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Isolating Biomarkers for Symptomatic States: Considering Symptom-Substrate Chronometry

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Abstract

A long-standing goal of psychopathology research is to develop objective markers of symptomatic states, yet progress has been far slower than expected. While prior reviews have attributed this state of affairs to diagnostic heterogeneity, symptom comorbidity, and phenotypic complexity, little attention has been paid to the implications of intra-individual symptom dynamics and inter-relatedness for biomarker study designs. In this critical review, we consider the impact of short-term symptom fluctuations on widely-used study designs that regress the "average level" of a given symptom against biological data collected at a single time-point, and summarize findings from ambulatory assessment studies suggesting that such designs may be sub-optimal to detect symptom-substrate relationships. While such designs play a crucial role in advancing our understanding of biological substrates related to more stable, longer-term changes (e.g., grey matter thinning during a depressive episode), they may be less optimal for the detection of symptoms that exhibit show high frequency fluctuations, are susceptible to common reporting biases, or may be heavily influenced by the presence of other symptoms. We propose that a greater emphasis on intra-individual symptom chronometry may be useful for identifying subgroups of patients with a common, proximal pathological indicators. Taken together, these three recent developments in the areas of symptom conceptualization and measurement raise important considerations for future studies attempting to identify reliable biomarkers in psychiatry.

Introduction

A major goal of psychiatry research is to develop objective tests of illness.[1-3] In recent decades, these efforts have been largely focused on the identification of biomarkers that may establish the presence, risk, or stage of a particular disorder.[4] Advances have been slower than expected, however, as many of the most promising biomarker candidates have been found to lack requisite sensitivity and specificity. As has been articulated previously,[3, 5]

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causes for this delayed progress include the vast heterogeneity of diagnostic categories, significant co-morbidity across disorders, and the sheer complexity of the phenotypes, all of which have hindered the identification of disorder-specific pathophysiology necessary to develop meaningful objective diagnostic or prognostic tests in psychiatry.

These factors do not, however, explain why the field still lacks proximal bio-signatures of symptom expression. As compared to the complex developmental trajectories that may hamper the discovery of ultimate biological diatheses, proximal, 'in-the-moment' correlates of psychiatric symptoms should be more easily identified. Panic attacks, for example, have a number of established biological sequelae that may be objectively measured to corroborate a subjective report, and these are much easier to detect than, say, genetic risk factors for the development of panic disorder. Indeed, in the related field of cognitive neuroscience, the ability to decipher the neural code associated with a given experience has become so advanced that neuroimaging data can be used to reconstruct perceived images,[6] enable direct brain-to-brain interaction,[7] and command remote-controlled machines.[8] Despite this progress, we still have no reliable biological indicator for most of the core symptoms of our field – the onset of a dysphoric mood, an intrusive negative thought, or a sudden craving.

This absence of markers for symptomatic states can be difficult to reconcile with the ever-growing number of reliable group-level findings in psychiatric patient populations. For example, numerous studies and meta-analyses have confirmed that anxiety is associated with increased amygdala responsivity,[9, 10] patients with major depression exhibit structural reductions in prefrontal and hippocampal areas,[11-14] and striatal dopamine levels are altered in schizophrenia.[15] Even more recent work has begun to uncover a number of broadly transdiagnostic markers.[16, 17] Unfortunately, however, such effects tend to only emerge on average, and fail to provide meaningful information at the level of an individual patient.[18] The promise of biomarkers is to bridge the gap between group-average differences and positive or negative predictive power for individuals, which is critical for the deployment of 'precision science' in psychiatry.[19] To date, however, this promise remains largely unfulfilled.

