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DEVELOPMENT OF A THEORETICALLY-DERIVED HUMAN ANXIETY SYNDROME BIOMARKER

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Abstract

"Anxiety disorders" are extremely common; and are a major source of health costs and lost work days. Their diagnosis is currently based on clinical symptom check lists and there are no biological markers to diagnose specific syndromal causes. This paper describes: 1) a detailed theory of the brain systems controlling anxiolytic-insensitive threat-avoidance and anxiolytic-sensitive threat-approach – where, in specific brain structures, activity generates specific normal behaviours, hyperactivity generates abnormal behaviours, and hyper-reactivity (hypersensitivity to input) generates specific clinical syndromes; 2) a rodent model of systemic anxiolytic action (rhythmical slow activity), linked to the theory, that over a period of 40 years has shown predictive validity with no false positives or false negatives – and which is likely to assay the sensitivity of endogenous systems that control anxiety; and, 3) derivation from this rodent-based theory of a specific non-invasive biomarker (goal-conflict-specific rhythmicity) for the threat-approach system in humans. This new biomarker should allow division of untreated "anxiety" patients, with superficially similar clusters of symptoms, into distinct high scoring (syndromal) and low scoring groups with different treatment-responses. This would be the first theoretically-derived biomarker for any mental disorder and should: 1) predict treatment efficacy better than current symptom-based diagnoses; 2) provide a human single dose test of novel anxiolytics; 3) provide a starting point for developing biomarkers for other "anxiety" syndromes; and so, 4) greatly improve treatment outcomes and cost-effectiveness.

Keywords

• Anxiety • Phobia • Conflict • Biomarker • Syndrome • Theta rhythm • Human

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The need for an anxiety syndrome biomarker

A cluster of defensive pathologies, usually referred to as "anxiety disorders", afflict as much as 15% of the population in any one year [1]. Diagnosis currently cannot identify syndromes and so treatments are applied with poor predictive success, which increases costs and societal impact. While the focus of this paper is on anxiety disorders, it should be noted that similar problems with diagnosis occur with mental disorders generally. Work days lost to mental disorders as a whole are about double those lost to other health issues [1]. "Patients with mental disorders deserve better" [2]. This paper describes a rodent-based neuropsychology for which Rhythmical Slow Activity (RSA; "theta rhythm") is a key functional substrate and the derivation from this of a human biomarker, Goal Conflict-Specific Rhythmicity (GCSR). GCSR should, for the first time identify a specific, theoretically-derived (bottom up), neurally-based syndrome within the 'anxiety disorders'. The paper does not attempt to review current attempts to derive psychiatric biomarkers using a top-down approach.

Development of this biomarker represents a significant attempt to apply to psychiatry the approach currently taken in more general medicine and is aligned with recent (April 29, 2013) statements from the US National Institute of Mental Health:

"[Current] diagnoses are … equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever. … Symptoms alone rarely indicate the best choice of treatment. ... NIMH has launched the Research Domain Criteria (RDoC) project to transform diagnosis. This approach began with several assumptions:

- *A diagnostic approach based on the biology as well as the symptoms must not be constrained by the current … categories,*
- *Mental disorders are biological disorders involving brain circuits that implicate specific domains of cognition, emotion, or behavior,*
- *Each level of analysis needs to be understood across a dimension of function, Mapping the cognitive, circuit, and genetic aspects of mental disorders will yield new and better targets for treatment.*

It became immediately clear that [RDoC] cannot design a system based on biomarkers … because we lack the data."[2]

Disorders of defensive reactions (often grouped as "anxiety disorders" [3]) are currently assigned many specific diagnoses within two main systems: The WHO International Classification of Diseases, now in its 10th Edition (ICD-10) [4]; and the American Psychiatric Association's Diagnostic and Statistical Manual, recently released in its 5th edition (DSM-5) [3]. Both DSM-5 and ICD-10 assign a single "diagnosis" per patient with neither certainty as to primary dysfunction nor allowance for comorbidity. However, patients usually present clinically with mixed symptoms, fitting multiple "diagnoses" (e.g., generalised anxiety, panic, social anxiety, depression) and so clinicians are inclined to assign co-morbid diagnoses. Neither anxiety, nor its distinction from fear/phobia, nor any of the current divisions of either fear or

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anxiety into subtypes, is biologically defined. DSM-5 [3] includes various phobias/anxieties indiscriminately within "anxiety disorders"; whereas ICD-10 [4] has separate subgroups of phobic disorders and anxiety disorders but groups them within a broader class of "neurotic, stress-related and somatoform disorders". The biggest problem is that ICD-10 and DSM-5 both distinguish only superficial patterns of symptoms (e.g. worry; panic attacks) or the situations associated with them (e.g. social scrutiny, specific objects) and have no objective biomarkers for any organic source of disorder.

