Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment

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While characterization of pathogenetic mechanisms underlying major depression is a fundamental aim of neuroscience research, an equally critical clinical goal is to identify biomarkers that might improve diagnostic accuracy and guide treatment selection for individual patients. To this end, a synthesis of functional neuroimaging studies examining regional metabolic and blood flow changes in depression is presented in the context of a testable limbic-cortical network model. 'Network' dysfunction combined with active intrinsic compensatory processes is seen to explain the heterogeneity of depressive symptoms observed clinically, as well as variations in pretreatment scan patterns described experimentally. Furthermore, the synchronized modulation of these dysfunctional limbic-cortical pathways is considered critical for illness remission, regardless of treatment modality. Testing of response-specific functional relationships among regional 'nodes' within this network using multivariate approaches is discussed, with a perspective aimed at identifying biomarkers of treatment non-response, relapse risk and disease vulnerability. Characterization of adaptive and maladaptive functional interactions among these pathways is seen as a critical step towards future development of evidenced-based algorithms that will optimize the diagnosis and treatment of individual depressed patients.

As our understanding of brain mechanisms mediating complex behaviours continues to grow, the arbitrary operational boundaries separating the clinical disciplines of psychiatry and neurology become increasingly blurred, requiring new integrative strategies for the study of neurobehavioural disorders such as depression. In this evolving integrative neuroscience environment where relationships between genetics, biochemistry, anatomy, functional neurocircuitry, and systems-levels behaviours are now being defined, new perspectives on the pathogenesis of depressive disorders with relevance to both disease classification and evidence-based treatment strategies are needed.

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There are, at this time, no definitive biological algorithms that can reliably determine the necessary and sufficient treatment of individual patients, as is the case for many medical conditions, such as diabetes and ischaemic heart disease. A future is nonetheless envisioned where quantitative measures of brain function is an integral step in determining the optimal treatment for a given patient presenting with a major depressive episode, just as the integrity and calibre of the coronary arteries in combination with myocardial functioning are critical determinants of the interventional strategy initiated following the diagnosis of an acute myocardial infarction. These cardiology decisions are neither arbitrary nor conciliatory, unlike many of the physician trial-and-error strategies or patient self-selection practices common in treating major depression. Rather, they are based on objective measurements of the primary organ of interest considered in context of other contributing risk factors including genetics, co-morbid medical conditions (*i.e.* hypertension, diabetes, hyperlipidaemia) life-style factors (smoking, diet, exercise) and past cardiac problems. In prioritizing a role for direct measures of brain functioning in the development of new algorithms for clinical management of depressed patients, the approach does not suggest to either bypass or minimize the critical contributions of genetics, early-life loss, or exogenous stressors, but rather to include formally these variables in the disease construct at the brain level. Minimally, this approach should yield brain biomarkers that can both identify which patients are likely (or unlikely) to respond to a given intervention, and predict which patients are vulnerable to relapse during maintenance treatment. Long-term, this approach in combination with genetic studies, might also reveal markers of disease vulnerability in family members at potential risk. It is with these optimistic goals in mind that the contributions of functional neuroimaging to our understanding of affective disorders are reviewed.

Limbic-cortical dysregulation model

Early aetiological theories of depression highlighted specific neuro-chemicals and neuropeptides (reviewed by Fava & Kendler[1]). It is now generally understood that depression is unlikely to be the result of a single brain region or neurotransmitter system. Instead, it can be conceptualized as a multidimensional, systems-level disorder affecting discrete, but functionally integrated, pathways[2]. Moreover, depression is not simply the result of dysfunction in one or more of these elements, but also involves failure of the remaining system to maintain homeostatic emotional control in times of increased cognitive or somatic stress. While mechanisms mediating this 'failure' are not yet characterized,

they are thought likely to be multifactorial, with genetic vulnerability, affective temperament, developmental insults and environmental stressors all considered important contributors[3]. Treatments for depression can be similarly viewed within this framework where different modes of treatment modulate distinct neural targets resulting in a variety of complementary chemical and molecular adaptations and homeostatic effects that re-establish a normal mood state[4–6].

