Neural Connectivity Subtypes Predict Discrete Attentional Bias Profiles Among Heterogeneous Anxiety Patients

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Abstract

On average, anxious patients show altered attention to threat—including early vigilance towards threat and later avoidance of threat—accompanied by altered functional connectivity across brain regions. However, substantial heterogeneity within clinical, neural, and attentional features of anxiety is overlooked in typical group-level comparisons. We used a well-validated method for data-driven parsing of neural connectivity to reveal connectivity-based subgroups among 60 adults with transdiagnostic anxiety. Subgroups were externally compared on attentional patterns derived from independent behavioral measures. Two subgroups emerged. Subgroup A (68% of patients) showed stronger executive network influences on sensory processing regions and a paradigmatic “vigilance-avoidance” pattern on external behavioral measures. Subgroup B was defined by a larger number of limbic influences on sensory regions and exhibited a more atypical and inconsistent attentional profile. Neural connectivity-based categorization revealed an atypical, limbic-driven pattern of connectivity in a subset of anxious patients that generalized to atypical patterns of selective attention.

Keywords

fMRI; individual-level functional connectivity; community detection; attentional bias; anxiety

Biological heterogeneity is common within psychological disorders. Anxiety disorders, the most common form of psychiatric disorder (Kessler, Chiu, Demler, Merikangas, & Walters, 2005), are replete with heterogeneity at the level of symptom presentation (Grisanzio et al., 2018), but little is known within this broad class of diagnoses regarding possible biobehavioral subtypes, and treatment indications that might track with such subtypes. Though genetic and neurocognitive studies suggest a broad taxonomy distinguishing anxiety...
disorders characterized predominantly by chronic distress from those characterized by acute fear (Kendler, Prescott, Myers, & Neale, 2003; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; McTeague & Lang, 2012), such broad distinctions at the level of clusters of symptoms or symptom-based diagnoses remain inherently heterogeneous with regard to specific biobehavioral mechanisms that are likely to vary within the scope of a single diagnosis—and which may represent important treatment targets.

In a complementary approach, biological heterogeneity across individual patients has been parsed with data-driven methods to identify subgroups of patients within broad disorder domains (Beltz, Moser, Zhu, Burt, & Klump, 2018; Clementz et al., 2016; Karalunas et al., 2014; Yang et al., 2014), including affective disorders such as depression (Drysdale et al., 2017; Price, Gates, Kraynak, Thase, & Siegle, 2017; Price, Lane, et al., 2017). Efforts to date suggest that such biologically-based subtyping can have external relevance to clinically relevant features across multiple levels of analysis, including gender, diagnosis (depressed vs. healthy; comorbid anxiety), symptom severity, history of depression recurrence, and behavioral performance on information processing tasks (Price, Gates, et al., 2017; Price, Lane, et al., 2017); and could possibly inform clinical decision-making (Drysdale et al., 2017).

One well-established, clinically relevant, transdiagnostic dimension of anxiety disorders involves altered attentional deployment towards threat (hereafter, “attentional bias”), which has been described at both early and later stages of threat processing. Specifically, anxious individuals may show a pattern of excessive vigilance towards threat during initial stages of threat processing (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007), but during later, more strategic stages of threat processing, may switch to an avoidant pattern of attention (Mogg, Bradley, Miles, & Dixon, 2004)—consistent with the marked degree of behavioral avoidance that is a core clinical feature of these conditions.

Both arms of this “vigilance-avoidance” pattern have been linked previously to altered functional connectivity between regulatory regions of the prefrontal cortex (PFC) and affective/limbic regions involved in stimulus-driven responses to threat-related stimuli (e.g., amygdala, hippocampus) (Bishop, 2007; Price, Allen, et al., 2016; Price, Eldreth, & Mohlman, 2011; Price et al., 2014; White et al., 2017). However, group-level observations of these attentional phenomena in anxious samples mask considerable within-group heterogeneity, which may contribute to notably mixed findings within the literature (Kruijt, Parsons, & Fox, 2018; Mogg, Waters, & Bradley, 2017; Rosen, Price & Silk 2019). Further contributing to heterogeneity, attention is itself a multifaceted phenomenon, with divergent subcomponents, and potentially unique neural substrates (Petersen & Posner, 2012), present not only as a function of time period (as predicted by vigilance-avoidance models), but also with respect to overt vs. covert components [i.e., observable “overt” eye movements vs. “covert” shifts in the ‘spotlight’ of attention within a stable visual field (Posner, Snyder, & Davidson, 1980; Weierich, Treat, & Hollingworth, 2008)], and engagement vs. disengagement processes [i.e., selective initial capture of attention by threat vs. selective difficulties disengaging from threat (Grafton & MacLeod, 2014)].
Individual differences in attentional patterns within anxious samples have been linked to longitudinal and treatment outcomes (Amir, Taylor, & Donohue, 2011; Legerstee et al., 2009; Price, Tone, & Anderson, 2011; Price, Rosen, et al., 2015; Price, Wallace, et al., 2016; Price, Woody, Panny, & Siegle, In press), suggesting that attending to heterogeneity may help to capture critical, clinically relevant information. Multiple treatment modalities (e.g., psychotherapy, pharmacology) produce acute reductions in attentional bias that may precede mood effects (Browning, Holmes, & Harmer, 2010), suggesting that attentional bias modification could be a final common pathway to symptom reduction. Recently, methods have been developed to alter attentional bias directly through computer-based tasks that consistently train initial attention towards neutral or positive cues. After establishing causal effects of the experimental manipulation of attentional bias on emotional reactivity in healthy samples (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002), this approach was extended to clinical populations (Heeren, Mogoase, Philippot, & McNally, 2015; Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; Price, Wallace, et al., 2016). However, given widely-noted mixed findings within this emerging mechanistic treatment literature (McNally, 2018), a better understanding of the underlying neural contributors to heterogeneous attentional patterns within anxious patients may offer key insights that are relevant to the refinement of mechanistic treatments targeting attention and/or patient-treatment matching algorithms.