The problem of defining anxiety

The difference in treatment of the fear/anxiety distinction in the two classification systems is not surprising given the variation in the normal uses of the words "fear" and "anxiety". For some people fear is unconditioned and anxiety conditioned, for others fear is normal and anxiety is pathological, for yet others fear is strong and anxiety is weak – with a clear contradiction between the last two meaning sets. Likewise, brief inspection of Collins German Dictionary finds that anxiety translates as Angst, Angst translates as dread (but not vice versa), dread translates as Furcht (but not vice versa) and Furcht translates as fear not anxiety – while the sequence as a whole equates fear with anxiety. The approach taken in this paper is to construct theory-specific definitions of these emotion words based on biological and pharmacological considerations.

What is an emotion? A challenge addressed to biological psychologists 130 years ago [5], this question still has no consensus answer. Our unique approach [6] is to define "an emotion" as a set of reactions that share a common teleonomy [7] (i.e. evolutionary "purpose"/ adaptive function). The common usages that we considered above see fear and anxiety as almost synonyms. In contrast, while seeing both fear and anxiety as defensive reactions, we [8] link fear to withdrawal from threat and anxiety to the opposite, approach to threat. That is we define fear as the set of all those behavioural, autonomic and hormonal reactions that has evolved to facilitate defensive *withdrawal* (i.e. simple avoidance where there is no conflict with other prepotent responses); and we define anxiety as the set of all those reactions that have evolved to facilitate defensive *approach* (i.e. that resolves approach-avoidance conflicts).

A second way to distinguish defensive systems is pharmacological. Individual drug classes used to treat "anxiety disorders" tend to have relatively non-specific main effects (Table 1) as well as a range of distinctive side effects. However, we can construct the laboratory equivalent of the "magic bullet" by looking at the intersection of the effects of different classes of drug. In particular, if we compare benzodiazepines with buspirone we can see that they share only a common anxiolytic effect (in that they have been shown to have some therapeutic effect in groups of patients classified as having generalised anxiety disorder); while they have disparate effects on panic, obsession, depression, muscle relaxation, epilepsy, addiction, headaches, etc. Thus any neural or behavioural measure that is affected similarly by both a benzodiazepine and buspirone should be linked to "anxiety" as defined pharmacologically. Importantly, these drugs are likely to be acting on receptors that are normally modulated by endogenous compounds [9-11] that can provide the basis for anxiety sensitivity.

A neuropsychology of anxiety and fear disorders

"Anxiety disorders" (including both fear and anxiety as defined above) involve the subjective experience of aversion together with characteristic behavioural and physiological responses (e.g. avoidance, vigilance and arousal). But these reactions can all occur normally; and so both DSM-5 [3] and ICD-10 [4] require them to be excessive, persistent, distressing, and functionally impairing to meet clinical criteria for an anxiety disorder. Given this, our approach has been to analyse the neurology of defence in normal rodents assuming that the structures involved will be homologous to those affected in human disorder – with dysfunction resting only in excessive *re*-activity to input stimuli or spontaneous, inappropriate, output (e.g. as a result of paroxysmal discharge of neurones).

Disorders of defensive reactions, then, reflect dysfunction of evolutionarily conserved neural systems [13-15] adapted for survival in the face of threat; for which we have developed, over several decades [8,15-41], a highly detailed two dimensional (2D: direction / distance) theory of defensive reactions and their disorders. The theory's fundamental axiom [42,43] is that anxiolytic drugs act on, and so define, the Behavioural Inhibition System (BIS; the "anxiety" system). Anxiolytics are defined here as drugs acting at benzodiazepine or $5HT_{1A}$ receptors, which *as a class* can improve some cases of anxiety disorders but do not necessarily improve panic, phobia, depression or obsession [34]. The BIS is activated by approach-avoidance conflict [8,22]. It gets its name from its initial inhibition of on-going behaviour prior to replacing it with, e.g., risk assessment behaviour. Its outputs also include increased arousal, attention and negative emotional bias. Anxiolytics, as a class, do not affect the Fight, Flight, Freeze System (FFFS; the "fear" system), which is sensitive to panicolytics such as fluoxetine. Most of the pharmacology that has characterised the BIS uses learning experiments [22,43]; but the same pharmacological separation occurs with innate responses [44-56] and is matched by functional (ethological) separation of these into "fear-" and "anxiety-"related behaviours [46,47,57].