In this evolving depression model (Plate XI see end of file p.*208), foci of 'network' dysfunction identified in the base-line depressed state are considered as potential aetiological abnormalities as well as sites of adaptive and maladaptive intrinsic compensatory processes, accommodating both the reported variations in pretreatment scan patterns and the well-recognized heterogeneity of depressive symptoms and premorbid functioning (*i.e.* mood, motor, cognitive, vegetative-circadian; neuroticism, early trauma). Furthermore, selective modulation of specific subcortical sites including brainstem, striatum and cingulate are additionally seen as primary targets facilitating the observed wide-spread, reciprocal changes in cortical and limbic regions across studies of various antidepressant treatments. The synchronized modulation of these dysfunctional cortical-limbic pathways is considered critical for illness remission, regardless of treatment modality, accommodating pharmacotherapy as well as cognitive and surgical interventions. Strategies to test and distinguish formally disease-specific and response-specific functional interactions among regions in this depression network using multivariate approaches are highlighted as a critical next step towards the eventual development of clinical algorithms that will discriminate patient subgroups, optimize treatment selection, predict relapse risk, and provide markers of disease vulnerability.

The concept of such a depression network can be seen as the natural evolution of a long tradition of behavioural localization. Lesion-deficit studies of depressed patients with acquired brain lesions provide a critical clinical perspective, consistently identifying involvement of frontal cortex and the striatum (reviewed in Starkstein & Robinson[7]). Anatomical findings in patients with primary affective disorders while less consistent, report focal volume loss in ventral and medial frontal cortices and hippocampus[8]. Interestingly, primary injury to limbic structures (such as the amygdala, hippocampus, hypothalamus or even brainstem) are not associated with primary depressive symptoms, despite their fundamental involvement in critical aspects of motivational, affective, and emotional behaviours (see, for example, LeDoux[9]). This apparent contradiction underlines the need for a more complex functional network linking stereotypic clinical symptoms to specific limbic, subcortical and cortical pathways. Functional neuroimaging studies of regional blood flow and metabolism have assumed a unique position in testing this hypothesis.

Studies of the untreated depressed state

Positron emission tomography (PET) and single photon emission tomography (SPECT) studies of both primary depression and depression associated with specific neurological conditions identify many common regional abnormalities (reviewed by Ketter *et al*[10] and Mayberg[11,12]). For example, in depressed patients with basal ganglia disorders such as Parkinson's disease, Huntington's disease and caudate strokes, resting-state paralimbic hypometabolism (ventral prefrontal cortex, anterior cingulate, anterior temporal cortex) differentiates depressed from non-depressed patients within each group, as well as depressed from non-depressed patients, independent of disease aetiology. These regional findings, replicated in other neurological disorders, suggested critical common pathways for the expression of depression in distinct neurological populations with potential relevance to primary mood disorders.

Studies of blood flow and glucose metabolism in patients with primary depression[13,14] also report frontal abnormalities, in general agreement with the pattern seen in neurological depressions (reviewed by Ketter *et al*[10] and Mayberg[11]). The most robust and consistent finding is decreased frontal lobe function, although normal frontal as well as hyperfrontal activity has also been reported. Localization within the frontal lobe includes dorsolateral and ventral lateral prefrontal (Brodmann areas 9, 46, 10, 47) as well as orbital frontal cortices (Brodmann areas 10,11). Findings are generally bilateral, although asymmetries are described. Cingulate changes are also commonly seen and consistently involve anterior dorsal sectors. Other limbic-paralimbic (amygdala, anterior temporal, insula), and subcortical (basal ganglia, thalamus) abnormalities have also been identified, but the findings are more variable. Use of different analytical strategies (voxel-wise *versus* region-of-interest) has been considered an important factor in explaining these apparent inconsistencies. Differences among patient subgroups (familial *versus* sporadic; bipolar *versus* unipolar, primary *versus* neurological), as well as heterogeneous expression of clinical symptoms is also thought to contribute significantly to this variance, but there is not yet a consensus[15,16]. In practice, the presence of such clinical symptom variability within a given patient cohort does not appear to explain fully the reported group effects (*i.e.* depression *versus* controls). Therefore, alternative explanations for frontal hyper- and hypometabolic profiles seen in seemingly comparable experimental groups are needed, particularly if these techniques are ever to have relevance to the clinical evaluation of individual patients.