The neural substrates of both anxiety and attentional bias have typically been studied through group comparisons (e.g., anxious patients vs. controls), but group-level summaries (e.g., brain maps) may not accurately represent even a single individual within the group (Beltz, Wright, Sprague, & Molenaar, 2016; Gates & Molenaar, 2012; Miller et al., 2002; Molenaar & Campbell, 2009). A more novel approach is to focus explicitly on heterogeneity (e.g., heterogeneity expressed within neural network connections) by analyzing data at the individual participant level, searching for detectable biologically-derived subgroups, and then characterizing these subgroups with respect to relevant observable characteristics and behaviors (Drysdale et al., 2017; Price, Gates, et al., 2017; Price, Lane, et al., 2017).

In the present study, we aimed to robustly characterize the functional connectivity patterns expressed by each individual within a transdiagnostic clinically anxious sample during the presentation of threatening and neutral images. As in our previous studies, we applied a connectivity method shown to reliably recover, for each individual, both the presence and the direction of connectivity among regions [i.e., does A predict B after controlling all other network-wide influences (including B’s influence on itself)? (Friston, 1994)]. Whereas concerns have been raised about the ability of many connectivity methods to reliably recover brain connections for individuals (Smith et al., 2011), validation tests suggest our selected approach, Group Iterative Multiple Model Estimation with subgrouping [S-GIMME; (Gates, Lane, Varangas, Giovanello, & Guiskewicz, 2017; Gates & Molenaar, 2012)], reliably recovers both the presence and direction of paths within heterogeneous individuals when the number of observations per person exceeds 120 (as is the case in most neuroimaging datasets), even in relatively small subsets of individuals (Gates & Molenaar, 2012; Lane, Gates, Pike, Beltz, & Wright, 2019; Mumford & Ramsey, 2014; Nichols, Gates, Molenaar, & Wilson, 2014).
This approach thus allowed for neural network maps, across a network of regions robustly modulated by the task, to be reliably constructed at the individual level, and with greater specificity than is possible in non-directed (e.g., correlational) approaches, while incorporating data-driven, subgroup categorization within these functional connectivity maps. In addition to being able to recover models in best-case scenarios, the GIMME algorithm robustly recovers individual-level directed paths in a number of conditions that emulate those seen in fMRI studies, such as nonstationarity and additional noise in the region of interests selected (Gates & Molenaar, 2012). Of particular relevance for subgrouping, GIMME has been strongly validated at the individual subject level, robustly recovering directed influences in heterogeneous individuals according to simulations (Gates & Molenaar, 2012).

With regard to subsequent subgroup detection based on connectivity maps, the S-GIMME approach has been validated in both simulated (Gates et al., 2017; Gates & Molenaar, 2012; Gates, Molenaar, Iyer, Nigg, & Fair, 2014; Lane et al., 2019) and empirical (Price, Gates, et al., 2017; Price, Lane, et al., 2017) datasets. S-GIMME has been shown to reliably recover the underlying subgroups across a range of conditions, such as varying number of subgroups, varying size and proportionality of subgroups, and differing sample sizes (Gates et al., 2017; Lane et al., 2019), including much smaller samples (e.g., N=25 in the total sample, prior to subgrouping) than the current sample (N=60). The stability and robustness of the subgroup solution produced by S-GIMME has been established using simulated and empirical data (Gates et al., 2014). Subgroups remain stable after randomly perturbing the similarity matrix of connectivity weights to generate random fluctuations in individual data points (while holding sample size/power constant).