There have been a number of excellent reviews on the challenges inherent to biomarker discovery in psychiatry, [3, 5, 20, 21] and proposed solutions have included a shift towards targeting of particular circuits and symptoms rather than whole disorders (e.g., the RDoC initiative), substantial increases in power–especially in genetic studies[17, 22-24]–and ever-increasing sophistication in the acquisition and analysis of biological data (e.g., graph-theoretical approaches to processing neuroimaging data).[25, 26] Issues of symptom assessment and interrelatedness, however, have received comparatively less attention; this represents an important oversight, as recent developments in the measurement and conceptualization of mood, affect and well-being raise important questions regarding methods for biomarker identification.

In this review, we focus on three core issues surrounding the accurate assessment of psychiatric symptoms that may undermine the detectability of biomarkers for symptom states in some cases: dynamic variation, reporting biases, and symptom inter-relatedness. While numerous reviews exist on these topics in the contexts of clinical assessment,[27, 28]

personality and well-being research,[29] and affective science,[30] the implications for the field of biological psychiatry have not, to our knowledge, been critically examined. Here, we suggest ways in which enhanced measurement and characterization of symptoms may be improved, thereby augmenting statistical power without the added expense of increasing sample sizes. While our points emphasize relationships spanning the level of individual biology and specific symptoms, we note that many of the issues raised are not limited to these two particular levels of analysis. However, we have focused on symptom-substrate relationships in part due to the substantial emphasis that has been placed on biomarker discovery in psychiatric research in recent years.

Symptom-substrate dynamics and 'average level' symptom inventories

When attempting to identify a biomarker, one critical question that must be addressed in advance is the hypothesized relationship between symptom and substrate variability. Most symptoms and substrates show periodic and/or stochastic fluctuations over time; if it is presumed that these oscillations are mainly a product of situational factors, measurement error, or other forms of noise, then it would make sense to utilize central tendency statistics that may help reduce such noise distortion. In contrast, if one believes such fluctuations in both symptom and substrate levels are meaningfully coupled, than the process of averaging may remove critical signal, and a time series design may be required. In practice, a substantial number of studies employ cross sectional designs in which measures of symptom severity are assessed using a retrospective report instrument that prompts patients to report their "average-level" of symptoms over various periods of time. These measures will then typically be regressed against a biological measure collected at a single time point. For ease of reference, we will refer to these as "average-level" study designs. Such studies have played a critical role in biological psychiatry to date, and have yielded a number of important discoveries. The appropriateness of this design should not go unexamined, however, and may depend on the dynamic nature of both the symptom and target substrate, as well as their respective sampling rates.

The easiest biomarkers to detect will be those with either minimal variance or highly regular patterns of expression. Consider the example of visual processing deficits following damage to area V1, which is associated with object misperception. While such lesions may prompt an initial period of cortical reorganization, afterwards the substrate (V1 lesion) and symptom (object perception) are relatively stable and therefore readily detectable using average-level designs.[31] Similar situations arise when symptom/substrate fluctuations are slow-moving relative to the sampling-rate of the measures used. For example, a number of studies suggest that hippocampal grey matter volume varies over time as a marker of current or remitted depression,[11, 12, 14, 32-34] and is differentially impacted by the number of past depressive episodes.[35-38] Importantly, these clinical findings are buttressed by a large animal literature suggesting that hippocampal atrophy may gradually occur after a period of sustained chronic stress.[39, 40] A key contribution of these preclinical data is to provide an estimate of the period frequency of hippocampal volume changes, suggesting that the temporal dynamics of a depressive episode and structural change may be approximately synchronized. Therefore, while neither depressive episodes nor hippocampal volume changes are as stable as a lesion, their oscillations may be slow enough that a symptom measure that averages over the past

week of experience (such as the BDI or HRSD) is suitable to detect a relationship. Consequently, structural changes in this region have been successfully identified as a marker for both depressive state as well as risk for relapse.[41, 42]