One alternative to the more classic lesion-deficit approach is to consider that a given metabolic pattern is a combination of 'functional lesion' and an on-going process of attempted self-correction or adaptation. In this construct, the current status of regional activity,

independent of the cause, drives the observed behaviour. For instance, frontal hyperactivity is now viewed as an exaggerated or maladaptive compensatory process resulting in psychomotor agitation and rumination, serving to over-ride a persistent negative mood generated by abnormal chronic activity of limbic-subcortical structures. In contrast, frontal hypometabolism seen with increasing depression severity is the failure to initiate or maintain such a compensatory state, with resulting apathy, psychomotor slowness and impaired executive functioning. With this perspective, treatment selection might be optimally tailored to augment selectively an ineffective compensatory state as measured by the pattern of regional abnormalities. To test such a hypothesis, response-specific and treatment-specific change patterns must first be defined.

Preclinical studies of treatment mechanisms lend support for this hypothesis. Pharmacotherapy findings emphasize a bottom-up cascade; brainstem, limbic and subcortical sites are viewed as the primary sites of drug action with secondary cortical changes seen as secondary effects of chronic treatment[4–6,17]. A similar mode of action has been hypothesized for electroconvulsive therapy and vagus nerve stimulation[18,19], although precise mechanisms are less well characterized than with medications. In contrast, non-pharmacological antidepressant treatments such as cognitive behavioural therapy and interpersonal psychotherapy work to facilitate alterations in depression-relevant cognitions, affective bias and maladaptive information processing[20,21], that may also modify specific, but alternative, neural processes not yet characterized. Lastly, surgical ablation provides the most compelling evidence for involvement of specific neural pathways. Three standard approaches – anterior capsulotomy, cingulotomy and subcaudate tractotomy – all show comparable clinical efficacy but disrupt different white matter targets[22]. Both top-down (cortico-thalamic, cortico-limbic) and bottom-up (thalamo-cortical, limbic-cortical) mechanisms can be postulated, although the precise limbic, subcortical and cortical targets or pathways necessary for amelioration of depressive symptoms are unknown.

Treatment effects

A critical step towards development of brain-based algorithms to optimize treatment selection is the systematic assessment of brain changes that best correlate with symptom remission across various treatment options. Based on the theoretical constructs articulated in the previous paragraph, one might postulate that different interventions with varying primary mechanisms of action should be equally effective, if there is preserved compensatory capacity in the obligatory depression circuit overall (Plate XI see end of file p.*208). Functional integrity of

these pathways might thereby explain the comparable clinical efficacy of pharmacological and cognitive treatments in randomized controlled trials conducted in non-refractory depressed patients. Similarly, progressively more aggressive treatments needed to ameliorate symptoms in some patients may reflect poor adaptive capacity of the network in these patient sub-groups. Published studies have already demonstrated preliminary correlations between specific base-line scan patterns and differential response to psychotherapy and pharmacotherapy in obsessive-compulsive disorder[23] although prospective studies based on these patterns have not yet been attempted. An expectation, nonetheless, is that a specific metabolic signature may ultimately provide a therapeutic road map for optimal treatment selection based on known patterns of differential change with different treatment interventions, if the contribution of these adaptive and maladaptive compensatory responses can be fully defined.

Changes in regional metabolism and blood flow with recovery from a major depressive episode consistently report normalization of many regional abnormalities identified in the pre-treatment state (reviewed by Mayberg[11] and Mayberg *et al*[24]). Changes in cortical (prefrontal, ventral prefrontal, parietal), limbic-paralimbic (cingulate, amygdala, insula, and subcortical (caudate/pallidum) areas have been described following various treatments including medication, psychotherapy, sleep deprivation, ECT, rTMS and ablative surgery. Normalization of frontal hypometabolism is the best-replicated finding, seen mainly with all classes of medication, although normalization of frontal hypermetabolism is also reported. Changes in limbic-paralimbic and subcortical regions are also seen, often involving changes in previously 'normal' functioning regions. Requisite changes mediating clinical recovery have not been determined, nor have clear distinctions been made between different modes of treatment.

The critical importance of systematic comparisons of diverse interventions is illustrated in the following examples. In a double-blind, placebo-controlled, in-patient study of depressed men, the time course of regional metabolic changes with fluoxetine treatment was measured after 1 and 6 weeks of treatment[24]. Fluoxetine responders and non-responders, while similar in both clinical response (none) and regional metabolic changes (brainstem, hippocampus increases; posterior cingulate, striatal, thalamic decreases) after 1 week of treatment, were differentiated by their 6-week metabolic change pattern. Clinical improvement at 6 weeks was uniquely associated with limbic-paralimbic and striatal decreases (subgenual cingulate, hippocampus, pallidum, insula) and brainstem and dorsal cortical increases (prefrontal, anterior cingulate, posterior cingulate, parietal; Plate XIIA see end of file p.*209). Failed response to fluoxetine was associated with a persistent 1-week pattern (hippocampal increases; striatal, posterior cingulate decreases) and absence of either subgenual cingulate or prefrontal changes.

