Review

Topography of the Anxious Self: Abnormal Rest-Task Modulation in Social Anxiety Disorder

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Abstract

Social anxiety disorder (SAD) is characterized by social anxiety/fear, self-attention, and interoception. Functional magnetic resonance imaging studies demonstrate increased activity during symptom-sensitive tasks in regions of the default-mode network (DMN), amygdala (AMG), and salience network (SN). What is the source of this task-unspecific symptom-sensitive hyperactivity in DMN? We address this question by probing SAD resting state (rs) changes in DMN including their relation to other regions as possible source of task-unspecific hyperactivity in the same regions. Our findings show the following: (1) rs-hypoconnectivity within-DMN regions; (2) rs-hyperconnectivity between DMN and AMG/SN; (3) task-evoked hyperactivity in the abnormal rs-regions of DMN and AMG/SN during different symptom-sensitive tasks; (4) negative relationship of rest and task changes in especially anterior DMN regions as their rs-hypoconnectivity is accompanied by task-unspecific hyperactivity; (5) abnormal top-down/bottom-up modulation between anterior DMN regions and AMG during rest and task. Findings demonstrate that rs-hypoconnectivity among DMN regions is negatively related to task-unspecific hyperactivity in DMN and AMG/SN. We propose a model of "Topography of the Anxious Self" in SAD (TAS-SAD). Abnormal DMN-AMG/SN topography during rest, as trait feature of an "unstable social self", is abnormally aggravated during SAD-sensitive situations resulting in task-related hyperactivity in the same regions with an "anxious self" as state feature.

Keywords

social anxiety disorder, default-mode network, rest-task interaction, fMRI, resting state functional connectivity, amygdala, salience network, task-induced activity, anxious self, unstable social self

Introduction

Social anxiety disorder (SAD) is a common psychiatric disorder characterized by various symptoms including heightened social anxiety/fear, self-referential attention/rumination, and somatic interoceptive sensation (American Psychiatric Association 2013; Bögels and Lamers 2002; Bögels and Mansell 2004; Clark and Wells 1995; Etkin and Wager 2007; Gross 1998; Hofmann 2007; Rapee and Heimberg 1997; Spurr and Stopa 2002). Functional magnetic resonance imaging (fMRI) studies highlight the role of particular regions' neuronal changes that supposedly mediate these SAD-related symptoms. Alterations in the core default-mode network (DMN) regions, that is, cortical midline structures (CMS), as well as fear-related regions like the amygdala (AMG) and insula, that is, salience network (SN), and the dorsolateral prefrontal regions of the central executive network (CEN) regions figure most prominently in SAD (see below). These regions are related to key dimensions of SAD like self-referential processing (SRP; Qin and Northoff 2011; Qin and others 2020), emotional processing (Bas-Hoogendam and Westenberg 2020), interoception (Craig 2002), and cognitive control (Brühl and others 2014; Bunge and others 2001). Their exact role in generating

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the typical SAD symptoms like an "anxious self" (e.g., Etkin and Wager 2007) and an "unstable social self" (e.g., Clark and Wells 1995) remains unclear, though.

DMN regions and especially AMG show hyperactivity during different paradigms applying symptom-sensitive tasks. This can be observed during (1) self-referential stimuli, that is, self-recognition, negative self-beliefs, self-referential comments (Blair and others 2008a; Blair and others 2011b; Brown and others 2019; Dixon and others 2020; Goldin and Gross 2010; Goldin and others 2009a; Yoon and others 2019); (2) social anxious and fearful stimuli, for example, visual scenes, aversive auditory and social stimuli (Blair and others 2010; Boehme and others 2013; Heitmann and others 2016; Heitmann and others 2017; Nakao and others 2011; Quadflieg and others 2008; Schmidt and others 2010; Schneier and others 2011); (3) social cognition tasks like emotional faces paradigm (Gentili and others 2016); (4) disorder-irrelevant stimuli (emotional stimuli without social content, reward anticipation/outcome, human-computer interaction, cognitive tasks; Richey and others 2012; Sareen and others 2007; Shah and others 2009; Sripada and others 2009; Sripada and others 2013).

Together, these findings suggest that exaggerated activity in DMN and AMG and others occur across different stimuli/tasks and domains in a more or less task-unspecific way. At the same time, the exaggerated activity seems to be related to specific symptoms of SAD, that is, symptom-sensitive. Are there already resting state changes in regions like DMN, AMG, SN, and CEN, which, as psychological trait features ("unstable social self"), predispose SAD subjects to react anxiously in especially social situations that, as probed in task states, mirror psychological state features ("anxious self")? Addressing this question is the main goal of our investigation.

Complementing task-evoked studies, changes in SAD are also observed in resting state, that is, during the absence of any specific stimuli/task with eyes opened or closed (for generally about 5–8 minutes; Logothetis and others 2009). Resting state fMRI (rsfMRI) in SAD show alterations in resting state functional connectivity (rsFC) of the DMN, as well as of fear-related regions like AMG and SN. How these changes in resting state activity are related to task-unspecific but symptom-sensitive hyperactivity in more or less the same regions remains unclear, though. We here present a first step toward addressing this yet open issue. Specifically, we ask whether SAD resting state changes in especially DMN regions and amygdala are related to task-unspecific symptom-sensitive hyperactivity in the same regions.

The goal of our study is to address the question whether resting state changes in DMN, AMG, SN, and CEN regions of SAD are related to task-unspecific symptom-sensitive hyperactivity in the same regions. In accordance with our findings, our investigation will focus predominantly on DMN and SN regions including amygdala, that has been extensively associated with anxiety and the so-called fear-related circuit (Bas-Hoogendam and Westenberg 2020; Etkin and Wager 2007). As the amygdala is a key region of the SN (Menon 2015; Menon and Uddin 2010), from here on we will refer to AMG/SN. Based on the special role of DMN for both rest and task states (Anticevic and others 2012; Raichle 2015; Raichle and others 2001), as well as its changes in SAD (see below), we hypothesize that those DMN regions (and their connections to AMG/SN regions and CEN regions) showing decreased rsFC exhibit increased activity during different tasks, that is, task-unspecific but symptom-sensitive hyperactivity.

To probe this hypothesis, we conduct a systematic narrative review of fMRI studies with the following specific aims: (1) review inter-regional (rsFC) measures of resting state activity in especially DMN of SAD to define relevant regions of interest (ROI); (2) apply these resting state-based ROIs to the review of task-evoked studies in SAD during various stimuli/tasks to test for rest-task relationship; (3) review those studies in SAD that measure and compare both rest and task in the same subjects to support our hypothesis of abnormal rest-task modulation in SAD; (4) investigate those studies that employ effective functional connectivity to probe for the directionality of especially the relationship of DMN and AMG (see Fig. 1 for overview).

Materials and Methods

Search Strategy and Selection Criteria

To be included in this work, studies had to have been published in scientific journals in order to be considered of comparable quality. The systematic literature search and study selection approach followed PRISMA guidelines. PubMed and Web of Science were the source of information and an online search was conducted using the following keywords: "social anxiety disorder" OR "social phobia" AND "resting state" AND "task-evoked activity" OR "task/stimulus-induced" AND "fMRI" for the time frame up to May 2021.

The study selection followed a four-stage approach in order to search: (1) studies using resting state fMRI in SAD, (2) task-evoked fMRI studies in SAD, (3) combined rest and task fMRI studies in SAD. Additionally, (4) we searched for effective connectivity (EC) fMRI studies in SAD to investigate the directionality between the different examined regions, to test our prior hypothesis of rest-task modulation.

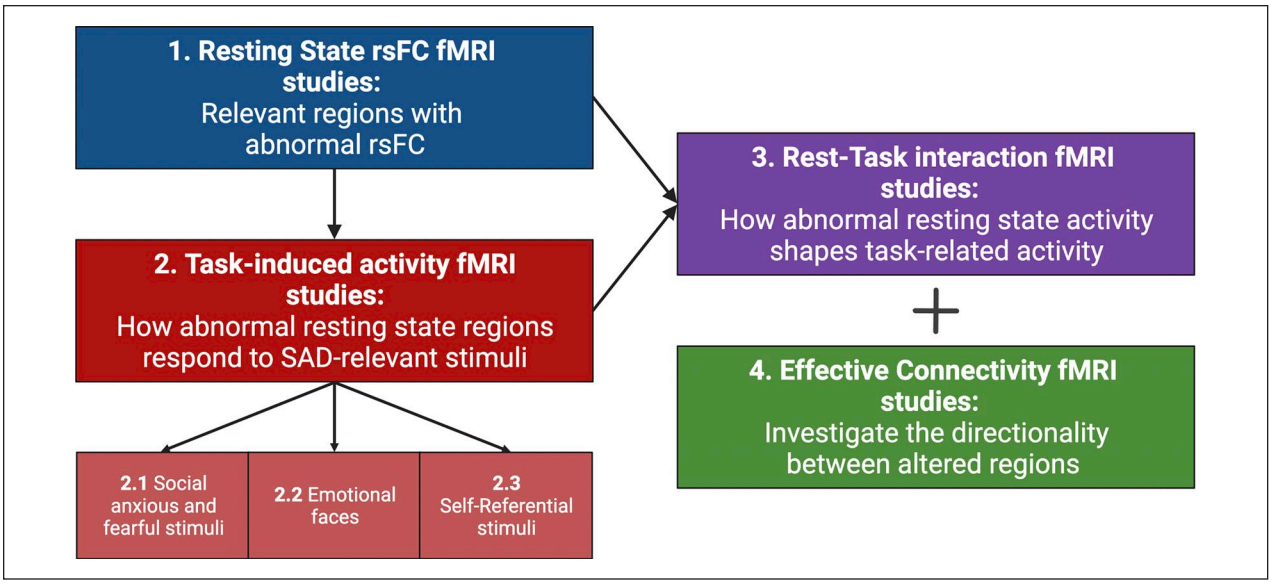


Figure 1. Schematic organization of the review.

rsfMRI Studies in SAD. We obtained 130 results in which we further refined the search assessing from the title and abstract whether the studies: (1) were fMRI studies, (2) used resting state paradigm, and (3) included both a group of patients with SAD and a healthy control group. At this stage, we excluded all studies that were systematic and narrative reviews, and meta-analysis.

We finally identified 16 studies (T1) that examined SAD patients and healthy controls during resting state conditions. From the 16 studies mentioned above, we obtained the brain regions with abnormal activity during resting state conditions when compared to the control group (T2).

Task-Evoked fMRI Studies in SAD. In the second stage, we identified 37 task studies (T1) in SAD using as main reference point the various meta-analyses present in the literature regarding task-evoked activity in SAD (e.g., Brühl and others 2014; Gentili and others 2016; Yoon and others 2019) together with a literature search via PubMed and Web of Science as previously illustrated.

Furthermore, we differentiated these studies in three categories on the base of stimulus type and induced outcome: (1) eight studies about how the subject experiences himself (internal-cognitive processing): *self-referential tasks*, for example, self-recognition, negative self-beliefs, self-referential comments; (2) eight studies about how the subject reacts in a social context/fearful situation (external-emotional processing): *social anxious and fearful stimuli*, that is, visual scenes, aversive auditory and social stimuli; (3) 21 studies about how the subject experiences the other, that is, social cognition, (external-emotional processing): *emotional faces tasks*.