In many ways, the importance of this type of symptom chronometry has been previously recognized by the classic state vs. trait distinction in psychiatry. However, the maximum temporal window for a given symptom state is often not well-characterized empirically,[43] and many clinical symptom measures used in ”average level” designs assume, at least in practice, that symptom states show relatively little meaningful variation over time periods as long as a few weeks or more[44-53]. The growing availability of daily and multi-day assessment data (referred to herein as Ambulatory Assessment; “AA”) suggests that many symptom domains–especially those related to mood, anxiety and stress–show significant day-to-day[27, 30, 54-56] and even within-day[57-59] variation in both clinical and non-clinical populations. Similarly, various classes of biomarkers, including hormone levels, gene expression and functional connectivity, exhibit dynamic patterns over multiple timescales,[60, 61] for which possible relationships to symptomatic mental states are only beginning to be uncovered.[60, 62, 63] In rodent models, cellular rhythms involving transcriptional and translational and post-translational feedback mechanisms have been shown to predict the development of depressive symptoms [64], as well as antidepressant response to SSRIs.[65] Consequently, to the extent that these fluctuations are meaningfully correlated, average-level designs may be sub-optimal for detecting and/or interpreting these relationships. For example, while average severity levels of common symptoms related to mood, anxiety, and distress may differ significantly between healthy controls and psychiatric patient populations, there is nevertheless substantial overlap in these distributions.[27, 28, 55, 66] An average-level design relying on a single time-point for assessment of a biological variable (e.g., an MRI scan session) may include a subset of patients that were scanned on a relatively “low-symptom” day as well as controls who were scanned on a comparatively “high symptom” day, despite robust differences when averaging over time for each individual (e.g., by using a retrospective report).

To better quantify this issue, we conducted a pubmed search to identify papers that have used AA measures of mood, affect and stress in healthy controls and various patient groups. The studies included a total of 9,628 healthy/low-symptom subjects and 2,815 patients with various disorders (please see Supplementary Information and Table S1). Importantly, these studies reported both the mean and standard variation for group *level* of positive affect (PA) and negative affect (NA) ratings averaged individually within-subjects over time, but also the mean and standard variation for *variability* of affect.[67, 68] This allowed us to first examine the magnitude of within subject variability (average of the standard deviation for daily, within subject ratings) relative to mean affect level for healthy controls and different patient groups. Across studies, values for group within-subject variability (WSD) were first divided by group average level to standardize values across the different instruments used. This provides a simple index of the proportion of within-subject variability that was observed relative to affect level, with zero indicating no within-subject variability. We found that for both patients and controls, within subject variability ranged from 24%-37% of the mean level for PA and NA (**Figure 1A**). The effect was significantly higher for PA in patients

compared to controls (Mann-Whitney, p = 0.003), but not for NA (Mann-Whitney, p = 0.785) (see Supplemental Materials). In addition to examining within-subject variability relative to mean affect level, we also examine within-subject variability relative to between subject variability. For both positive and negative affect, within/between variability ratios were close to 1 (NA: 0.94; PA: 0.87) suggesting that within-subject variability in both positive and negative affect over time is almost as large as between-subject variability (**Figure 1B**).

In sum, contrary to prior studies positing that psychiatric disorders were associated with extremely low levels of within-subject variability,[69] this analysis of the existing AA literature on affect in psychopathology suggests that daily lability in both negative and positive affect is relatively high compared to the differences in average level commonly found between patients and controls, which may result in “average” experience ratings are significantly different from “day-of” experiences during biological measurement. Additionally, this variability appeared to be consistent across both clinical and non-clinical samples.