Additionally, an extensive Monte Carlo simulation study was conducted to identify which clustering algorithms return the correct subgroups in the context of GIMME-derived features (Gates et al., 2017). Walktrap (Pons & Latapy, 2006), the clustering approach used in S-GIMME, outperformed all the others. Furthermore, Walktrap is an unsupervised classification approach which does not rely on an a priori number of subgroups specified by the researcher. Instead, it produces an optimal number of subgroups based solely on shared patterns of connectivity across individuals, and, if there are no subgroups, Walktrap is among the few methods that will return only one subgroup. This indicates to the researcher that, if subgroups are obtained, they explain more variance than considering the sample as one group. In summary, S-GIMME provides a robust and exceedingly well-validated data-driven approach to parsing heterogeneity within the functional connectivity of a sample, even in the absence of “big data” cohorts.

Given previous findings suggesting functional connectivity patterns across PFC and limbic/affective are key substrates of attentional bias, we hypothesized that subgroups, derived by S-GIMME based solely on functional connectivity maps, might differ on externally measured behavioral indices of attention to threat. Attentional bias variables collected outside the scanner (eyetracking, reaction times) were thus used to compare connectivity-based subgroups across multiple subcomponents of attention, including varying time periods (initial vs. later stages of threat processing) and discrete subcomponents of attention (overt vs. covert attention, engagement vs. disengagement patterns), allowing us to further
characterize the subgroups and assess their external relevance to a putative treatment target in anxiety. Resulting connectivity-based subgroup characteristics could ultimately suggest novel mechanistic targets for treatment by revealing discrete attentional profiles that would be overlooked when averaging across heterogeneous anxious individuals.

Methods

Participants were 60 individuals with clinically impairing anxiety recruited for a larger treatment study [see (Price et al., 2018); Table and Supplement].

fMRI task.

As described in detail previously (Price et al., 2018) and adapted from Somerville and colleagues (Somerville et al., 2013), participants were shown a total of eight 78s blocks that were either “Negative,” containing a series of 10 negative/threatening images, presented for 3s each, from the International Affective Picture Set (IAPS; (Lang, Bradley, & Cuthbert, 2008)), or “Neutral,” consisting of 10 neutral IAPS images. Images were jittered with a pseudorandom number of numerals relating to either a numerical countdown (e.g., 3-2-1) (“Predictable” blocks) or a random string of numbers (“Unpredictable” blocks). Participants were alerted by a 2s text cue, presented at the start of each block, as to the nature of the upcoming block (e.g., “Predictable Negative”). To encourage continued attention to the images, participants completed an incidental task by responding via button press to indicate whether each image depicted an indoor or an outdoor scene.

fMRI acquisition and preprocessing.

T2*-weighted images depicting BOLD contrast (TR=2000;TE=28;flip angle=73°;slices=38;FOV=200×200;3.125×3.125×3.2mm voxels) were acquired on a 3T Siemens Trio. Standard preprocessing steps were applied using Analysis of Functional Neuroimaging (AFNI; see Supplement).

11 functionally defined ROIs were selected because they showed robust group-level activations or deactivations to negative/threatening images during the task (map-wise p<.05; see details in Supplement), ensuring that connectivity was quantified within a network relevant to the processing of visual threat cues. To improve interpretability of findings, these 11 regions were then classified based on their known functions (e.g., Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Laird et al., 2011) as belonging to networks predominantly relevant to affective processing (AN), sensory processing, and executive control (ExN). See Supplement and Figure 1A for details of ROI definitions. Mean, preprocessed timeseries data were extracted per-participant for each ROI. Of 69 participants who completed the task, 9 (13%) were excluded from analysis due to excessive motion during the task (>30% of timepoints showed framewise motion >0.2mm or >0.2°). To further protect against spurious connectivity patterns related to motion, we removed individual timepoints with framewise motion >0.2mm or >0.2° from analysis [which are then accounted for during full information maximum likelihood estimation during GIMME; see (Beltz & Gates, 2017)] and verified that participants’ motion parameters were unrelated to any finding (Supplement).
Directed connectivity and subgrouping.

Directed paths (i.e., establishing which ROIs statistically predict others) were derived for each individual in a data-driven fashion using S-GIMME (Gates et al., 2017; Lane, Gates, & Molenaar, 2015), while controlling for contemporaneous influences of the task on each ROI (i.e., threatening and neutral word blocks convolved with a smoothed finite impulse response)(see (Gates, Molenaar, Hillary, & Slobounov, 2011). Paths could be contemporaneous (marking prediction at the same TR) or lagged (marking prediction from one TR to the next); and could be present for the full sample, only a subgroup of the sample, or just for an individual. Large-scale simulations show that S-GIMME is a valid and reliable connectivity mapping approach particularly when timeseries are long (as is the case for fMRI data) and lagged autoregressive effects are modeled (as was done here) (Gates et al., 2017; Lane et al., 2019)].