In these studies, we investigated how the previously defined rs-ROIs responded in accordance with the different symptom-specific tasks in SAD patients versus healthy controls. This step served us to make hypotheses about the changes in activity from rest to task and how they might be intrinsically related.

Combined Rest-Task Studies in SAD. In the third stage we obtained five studies including both rest and task conditions (T1). These studies served the aim to test our initial hypothesis of direct rest-task relationship in SAD.

Effective Connectivity Studies in SAD. Finally, in a fourth stage, in order to define the directionality in the interaction of different regions during rest and task states, we reviewed EC studies in SAD. We found four studies examining EC in SAD (T1), using different types of paradigms, that is, resting state and emotional tasks, and type of analysis (Granger causality analysis [GCA] and dynamic causal modelling [DCM]). See Tables 1 and 2.

Results

Intra- and Inter-Network Functional Connectivity in Resting State

Resting state activity is predominantly investigated using functional connectivity (rsFC). rsFC can be explored among the regions within a specific network like DMN or the salience network (SN) that includes the amygdala. Additionally, one can also investigate rsFC between the regions of different networks like DMN and SN. Both

Table 1. Studies included in the review.

Resting State Studies	Sample (SAD vs. HC)	Type of Paradigm
1. Liao and others 2010a	20 vs. 19	Resting state (RS)
2. Liao and others 2011	18 vs. 18	RS
3. Ding and others 2011	17 vs. 19	RS
4. Pannekoek and others 2013	12 vs. 12	RS
5. Liu and others 2015a	20 vs. 20	RS
6. Liu and others 2015b	20 vs. 20	RS
7. Anteraper and others 2014	17 vs. 17	RS
8. Manning and others 2015	53 vs. 33	RS
9. Geiger and others 2015	18 vs. 15	RS
10. Cui and others 2017	21 vs. 20	RS
11. Rabany and others 2017	8 vs. 19	RS
12. Zhu and others 2017	42 vs. 42	RS
13. Yun and others 2017	28 vs. 27	RS
14. Yuan and others 2018	43 vs. 43	RS
15. Jung and others 2018	36 vs. 42	RS
16. Yang and others 2019	33 vs. 32	RS
Task Studies	**Sample (SAD vs. HC)**	**Type of Paradigm**
1. Quadflieg and others 2008	12 vs. 12	Emotionally spoken words
2. Blair and others 2010	16 vs. 16	Social norm processing task
3. Schmidt and others 2010	19 vs. 18	Phobia related words
4. Nakao and others 2011	6 vs. 9	Social situation task
5. Schneier and others 2011	16 vs. 16	Direct vs. away eye gaze
6. Boehme and others 2013	17 vs. 17	Anticipation of public speech
7. Heitmann and others 2016	54 vs. 54	Disorder-related visual scene
8. Heitmann and others 2017	54 vs. 54	Disorder-related visual scene
9. Stein and others 2002b	15 vs. 15	Emotional faces (EF)
10. Straube and others 2005	9 vs. 9	EF
11. Amir and others 2005	11 vs. 11	EF
12. Phan and others 2006	10 vs. 10	EF
13. Cooney and others 2006	10 vs. 10	EF
14. Yoon and others 2007	11 vs. 11	EF
15. Evans and others 2008	11 vs. 11	EF
16. Gentili and others 2008	8 vs. 7	EF
17. Blair and others 2008b	17 vs. 17	EF
18. Goldin and others 2009b	15 vs. 17	EF
19. Klumpp and others 2010	12 vs. 12	EF
20. Blair and others 2011a	25 vs. 23	EF
21. Labuschagne and others 2012	18 vs. 18	EF
22. Klumpp and others 2012	29 vs. 26	EF
23. Klumpp and others 2013	29 vs. 27	EF
24. Frick and others 2013	14 vs. 12	EF
25. Ziv and others 2013	67 vs. 28	EF
26. Phan and others 2013	21 vs. 19	EF
27. Pantazatos and others 2014	14 vs. 17	EF
28. Wheaton and others 2014	23 vs. 24	EF
29. Fonzo and others 2015	14 vs. 15	EF
30. Blair and others 2008a	17 vs. 17	Self vs. other referential criticism and praise
31. Goldin and others 2009a	16	Self-referential processing (SRP) task
32. Goldin and Gross 2010	16	Negative self-beliefs (NSB) task
33. Blair and others 2011b	15 vs. 15	Response to own/other opinion
34. Pujol and others 2013	20 vs. 20	Public self-exposure

(continued)

Table 1. (continued)

Task Studies	Sample (SAD vs. HC)	Type of Paradigm
35. Gaebler and others 2014	21 vs. 23	Self-focused emotion regulation task
36. Brown and others 2019	51 vs. 13	SRP task
37. Dixon and others 2020	113 vs. 35	NSB task
Rest-Task Studies	**Sample (SAD vs. HC)**	**Type of Paradigm**
1. Hahn and others 2011	10 vs. 27	RS + EF
2. Prater and others 2013	20 vs. 17	RS + EF
3. Cremers and others 2015	20 vs. 20	RS + Anticipation of public speech
4. Choi and others 2016	22 vs. 20	RS + EF + Interoceptive task
5. Yoon and others 2016	20 vs. 20	RS + Working memory task
Effective Connectivity Studies	**Sample (SAD vs. HC)**	**Type of Paradigm**
1. Liao and others 2010b	22 vs. 21	RS
2. Sladky and others 2015	15 vs. 15	EF
3. Tadayonnejad and others 2016	21 vs. 19	EF
4. Minkova and others 2017	15 vs. 15	Emotional Stroop task

SAD = social anxiety disorder; HC = healthy controls.

Table 2. Summary of Brain Regions with Abnormal Resting State Activity.

Brain Region	Resting State Studies (from Table 1) in Which Abnormal Activity Is Reported	Total
MPFC (VMPFC + DMPFC)	1, 3, 7, 8, 9, 11, 12, 14, 15, 16	10
PCun	1, 3, 4, 5, 6, 7, 10, 12, 15, 16	10
IPG (IPL + AG + SMG)	1, 3, 4, 5, 7, 9, 11, 15, 16	9
ACC (PGACC + SGACC + DACC)	1, 4, 7, 8, 9, 10, 11, 15	8
MTG	1, 2, 4, 7, 9, 13, 15, 16	8
SMC (PMC + PSCG + PRCG + SMA)	1, 3, 5, 7, 8, 10, 16	7
DLPFC	1, 3, 7, 14, 15, 16	6
INS	1, 5, 9, 10, 14, 16	6
PCC	3, 7, 10, 11, 14, 15	6
AMG	3, 4, 7, 9, 11, 16	6
FFG	3, 6, 8, 14, 15, 16	6
OC (SOG + MOG + IOG)	1, 2, 3, 4, 5, 15	6
ITG/PHG	2, 7, 12, 14, 15, 16	6

VM/DMPFC = ventro/dorsomedial prefrontal cortex; IPG = inferior parietal gyrus; IPL = inferior parietal lobule; AG = angular gyrus; SMG = supramarginal gyrus; PCun = precuneus; PG/SG/DACC = perigenual/subgenual/dorsal anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; SMC = somatomotor cortex; PMC = premotor cortex; PSCG = postcentral gyrus; PRCG = precentral gyrus; SMA = supplementary motor area; OC = occipital cortex; SOG = superior occipital gyrus; MOG = middle occipital gyrus; IOG = inferior occipital gyrus; FFG = fusiform gyrus; MTG = middle temporal gyrus; INS = insula; PCC = posterior cingulate cortex; ITG = inferior temporal gyrus; PHG = parahippocampal gyrus; AMG = amygdala.

intra- and inter-network rsFC have been extensively conducted in SAD.

Intra-Network rsFC

Within-DMN rsFC. In a first step, we investigated resting state studies in SAD to identify ROIs showing abnormal resting state connectivity among the regions of the DMN. Weaker rsFC between anterior (dorsomedial prefrontal cortex [DMPFC], ventromedial prefrontal cortex [VMPFC], perigenual anterior cingulate cortex [PGACC], subgenual anterior cingulate cortex [SGACC]) and posterior (posterior cingulate cortex [PCC], precuneus [PCun], inferior parietal lobule [IPL]) have been consistently reported (Cui and others 2017; Yuan and others 2018; Zhu and others 2017). Three fMRI studies also observed decreased rsFC among the anterior DMN regions themselves, that is, between VMPFC/DMPFC and PG/SGACC (Cui and others 2017; Manning and others 2015; Yuan and others 2018).

Some conflicting results shall be mentioned. One study found an enhanced anterior-posterior rsFC, specifically between the VMPFC and PCC (Rabany and others 2017). This conflicting result may be related to the small SAD sample, that is, eight SAD patients. Another fMRI

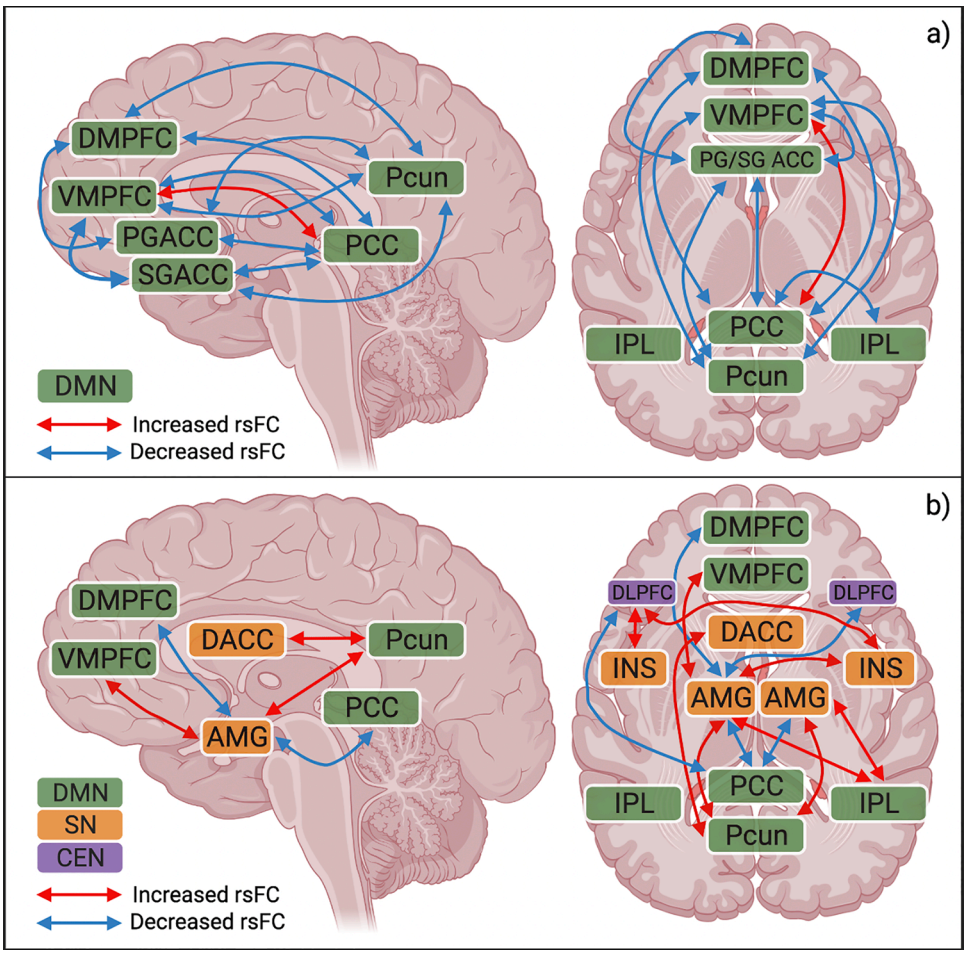


Figure 2. Resting state studies: (a) Intra-network rsFC (within-DMN). (b) Inter-networks rsFC (DMN, AMG/SN, CEN). VMPFC = ventromedial prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; SGACC = subgenual anterior cingulate cortex; PGACC = perigenual anterior cingulate cortex; PCC = posterior cingulate cortex; PCun = precuneus; IPL = inferior parietal lobule; DACC = dorsal anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; AMG = amygdala; INS = insula; PCC = posterior cingulate cortex.