A closely related challenge is the dynamic fluctuations of biomarkers themselves. While some sources of variance may be known and controlled for (e.g., diurnal variation), many are likely unknown. When single ‘basal’ measures are taken, as in a single measure of a target protein or imaging of the brain “at rest”, these sources of variability may significantly attenuate potential relationships. For example, many fMRI studies using functional connectivity techniques have identified networks that appear to be remarkably stable across different individuals and cognitive/emotional states, suggesting a trait-like nature; [70, 71] yet other studies have reported significant changes in network connectivity as a consequence of short-term (e.g., 10-30 minutes) dynamic state change. [72-74] Indeed, one recent paper using a large (n = 575) imaging sample of healthy individuals found that different cognitive states accounted for almost half of the variance in functional connectivity networks. [75] Many studies seek to control this issue by using repeated laboratory assessments of a target biomarker in response to conditions of interest (e.g., change following cognitive or emotional task conditions, a lab stressor, or a pharmacological challenge). While a significant improvement, without some extended characterization of a biomarker's normal range within an individual, such assessments may still suffer from intra-individual variability across different days. Additionally, it is often unknown the extent to which the dynamic range of a target biomarker within the lab matches relevant external environments. Finally, some biomarker relationships may not be readily observable without prolonged, high-density sampling, similar to how ambulatory blood-pressure monitoring studies were necessary to identify cardiovascular disease risks associated with so-called “non-dippers”–individuals with a flattened diurnal variation–that could not be detected using average-level designs [76]. In some cases, the relative stability of target biomarkers is unclear.

Taken together, the short-term temporal structure of both symptoms and candidate biomakers is under-studied, and may exert significant impact on the measurement of symptom-substrate relationships. While the classic trait-state distinction has long been recognized in psychiatry, in practice, ‘states’ are often operationalized to extend from several weeks to several months. Available data from the AA literature suggests that

variability may exist in this window, highlighting the importance of alternative approaches to data collection.

The Effects of Symptom-Specific Measurement Bias on Symptom-Substrate Relationships

A related concern for 'average-level' designs is the use retrospective measures that call upon the individual patient to perform a "mental averaging" of their daily experience. A substantial amount of AA data has emerged in the last decade to suggest that, contrary to expectations, such retrospective measures correlate only moderately with average experience sampled using AA approaches.[28, 55] This lack of strong agreement between retrospective and AA reports of the same experiences has led researchers to posit the existence of two distinct "selves"; the "experiencing self" and the "believing self". [28-30, 77-79] The former reflects an aggregate of reported "in-the-moment" experiences, while the latter is influenced by retrospective reporting biases.

The potential biases that arise from retrospective report, including "peak-and-end effects", mood-congruent recall, focusing illusions and heuristic-based reconstruction, have been thoroughly reviewed elsewhere.[28-30, 79, 80] Here, we raise the question of how these different "selves" may influence symptom reports in average-level designs, and, in turn, biomarker detection. As most symptom inventories are retrospective in nature, they will be susceptible to some reporting biases that more strongly reflect personal narratives about experience rather than experience itself. Importantly, the effect size of these biases may differ both across disorders, as well as across symptom domains within a disorder. For example, a substantial amount of evidence now supports the presence of significant discrepancies among patients with schizophrenia regarding their believed and experienced negative symptoms; patients report significantly less expected enjoyment to laboratory stimuli as compared to their actual enjoyment;[81-85] are found to have difficulty reporting consistently about their preferences[86-88] and appear unable to translate reported anticipation of pleasure into goal directed behavior.[89] Consequently, retrospective reports on rewarding experiences might be expected to substantially diverge from 'in-the-moment' reports, reducing observed relationships between average-level symptom scores and biological measures. Similarly, while panic attacks have often been described as occurring unexpectedly, AA data suggest clear alterations across multiple physiological domains prior to onset,[90] and studies using actigraphy have identified clear inconsistencies between recorded and retrospectively reported levels of physical activity,[91] which may be relevant for predicting the onset of depressive symptoms.[92] In short, these studies illustrate that asking patients to report retrospectively on certain types of experiences may access self-related beliefs that are unlikely to be predictive of "in-the-moment" experiences or their neurobiological correlates. Further, the extent to which retrospective reports may be more or less accurate is likely to depend on the individual, the symptom and the disorder.

Conversely, there may be other symptom domains for which isolated assessment of the 'believing self' and its associated biomarkers are especially relevant. For example, repeated studies have shown the presence of a persistent negative bias in disorders such as

depression,[93-96] leading to affective forecasting predictions that are often worse than experienced.[97, 98] Consequently, neuroimaging studies seeking to identify the mechanisms of such biases may do better to avoid “in-the-moment” measures of negative affect –which may be less differentiated from controls than reported–and focus on markers of negative forecasting judgments.