S-GIMME implements unified structural equation models (Kim, Zhu, Chang, Bentler, & Ernst, 2007) and utilizes a Bayes net formulation. It first detects (only if they exist) lagged or contemporaneous directed connections for the majority (defined here and in most simulations as 75%) of the sample. Next, it detects subgroups by using the individual-level estimates of these group-level connections as well as anticipated estimates for candidate connections and employing an ‘unsupervised’ community detection algorithm (i.e., Walktrap). These ‘shared’ patterns are defined based on their sign (positive/negative), significance (p<.05 vs. p>.05, after Bonferroni correction for the number of subjects), direction of influence (e.g., region A→region B), and temporal pattern (contemporaneous or lagged). If subgroups are identified, S-GIMME then detects lagged or contemporaneous directed connections for the majority (defined here and in most simulations as 50%) of a subgroup. Finally, S-GIMME iteratively detects (if they exist) additional individual-level connections. The identification of all connections is based on LaGrange Multiplier Equivalents, which indicate which connections (if added to a map) will maximally increase the map’s explanatory power (i.e., model fit).

Characterization of subgroup connectivity.

For each participant, S-GIMME generated a connectivity map with group-level, subgroup-specific, and individual-level connections. To understand the nature of the disparate connectivity patterns found across subgroups, subgroups were characterized by the unique subgroup-level connections that were identified by the algorithm, and by comparing the strength of each group-level path (excluding auto-regressive paths) via independent t-tests (across subgroups) comparing individuals’ path beta weights, with False Discovery Rate (FDR) correction.

External variables.

Connectivity-based subgroups were compared across several attentional bias indices described in detail previously [(Price, Brown, & Siegle, 2019; Price et al., In press); see details, missing data explanations, and resulting subgroup sample sizes for each analysis in Supplement]. Briefly, a standard dot-probe task, consisting of threat-neutral word pairs presented for short (500ms) and longer (1500ms) durations, was completed with concurrent eyetracking. This task provided four indices for analysis, all of which demonstrated
adequate-to-strong psychometric reliability within this sample, as discussed in detail previously (Price et al., 2019; Price et al., In press), which is critical given that attentional bias indices can be prone to poor reliability (Price, Kuckertz, et al., 2015; Rodebaugh et al., 2016). Two were reaction time indices that were derived following computational modeling [Drift Diffusion Modeling; (Ratcliff & McKoon, 2008)] of trial-by-trial data from each individual dataset in order to separate the attentional parameters of interest from incidental decision processes. Our previous publication in the current sample (Price et al., 2019) illustrated marked improvement in split-half and test-retest reliability for these attentional bias indices relative to conventional analysis methods for the dot-probe; thus, we exclusively analyzed the DDM-derived dot-probe indices, which were quantified separately for each of the two stimulus durations (short: 500ms and long: 1500ms), enabling us to detect time-sensitive patterns consistent with the “vigilance-avoidance” hypothesis. Two concurrently collected eyetracking indices reflected overt gaze patterns: initial fixation to threat (as a % of all trials); and disengagement delay bias (see Supplement for further details). Both overt/eyetracking indices demonstrated moderate split-half reliability in the present sample [≥52; (Price et al., In press)]. Finally, a separate, widely used reaction time index of covert attentional bias, the spatial cueing task (Bar-Haim, Morag, & Glickman, 2011; Price et al., In press), was used to separately quantify biases in covert engagement and covert disengagement from threat-related faces (see Supplement). The split-half reliability of the spatial cueing task indices was strong in the present sample [≥56; (Price et al., In press)].

As a comparison, attentional bias variables were also compared across more conventional, symptom-based subgroups within the anxious participants (+/- generalized anxiety disorder, +/- comorbid depression, primary distress- vs. fear-related disorder).

Results

Connectivity maps.

Group-level: At the group level, connectivity paths depicted in Figure 1A were present, in addition to lagged autoregressions at every ROI. As expected, ROIs behaved as a strongly interconnected network. All contemporaneous network influences were in the positive direction, while two lagged influences were negative, and redundant with positive contemporaneous paths, suggesting possible negative feedback mechanisms. No group-level paths were found for task vectors (i.e., negative and neutral blocks) predicting ROI timeseries in the context of the observed ROI-to-ROI network influences. Subgroups. Based on unsupervised search for the optimal number of subgroups, two subgroups emerged (see Supplement for subgroup quality analyses). Subgroup A contained 68% (n=41) of participants; hence, Subgroup B (32% of participants; n=19) was considered to exhibit ‘atypical’ connectivity patterns relative to the majority of anxious patients. Subgroup was unrelated to motion and other data quality measures (Supplement). In t-tests, Subgroup A exhibited stronger connectivity than Subgroup B in two specific group-level paths (Figure 1A; FDR p<.05): a ExN->sensory path (DMPFC->thalamus) and an ipsilateral occipital lobe (sensory) path. Similarly, the paths unique to each subgroup (Figures 1B–C) were also consistent with additional unique influences connecting ExN and sensory regions in

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Subgroup A. By contrast, there were multiple unique directed influences of AN regions on sensory regions in Subgroup B, including three AN paths converging on the thalamus.