Table 1. Clinical profile of drugs used to treat defensive disorders. Note that no drug has a specific effect on a single type of disorder but that benzodiazepines (classical, GABA-A agonists) and buspirone (novel, 5HT-1A agonist) share only an effect on generalised anxiety disorder (GAD). OCD = obsessive compulsive disorder. Adapted from [12].

	PANIC	GAD	OCD	DEPRESSION
BENZODIAZEPINES	0/ –	–	0	0
BUSPIRONE	0	–	0	–
IMIPRAMINE	–	–	0	–
CLOMIPRAMINE	–	–	––	–

We attribute these separations to polar opposition on a dimension of “defensive direction”: defensive withdrawal versus defensive approach [22,36]. The same functional analysis [46,47] defined a second dimension of “defensive distance” (essentially perceived immediacy of threat), along which specific functional behaviours are hierarchically organised [46,47]; leading to the suggestion that their neural control systems are also hierarchically organised [58]. We [8,22] distilled these and other data on functional *and dysfunctional* defensive behaviour into the 2D theory (Figure 1). This 2D theory of the control of defensive states is also the basis of the Reinforcement Sensitivity Theory of human personality [59].

Normality, morbidity and comorbidity

Each of the modules (Figure 1) in the hierarchies of the BIS and FFFS can be involved primarily or secondarily in mental disorder. Activity within any specific module will produce specific behavioural and autonomic output; but can do so for a range of different reasons. With a strong threat (e.g. a close encounter with a grizzly bear on a narrow track) and a normal module (e.g. periaqueductal grey, Figure 1) there will be normal output (e.g. heart rate increase, freezing, thoughts of death; i.e. normal, adaptive, panic). With a weak threat and a hyper-*re*active module there will be maladaptive, syndromal, output (e.g. panic resulting from hyper-reactivity of the periaqueductal grey [60-62]). With no apparent threat, panic could also occur unexpectedly as a result of spontaneous periaqueductal grey activity [63], such as epileptiform discharge, producing spontaneous panic [64].

An important complication for clinical diagnosis is that with normal external input, and a normal module, symptomatic output can nonetheless occur as a result of abnormality in another module. Activity in any module impacts immediately on others through extensive reciprocal excitatory and inhibitory neural connections (Figure 1). Excitatory connections allow a threat detected by only one level of the hierarchy to engage modules higher and lower in the hierarchy to increase the probability of an