It should be noted that while AA measures are potentially helpful against retrospective biases, they may be equally vulnerable to other forms of bias, including focusing effects, demand and social desirability biases, individual differences in item comprehension, and reporting effort among others [29, 30, 99]. Additionally, to the extent that momentary assessments clash with important self-narratives (e.g., one who is depressed but feeling ok in a given moment), cognitive dissonance and self-beliefs may still influence AA reports. In other cases, AA measures may introduce sources of bias that retrospective measures help avoid; for example, many assessments of interest can require a significant amount of mental or emotional effort to report on, which may confound their measurement as they unfold experientially. Indeed, it can at times be easier to report accurately on the nature of a particularly distressing experience after the fact.

These limitations aside, the growing evidence that AA and retrospective symptom measures often paint very different portrayals of subjective experience–even over relatively short time periods–should raise important questions about the most appropriate symptom measures selected average level-designs. As discussed in greater detail below, one solution is to increase the use of hybrid designs, that may compare measures of “in-the moment” neurobiological responses to laboratory stimuli with AA data,[100] which have helped identify predictive markers of behavior in both clinical and non-clinical populations.[101, 102] While such designs do not eliminate sources of bias for either AA or retrospective measures, they do offer a potential means of examining their shared and unshared variance in relationship to biological measures of interest.

Individual differences in symptom inter-relatedness

As noted in the introduction, one common explanation for the lack of biomarkers is the heterogeneity of diagnostic categories, case-control designs have largely failed to identify “final common pathways” for psychiatric disorders. The NIMH's Research Domain Criteria (RDoC) initiative has sought to address this issue in part by focusing on markers for specific symptoms rather than diagnostic entities as whole. However, it has long been recognized that like disorders, even a single symptom can reflect different pathologies.[103,104] One factor that may impede identification common of pathways at the individual symptom level is the potential for individuals differences in the interactions among symptoms. Consider an example of a hypothetical average-level study design seeking to identify resting functional connectivity relationships with depression severity using individual BDI scores. Patient A is highly self-critical, and often fails to enjoy things because of an active self-critical rumination process, which has frequently been associated with altered medial prefrontal activity.[105, 106] For her, anhedonic and fatigue symptoms of depression are not highly central, but are downstream in her symptom network from rumination, guilt and low self-esteem. Patient B, however, experiences chronic inflammation, which has been shown to

induce hypodopaminergia and subsequent symptoms of anhedonia and fatigue. [107-113] For him, the severity of immuno-linked anhedonic symptoms may be a primary factor that drives subsequent symptoms related to guilt, self-esteem and others. As result, patients A and B could theoretically present with near-identical scores across all symptoms on the BDI, but with markedly divergent biosignatures stemming from distinct patterns of causality within symptoms (**Figure 2**). While immuno-related effects on depressive symptoms are themselves heterogenous and complex, identifying patients for whom fatigue and apathy are driving symptoms may significantly enhance the ability to identify inflammation-related and non-inflammation related forms of depressive symptoms. Accomplishing this, however, will require more time-series assessment of symptom inter-relationships. Indeed, recent efforts to characterize intra-individual changes in personal omics [114] and neuroimaging data [115] and their relationship to mood and illness highlight the complexity of such relationships as they unfold over time.