External variables.

Dot-probe reaction times. In a repeated-measures ANOVA with subgroup as a between-subjects factor and stimulus duration (short vs. long) as a within-subjects factor, a group*duration interaction effect on attentional bias scores was found ($F_{1,58}=7.75, p=.007$; Figure 2). Specifically, subgroup A showed a “typical,” theoretically hypothesized vigilant-avoidant pattern of attention, as reflected in vigilance towards threat during short trials followed by avoidance of threat during long trials ($t_{40}=2.39; p=.02$). Subgroup B displayed an inverse pattern reflecting greater sustained vigilance to threat during long trials. Dot-probe eyetracking. Subgroup B had a higher percentage of trials with initial fixation to the threat cue than Subgroup A, suggesting greater overt engagement with threat ($t_{55}=2.32; p=.02$). The groups did not differ on overt disengagement bias ($t_{55}=1.27; p=.21$). Spatial cueing task reaction times. Patients in Subgroup A had a more vigilant pattern of engagement with threat relative to Subgroup B ($t_{55}=2.58; p=.01$). The groups did not differ with respect to disengagement from threat ($t_{55}=0.54; p=.59$).

In aggregate, analyses suggested connectivity-based subgroups had external behavioral relevance across multiple subdomains of attention, particularly for measures reflecting engagement with (rather than disengagement from) threat, and pointed to a more theoretically paradigmatic pattern of attention in Subgroup A relative to Subgroup B.

Symptom-category-based subgroups.

Attentional indices did not show significant differences across anxious participants with (n=50) vs. without (n=10) a generalized anxiety disorder diagnosis (the most prevalent diagnosis in the current sample), with (n=18) vs. without (n=42) comorbid depression diagnosis, or those with a primary distress-related (n=51) vs. a primary fear-related diagnosis (n=9), with only one specific exception: individuals with a comorbid depression diagnosis displayed a more vigilant pattern towards threat during long duration dot-probe trials relative to individuals without a comorbid depression diagnosis ($t_{58}=2.68; p=.01$).

Connectivity subgroups and clinical measures.

Connectivity subgroups were unrelated to diagnosis-based subgroups, as defined above ($\chi^2's<.76, p's>.39$). Furthermore, connectivity subgroups also did not predict clinical symptom severity on any of the Mood and Anxiety Symptoms Questionnaire (MASQ; (Watson et al., 1995)) subscales: anxious arousal, anhedonic depression, and general distress ($p's>.41$). Thus, clinical phenotypes were not strongly linked to connectivity-based subtypes in the current sample.

Discussion

In the present study, a robust method was applied to characterize heterogeneous individuals’ directed connectivity paths during threat and neutral image viewing (Gates et al., 2017; Gates & Molenaar, 2012), revealing two brain-based subgroups of anxious individuals.
The majority of anxious patients in our sample (68%; Subgroup A) showed relatively strong executive network influences on sensory processing regions (thalamus, occipital cortex), relative to the smaller, “atypical” subgroup (Subgroup B). In contrast, Subgroup B was defined by a larger number of directed influences from regions of the affective network onto sensory regions—including three AN-driven paths converging on the thalamus, a sensory gating hub (McCormick & Bal, 1994). Given the use of a robust and well-validated method (S-GIMME) for subgroup identification, which is an ‘unsupervised’ approach that has been shown in simulated data to arrive at accurate, complete, and stable subgroup solutions in total sample sizes as small as N=25, the current study provides initial evidence that these two subtypes of neural network patterns may well typify the larger population of anxious patients who share similar characteristics (e.g., clinical, demographic, neurobiological) with the individuals in our sample.

The two unique neural network patterns exhibited by subgroups of anxious patients also predicted unique attentional profiles at the behavioral level (Figure 2). Specifically, Subgroup A, the more “executive-driven” subgroup, displayed a paradigmatic “vigilance-avoidance” pattern on reaction time measures, which is consistent with influential theories of attentional processing in anxiety (Mogg et al., 2004). Subgroup B exhibited an atypical and inconsistent pattern across multiple measures of attentional bias, consistent with the multifaceted, neurobiologically complex nature of attention (Peterson & Posner, 2012; Weierich et al., 2008), including greater overt initial attention to threat (according to an eyetracking measure), accompanied by both later/sustained vigilance to threat and decreased covert engagement with threat on a distinct measure (Figure 2). Traditional diagnosis-based subgroups largely failed to predict distinct attentional profiles in the current sample, and connectivity-based subgroups were also unrelated to clinical variables (diagnostic subgroups, symptom scales), suggesting the connectivity-based subgroups provided unique information that may have had stronger behavioral impact than clinical phenotypes.