This same combination of reciprocal dorsal cortical and ventral limbic changes has also been demonstrated in unipolar depressed responders treated with paroxetine[25], and in a new study of fluoxetine treatment of depression in patients with Parkinson's disease (Plate XIID see end of file p.*209)[26]. Like the in-patient fluoxetine study[24], frontal and parietal increases were seen in Parkinson's disease responders, resulting in the normalization of a pretreatment hypometabolic pattern. Clinical improvement was also associated with metabolic decreases in the subgenual cingulate and hippocampus, again identical to that seen in the unipolar patients. These decreases were not found in Parkinson's disease non-responders who remained depressed, despite comparable treatment.

As improvement in depressive symptoms best correlated with increases in prefrontal cortex (F9/46) and decreases in subgenual cingulate (Cg25), it is additionally postulated that these changes are most critical for illness remission. This hypothesis is further refined by preliminary evidence of persistent Cg25 hypometabolism and posterior cingulate hypermetabolism in a new group of fully recovered patients on maintenance SSRI treatment (Plate XIIC see end of file p.*209). These findings might suggest that persistent limbic changes in remitted patients are the adaptive homeostatic response necessary to maintain a recovered state. In this context, it is interesting to note that the limbic leukotomy procedure performed to treat severe refractory depression[22] disrupts afferent and efferent subgenual cingulate pathways (subcaudate tractotomy component; Plate XIID see end of file p.*209, red arrow) as well as inter-cingulate connections (cingulotomy component, blue arrow)[27–29].

A final point is illustrated by the findings in placebo treated patients. The identical change pattern – increases in frontal, parietal and posterior cingulate, and decreases in subgenual cingulate – is also seen in placebo responders after 6 weeks of in-patient treatment (Plate XIIB see end of file p.*209)[30]. The presence of unique subcortical changes with fluoxetine (brainstem, hippocampal, caudate) not seen with placebo response provides initial support for the hypothesis that both treatment-specific and response-specific effects can be identified.

Despite this compelling convergence of findings, a further demonstration of comparable changes with a non-pharmacological therapy is needed. At issue is whether remission mediated by cognitive or psychotherapies involve similar or unique brain changes to those seen with medication. The few published studies thus far show no clear common patterns[31,32]. Preliminary analyses comparing remission with cognitive behavioural therapy and paroxetine studied in two separate out-patient cohorts[25,33] reveals some unexpected new findings. In a re-analysis of the paroxetine group, remission was associated with metabolic increases in prefrontal cortex and decreases in subgenual cingulate and hippocampus, as previously described. In contrast, CBT response was associated with a completely different set of changes: prefrontal

decreases, similar to those seen with interpersonal psychotherapy[31], as well as hippocampal and rostral cingulate increases, not previously described. These CBT-specific changes are particularly interesting given current cognitive models[20,21] and the known roles of rostral cingulate and hippocampus in emotional monitoring and memory and lateral and medial frontal cortices in perception, action and self-reference[34].

The differences in change patterns between the two interventions would, at first, appear to contradict interpretations offered thus far, suggesting treatment-specific effects rather than a common response-effect pattern. Furthermore, one must now also consider the contribution of variable base-line frontal findings, since no abnormalities were identified in dorsolateral prefrontal regions in either the paroxetine or CBT groups, unlike the frontal hypometabolism seen in all of our previous studies. This in spite of a near identical change pattern in both groups of pharmacotherapy-treated patients. This base-line variability is not explained by demographic characteristics or standard indices of clinical severity, suggesting a more complex interaction between pretreatment abnormalities, attempted compensatory responses and actual treatment effects. Testing of this hypothesis is best addressed by a multivariate statistical approach, where relationships between independent and dependent variables can be simultaneously observed[35–38]. As pre-amble to considering such a strategy, metabolic patterns predicting treatment response within a given treatment group is first considered.