Fortunately, a number of analytical approaches for analyzing the influences of symptoms on other symptoms as they unfold through time have begun to emerge. One such approach has emerged from dynamical systems theory. Given the hypothesis that symptoms may be influenced by each other, it would be expected that increasing inter-correlation among symptoms may indicate a “tipping point” at which symptom convergence results in a transition to a clinical state[116]. One could easily imagine adopting a similar strategy of identifying such “tipping point” periods and then assessing biomarkers within this time, similar to the strategy recently adopted by Rahdar and Galvan [117]. A second approach to such time-series data is the study of symptom networks and network dynamics. [118, 119] Network analysis has received growing attention across a number of closely related fields, and a variety of software tools for the purposes of analysis and visualization of networks have been developed ([120, 121] that can help characterize the ebb and flow of individual symptom expression in a variety of ways [122, 123]. While most network analyses have been applied at the group level, recent studies have begun to focus on using individual networks to capture multi-level phenotypes over time (e.g., [115]).

Future Directions

As summarized above, the combination of symptom fluctuation, well-established reporting biases and individual differences in symptom inter-relationships can all pose challenges for biomarker detection. These issues are not insuperable, however, and in this final section we point to several approaches through which they may be addressed. As mentioned in the introduction, these challenges are also relevant for other aspects of measurement in psychopathology. Indeed, some of these recommendations may be useful for improving the measurement of psychopathology without the end goal of identifying biomarkers, and could help developing novels means of predicting onset or recurrence (e.g., [116]).

First, we wish to reiterate that while we have focused on some of the limitations of average-level designs, this critique should not to be taken to imply that such designs are without substantial merit. As noted at the outset, average level designs can have important advantages by reducing noisy fluctuations in symptom expression that may be unrelated to biological variables of interest as well as measurement noise in the assessment of biological

measures themselves. Here, we suggest that for some target biomarker relationships, such designs may "average-over" important intra-individual variance. To address this issue, one approach will be an increased use of intra-individual designs with repeated assessments for both symptoms and target biomarkers. While AA measures of symptom severity are not without bias, the collection of both AA and retrospective measures provides a means of potentially identifying the magnitude of these discrepancies for different symptoms and different individuals. This strikes us as an important starting place for improving our understanding of how "believing" and "experiencing" selves may impact the identification of relevant biomarkers. Such data will also help better characterize the short-term temporal structure of various symptoms. While our literature search of available AA studies suggested that there may significant daily variability in positive and negative affect, other symptoms may show greater stability, and it would be useful for future studies to be able to select AA or retrospective measures on this basis. In some cases, AA measures may allow for the comparison of objective and subjective measures, as metrics such as actigraphy, cardiovascular physiology, or estimates of social contact, all of which can be used to assess symptomatic states without some of the biases of self-report. Optimally one could collect, subjective, objective and target biomarkers at a comparable sampling rate; the necessary technology for real-time analysis of saliva, EEG measures and movement is increasingly rapidly (e.g. [124]), and this provides new possibilities for measuring symptoms and substrates at an heretofore unprecedented temporal resolution.

There are, however, some limitations to this strategy that will need to be addressed. The first is that for many biomarkers, inexpensive, wearable technology remains some ways off, and is simply not possible at present. The increase in cost is partially offset by the significant increases in statistical power that may be achieved as has been evident by the success of multi-session imaging studies in identifying neural mechanisms underlying dynamic cognitive processes over time (e.g.,[125, 126]). However, such studies are still difficult and expensive to run. A second challenge is that many biomarkers of interest may only be detectable in particular contexts (e.g., extreme stress or negative affect), and may show relatively little or no association during euthymic periods, requiring long periods of passive data collection. A third option is a hybrid approach that would use repeated-measures assessments of both symptom and substrate measures over a brief amount of time, such as a single 3-4 hour laboratory visit, and then examine how these fluctuations relate to "real world" fluctuations during an extended AA follow-up period.[127-129] Ongoing AA can also be used as an alternative to random sampling to help characterize their intra-individual variance patterns prior to biologic assessment, which can help ensure that such assessments are performed when everyone is in a comparable state relative to an individualized baseline. [117]