The field of attentional bias research has been fraught with mixed and inconsistent findings, which may stem from a variety of sources including psychometric limitations of widely-used behavioral indices (Price, Kuckertz, et al., 2015); inadequate dissection of the relevant subcomponents of attention (Grafton & MacLeod, 2014; Price et al., In press); and dominant theoretical and intervention models which presume anxious patients will exhibit fairly uniform patterns of attentional bias relative to healthy individuals. Notably, in the present analyses we utilized only attentional bias measures which we have previously demonstrated to show adequate-to-strong reliability levels within this sample (Price et al., 2019; Price et al., In press); thus, the divergent attentional profiles we uncovered are less likely to be heavily polluted by measurement error, and more likely to reflect true heterogeneity that would be overlooked in a conventional analysis averaging across anxious individuals.

The present findings suggest there is meaningful and consequential neural heterogeneity expressed within this transdiagnostic sample with predominantly distress-related disorders (e.g., Generalized Anxiety Disorder; Table), and that these brain-based subgroups are predictive of divergent attentional profiles that are complex and would be difficult to detect without first parsing the sample on the basis of the neural patterns (or another impactful, independent variable). In particular, divergent patterns exhibited by the “atypical” subgroup...
would dilute, and thereby mask, the more paradigmatic patterns of attentional bias (e.g., vigilance-avoidance; increased covert threat engagement) that were indeed displayed by the majority subset. Conversely, while with increasing sample sizes the dominant attentional profile exhibited by the majority would likely emerge as a detectable pattern at the full-group level (as in meta-analyses, e.g. (Bar-Haim et al., 2007), this approach would mask the significant minority of anxious patients who deviate from it systematically.

Our findings suggest multiple novel conclusions regarding the neural substrates of anxiety and attentional bias that highlight future avenues for replication and extension. First, the vigilance-avoidance model posits that bottom-up attentional capture by threat-related cues is insurmountable in the early, relatively automatic stages of processing, but is then strategically overcome and reversed (in favor of avoidance of threat) once stimuli are presented for a sufficiently long duration (Mogg et al., 2004). The connectivity subgroup that was associated with this pattern of attention in the current sample displayed additional directed influences of executive control regions (DMPFC, parietal cortex) over sensory processing regions (thalamus, occipital cortex; Figure 1B). Thus, the subgroup’s behavioral patterns may reflect that, when anxious patients have enhanced prefrontal control of sensory processing at their disposal, they may apply it in the service of threat avoidance at later stages of stimulus processing. Future studies are needed to determine if this link between neural connectivity and attentional threat avoidance is related to subsequent maintenance of anxiety in the long-term (e.g., Price, Allen, et al., 2016).

Subgroup B, by contrast, exhibited numerous unique directed paths from AN regions to sensory regions, with a particular preponderance of AN-driven paths converging on the thalamus—a region with a central role in gating the sensory information that will be passed on for further, elaborative processing (McCormick & Bal, 1994). Interestingly, this subgroup also exhibited increased initial overt eye fixations to threat cues, relative to Subgroup A. Thus, AN-driven influences on sensory processing regions—which included AN-driven paths to both thalamus and occipital cortex—might be a corollary of increased overt eye saccades to threat during early stages of attention. According to reaction time measures, this subset of individuals also became increasingly attentive to threat cues over time (i.e., after longer presentation intervals on the dot-probe task), suggesting that this subgroup’s unique AN influences on the thalamus might reflect affectively driven ‘tagging’ of threat cues to be retained as foci of attention during later, more elaborative stages of processing. Of note, no significant differences across subgroups were observed on either of two [overt (eyetracking) and covert (spatial cueing)] threat disengagement indices, suggesting the degree of difficulty with disengagement from threat was relatively homogeneous within the current sample—as were the numerous directed influences apparent across brain regions in group-level (i.e., homogenous) paths (Figure 1A).

Overall, findings suggest that, while numerous influences across brain regions were robustly characteristic of the full sample of anxious patients (as reflected in group-level paths), unique patterns of neural connectivity, which distinguished one anxious subgroup from the other, were impactful in predicting attentional profiles measured on a distinct, external battery of tasks. This novel, data-driven taxonomy of anxious neural subtypes, which is based on proximal neural processes that support affective visual information processing,
may have a tighter coupling with behavioral information processing patterns relative to symptom-based categories (e.g., diagnoses—which were unrelated to both connectivity subgroups and nearly all attentional indices), and might extend to other, unassessed domains of information processing with clinical relevance. With regard to diagnostic subgroups, patients with comorbid depressive diagnoses exhibited greater attentional bias towards threat during long-duration dot-probe trials—which is consistent with an existing literature suggesting attentional biases characterize depressed patients predominantly at later stages of processing (de Raedt & Koster, 2010; Gotlib & Joormann, 2010). However, no other link was found between diagnostic subgroups and any attentional pattern examined. While this may lend preliminary support to the unique utility of connectivity-based subtyping, larger and more heterogeneous transdiagnostic samples are necessary to adequately test this hypothesis—particularly given previous reports of attentional patterns that were moderated by specific anxiety diagnoses (Salum et al., 2012).