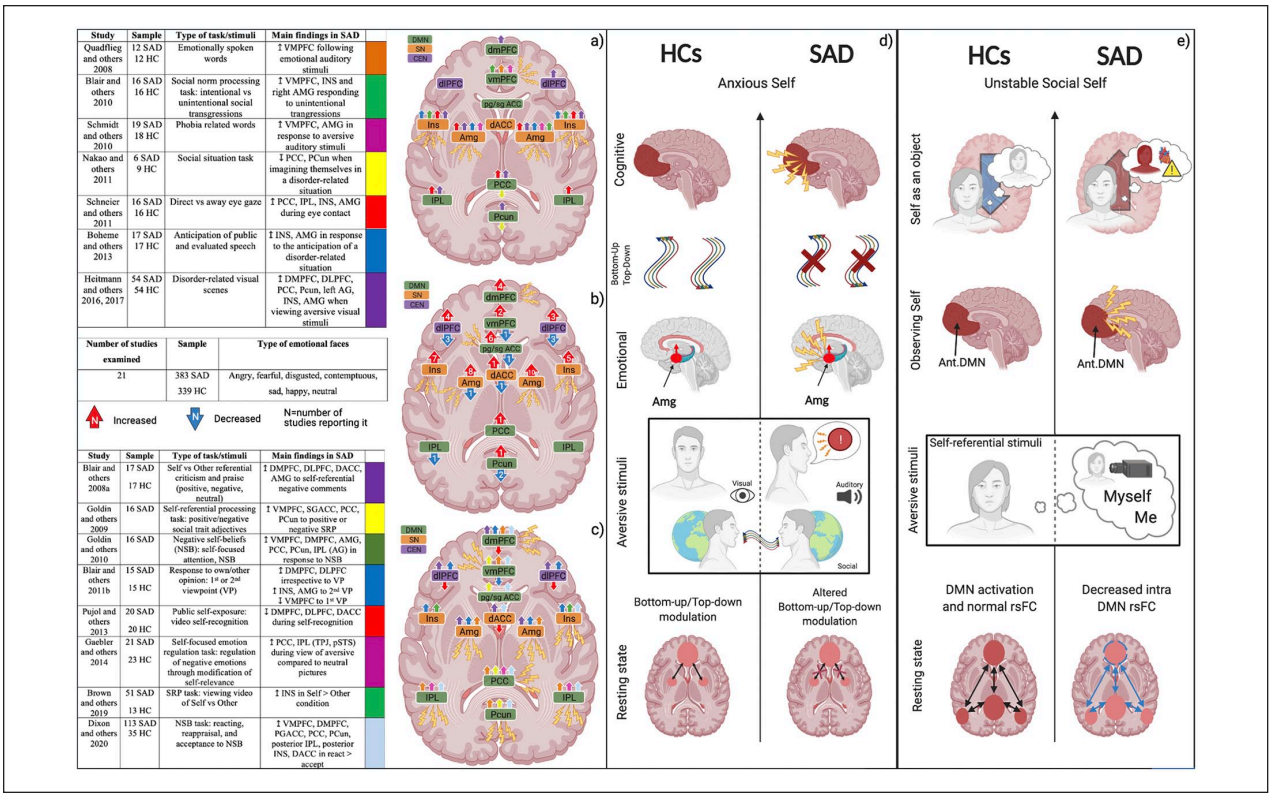
study on SAD reported no significant differences of the rsFC within the DMN between SAD patients and controls (Pannekoek and others 2013).

Altogether these findings indicate that most of the studies on SAD investigating rsFC within DMN observe mainly (1) decreased rsFC between anterior and posterior DMN and (2) decreased rsFC among the different anterior regions of DMN. This highlights the key role of anterior DMN regions in SAD showing resting state hypoactivity indicating lower degrees of cross-regional synchronization (as measured by functional connectivity; Fig. 2a).

rsFC among amygdala and insula. A few studies report increased resting state connectivity of the amygdala with the insula and other regions of the SN in SAD. Specifically, Jung and other (2018) observed enhanced rsFC between amygdala and insula (Fig. 3b) in SAD patients when compared with HC. A graph theoretical topological approach shows abnormal nodal properties of the insula relative to other regions in SAD (Yang and others 2019). Tentatively, these findings suggest abnormal subcortical rsFC with a focus on amygdala and insula.

Inter-Network rsFC

rsFC between amygdala and DMN. Various fMRI studies show altered rsFC between DMN and AMG/SN regions in SAD. Amygdala is reported to have increased rsFC with some DMN regions including VMPFC, PCun, and IPL (Anteraper and others 2014; Geiger and others 2015; Jung and others 2018). Like the amygdala, another region of SN, the dorsal anterior cingulate cortex (DACC) shows enhanced rsFC with the precuneus (Pannekoek and



Study	Sample	Type of task/stimuli	Main findings in SAD
Quadflieg and others 2008	12 SAD 12 HC	Emotionally spoken words	↕ VMPFC following emotional auditory stimuli
Blair and others 2010	16 SAD 16 HC	Social norm processing task: intentional vs unintentional social transgressions	↕ VMPFC, INS and right AMG responding to unintentional transgressions
Schmidt and others 2010	19 SAD 18 HC	Phobia related words	↕ VMPFC, AMG in response to aversive auditory stimuli
Nakao and others 2011	6 SAD 9 HC	Social situation task	↕ PCC, PCun when imagining themselves in a disorder-related situation
Schneier and others 2011	16 SAD 16 HC	Direct vs away eye gaze	↕ PCC, IPL, INS, AMG during eye contact
Boheme and others 2013	17 SAD 17 HC	Anticipation of public and evaluated speech	↕ INS, AMG in response to the anticipation of a disorder-related situation
Heitmann and others 2016, 2017	54 SAD 54 HC	Disorder-related visual scenes	↕ DMPFC, DLPFC, PCC, Pcun, left AG, INS, AMG when viewing aversive visual stimuli

Number of studies examined	Sample	Type of emotional faces
21	383 SAD 339 HC	Angry, fearful, disgusted, contemptuous, sad, happy, neutral

↑N Increased ↓N Decreased N=number of studies reporting it

Study	Sample	Type of task/stimuli	Main findings in SAD
Blair and others 2008a	17 SAD 17 HC	Self vs Other referential criticism and praise (positive, negative, neutral)	↕ DMPFC, DLPFC, DACC, AMG to self-referential negative comments
Goldin and others 2009	16 SAD	Self-referential processing task: positive/negative social trait adjectives	↕ VMPFC, SGACC, PCC, PCun to positive or negative SRP
Goldin and others 2010	16 SAD	Negative self-beliefs (NSB): self-focused attention, NSB	↑ VMPFC, DMPFC, AMG, PCC, PCun, IPL (AG) in response to NSB
Blair and others 2011b	15 SAD 15 HC	Response to own/other opinion: 1st or 2nd viewpoint (VP)	↕ DMPFC, DLPFC irrespective to VP ↕ INS, AMG to 2nd VP ↕ VMPFC to 1st VP
Pujol and others 2013	20 SAD 20 HC	Public self-exposure: video self-recognition	↕ DMPFC, DLPFC, DACC during self-recognition
Gaebler and others 2014	21 SAD 23 HC	Self-focused emotion regulation task: regulation of negative emotions through modification of self-relevance	↕ PCC, IPL (TPJ, pSTS) during view of aversive compared to neutral pictures
Brown and others 2019	51 SAD 13 HC	SRP task: viewing video of Self vs Other	↕ INS in Self > Other condition
Dixon and others 2020	113 SAD 35 HC	NSB task: reacting, reappraisal, and acceptance to NSB	↕ VMPFC, DMPFC, PGACC, PCC, PCun, posterior IPL, posterior INS, DACC in react > accept

Figure 3. (a) Brain activity during *social anxious and fearful stimuli tasks*; (b) Brain activity during *emotional faces tasks*; (c) Brain activity during *self-referential tasks*; (d) Anxious Self paradigm: a proper communication between amygdala and anterior DMN regions is essential to modulate strong emotional feelings (Phelps and LeDoux 2005). This bidirectional relationship is already present in the absence of stimuli, that is, at rest. In fact, under normal conditions, a strong amygdala activation (caused by an aversive stimulus), that is, bottom-up modulation, is counterbalanced by anterior DMN regions activation (cognitive), which in turn modulates the emotional activation of the amygdala, lowering the levels of anxiety/fear, that is, top-down modulation. Conversely, an abnormal relationship between amygdala and anterior DMN regions is already present at rest in SAD patients. This determines that, when these individuals experience an aversive stimulus (visual, auditory, or social), the synchronized activation of amygdala and anterior DMN regions occurs independently (Phelps and LeDoux 2005). By not communicating adequately, an altered bottom-up/top-down modulation causes an emotional dysregulation which leads these subjects to experience an Anxious Self, characterized by high levels of (social) anxiety and fear. (e) Unstable Social Self paradigm: studies suggest that rsFC within the DMN is related to internally oriented cognition (such as SRP and social cognition; Frewen and others 2020; Qin and Northoff 2011; Qin and others 2020). Under normal conditions, there is an appropriate rsFC between DMN regions at rest. Consequently, when a self-referential stimulus is experienced, the co-activation of the same active regions during rest allows an adequate processing of external and internal stimuli. This seems not to happen in SAD patients. Indeed, the DMN hypoconnectivity we have reported (1) within the anterior regions and (2) between anterior and posterior regions seems to have a pivotal role in these individuals' reactions to self-referential stimuli. Specifically, the anterior DMN hyperactivity competes for cognitive resources with brain regions supporting attention control, memorization, and analytical reasoning leading to a heightened attention to the self in the environment, that is, self as an object. This causes an enhanced self-focused attention which compromises social performances and feeds negative self-beliefs (Clark and Wells 1995). VMPFC = ventromedial prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; DACC = dorsal anterior cingulate cortex; PGACC = perigenual anterior cingulate cortex; SGACC = subgenual anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; AMG = amygdala; INS = insula; PCC = posterior cingulate cortex; IPL = inferior parietal lobule; PCun = precuneus.

others 2013). At the same time, the amygdala also shows reduced rsFC with other DMN regions like DMPFC and PCC (Jung and others 2018; Rabany and others 2017). In contrast to the amygdala, the insula does not show altered rsFC with anterior and/or posterior DMN regions.