Response predictors

Baseline predictors

In light of the described differences between responders and non-responders with treatment, a related clinical question is whether base-line findings predict eventual treatment outcome to a given treatment. Studies report that pretreatment metabolic activity in the rostral (pre-genual) anterior cingulate (Cg24a) uniquely distinguishes medication responders from non-responders (Plate XIIIA,B, see end of file p.*209)[39,40]. The pattern of cingulate hypermetabolism in responders and hypometabolism in non-responders has been replicated in depressed Parkinson's disease patients (Plate XIIIC see end of file p.*209)[26]. A similar hypermetabolic pattern in a nearby region of the dorsal anterior cingulate has also been shown to predict good response to one night of sleep deprivation[41]. This is also the pattern seen in both paroxetine and CBT responders described in the previous section. Preliminary studies using multivariate techniques revealed a more wide-spread network of regions to co-vary with Cg24a activity that further distinguishes

medication responders from non-responders prior to treatment initiation[42]. Interestingly, these regions were not revealed by more conventional univariate analysis strategies. These additional regions, influenced by on-going changes in activity in rostral cingulate, are those directly altered by specific antidepressant treatments. Furthermore, Cg24a metabolism while not itself altered by treatment in either the paroxetine or fluoxetine studies, showed further metabolic increases with successful CBT. Additional evidence of persistent hypermetabolism in patients in full remission on maintenance SSRI treatment for more than a year, further suggests a critical compensatory or adaptive role for rostral cingulate in facilitating and maintaining clinical response long-term (Plate XIIID see end of file p.*209). Taken together, these data would suggest not just focal differences but also network differences among patient subgroups relevant to mechanisms mediating brain plasticity and adaptation to illness with potential future implications for clinical management of individual patients.

Early treatment effects predicting later response

In the fluoxetine time-course study[24], subcortical metabolic changes were seen after 1 week of treatment, although patients showed no change in symptoms. The reversal of this week-1 pattern at 6 weeks was seen uniquely in those patients showing a clinical response, might suggest a requisite process of neural adaptation in specific brain regions over time with chronic treatment. The presence of an inverse pattern in responders and non-responders at the 6-week time point further suggests that failure to induce these adaptive changes underlies treatment non-response. Needed are careful time-course experiments to identify the point of regional metabolic 'switching' that may actually predict fluoxetine response down the line. Furthermore, this approach may be useful in evaluating new antidepressant agents with purported earlier onset of clinical effects.

An additional observation from this same fluoxetine-placebo, time-course study involves early changes in the eventual placebo responders[30]. Early increases in posterior cingulate activity seen uniquely in the placebo group – a finding also reported midway through a 12-week course of interpersonal psychotherapy[32] – were identified, preceding both clinical response and the final increases seen in this region in both responder groups. Known anatomical connections from posterior cingulate to the common frontal and subgenual cingulate changes seen with both active fluoxetine and placebo[29] might suggest that the posterior cingulate change may be a more general marker of treatment responsivity, identifiable during the initial phase of a clinical trial[43]. Additional evidence that placebo and psychotherapy non-

responders fail to show this 1-week posterior cingulate change would strongly support this hypothesis.

Relapse risk and illness vulnerability

A further need concerns identification of patients at risk for illness relapse as well as those vulnerable to illness onset. Challenge or stress tests might be seen as possible avenues towards this goal. As such, mood-induction experiments initially studied in healthy subjects to define brain regions mediating modulation of acute changes in mood state relevant to the depressive dysphoria[44] have been similarly performed in acutely depressed and remitted depressed subjects, and have identified disease-specific modifications of these pathways[45]. Specifically, with acute sad-mood induction in healthy volunteers, anterior cingulate increases are consistently described (reviewed by Mayberg[11]). These cingulate increases are not found in depressed patients comparably provoked, where unique dorsal cingulate increases and medial and orbital frontal decreases are instead seen. Similar findings in both euthymic-remitted and acutely depressed patients suggest that these differences may be depression trait markers. In addition, the pattern seen with memory-provoked sadness shows striking similarities to resting state studies of refractory unipolar and neurologically depressed patients, as well as the changes seen following acute tryptophan depletion during the early phase of SSRI treatment[46]. This pattern has also been described using fMRI in a recent case of iatrogenic mood symptoms induced by high-frequency deep-brain stimulation of the right subthalamic nucleus for treatment of intractable Parkinson's disease in a patient with a remote history of major depression[47]. Consistent with recent clinical studies demonstrating increased relapse risk in those remitted, depressed patients with persistent hypersensitivity to negative emotional stimuli[21,48], the converging imaging evidence suggests strategies for future studies of potential neural mechanisms of relapse vulnerability.