Using AA data to classify symptom relationships prior to biological measurement may also increase the likelihood of identifying subgroups of patients with a shared biological diathesis. For example, by collecting daily symptom data for a period of time prior to biological assessment, one may be able to identify individuals who share common "driving symptoms" who are therefore more likely to exhibit common circuit-level abnormalities than individuals who merely exhibit similar symptom severity. As outlined in figure 2, a group of patients with fatigue as a common symptom of high centrality may be more likely to exhibit

abnormalities in inflammation and striatal circuitry than patients for whom fatigue is a consequence of anxious rumination and insomnia. Conversely, one can also take the approach of stratifying patients along a particular candidate biomarker to identify symptom clusters that differentiate between high and low marker expression levels.[130]

In sum, this review has focused on how recent developments in the conceptualization and measurement of symptoms have raised important caveats for the detection of symptom-substrate relationships. Adoption of recently developed symptom measurement and analysis techniques will help increase power to detect reliable markers of symptom expression, thereby facilitating the development of objective tests for symptoms of psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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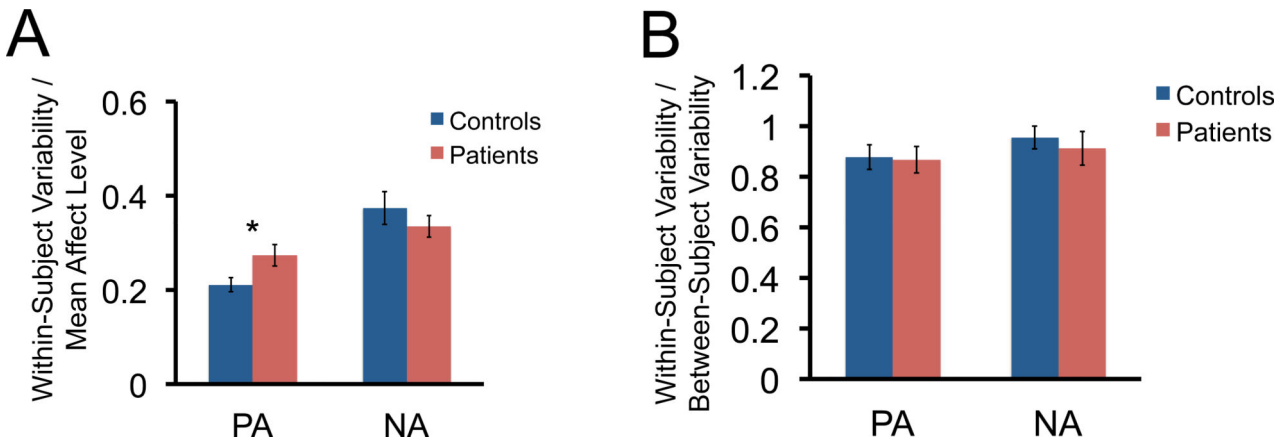

Figure 1.

Summary of within-subject variability in positive affect (PA) and negative affect (NA) relative to mean affect level. A. Depictions of EMA-based measures of within-subject variability in PA and NA relative to mean affect in patients and controls. Larger values indicate greater change over time relative to mean. **B.** Depictions of EMA-based measures of within-subject variability in PA and NA relative to mean affect in patients and controls. Values ≥ 1 indicate within-subject variability in PA and NA over time is as large or larger than between-subject variability. * Indicates a $p<0.05$ (Mann-Whitney).