Taken together, we observed altered rsFC of the amygdala with anterior and posterior DMN regions, whereas no rsFC changes can be observed for the insula with the DMN. The direction of the changes of amygdala-DMN rsFC is increased in some studies while decreased in other studies. The reasons for such discrepancy are not fully clear and may be related to different steps in preprocessing as well as the inclusion/exclusion of global signal regression (GSR; see Scalabrini and others 2020b for a

discussion on the relevance of global signal in psychiatric disorders; Fig. 2b).

rsFC between other networks. Abnormal rsFC is also reported in other networks outside DMN and AMG/SN. A prominent CEN region, that is, DLPFC, shows reduced rsFC with PCC and amygdala as well as increased rsFC with bilateral insula (Jung and others 2018; Yang and others 2019; Zhu and others 2017). Decreased rsFC can also be observed in the temporal lobe as involved in the auditory network (AN) with frontal, somatosensory and occipital regions (as parts of DMN, somatomotor network [SMN], and visual network [VN], respectively; Cui and others 2017; Ding and others 2011; Zhu and others 2017).

Summary of Intra- and Inter-Network rsFC Studies. Taken together, the intra- and inter-network rsFC findings show (1) hypoconnectivity among anterior and posterior DMN regions; (2) decreased rsFC among the anterior DMN regions themselves; (3) increased and decreased rsFC of the amygdala with different DMN regions; and (4) reduced rsFC of the DLPFC with posterior DMN and amygdala.

Task-Evoked Activity in Abnormal Resting State Regions

How does resting state DMN hypoconnectivity and amygdala-related hyperconnectivity impact task-evoked activity? This will be addressed in two steps. First, in order to draw relationship of rest and task states in SAD, we now select exactly those regions that show consistent resting state changes, that is, especially DMN and AMG/SN, for analysis of their task-evoked activity. Second, we also raise the question of task-specificity versus task-unspecificity: do the DMN and AMG/SN regions that show abnormal resting state activity exhibit distinct task-evoked activity changes during different kinds of stimuli/tasks? For that purpose, we focus on the main stimuli/tasks applied in SAD fMRI imaging studies; these include social-emotional, emotional, and self-referential cognition tasks.

Social Anxious and Fearful Stimuli. The most used method to investigate abnormal activity in anxiety disorders is to expose patients to external social and fearful stimuli as to probe the subjects' emotional response. The examined fMRI studies highlight a consistent hyperactivation of most of the altered resting state regions in response to social-emotional stimuli and their anticipation in different sensory modalities, that is, visual and auditory stimuli. This includes the midline DMN regions and especially the amygdala and insula which is one of the best replicated findings in SAD (Blair and others 2010; Boehme and others 2013; Heitmann and others 2016; Heitmann and others 2017; Nakao and others 2011; Quadflieg and others 2008; Schmidt and others 2010; Schneier and others 2011). Altogether, SAD patients mainly report hyperactivations in response to social anxious and fearful stimuli in amygdala and insula as well as in various DMN regions, that is, VMPFC, PCC, and IPL (Fig. 3a).

Emotional Faces. Yet another widely used paradigm are emotional faces. This showed consistent hyperactivation of amygdala and insula in SAD (Etkin and Wager 2007) during especially negative-emotional faces, that is, fearful, angry, disgusted (Amir and others 2005; Blair and others 2008b; Blair and others 2011a; Evans and others 2008; Fonzo and others 2015; Gentili and others 2008; Klumpp and others 2010; Klumpp and others 2012; Klumpp and others 2013; Phan and others 2006; Phan and others 2013; Stein and others 2002b; Straube and others 2005; Yoon and others 2007). Various studies also report abnormal activity in the frontal regions: an increased activity following negative-emotional faces have been found in anterior midline DMN regions like DMPFC, VMPFC, PGACC, SGACC, and also DACC (Amir and others 2005; Blair and others 2008b; Blair and others 2011a; Evans and others 2008; Goldin and others 2009b; Klumpp and others 2012; Labuschagne and others 2012; Wheaton and others 2014; Ziv and others 2013; Fig. 3b).

In contrast to anterior DMN, few studies have observed task-related abnormalities in posterior DMN regions. A study focusing on the DMN reveals a lower deactivation of PCC/PCun in SAD patients (Evans and others 2008; Gentili and others 2009), whereas other studies highlight hypoactivity of PCun and IPL (Gentili and others 2008; Goldin and others 2009b). Finally, the DLPFC also often exhibits differential activity, most often hyperactivation (Blair and others 2008b; Evans and others 2008; Frick and others 2013; Gentili and others 2008; Klumpp and others 2010; Pantazatos and others 2014; Phan and others 2013; Yoon and others 2007; Ziv and others 2013). Together, the activity pattern during emotional faces resembles the one during social anxious stimuli as both show hyperactivity in amygdala/insula and anterior DMN (while only the social tasks also elicit hyperactivity in posterior DMN).

Self-Referential Tasks. A third set of studies evaluated neural activity linked to self-referential processing (SRP) during self-referential tasks in SAD for which different types of paradigms, for example, negative self-beliefs, public self-exposure, response to own/other opinion are used. Hyperactivity can again be observed in amygdala, insula, and DACC during self-referential tasks (Blair and others 2008a; Blair and others 2011b; Brown and others 2019; Dixon and others 2020; Goldin and Gross 2010). There is also strong evidence for anterior and posterior midline DMN regions showing hyperactivity during

attention to internal self-referential cognition as distinguished from external emotional responses (Blair and others 2008a; Blair and others 2011b; Brown and others 2019; Dixon and others 2020; Gaebler and others 2014; Goldin and Gross 2010; Goldin and others 2009a; Pujol and others 2013; Fig. 3c). Hence, as in social and emotional tasks, self-referential cognition elicits hyperactivity in amygdala/insula and anterior (and posterior) DMN regions in SAD.

Rest-Task Modulation in SAD

Summary of Task-Related Studies. Are resting state changes in amygdala/insula as well as in anterior and posterior DMN related to task-evoked changes in the same regions? We here took those regions showing resting state changes as regions of interest for investigating different task states in SAD. We obtained the following findings. (1) Our approach revealed task-related hyperactivity most consistently in amygdala and insula during all three paradigms (social, emotional, and self-referential cognition). (2) Similarly, especially anterior (and, in part, posterior) DMN regions also exhibit task-related hyperactivity in all three paradigms. (3) Given that task-related hyperactivity was observed across all three paradigms, we assume some degree of task-unspecificity holding across emotional, social, and self-referential tasks; this suggests some basic neural changes holding in response to SAD-sensitive or SAD-relevant stimuli of different kinds.

Together with the resting state findings, this amounts to the following hypotheses. Resting state hyperactivity in amygdala and insula is related to hyperactivity in all three task states, that is, task-unspecific—this suggests positive rest-task modulation. While resting state hypoactivity in anterior (and posterior) DMN also yields task-related hyperactivity in again a task-unspecific way—this suggests negative rest-task modulation.

We need to be careful, though. The various rest and task studies were obtained in different subjects and different scanners. This raises the question for direct interaction of rest and task states within the same regions of the same subjects in the same scanner. This leads us to review those studies in SAD that combine both rest and task within the same subjects addressing the question for abnormal rest-task modulation (see in healthy subjects: Huang and others 2017; Northoff and others 2010; Wainio-Theberge and others 2021; Wolff and others 2019).

Rest-Task Modulation in SAD. Is there abnormal rest-task modulation in DMN and amygdala in SAD? Specifically, we raise the following assumptions as formulated as questions: (1) Is the task-related hyperactivity in amygdala related to its abnormal resting state functional connectivity with regions of the DMN (and other cortical regions)? (2) Is the increased task-related activity in DMN inversely related to their decreased functional connectivity in the resting state in the same regions of the DMN? To test the assumption of abnormal rest-task modulation in amygdala and DMN of SAD, we now review those fMRI studies that combined both rest and task within one and the same subject. We found only five studies combining both rest and task within the same SAD (and healthy) subjects. As the studies are rather heterogeneous, we describe the main results of each of them.

Study	fMRI Paradigm	Sample	Rest Findings	Task Findings
Hahn and others 2011	RS + facial expression discrimination task (FEDT)	*10 SAD*	Reduced rsFC between amygdala and VMPFC, PCC/PCun	Increased activity of amygdala
		27 HC	Increased rsFC between amygdala and VMPFC	—
Prater and others 2013	RS + emotional face matching task (EFMT)	*20 SAD*	Reduced rsFC between amygdala and VMPFC	Reduced FC between amygdala and VMPFC; increased activity of amygdala (fear vs. happy faces)
		17 HC	—	Increased FC between amygdala and VMPFC
Cremers and others 2015	RS + social evaluative stress procedure (SESP)	*20 SAD*	Negative rsFC between amygdala and CER (VMPFC, DLPFC, etc.)	Reduced FC between amygdala and CER regions
		20 HC	Negative rsFC between amygdala and CER (VMPFC, DLPFC, etc.)	Increased FC between amygdala and CER regions
Yoon and others 2016	RS + self-referential working memory task (encoding + maintenance + retrieval)	*20 SAD*	Increased rsFC between amygdala and DMPFC, TPJ (encoding), DLPFC (retrieval)	Increased activity of DMPFC, PCC, insula, TPJ (encoding); reduced activity in DLPFC (retrieval)
		20 HC	—	—
Choi and others 2016	RS + emotional faces + interoceptive task	*22 SAD*	Reduced rsFC between PCC with others DMN regions	Increased activity of PCC (target condition) and insula (internal focus)
		20 HC	—	—

Combined rest and task studies in SAD. Hahn and others (2011) investigated the functional connectivity network of the amygdala subjecting SAD patients and HCs to a facial emotion processing task as well as a resting state period. They observed (1) task-evoked hyperactivity (during emotional face stimuli) in right and left amygdala; (2) amygdala shows decreased rsFC with anterior (VMPFC) and posterior (PCC/PCun) DMN regions in SAD which correlated negatively with symptom severity (lower rsFC leads to higher symptom severity). Together, these findings show that task-related hyperactivity and resting state hypoactivity in the amygdala occur within the same region and within the same subjects. Though unfortunately, they did not calculate correlation of rest and task states in the amygdala, these findings nevertheless lend support to the assumption that rest and task changes in amygdala (including its connectivity to DMN) are related to each other.