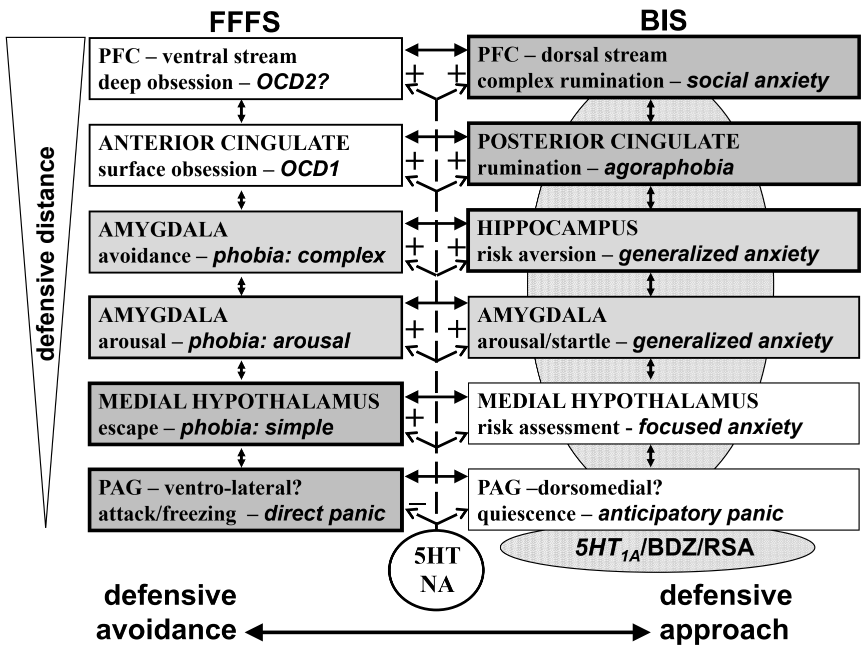

Figure 1. The 2D defence system (direction x distance), updated from [8]. Brain area in capitals, normal function lower case, nominal disorder (closest current diagnosis) in italics. Note the reciprocal (excitatory and inhibitory) connections between levels and systems. The light grey oval represents areas that show RSA (see text), which is modulated by 5HT1A and BDZ receptor agonists. Dashed lines = 5HT/NA modulation. 5HT = 5-hydroxytryptamine /serotonin; 5HT1A = 5HT1A receptors; BDZ = benzodiazepine receptors; NA = noradrenaline; OCD = obsessive compulsive disorder; PAG = periaqueductal grey; PFC = prefrontal cortex; RSA = rhythmical slow activity.

appropriate response being generated at that point in time, or in the future via conditioning. Inhibitory connections determine which level of the hierarchy is in immediate control of responding – for example, if avoidance is possible then undirected escape needs to be inhibited.

On a longer time scale, modules can become co-activated as a result of environmental feedback and learning. For example, panic – in the FFFS – can later result in anxiety [65] via activation of the BIS by conditioned stimuli (such as the place in which spontaneous panic first occurred), particularly in neurotic individuals. So, patients presenting with, for example, symptoms of panic and anxiety may have primary panic disorder with consequential anxiety [66], primary anxiety disorder with increased arousal generating consequential panic [67-69], or a combination of these problems. There are also conditions under which reduced anxiety releases panic from inhibition [58]. The same general scenarios will apply to all modules of both systems. Hyper-*re*activity [70] of a module will generate a syndrome [8], produce specific primary symptoms; and activate other modules, producing secondary symptoms [71]. As a result, symptoms will not be a good guide to syndromes.

The 2D theory predicts [8,22] not only multiple distinct syndromes (Figure 1) but also explicitly allows comorbidities. Hyper-reactivity [72,73] of (or spontaneous discharges in [63]) the ventro-lateral periaqueductal grey would produce a “pure panic disorder” that would be approximately equivalent to the current diagnosis of “irritable heart syndrome” [64]. (This pure panic disorder would not usually present in the psychological clinic until it was combined with additional secondary BIS-related symptoms.) Hyper-reactivity of specific modules of the FFFS would generate phobic (primary avoidance) syndromes ranging from relatively “simple” (hypothalamus) to “complex” (frontal cortex). Likewise, hyper-reactivity of the hypothalamus *or* amygdala *or* hippocampus *or* frontal cortex would generate a similar range of BIS syndromes. The disorder labels in Figure 1 are preliminary and approximate mappings to the closest equivalent current diagnosis, if one exists. The more limited distribution of $5HT_{1A}$ receptors compared to 5HT terminals (Figure 1) explains why $5HT_{1A}$ agonists like buspirone can treat anxiety but not panic [74], whereas broader 5HT drugs like fluoxetine can treat both. The specific nature of the 5HT terminals in the anterior cingulate compared to other areas explains why clomipramine but not desipramine can be effective in some cases of obsessive compulsive disorder [75]. Genuine co-morbidity (as opposed to a mixture of primary and secondary symptoms) would occur when more than one module (or more than one system-wide modulatory input) is dysfunctionally hyper-reactive.

Rhythmical Slow Activity (RSA, theta) as a potential anxiety syndrome biomarker

Despite the apparent complexity of the relation between symptoms and syndromes, syndromes should be distinguishable by biomarkers. A key assumption of the 2D theory is that distinct disorders will represent *hyper-reactivity* of distinct modules within a system or of inputs that modulate multiple modules of a system. That is, no symptoms need be shown currently; but a particular level of stimulus input to that module, delivered as a challenge, will produce greater than normal output. Panic, for example, can be provoked by a variety of physical challenges (CO_2, lactate, etc.). Patients currently diagnosed with "panic disorder" and "irritable heart syndrome" often show a lower threshold (i.e. hyper-reactivity) to these challenges than do controls. However, with panic, there is as yet no strong theoretical link between the nature of the challenge and the cause of the underlying disorder [66]. What is required, therefore, are biomarkers for activity in specific modules of the defense systems and for the modulating systems that control the global sensitivities of the BIS and/or FFFS.

