compared with healthy control subjects. These findings were partially replicated by Liao et al.[46] In this study, increased functional coupling between the right amygdala and the medial OFC was demonstrated in patients with SAD. Additionally, increased coupling was found between the left amygdala and the MFG, temporal cortex, somato—motor and visual, as well as parahippocampal regions in patients with SAD, compared with healthy control subjects. Liao et al[46] also examined the relation between functional connectivity and morphometry of grey matter. When compared with healthy control subjects, decreased grey matter volumes in the right posterior inferior temporal gyrus, and right parahippocampal–hippocampal gyrus were observed in patients with SAD. Grey matter volumes in these 2 regions were negatively correlated with symptom severity. Structural analysis, combined with resting-state studies, may provide yet another means of evaluating the neurobiological underpinnings of anxiety disorders.

Obsessive–Compulsive Disorder

Previous research on OCD has demonstrated alterations of orbitofrontal-striatal–associated brain structures.[52] With these results in mind, an electronic search of OCD resting-state studies, between 2009 and 2013, returned 7 investigations.[53–59] These studies have also primarily examined resting-state functional connectivity using an ROI methodology. Two studies investigated functional connectivity of brain regions related to the DMN.[55,58] Jang et al[55] and Stern et al[58] demonstrated decreased connectivity

among brain structures within the DMN of patients with OCD, compared with control subjects. Decreased connectivity was correlated with symptom severity in patients with OCD.[55] One of the 7 studies also examined connectivity within SN-associated brain regions.[57] This study demonstrated increased connectivity between the right anterior PFC and the right insula, as well as the middle cingulate cortex in patients with OCD, compared with control subjects.[57]

Given that previous research has demonstrated alterations of orbitofronto-striatal–associated brain structures in patients with OCD,[52,60] investigators have also begun to shed light on the functional connectivity of resting-state orbitofronto-striatal functional connectivity.[53,56] Two of the 7 studies focused on resting-state orbitofronto-striatal connectivity and found increased functional coupling within those structures in patients with OCD, compared with healthy control subjects.[53,56] Additionally, the strength of connectivity between the ventral caudate–nucleus accumbens and the anterior OFC predicted overall OCD symptom severity, suggesting an enhanced engagement of central structures of the basal ganglia, with increased OCD symptom severity.

Zhang et al[59] focused on the cortical-control network connectivity and demonstrated a decreased connectivity in posterior temporal regions in patients with OCD, compared with healthy control subjects. Additionally, increased functional coupling in the cingulate, precuneus, thalamus, and cerebellum was also demonstrated in patients with OCD, compared with healthy control subjects. Moreover, patients with OCD showed significant changes in small-world network parameters, compared with healthy control subjects. Small-world analysis indicates the extent of interconnectivity of a network at a local and global level, comprising 2 features: high clustering and short path. Both features are needed to ensure functional segregation (high clustering) and integration, as well as rapid transfer of information between brain structures (short paths). Patients with OCD showed higher local clustering. Further analysis revealed changes to network properties predominantly occurred in brain regions showing increased functional connectivity strength in patients with OCD, namely, the cingulate, precuneus, thalamus, and cerebellum.

Panic Disorder

An electronic search of PD resting-state studies, between 2009 and 2013, returned only one investigation.[61] Pannekoek et al[61] examined resting-state functional connectivity of limbic structures as well as regions related to the SN. In detail, they found an increased functional connectivity between the amygdala and the bilateral precuneus and overall altered functional coupling within the SN in patients with PD, compared with healthy control subjects.[61] Given that there is only one investigation focusing on resting-state network activation in the PD patient population, more research is needed to reveal the neural connectivity underpinnings of PD.

Specific Phobia

An electronic search of resting-state studies in SP returned zero investigations. To our knowledge, no resting-state studies have been conducted in patient samples with SP as a primary diagnosis. However, it should be noted that at least one study we reviewed contained patient samples with comorbidities of SP.[50] Further research on resting-state connectivity in SP may find these studies an informative point of departure.

Discussion

Resting-state studies are beginning to elucidate different brain networks underlying anxiety disorders (see online eTable 1). Overall, there appears to be a certain degree of overlap within the neural networks underlying different anxiety disorders. Broad connectivity alterations between limbic regions—namely, the bilateral amygdalae, insula, and amygdalar subregions—and regions associated with the DMN, CEN, and SN were observed in PTSD, GAD, SAD, and PD. However, connectivity strength between limbic regions and these respective networks appears highly variable. The dominant resting-state feature of OCD appears to be alterations within corticostriatal regions and the DMN.[53,54] Therefore, future studies to determine the precise pattern of connectivity changes within SN, DMN, limbic, and corticostriatal networks across different anxiety disorders are warranted.

Finally, structural alterations to cortical regions that were predictive of functional alterations were demonstrated in 2 studies examining PTSD[32] and SAD.[47] Further research is needed before such findings can be deemed prognostically significant. However, positive correlations between functional connectivity and structural integrity lead us to believe that similar anatomical changes may be found in other neural circuits involved in resting-state abnormalities. Future research, employing a combination of resting-state functional imaging and structural imaging (for example, diffusion tensor imaging), may be instructive for identifying neurobiological distinctions among anxiety disorders.

Conclusion

Research examining functional connectivity during the resting state in subjects diagnosed with anxiety disorders is still in its infancy. Nevertheless, resting-state studies are beginning to associate alterations in various neural networks with anxiety disorders and, overall, there appears to be some similarity in the findings across studies and diagnoses. Such findings are consistent with emerging studies that have used specific, hypothesis-driven fMRI tasks.[62] However, some differences in functional connectivity are apparent. In PTSD, abnormalities within emotion regulatory networks, the DMN, and the SN appear prominent. In GAD, a single study points to the disruption of the SN and CEN. In SAD, it appears that the DMN, CEN, and SN may be altered, yet further changes are also observed in visual, somatosensory, and dorsal attention networks. OCD appears to be most reliably associated with abnormalities in the corticostriatal

networks, as well as the DMN. Finally, self-referential and somatosensory networks may play a central role in PD progression.

Overall, there appears to be a distinct need for resting-state studies that directly compare network connectivity between subjects with different anxiety disorders. Indeed, such an experimental design may improve our understanding of the neural underpinnings of these disorders, thereby clarifying diagnostic nosology and facilitating disorder-specific therapies. Resting-state designs that examine the relation between disorders, symptom profiles, underlying network abnormalities, and symptom severity will be important areas for neuropsychiatric investigation in the future.

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