Prater and others (2013) administered a resting state period followed by an emotional face matching task, that is, fearful faces, to SAD patients and HCs. Their main findings in SAD are the following: (1) greater activity in bilateral amygdala (and the DLPFC) during fearful versus happy faces; (2) decreased task-related functional connectivity between the amygdala and the anterior DMN (VMPFC) (during fearful vs. happy faces); (3) decreased functional connectivity between bilateral amygdala and the anterior DMN (VMPFC) during resting state; (4) significant overlap (40%) among rest and task voxels in amygdala which show decreased functional connectivity with anterior DMN during rest and task. Together, these findings show close relationship of task-related hyperactivity and resting state hypoconnectivity of the amygdala (and its relation to anterior DMN). The authors therefore propose that aberrant amygdala–VMPFC connectivity in SAD may already exist at baseline (in rest) even in the absence of any (task-related) detection of social threat in the environment (Prater and others 2013).

Cremers and others (2015) investigated resting state functional connectivity before, during, and after a social-evaluative task, namely, the anticipation of giving a public speech. They extracted the time series of right and left amygdala and correlated that with the time series of a complex of regions all being involved in cognitive emotion regulation (CER; which includes DLPFC, VMPFC, etc.) without distinguishing the latter regions into DMN and non-DMN regions. Their findings are the following: (1) functional connectivity of amygdala and the complex of all cortical CER regions increased in healthy subjects during the anticipation of a public speech (relative to before and after); (2) SAD subjects show decrease rather than increase in FC of amygdala-CER regions during the anticipation of the public speech; (3) significant correlation of stress-related changes in FC and symptom severity. Together, these findings show that resting state FC of the amygdala to diverse cortical regions reacts in an abnormal way, that is, decrease rather than increase, during a socially anxious task. That further supports the assumption of close relationship of rest and task changes in the amygdala.

Yoon and others (2016) applied a working memory task (encoding, maintenance, retrieval) with self-referential stimuli (faces with self-referential positive or negative comments). The observed (1) task-related hyperactivity in PCC and insula (and various other regions like DMPFC and TPJ) during specifically the encoding phase of the working memory while retrieval induced hypoactivity in DLPFC (and others); (2) increased resting state functional connectivity of the amygdala with the DMPFC and DLPFC (and others like TPJ) as showing task-related changes; (3) significant correlation of task-related activity changes in insula and DLPFC with symptom severity. Together, these findings show that the amygdala shows abnormal resting state functional connectivity to those regions that exhibit task-related hyperactivity (during a self-referential emotional working memory task). This further emphasizes the key role of the amygdala in SAD with respect to specifically subcortical-cortical rest-task modulation.

The studies so far support the key role of the amygdala and its relation to DMN for rest-task modulation as per our first assumption. How about our second assumption of abnormal rest-task modulation within the DMN itself? Choi and others (2016) investigated the neural basis and underlying resting-state pathology of attentional bias toward internal, that is, interoceptive attention and external social attention to threats (high or low number of persons) in SAD patients compared to HCs. A face-in-the-crowd-effect task was used for detecting a target face, that is, a contemptuous face among distracter faces. During the task, participants' attention to the own heartbeat (vs. attention to a control sound) while viewing the crowdedness of the faces, that is, eight-person (high threat) versus four-person (low threat) crowd, were presented.

They obtained the following main findings. First, during interoceptive attention to the own heartbeat (during both low and high social threat with the four and eight persons, respectively), SAD subjects exhibited task-related hyperactivity in rostral anterior cingulate (part of DMN) as well as in both left and right anterior insula. Second, the PCC as part of the DMN showed task-related hyperactivity during the target condition (high social threat—eight 8 persons—during interoceptive attention of the own heartbeat). Third, resting state FC was decreased within DMN including PCC. Fourth, the elevated task-related hyperactivity in PCC correlated

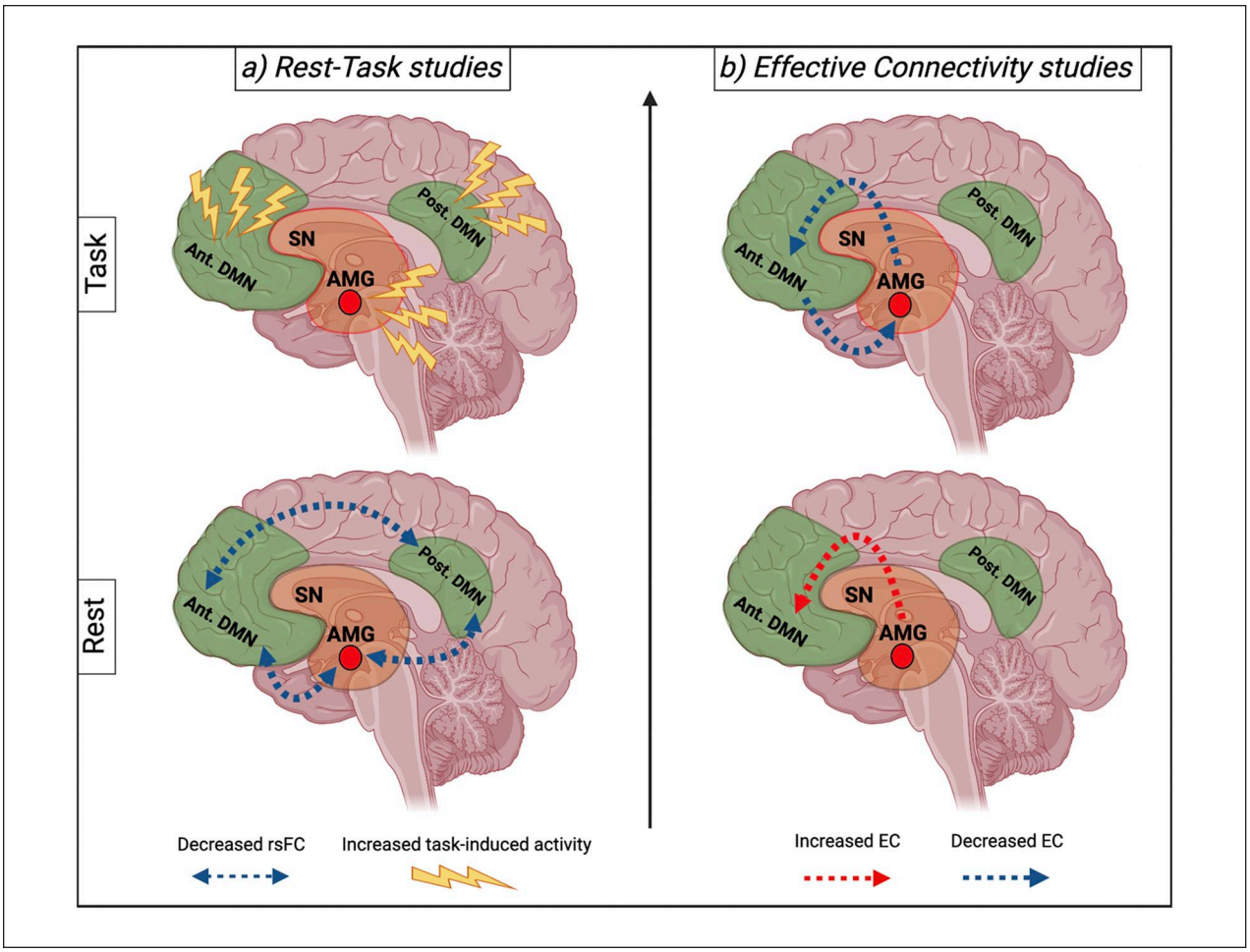


Figure 4. Brain activity across rest and task in (a) Rest-Task studies and (b) Effective Connectivity studies. Ant. DMN = anterior default mode network (e.g., vmPFC, pgACC); Post. DMN = posterior default mode network (e.g., PCC, TPJ); SN = salience network; AMG = amygdala; rsFC = resting state functional connectivity; EC = effective connectivity.

negatively with decreased rsFC of PCC-DMN as well as positively with symptom severity of social anxiety. Together, these findings confirm the observation of task-related hyperactivity in insula and resting state hypoconnectivity in DMN. Importantly, they establish negative rest-task relation within the PCC as part of the DMN: decreased PCC-DMN resting state hypoconnectivity within DMN goes along with increased task-related activity in DMN, which, in turn, positively relates to SAD symptom severity. This lends support to our second assumption, negative rest-task modulation within DMN.

Summary of combined rest and task studies in SAD. Together, these combined rest-task studies support the assumption of a relationship between resting state changes and task-related hyperactivity within both (1) amygdala and (2) anterior (and posterior) DMN, respectively. Albeit rather tentatively, the findings suggest that (3) resting state changes in amygdala and, in part, anterior (and posterior) DMN may be instrumental for task-related changes in the amygdala itself, anterior and posterior DMN, and non-DMN regions like DLPFC (Fig. 4).

Does this amount to a causal relationship from subcortical amygdala to cortical DMN and non-DMN during rest, task, or even across the rest-task divide? In order to address this question, we investigate studies using effective connectivity in SAD as that allows probing for directionality in the functional connectivity pattern between different regions.

Bottom-Up and Top-Down Modulation between Amygdala and DMN. Our findings so far show alterations during both resting state and task states in amygdala and DMN of SAD as well as, albeit tentatively, abnormal rest-task modulation within and between these regions. This raises the question whether there is a certain directionality in the interaction of especially amygdala and anterior DMN in SAD—this can be investigated using effective

connectivity. Do the resting state changes in amygdala drive the task-related hyperactivity in especially anterior DMN? Or does the latter drive the former? The findings of the studies showing rest-task modulation suggest the former, namely, that resting state changes in the amygdala may drive resting state and task-related activity changes in anterior (and posterior) DMN (and non-DMN).

Study	Sample	fMRI Paradigm	SAD Findings
Liao and others 2010b	22 SAD vs. 21 HC	Resting state (RS)	Increased EC from AMG to VMPFC Increased EC from PCC to AMG
Sladky and others 2015	15 SAD vs. 15 HC	Emotional face matching task (EFMT)	Reduced EC from AMG to DMPFC, DLPFC
Tadayonnejad and others 2016	21 SAD vs. 19 HC	Emotional face matching task (EFMT)	Increased EC from OFC to pulvinar
Minkova and others 2017	15 SAD vs. 15 HC	Emotional Stroop task	Reduced EC from VMPFC to AMG

Studies on effective connectivity of amygdala-DMN modulation. Testing the directionality, we now report the few studies that investigate effective connectivity in SAD; as there are only four such studies, we will describe each single study. Using Granger causality, Liao and others (2010b) observed increased effective connectivity from right and left amygdala to the anterior DMN, that is, VMPFC, which also correlated positively with symptom severity. While, reversely, regions of the posterior DMN like the PCC and DMPFC (and others like visual cortex, TPJ, etc.) show increased effective connectivity to right and left amygdala. Together, these findings suggest abnormally strong directionality from amygdala to anterior DMN (and reversely, too strong directionality from posterior DMN to amygdala) during the resting state itself.

Sladky and others (2015) used dynamic causal modelling (DCM) to test for effective connectivity during a task state, namely, emotion discrimination. Based on task-related hyperactivity in right amygdala, DLPFC, and anterior DMN (which the authors coin as orbitofrontal) as observed in their previous study (Sladky and others 2012), the authors determine the amygdala-prefrontal network to which they applied DCM during task-related activity, target, and control. Both healthy and SAD subjects showed bottom-up connectivity from amygdala to anterior DMN albeit SAD exhibit decreased effective connectivity from amygdala to anterior DMN (and also the DLPFC) during the task. The reverse direction, from anterior DMN to amygdala was negative in healthy subjects but positive in SAD. While the connection from anterior DMN to DLPFC was negative in healthy subjects, that is, opposite modulation of medial and lateral (Northoff and others 2004), it was less so in SAD. Together, these findings suggest weakening of amygdala-DMN bottom-up modulation during task states in SAD (see also Tadayonnejad and others 2016) accompanied by decreased DMN-amygdala top-down modulation.