We have developed the first such biomarker based on the fact [16,22,76,77] that the BIS depends on Rhythmical Slow Activity (RSA; 4-12 Hz rhythmic cell firing – often referred to as "theta" despite its wide frequency range). We have repeatedly shown [77-85] with intracranial EEG in rats that RSA frequency reduction, measured in the hippocampus, predicts clinical "anxiolytic" action (see [86] for review), with no false positives (even with sedatives) or negatives (even with drugs ineffective in panic or depression). The predictive value of our rat test has been confirmed by others [87-90]. We also proved that artificial replacement of blocked RSA repairs behavioural dysfunction [91] (the first proof that any EEG rhythmicity is functional in and of itself); and that changes in RSA mediate the action of anxiolytics on behavioural inhibition in an approach-avoidance conflict [92]. Thus RSA appears to be not just a reliable model of anxiolytic action but to be a significant neural substrate of an anxiety-related process.

A human homologue of RSA

We developed a human homologue of rat RSA as a biomarker for BIS hyper-reactivity. Hippocampal depth recording is impractical for assessing anxiety disorders in humans. However, in rats, rhythmicity in frontal cortex becomes coherent (phase-locked) with hippocampal RSA during risk assessment behaviours [93]. Since the hippocampus itself shows RSA even when it is not in control of behaviour, this outflow of RSA to prefrontal cortex should be more predictive of BIS functional output and act as a better biomarker than hippocampal recording. We therefore searched for rhythmicity in human frontal cortex that was generated by goal (approach-avoidance) conflict and sensitive to anxiolytic drugs.

We measured human scalp EEG during approach, conflict, and avoidance, subtracting the average power in approach and avoidance from conflict to measure *goal conflict-specific rhythmicity* (GCSR). We found GCSR at a right frontal cortex site (F8) [94,95]. Right frontal cortex (particularly the inferior frontal gyrus) controls stopping [96-99] (a major output of the BIS) in the Stop Signal Task (SST) [100]. The SST is extremely simple to administer and has already been used with clinical cases such as ADHD and schizophrenia [101]. We used the SST to extract GCSR from F8 and found that this correlated *positively* with both trait anxiety and neuroticism [102]. Critically, we later showed that F8 GCSR was *reduced* by both benzodiazepine and $5HT_{1A}$ drugs [103] that share, in the clinic, only BIS and not FFFS or antidepressant actions. So, right frontal GCSR elicited in the SST task in humans is pharmacologically homologous to RSA elicited by electrical stimulation in rats.

Goal-conflict-specific rhythmicity as a basis for an anxiety syndrome

Dysfunctional control of GCSR may support a specific BIS syndrome. In the clinic, anxiolytics can take weeks to achieve their full therapeutic effects. Even the benzodiazepines (which have immediate, but temporary, euphoriant and muscle relaxant effects) need time for their full core anxiolytic effects [104,105]. In normal rats, acute administration of anxiolytics is effective if anxiety is an *immediately elicited* state or being learned [43,106]; and both in animal RSA [86] and in human GCSR [103], all anxiolytics are effective immediately; with no change in this effect over chronic administration [107]. Elicitation of GCSR, then, assesses the output from a mechanism, the chronic hyper-reactivity of which could both predispose to and perpetuate clinical anxiety by modulating (stippled $5HT_{1A}$/BDZ/RSA zone in Figure 1) the entire BIS.

GCSR provoked by the SST's approach-avoidance challenge should identify BIS hyper-reactivity. As noted above, GCSR amplitude correlates both with neuroticism (a general risk factor for multiple disorders [108]) and trait anxiety (a more focussed measure of the chronic tendency to be "anxious" [109]). Importantly, the SST involves no threats and stopping behaviour itself does not correlate with neuroticism or trait anxiety and is not affected by benzodiazepine or $5HT_{1A}$ drugs [103]. The strength of elicited GCSR in the SST, thus measures the reactivity of a BIS circuit, un-confounded by concurrent challenges to the panic system or by changes in behaviour controlled by act and action circuits [102] that operate in parallel to each other and to goal control by the BIS (Figure 2).