Findings have possible clinical implications for mechanistic treatments targeting attentional patterns. By highlighting the divergent attentional profiles of subgroups, the study suggests no one-size-fits-all approach to attentional remediation is likely to have a robust impact on symptoms across all anxious patients. However, with further replication and extension of the observed subgroups in larger validation samples, the present approach could eventually prove useful in matching specific subgroups of patients to specific attention retraining batteries, e.g., to automated interventions that explicitly target executive deficits vs. perceptually-driven aberrations (Best, Milanovic, Iftene, & Bowie, 2019). With an eye towards clinical translation, connectivity-based subtypes might also help to define a set of complex attentional profiles (exhibited across a battery of simple behavioral attentional measures) that would best reflect underlying neural subtypes, but may nevertheless be measurable without the need for cost-prohibitive fMRI assessment. Refinements to attention modification procedures might be informed by such future work. For instance, modification procedures might be made more clinically impactful if they are designed to target such complex profiles by simultaneously retraining multiple attentional subfeatures (e.g., vigilance and avoidance; overt and covert attention). Furthermore, a nuanced understanding of connectivity-based subtypes could ideally prove useful in designing synergistic treatment combinations that can leverage both neural (e.g., neuromodulation; neurofeedback) and behavioral (e.g., attention retraining) components of information processing simultaneously to optimize behavioral and clinical effects (Wilkinson, Holtzheimer, Gao, Kirwin, & Price, 2019).

The present sample did not include healthy comparison participants, and, though participants were recruited transdiagnostically, the sample included a preponderance of distress-related disorder (e.g., Generalized Anxiety Disorder) patients. Future work should explore the degree to which connectivity-based subtypes overlap across healthy and disordered states, and across a wider range of affective diagnoses. In our previous work applying S-GIMME to a sample that included both depressed patients and healthy controls, patient status (healthy vs. depressed) tracked statistically with data-driven connectivity-based subgroups, but did not overlap perfectly with it (Price, Lane, et al., 2017). In particular, the connectivity-based subgroup that contained the majority of depressed patients also contained 50% of rigorously screened healthy controls. If a similar pattern were to emerge for anxious patients and
controls when adopting a focus on threat processing, such findings would suggest interesting novel avenues for understanding potential latent risk factors and the nature of resilience or compensatory factors among healthy controls who overlap neurobiologically with anxious patients. Alternatively, if anxious and healthy subgroups were more cleanly divergent from one another when using data-driven connectivity-based grouping, it would suggest connectivity-based subgroups may be useful biomarkers that could potentially improve classification algorithms for clinical diagnosis by explicitly accounting for patient heterogeneity, as previously suggested in depression research (Drysdale et al., 2017).

**Limitations.**

Connectivity subgroups were unrelated to available clinical measures (diagnostic subtypes, continuous self-report measures) in the present dataset. Although the ability to detect such relationships may have been constrained by the specific diagnostic composition and/or small sample sizes of the present sample, these null relationships could also limit clinical applications of the current findings if subtypes can only be identified via less clinically available measures (i.e., fMRI and/or attention bias assessments). Nevertheless, our general S-GIMME approach shows relevance in the current analysis to transdiagnostic behavioral profiles in anxiety, and thus could be readily tested in future studies for its clinical utility in predicting, for example, treatment response to conventional treatment options for anxiety (e.g., psychotherapy, medications). This goal may be facilitated if more generalized forms of fMRI connectivity (e.g., resting state)––rather than strictly the connectivity patterns relevant to threat processing/attention measures per se––were incorporated as alternative (or additional) inputs to S-GIMME. Our research group’s use of S-GIMME in patient samples to date suggests that quantifying directed connectivity during both the resting state (Price, Gates, et al., 2017) and two distinct task states [threat processing, in the current study; and positive mood induction (Price, Lane, et al., 2017)] can yield subgroups that differ on external, clinically relevant variables. Future work may benefit from incorporating connectivity patterns drawn from multiple fMRI tasks/states into a unitary clustering algorithm, in an effort to consolidate the unique information contained in each type of connectivity data into a single overarching classification scheme.

S-GIMME relies on accurate specification of a relevant network of ROIs. Results may have differed with the inclusion of different regions in the connectivity models and/or with a different fMRI task design, particularly given that the functional network of ROIs was identified based on task activation patterns, which may have been sensitive to the overall sample size. Our sample size of N=60 was well-powered to detect fMRI activations of medium-to-large, but not small, effect size. The relatively small subgroup sample sizes (particularly Subgroup B) also constrained power for comparisons on external variables and may increase risk of both Type I and Type II error. The clinical utility of connectivity-based subgroups (e.g., patient sub-classification for treatment assignment) is contingent upon establishing the robustness of these subgroups in additional samples, and across time. In particular, although S-GIMME subgroup solutions are robust and stable in simulated datasets as small as N=25, a direct empirical test of subgroup stability and characteristics, both within and across anxious samples, is essential to build further confidence in the current findings.
Conclusions.