Minkova and others (2017) applied an emotional Stroop task using DCM to analyze task-related effective connectivity. They observed hyperactivity in right and left amygdala as well as in MPFC (medial orbitofrontal as part of anterior DMN) during emotional-cognitive interference in the SAD subjects. The medial OFC (MOFC, as part of anterior DMN) showed stronger top-down modulation of amygdala in healthy subjects while that was diminished in SAD. Precisely, they observed an inverse pattern of activity between patients and HCs during passive viewing, i.e., low cognitive load: HCs exhibited increased (inhibitory) connectivity from MOFC to the amygdala, that is, reducing amygdala activity, whereas SAD individuals showed a rather positive (excitatory) connectivity from MOFC to amygdala, resulting in increased amygdala activity during passive viewing. Together, these findings support the assumption of decreased top-down modulation of the amygdala by the anterior DMN during task states.

Summary of studies on amygdala-DMN modulation. Together, the few studies on effective connectivity demonstrate abnormalities in bottom-up and top-down modulation between amygdala and anterior DMN during both rest and task. (1) There seems to be converging evidence that the inhibitory top-down modulation of the amygdala by the anterior DMN is decreased if not replaced by excitatory modulation of the amygdala. (2) In contrast, bottom-up modulation from amygdala to anterior DMN is not fully clear as it is either enhanced (during rest) or decreased (as during task; Fig. 4)—whether the latter is related to the former as form of abnormal rest-task modulation remains unclear, though. Accordingly, it is clear that there are abnormalities in bottom-up and top-down modulation of amygdala and anterior DMN during rest and task with the exact nature of the directional changes remaining to be explored in future studies.

Discussion

What is the source of task-unspecific but symptom-sensitive hyperactivity in especially DMN regions of SAD? To address this yet open question, we conducted systematic fMRI review of resting state, task-evoked, and rest-task studies in SAD. Our main findings concern the following: (1) rsFC hypoconnectivity within-DMN; (2) rsFC hyperconnectivity between DMN-AMG/SN; (3) task-evoked hyperactivity in the altered rs-regions during different symptom-sensitive tasks; (4) mainly negative relationship of rest and task changes in DMN regions as their rs-hypoconnectivity is accompanied by task-unspecific hyperactivity; (5) bottom-up and top-down modulation of AMG and anterior DMN regions during task and rest states, respectively.

Together, our findings show intimate relationship of rest and task changes in especially DMN regions and their relation to AMG/SN and CEN regions in SAD. This supports our initial hypothesis that decreased resting state connectivity in DMN of SAD (including its connections to AMG/SN and CEN regions) may provide a possible source of task-unspecific but symptom-sensitive hyperactivity in DMN and AMG/SN regions. In accordance with our findings, we tentatively propose a topographic model of an abnormal self in SAD (TAS-SAD). We assume that abnormal rest-task modulation of DMN-AMG/SN topography plays a key role in connecting psychological trait and state features of the self. Specifically, it may connect the basic disturbance or trait feature of the self in SAD, an "unstable social self", to its state feature, an "anxious self" in especially social situations, and its associated symptoms like enhanced interoceptive awareness, high social fear/anxiety, and strong self-attention/rumination. Therefore, we describe our model as "Topography of the Anxious Self" in SAD (TAS-SAD).

From Abnormal Resting State to Task-Unspecific Hyperactivity

Our first main finding concerns resting state activity in DMN itself. Despite using different methods when analyzing different variants of rsFC, for example, multivariate pattern analysis and graph theory, all approaches demonstrate similar findings, namely, rsFC hypoconnectivity in mainly the core DMN, that is, midline structures. Specifically, our findings show decreased rs connectivity (1) between anterior and posterior DMN and (2) within the different anterior regions of DMN.

Complementary to within-DMN rsFC hypoconnectivity, our systematic review demonstrates mostly rsFC hyperconnectivity outside the DMN including DMN-AMG/SN rsFC. One of the most robust findings is the increased rsFC of especially posterior DMN regions with the amygdala as well as, in line with the SAD literature, hyperconnectivity among mostly regions of the SN like dorsal anterior cingulate cortex (DACC), insula, and DLPFC (as part of CEN). Together, resting state findings in SAD show rsFC hypoconnectivity within-DMN accompanied by mostly rsFC hyperconnectivity to non-DMN regions, that is, SN and CEN, like amygdala, insula, DACC, and DLPFC.

How are these resting state findings in DMN and non-DMN regions related to their task-evoked activity? Using the abnormal resting state regions as ROIs for task-evoked studies, we demonstrate that they all exhibit exaggerated task-evoked responses to different symptom-sensitive tasks/stimuli including social anxious and fearful stimuli, emotional faces, as well as self-referential stimuli. These also include regions known to be involved in the fear circuit, that is, amygdala, insula, PFC, and ACC, in line with SAD literature (Bas-Hoogendam and Westenberg 2020). This is further supported by the few studies that directly compare rest and task, where we observe negative modulation of task-evoked activity by rsFC: decreased DMN rsFC modulate task-unspecific hyperactivity in the same regions.

Together, this suggests negative rest-task relationship in DMN regions of SAD: the decoupling of anterior and posterior DMN regions, that is, decreased rsFC prones these DMN regions to react in an abnormally strong and task-unspecific way to different stimuli or tasks. That suggests negative rest-task modulation in SAD: the more the within-DMN rsFC is reduced, the more the same regions exhibit stronger task-unspecific response to symptom-sensitive stimuli. Such negative rest-task modulation of DMN is in line with analogous observations in healthy subjects that also demonstrate negative relation of DMN regions' rsFC to their task-evoked amplitude in DMN (Mennes and others 2010; Mennes and others 2011). The here observed negative rest-task relationship in SAD may thus reflect an extreme degree of the same albeit yet unclear mechanism of rest-task modulation which is also at work in healthy subjects (although in less extreme ranges): "average is good and extremes are bad" (Northoff and Tumati 2019).

In contrast to negative rest-task modulation in DMN regions, we observe positive relationship in AMG/SN regions. Specifically, regions like insula and amygdala show increased rsFC and task-unspecific hyperactivity. That, again, is in accordance with findings in healthy subjects showing analogous positive rest-task modulation in non-DMN regions (Mennes and others 2010; Mennes and others 2011), and it may be traced to the role of these regions in induced and pathological anxiety in SAD (Chavanne and Robinson 2021). We therefore postulate abnormally strong degrees of positive rest-task modulation in non-DMN regions of especially AMG/SN and CEN in

SAD: higher resting state functional connectivity in non-DMN regions leads to higher task-evoked activity. This suggests that resting state activity in non-DMN regions exerts a differential if not opposite impact on task-evoked activity, that is, positive rest-task modulation, compared to DMN regions, that is, negative rest-task modulation.

The reasons for opposite resting state modulation of DMN and non-DMN in SAD remain yet unclear and could, in part, be related to opposite subcortical biochemical modulation of DMN and non-DMN regions (Buckner and DiNicola 2019; Buckner and others 2008; Conio and others 2019; Scalabrini and others 2020a). Intriguingly, data in healthy subjects show opposite modulation of cortical DMN and non-DMN regions/networks by serotonin and subcortical raphe nucleus (RN; Conio and others 2019). At the same time, SAD is known to involve changes in the serotonergic system and the raphe nucleus (Furmark 2009; Stein and others 2002a). Whether these subcortical serotonergic changes in SAD modulate DMN and AMG/SN and other non-DMN regions' rest-task modulation in opposite ways, that is, negative and positive, and ultimately lead to their task-unspecific hyperactivity remains to be investigated in the future (see Box 1 for differences of SAD to other anxiety disorders).

Box 1. The Self in SAD: Converging Psychological Approaches and Our Topographic Model (TAS-SAD).

Models of SAD highlight the role of the self in the etiology and maintenance of this condition mainly from a cognitive perspective (Clark and Wells 1995; Hofmann 2007; Moscovitch 2009; Rapee and Heimberg 1997; Stopa 2009; see Gregory and others 2016 for a detailed review).

Beck and others (1985) developed a cognitive model of anxiety which have set the foundations for subsequent models. They proposed that anxiety disorders are maintained by a cognitive–affective–physiological interaction that is fed by self-knowledge in long-term memory. This knowledge includes rigid and inflexible beliefs about the self, others, the world and their relationships, which in turn create maladaptive schemas. These distorted beliefs influence the processing of information in anxiety, hyperactivating negative schemas and consequently leading to preferential processing of threat-consistent information. Specifically in SAD, social situations involving possible social scrutiny activate these dysfunctional schemas, with selective processing of negative self-related information (and how the self is perceived from others, i.e., perceived self). This increases the sense of self-vulnerability, enhancing anxiety and suggesting the key role of self in the maintenance of SAD.

Consistent with this model (Beck and others 1985), the role of dysfunctional beliefs in misinterpreting situations in a threatening manner is also pivotal in Clark and Wells' (1995) cognitive model of SAD. They proposed a model in which an interactive relationship between heightened self-focused attention—increasing the focus on internal sensations of anxiety—and negative self-beliefs contribute to maintain the dysfunctional patterns of social anxiety. Accordingly, the belief of an inability to make a good impression in social environments of socially anxious individuals, triggers a processing mode that they have termed as "self-as-an-object," namely, Me-self (echoing the Jamesian distinction between "I-self" and "Me-self"), confirming an experiential sense of the self that the authors defined as "compelling feeling of weakness or incompetence." This shifts the focus from the environment to the self, resulting in self-focused attention.

Rapee and Heimberg (1997) also consider increased self-focus as central to SAD. Nevertheless, respect to the latter model, they posit that SAD individuals have a biased attention not only for self-related information, but also for external threat stimuli (e.g., behaviors indicating negative evaluation from the others). The interaction of the two attentional processes can heighten anxiety and precludes the modification of negative self-beliefs typical of SAD.

Hofmann (2007), in accordance with the previous models, also adds an emphasis on the structural parts of the self-concept. The author argues that individuals with SAD are characterized by enhanced self-discrepancies, that is, between actual, ideal and ought self, and that these self-discrepancies may underlie their fears in the ability to maintain a desired image in the eyes of others. Additionally, Hofmann suggests that the combination of high perceived social standards and a deficiency in the capacity to set attainable social goals (e.g., impress others) in socially anxious individuals lead to increases in social apprehension and self-focused attention.

In contrast, Moscovitch (2009) postulates that the previous SAD models confused feared stimuli (e.g., SAD-relevant stimuli) with feared consequences (e.g., feared outcomes when SAD-relevant stimuli are present). This assumption highlights the importance of identifying specific self-attributes that underlie individuals' negative self-concept, rather than simply discussing the generally negative contents of their self-beliefs. According to the author, SAD patients are characterized by three self-fears that include concerns about (1) social competence (e.g., "I will act inappropriate"), (2) physical appearance (e.g., "I'm unattractive"), and (3) signs of anxiety (e.g., "I will sweat").