An improved goal-conflict-specific signal – homology with RSA

While satisfactory from a theoretical standpoint, our reported SST results [102,103] have some limitations in relation to clinical translation. They involved a novel method of analysis that separated trials into three groups to allow application of a quadratic contrast [110] to extract conflict-specific rhythmicity. All details of the task were carefully kept the same as in a study that demonstrated control of stopping by the right inferior frontal gyrus [97] but which was not optimised statistically for conflict detection. Based on other forms of the SST [101], we have now developed a statistically optimised version of the task in which GCSR correlates with neuroticism and trait anxiety [111].

This GCSR appears homologous to RSA. GCSR shows (Figure 3) a similar frequency range (RSA = 4-12 Hz) that spans the conventional theta (4-7 Hz) and alpha (8-12 Hz) bands. The frequency range observed (in particular the substantial power below 6Hz compared to rodent RSA) is also consistent with human hippocampal reports [37,112,113].

Importantly, we also have unpublished data showing that, as with the original SST [102,103], this GCSR is sensitive to buspirone ($5HT_{1A}$) and triazolam (a short-acting benzodiazepine). Buspirone and benzodiazepines are both clinically anxiolytic [104,105] but use completely independent neural systems to affect RSA [80]. Buspirone is neither panicolytic [74] (unlike other antidepressant drugs) nor anticonvulsant, euphoriant, muscle relaxant or addictive (unlike benzodiazepines) [104,114]. We also found that GCSR was sensitive to pregabalin (a calcium channel inhibitor), which is positive in our rodent RSA test [90], effective in generalised anxiety disorder [115], and has not been reported to be clinically either panicolytic or antidepressant. The sensitivity of GCSR to all three quite distinct classes of anxiolytic drug is strong evidence for it as an anxiety biomarker as well as clearly linking it to the BIS. However, GCSR may not be useable directly for individual diagnosis in the clinic – it involves a single challenge test format without the capacity for repeat testing, occasional loss

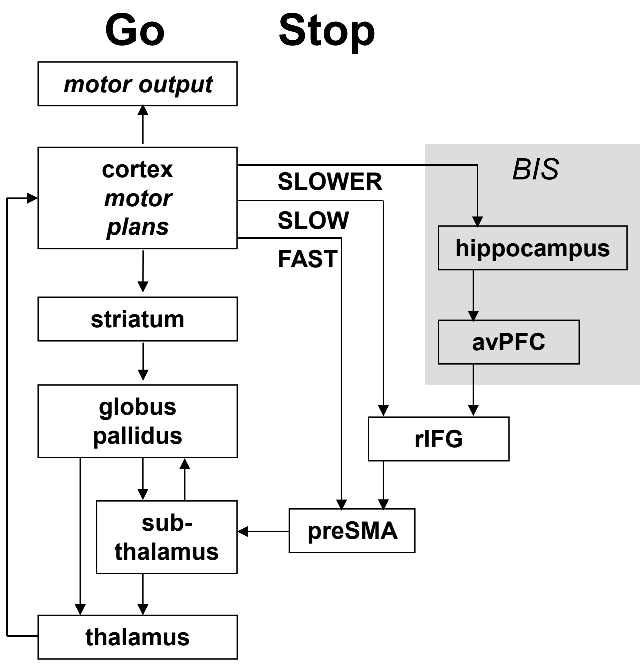

Figure 2. Layered control of SST stopping. With extremely fast go responses, stopping in the SST is controlled primarily by the preSMA [99] With somewhat slower go responses stopping is controlled primarily by rIFG [97,98] but BIS output is too slow to affect stopping in the SST [102].With even slower go responses (as in go/no go tasks) activation of the BIS would generate response inhibition via rIFG/preSMA. avPFC = anteroventral prefrontal cortex; preSMA = presupplementary motor area; rIFG = right inferior frontal gyrus. From [102].