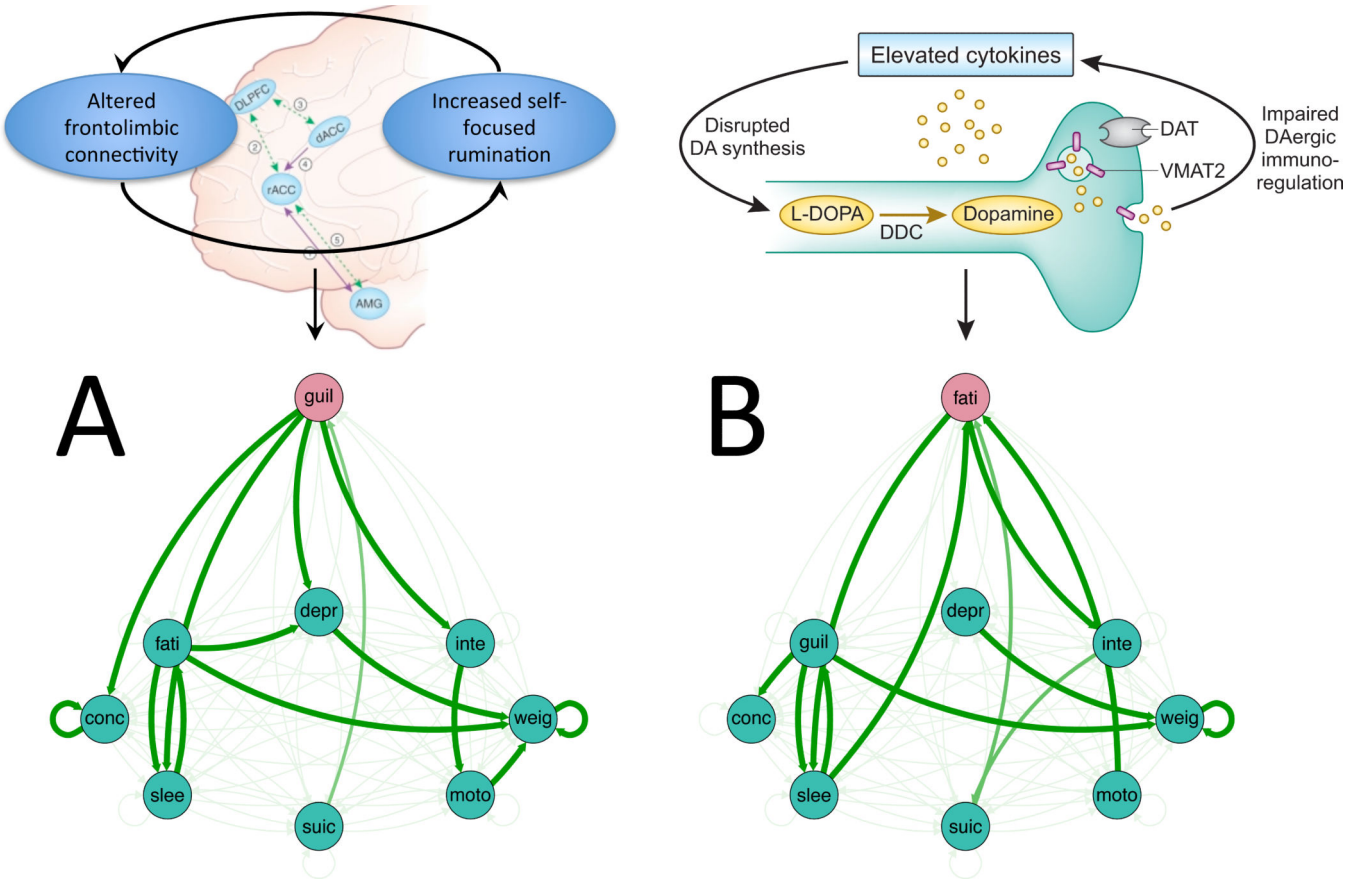

Figure 2.

Schematic of how symptom inter-relationships may result in different symptom networks that produce similar scores on a dimensional measure of depressive symptom severity despite unique pathophysiologies. **A.** Patient A has altered connectivity patterns in corticolimibic circuitry that underlie and reinforce self-focused rumination,[106] leading to frequent experiences of guilt and low self-esteem.[131, 132] **B.** For patient B, high-inflammation disrupts dopamine synthesis, leading to a chroming hypodopaminergic state and feelings of fatigue and anergia[107-113], which in turn precipitates social withdrawal, feelings of failure and subsequent other depressive symptoms. In both examples, the activation of a single symptom with differing pathologies can activate interconnected depressive symptoms, resulting in similar levels of symptom expression.