Interestingly, Stopa (2009) argues that the previous conceptualization of the disorder did not fully considered the complexity of the self, mainly focusing on the content of self-beliefs, and on the process of self-focused attention. Thus, the author proposes a broader organization of the self into three main aspects: content, structure, and process. She suggests that more attention needs to be given to various aspects of self-structure (such as self-complexity), and to additional processes (such as post-event processing) to fully understand how social anxiety may impact the self.

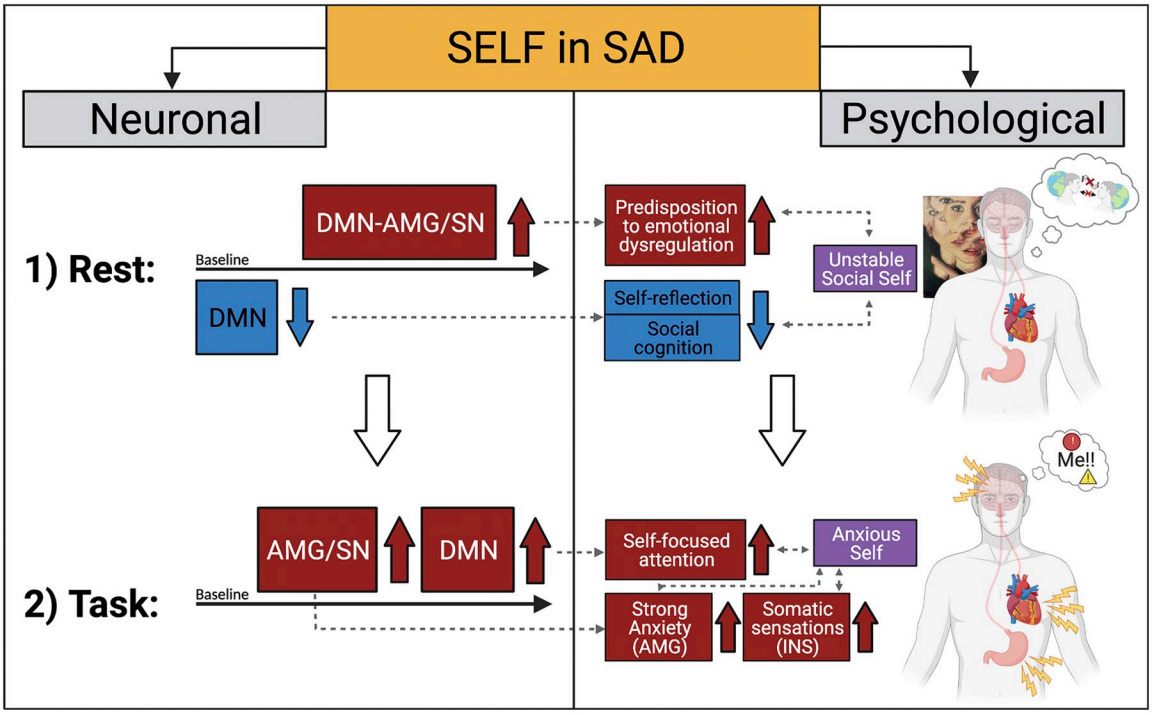
(continued)

Box 1. (continued)

Finally, stemming from an evolutionary perspective, Gilboa-Schechtman and others (2020) propose a model of self based on the Jamesian differentiation between (1) representational-self (Me-self, which concerns the attributes related to, and characterizing the self, like the traits that are ascribed to oneself, and autobiographical memories; Northoff 2016), and (2) experiential-self (I-self, which reflects the experiencing self, the entity that experiences itself and external objects or events; Northoff 2014a, 2014b).

These two types of self are evaluating in their interplay with two biopsychosocial factors as affiliation and social rank. They suggest that Me-self in SAD is under a strong influence of social-rank themes centering on shame, and that a negative representational-self (Me-self) is increased from self-focused attention and attentional bias for threat. Consistent with previous cognitive theories, the latter two processes serve as a bridge between I-self and Me-self, shifting the focus from the environment to the internal-cognition.

In summary, in a different way, SAD models mainly focused on the content of self-concepts and on attentional processes trying to define provoking and maintaining factors in SAD. However, there is still much to learn about how the self is positioned within models of SAD, and particularly how SAD treatment affects the self and its relationship with social anxiety. It shall be noted that the distinction of the two selves in several of the cognitive theories is will in accordance with the here suggested distinction of an unstable social self as trait and an anxious self as state. Hence, our TAD-SAD model may provide an approach to integrate the different cognitive approaches of self in SAD and, at the same time, put them on a more neuronal footing (see Figure in this box).



Going beyond anxiety disorder, the neuronal and psychological changes in self may also serve for differential diagnosis of anxiety disorders in general and others. For instance, a recent study observed hypoactivity in resting state in autism spectrum disorder (ASD; Lian and Northoff 2021). This resembles the findings in anxiety disorders which symptomatically may be mirrored in an unstable social self as psychological trait feature in both ASD and SAD. However, unlike in SAD, subjects with ASD exhibit decreased task-related activity in response to self-referential and emotional stimuli which symptomatically may be reflected in a decreased mental self (Lian and Northoff 2021; as distinguished from the increased mental self with higher self-attention in SAD). Accordingly, our combined rest-task approach holds the promise of providing differential-diagnosis of different changes of self in a variety of different psychiatric disorders like ASD (Lian and Northoff 2021) and schizophrenia (Northoff and Gomez-Pillar 2021).

From Abnormal Rest-Task Modulation to Psychopathological Symptoms

How can the abnormal rest-task modulation play a role in SAD-related symptoms? To address this question, we consider the close connection of rest and task states with multidimensional trait and state aspects. As a matter of fact, rsFC is often treated as a trait, used, for example, to draw inferences about individual differences in cognitive function, or differences between healthy or diseased populations (Scalabrini and others 2018; Uddin and others 2010). In contrast, changes in task-related activity during different mental states have been linked to task performances (Hermundstad and others 2014). Abnormalities in rest and task states, as observed in SAD, may thus be related on the psychological level to abnormalities in both trait and state anxiety respectively (Kennedy and others 2001).

A recent fMRI study reports a role of DMN and SN regions in differentiating trait and state anxiety: (1) trait anxiety was associated to both structural covariance of DMN, with an increase in dorsal nodes and a decrease in its ventral part, and to rsFC of DMN within anterior regions; (2) state anxiety, instead, was widely related to rsFC of SN and of DMN, specifically in its ventral nodes (Saviola and others 2020). Interestingly, abnormal activity in the abovementioned networks/regions can be observed during both rest and task states in SAD. This suggests a pivotal role of the abnormal resting state topography of DMN and AMG/SN for trait anxiety while task-related hyperactivity of the same regions may be related to their state anxiety.

Specifically, the role of rsFC in anterior DMN in trait-related anxiety of the self may be reflected by the DMN rsFC hypoconnectivity (1) within anterior, (2) between anterior and posterior regions, as well as (3) abnormal amygdala-prefrontal cortex modulation as reported in SAD patients. Interestingly, (1) alterations in the anterior regions of DMN may suggest impaired internally oriented cognition, that is, SRP and self-regulation (Frewen and others 2020; Qin and Northoff 2011; Qin and others 2020); (2) alterations in DMN rsFC between anterior and posterior regions might indicate deficits in self-other integration (Murray and others 2012; Murray and others 2015); and (3) an abnormal relationship between amygdala and anterior DMN regions could lead to emotional dysregulation (Phelps and LeDoux 2005).

Together, these findings indicate that alterations in internally oriented cognition, emotion regulation, and self-other relationship engender an "unstable social self," which is already present at rest, as personality trait of the self in SAD individuals (see Box 1 for current cognitive theories of self in SAD). Future studies may want to investigate how such "unstable social self" impacts different forms of internally-oriented cognition like episodic simulation, that is, mental time travel and mind-wandering. Since both episodic simulation (Northoff 2017; Schacter 2012) and mind-wandering (Christoff and others 2016; Northoff 2018) are mediated by the core DMN, one would assume that resting state hypoactivity in core DMN also renders unstable both episodic simulation and mind-wandering in SAD. Yet another line of research is the link of the brain's resting state with the cardiac input of the heart which is known to be altered in anxiety disorders including SAD (Tumati and others 2021).

The assumption of such "unstable social self" is consistent with studies about a history of childhood trauma in SAD patients. Studies of adults with SAD indicate that these individuals report childhood experiences associated with emotional abuse and/or neglect (Arrindell and others 1983; Arrindell and others 1989; Bruch and Heimberg 1994; Kuo and others 2011), with childhood emotional abuse or neglect associated with greater severity of social anxiety, trait anxiety, depression (neglect only), and self-esteem (Kuo and others 2011; Simon and others 2009). Moreover, studies show that early traumatic childhood experience induce strong changes in amygdala (Williams and others 2006) and anterior DMN regions (Duncan and others 2015) that are still present during adulthood. Albeit tentatively, we therefore assume that early traumatic childhood experience may provide a key source of the topographic resting state and rest-task abnormalities (Northoff and others 2010; Scalabrini and others 2018; Scalabrini and others 2019) in SAD revolving around DMN and AMG/SN. While psychologically, these early traumatic experiences may be manifested in an "unstable social self" as characterized by high degrees of trait anxiety (see Box 2).

Box 2. rsFC in GAD and PD.

Are our findings specific for SAD? Can they serve as diagnostic markers of SAD as distinguished from other anxiety disorders like panic disorder (PD) and generalized anxiety disorder (GAD)? To address these questions, we, in a first step, compare the resting state findings among these different anxiety disorders.

The DMN shows both increased and reduced rsFC in GAD and PD. In GAD, an increased anteroposterior rsFC within the DMN, that is, PGACC, PCC (Andreescu and others 2014), and an augmented connectivity of the MPFC are reported (Xiong and others 2020). This increased connectivity between the DMN components, found to be typical of younger GAD

(continued)

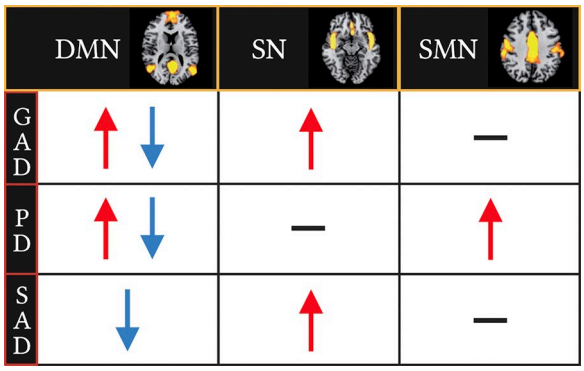
Box 2. (continued)

patients, seems to change during aging: older GAD patients in fact, were characterized by a greater rsFC between the PCC and the insula, which is supposed to be the neurobiological counterpart of the worsening of the worry for physical symptoms, that is, interoception. However, another study found both increased and decreased rsFC within regions of the DMN (Wang and others 2016).