Our data-driven, brain-based categorization approach suggested that transdiagnostic anxiety can be parsed into two unique subtypes, even among an anxious sample with predominantly distress-related disorders. The two connectivity-based subgroups generalized to external behavioral measures, displaying divergent patterns according to multiple indices of attentional bias—a widely studied, transdiagnostic, clinically relevant behavioral marker of anxiety. While a more executive-driven pattern of influences on sensory regions was predictive of a relatively paradigmatic attentional profile [vigilance-avoidance; covert engagement bias; (Mogg et al., 2004)], a sizable minority displayed a more affectively-driven pattern of sensory processing, which was predictive of a divergent and atypical attentional profile (e.g., late/sustained vigilance in reaction times, coupled with greater initial orienting to threat in overt eyetracking). DSM-based subgroups did not robustly predict attentional patterns or connectivity subtypes, suggesting the connectivity-based subgroups provided unique, clinically relevant information that may inform efforts to both characterize and mechanistically target attentional patterns in anxiety. Connectivity-based subgrouping, a novel extension of biological subtyping, could provide new insights into the diverse pathways that lead to anxiety—and, consequently, the diverse intervention pathways that may lead back to more adaptive functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1B: Subgroup A paths

Dorsal

Ventral

Anterior

Posterior

DMPPC

pgACC

L Insula

R Insula

Thalamus

R Amygdala

L Amygdala

L Parietal

R Parietal

R Occipital

L Occipital
Figure 1:
(A) Functional regions of interest represented as nodes in rough anatomical space. Nodes of the affective network (AN) are presented in blue; sensory processing regions in green; and executive network (ExN) in purple. Group-level directed connectivity paths between regions are depicted with arrows. Black, solid arrows represent positive, contemporaneous paths; red, dashed arrows represent negative, lagged paths. Brown, solid arrows represent positive, contemporaneous paths present in the whole group, but significantly stronger in Subgroup B (corrected for multiple comparisons). Not shown: positive, lagged autoregressive paths were also present for every region.
(B) Directed connectivity paths unique to subgroup A (green/solid=positive, contemporaneous path; red/dashed=negative, lagged path), superimposed on group-level connectivity map (in grey).
(C) Directed connectivity paths unique to subgroup B (in green), superimposed on group-level connectivity map (in grey).
Figure 2:
Behavioral attention bias indices as a function of connectivity-based subgroups (Subgroup A: blue gradient; Subgroup B: solid orange). All attention bias measures are quantified on a continuum such that higher/more positive scores indicate increasing vigilance to threat cues, while lower/more negative scores indicate relative avoidance of threat cues. Top left panel: dot-probe reaction time bias scores after applying drift-diffusion modeling (in seconds); top right panel: spatial cueing task reaction time bias scores (in milliseconds); bottom left panel: % of trials with initial overt eye fixation made to threat cue during dot-probe task (as % of all trials); bottom right panel: bias in the delay to disengage overt eye gaze from threat vs. neutral cues during dot-probe task (units = eyetracking samples; 1 unit=16.7ms). P-values displayed reflect all significant (p<.05) and trend-level (p<.10) effects according to t-tests.
### Table.

Demographic and Clinical Characteristics of the Transdiagnostic Anxiety Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian, n (%)</td>
<td>31 (63%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>38 (78%)</td>
</tr>
<tr>
<td>Age</td>
<td>30.07 (9.70)</td>
</tr>
<tr>
<td>Anxiety diagnoses met, n (%):</td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>50 (83%)</td>
</tr>
<tr>
<td>SAD</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Panic/agoraphobia</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>OCD</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Comorbid depressive disorder, n (%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Primary distress-related anxiety diag</td>
<td>51 (85%)</td>
</tr>
<tr>
<td>Number of anxiety diagnoses</td>
<td>1.72 (1.04)</td>
</tr>
<tr>
<td><strong>Self-report symptom indices</strong></td>
<td></td>
</tr>
<tr>
<td>MASQ: Anxious Arousal</td>
<td>32.65 (10.82)</td>
</tr>
<tr>
<td>MASQ: General Distress</td>
<td>58.77 (16.26)</td>
</tr>
<tr>
<td>MASQ: Anhedonic Depression</td>
<td>74.30 (11.52)</td>
</tr>
<tr>
<td>PSWQ</td>
<td>65.95 (9.34)</td>
</tr>
</tbody>
</table>

Note: Data presented as mean (SD) unless otherwise noted. PSWQ=Penn State Worry Questionnaire; MASQ=Mood and Anxiety Symptoms Questionnaire; GAD=Generalized Anxiety Disorder; SAD=Social Anxiety Disorder; PTSD=Posttraumatic Stress Disorder; OCD=Obsessive-Compulsive Disorder; NOS=Not Otherwise Specified.