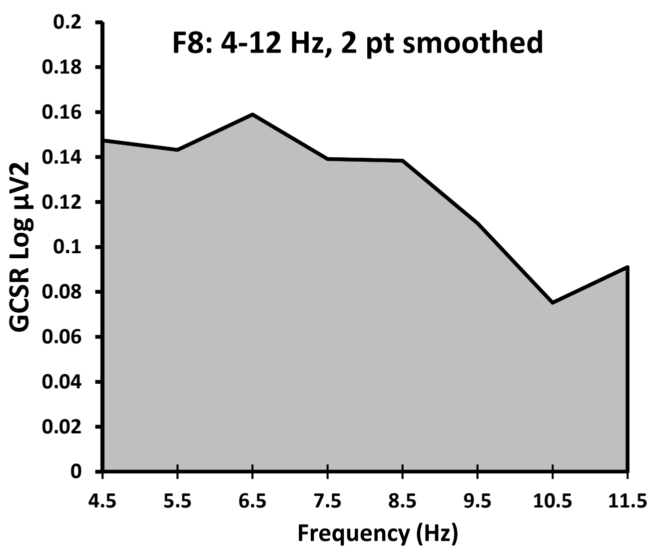

Figure 3. Frequency distribution of GCSR in the Stop Signal Task (SST) at F8 averaged for 50 participants (unpublished data pooled from 3 separate experiments). GCSR was calculated as the difference in stop-signal specific Fourier transform power between groups of trials with a stop signal delay that results in stop and go being in balanced conflict (50% of trials each) with the average power for groups where go or stop predominated. A positive value indicates an increase in rhythmic power specific to the presence of goal conflict. In this new version of the SST, power is increased in both the conventional theta (4-7 Hz) and conventional alpha (8-12 Hz) bands and so has a range that is very similar to the frequency range of the rodent RSA from which the test is theoretically derived.

of participants as a result of artefact, and may have insufficiently low error variance. However, our drug data show that it has the capacity to distinguish groups with N of the order of 10 and so it can be used as an anchor for the development of more clinically convenient instruments. We are currently starting a study to test this in anxiety disorder patients.

GCSR as a test for novel anxiolytic compounds

An important feature of GCSR (and its homologue RSA) is that these are tests that *on a single occasion* show an immediate response to anxiolytic drugs ($5HT_{1A}$, benzodiazepine, calcium channel inhibiter). The rat RSA test is well established as a predictor of clinical anxiolytic efficacy [87-90], with no false positives or false negatives [86]. GCSR should, therefore, be an effective screening test in *normal* humans for clinical efficacy of novel compounds without the need for chronic dosing. This would greatly increase the cost-effectiveness and reduce the risk of screening novel compounds in humans by demonstrating which compounds are *not* effective. Effective compounds would still require clinical trials for long-term safety and for additional (e.g. anti-panic) actions. But such trials could be restricted to compounds with highly predictive efficacy. It should be noted that while "anxiolytics", as defined earlier, affect RSA, so do a wide range of other less specific drugs that have known additional effects on anxiety to their other effects (e.g. panicolytic, antidepressant).

GCSR as a test for syndromal anxiety and comorbidity

Importantly, GCSR should, for the first time, allow identification of a neurally distinct, syndromal, subgroup of "anxiety disorder" patients and should provide both a practical and theoretical starting point for the identification of other biomarkers for syndromes within the cluster of "anxiety disorders". This should lead ultimately to *a rational diagnostic structure for anxiety disorders* in the clinic; and lead the way for similar biomarker-based structures for other mental disorders. Importantly, with more than one biomarker, such an approach can lead to multiple concurrent diagnoses and so provide a clear basis for *screening for comorbidity*. Current systems are designed to avoid comorbid diagnosis, in the name of simplicity for primary treatment. However, major depression and anxiety in particular, which are already high among all medical illnesses for disabling impact [116], are often comorbid. Comorbid anxiety with depression may include a separate condition distinct from the combination of simple anxiety with simple depression, being more chronic and severe, with higher suicide risk [117,118]. Only biomarkers can determine if this is the case. In addition, use of biomarkers would allow distinctions to be made between true comorbidity, where there is more than one locus of dysfunction, and cases where a primary morbidity (e.g. "spontaneous panic/ irritable heart syndrome") gives rise through either neural or societal links to secondary symptoms (e.g. "agoraphobia") that are also typical of some other primary morbidity ("pure agoraphobia").

Conclusion

In summary, GCSR is a non-invasive human measure that, like the rodent RSA model is sensitive to three distinct classes of anxiolytic drug (benzodiazepine, $5HT_{1A}$ agonist, calcium channel inhibitor) linking it to anxiety but not panic or depression. GCSR is derived from a well-developed and detailed preclinical neuropsychology. Independently of its theoretical basis its drug sensitivity is evidence that it is a biomarker for individual variation in a neural system, disorder in which would generate a specific syndrome within the "anxiety disorders". It should provide the first theoretically based biomarker for such a syndrome and initiate replacement [2] of symptom-based [3,4] diagnosis of anxiety and other mental disorders.

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