In PD, both increased and reduced rsFC within the DMN were reported (Lai and others 2014; Shin and others 2013). While in the SMN, changes in rsFC appear to be specific to PD. Using a whole-brain approach, Cui and colleagues (2016) observed increased rsFC between the postcentral cortex (i.e., sensory cortex) and the thalamus, which also correlated with the degree of anxiety.

Together, this comparison shows that resting state hypoconnectivity in DMN seems to be the most consistent in SAD; the same applies to AMG/SN changes which, though, can also be observed in GAD (see also Xu and others 2019). Importantly, the finding of task-unspecific but symptom-sensitive hyperactivity in DMN and AMG/SN seems to be specific for SAD as distinguished from both GAD and PD. Finally, resting state and task-related hyperactivity in SMN seems to be specific for PD as distinguished from both GAD and SAD. Accordingly, albeit tentatively, one may want to characterize the three anxiety disorders by partial overlap in resting state DMN but differential changes in task state in DMN, AMG/SN, and SMN.

In sum, these observations further support the importance of taking into view both rest and task changes to achieve better neuronal and topographic differentiation of the distinct anxiety disorders. Hence, all three anxiety disorders may be characterized by partial overlaps in especially their DMN topography accounting for the anxious self as trait feature—topography of anxious self (TAS). At the same time, topographical differences emerge especially during task states which may be related to their different state features of self, that is, TAS-SAD, TAS-GAD, and TAS-PD.



Unlike resting state changes, task-related hyperactivity in (1) AMG/SN and (2) anterior DMN regions as observed in SAD individuals may reflect state-dependent changes. The ineffective frontal modulation of the amygdala determines an amygdala hyperreactivity to SAD-sensitive stimuli; (1) this amounts to the feeling of a strong social anxiety/fear, which in turn leads to heightened somatic interoceptive sensation (Craig 2002; Phelps and LeDoux 2005). Furthermore, (2) the hyperactivation of anterior DMN regions may be the state-dependent counterpart of increased self-focused attention, a core symptom in SAD patients (Clark and Wells 1995).

Increased self-focused attention may be connected to task-related hyperactivation of the brain regions related to the self, that is, anterior DMN and AMG/SN, as they are hyperactivated during exposure to self-referential or symptom-sensitive stimuli in SAD (e.g., Blair and others 2008a; Blair and others 2011b; Goldin and others 2009a; Goldin and Gross 2010). Psychologically, this may connect self and emotions/anxiety in an abnormal way by enhancing negative self-beliefs and aggravate the instability of the social self with the subsequent intensification of its social anxiety (Bögels and Lamers 2002; Bögels and Mansell 2004). Together, this may generate an "anxious self" in SAD individuals which, as state feature of the self, is activated whenever a SAD-sensitive stimulus occurs leading to high degrees of state anxiety.

Taking everything into account, we propose a topographic model of an anxious self in SAD (TAS-SAD). The TAS-SAD postulates that topographic changes during rest and task engender a basic disturbance in the relationship of self and emotion leading to an "unstable social self" (as trait feature) and an "anxious self" (as state feature). Specifically, the topographic changes of the resting state revolving around DMN and AMG/SN, as possibly related to early childhood trauma, may mediate an "unstable social self" with deficits in self-representation, other-representation, and self-other relationship. As it is based

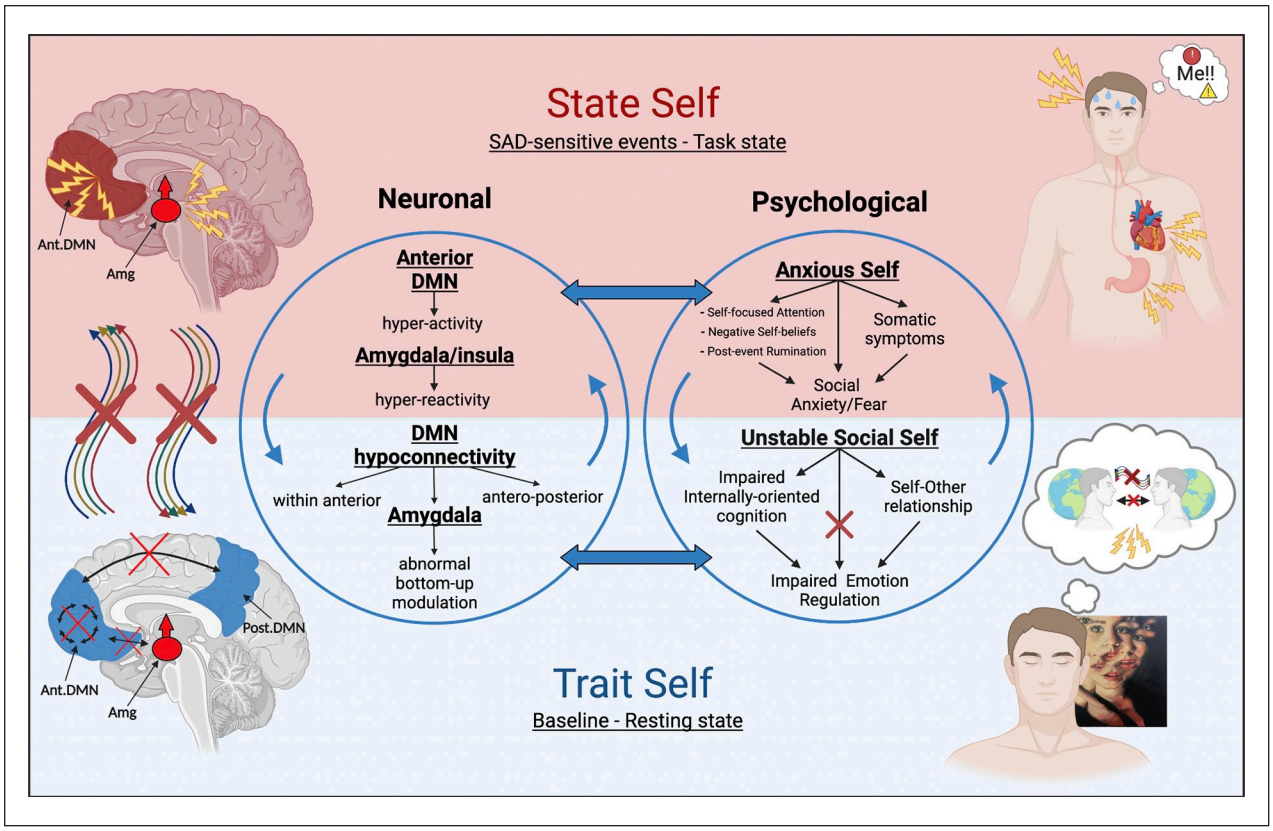


Figure 5. Topographic model of an anxious self in SAD (TAS-SAD): as neuronal (left circle) underpinning of trait self (lower in blue), the DMN hypoconnectivity (1) within anterior regions, and (2) between anterior and posterior regions, together with (3) an abnormal rsFC with amygdala during resting state (lower left), have an important role in mediating brain activity during SAD-sensitive events, that is, state self (upper in red). These topographic changes are abnormally aggravated and accentuated in the same regions during symptom-sensitive situations, that is, task-related hyperactivity in anterior DMN regions, amygdala, and insula (upper left). The psychological (right circle) counterpart of the neuronal trait self seems to be influenced by the abovementioned DMN abnormal rsFC. Indeed, the latter are reflected by an impaired emotion regulation, which, together with alterations in internally oriented cognition and self-other integration, concurs engendering an unstable social self (lower right). Being considered a trait feature of the personality in SAD, the unstable social self remains strongly activated when a SAD-sensitive event occurs. Psychologically, this may connect self and emotions/anxiety in an abnormal way by enhancing characteristic cognitive SAD symptoms (such as self-focused attention, negative self-beliefs, and post-event rumination) and aggravating the instability of the social self with the subsequent intensification of its social anxiety and somatic symptoms. Together, this may generate an anxious self in SAD individuals which is activated whenever a SAD-sensitive stimulus occurs leading to high degrees of state anxiety (upper right). Ant. DMN = anterior default mode network; Post. DMN = posterior default mode network; AMG = amygdala.

on topographic changes in the resting state, the "unstable social self" must be considered a trait feature of the personality in SAD.

These topographic changes are abnormally aggravated and accentuated in the same regions during symptom-sensitive situations, that is, task-related hyperactivity. That is manifested in an "anxious self" with the typical high state anxiety in SAD patients. This, in turn, increases self-focused attention/rumination, negative self-beliefs, social anxiety/fear, and somatic symptoms (Bögels and Lamers 2002; Bögels and Mansell 2004; Clark and Wells 1995; Hofmann 2007; Rapee and Heimberg 1997; Scalabrini et al., 2020a and others 2020b; Spurr and Stopa 2002). Together, the TAS-SAD provides an integrative model that intrinsically connects rest and task states on the neuronal level with psychological trait and state features of the self in SAD. The self and its relationship to especially social emotions are here considered a basic or generative disturbance of SAD which, on a deeper level, underlie and mediate the symptoms on the surface level of affective and cognitive functions (Fig. 5).

Conclusion

Social anxiety disorder is characterized by hyperactivity in response to self-referential, social anxious and fearful

stimuli, and emotional faces tasks in especially DMN and AMG/SN regions. The source of such task-unspecific hyperactivity in DMN remains unclear, though. Providing a first step toward addressing this question, we demonstrate that the same DMN (and non-DMN like AMG/SN) regions showing reduced inter-regional resting state connectivity also exhibit task-unspecific but symptom-sensitive hyperactivity. This strongly suggests abnormal rest-task modulation which, as in accordance with healthy subject findings, seems to operate in opposite ways in DMN and non-DMN, that is, negative and positive.

We propose that abnormal rest-task modulation is key in connecting abnormal psychological trait features of the self ("unstable social self") with its state features ("anxious self") in SAD. Abnormal DMN-AMG/SN topography during rest, mirroring the trait feature of an "unstable social self", is abnormally accentuated and aggravated during SAD-sensitive situations—this is manifested in task-related hyperactivity in the same regions and an "anxious self" as psychological state feature. Together, this amounts to a novel model of the self in SAD which we describe as "Topography of the Anxious Self" in SAD (TAS-SAD). The TAS-SAD provides a novel model of the self in SAD that integrates rest and task changes on the neuronal level with trait and state features of self on the psychological level.

Such integrative model allows for deeper insight into the generative mechanisms of SAD as first steps toward the development of diagnostic markers and more efficient individualized brain-based therapy. For instance, rest-task difference seems to be reduced in schizophrenia in both EEG and fMRI (Northoff & Gomez-Pillar 2021). That contrasts with the here observed enlargement of rest-task differences: resting state hypoactivity in DMN is accompanied by task-related hyperactivity in the same regions and AMG in SAD. Hence, pending further details, rest-task modulation may provide one important differential-diagnostic marker in the future.

Author Contributions

LLA, GN, and AS conceptualized and designed the study. LLA and GN wrote the first and final drafts of the paper that was critically revised by AS and VR. All authors approved the final version of the manuscript.

Declaration of Conflicting Interests

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