Challenge experiments of this type may additionally identify presyndromal subjects with high illness risk as suggested by preliminary studies demonstrating differential rest and mood-stress induced patterns of change in healthy control subjects selected for high and low neurotic temperaments[49,50]. The activation pattern seen in the high neuroticism group is similar, but not identical, to that in remitted, depressed patients suggesting a potential vulnerability marker, unmasked only with emotional stress. This is of interest since high neuroticism is not only highly associated with the presence of an affective disorder[51], but also appears to be a significant illness risk factor[1,3]. Further development of these types of paradigms might eventually prove useful for pre-clinical testing of unaffected family members of genetically defined cohorts.

Towards development of brain-based algorithms for treatment selection

A final approach is to consider that if a given metabolic pattern reflects a 'functional lesion' and an on-going process of attempted, but inadequate, self-correction, the pattern itself might effectively guide treatment selection. This construct would begin to explain potentially those studies reporting similar change patterns associated with both pretreatment frontal hypometabolism and hypermetabolism[24,25]. It also lays the foundation for directly examining whether clinical response to a particular mode of treatment can be effectively predicted by a particular pretreatment metabolic scan pattern. To test such a hypothesis, base-line patterns in patients with known clinical response to various treatments is required. In addition, a more deliberate assessment of these state-region-treatment interactions is needed. The multivariate technique partial least squares (PLS) combined with structural equation modelling provides one such approach[35–37].

As a first attempt at defining such predictive pathways, disease, treatment, and response-specific functional interactions among a cortical-limbic subset of regions, derived from past studies were modelled[52,53]. Using resting state FDG PET scans from three independent cohorts of acutely-ill depressed patients, PLS was used to confirm differences between groups in a network linking 7 brain regions repeatedly identified in treatment studies: dorsal prefrontal (F9), medial frontal (mF10), orbital frontal (OF11), rostral cingulate (Cg24a), subgenual cingulate (Cg25) anterior thalamus (aTh) and hippocampus (Hc). Path analysis was then conducted to estimate the strength and direction of effective connections between these regions within a predefined model structure, informed by known anatomical and physiological pathways in the published literature[27–29]. The model showed good stability for all three depressed cohorts in distinction to healthy controls, suggesting depression specificity. Furthermore, there were significant path differences that distinguished 5 subgroups defined as a function of treatment type and treatment response. Examination of clinical and demographic variables did not similarly distinguish the groups or the response effects. These differences are illustrated in Plate XIV (see end of file p.*210) and demonstrate sites of functional differences within this new 'depression network' that correlates with treatment outcomes to CBT, paroxetine and unspecified medication selected at the physician's discretion.

These preliminary results provide a perspective not possible using standard univariate techniques, revealing functional interactions among regions and not merely independent regional change effects. Interestingly, absolute frontal cortex metabolic status does not differentiate the groups, although anterior cingulate hypermetabolism consistently distinguished responders from non-responders in each of the three cohorts. An apparent

progression from a pure cortical pattern to a combined limbic-cortical pattern distinguished CBT responders (OF11→mF10; Plate XIV [see end of file p.*209] left, in green) from paroxetine responders (Hc→F9; Plate XIV [see end of file p.*209] left, in blue), whereas a more pure limbic pattern characterized drug non-responders including multiple drug failures (Cg24←Cg25←OF11; Plate XIV [see end of file p.*209] centre, in red). Group differences were otherwise unexplained by demographic, severity or behaviour measures. These findings would suggest that discriminate functional analyses of these regional patterns might serve a diagnostic and management function in future. On-going studies are examining this possibility with hopes for prospective studies of various treatments using randomization strategies based on base-line scan patterns.

Conclusions

Resting state PET measures of regional glucose metabolism and blood flow have proven to be sensitive indices of brain function in both the untreated state and following disparate treatments, offering a potential functional-anatomical template for more fundamental studies of *in vivo* and *post-mortem* pathology and chemistry[8,54] as well as simplified paradigms for new treatment algorithms. While the described network approach is by definition reductionistic in nature, it provides a flexible platform to consider systematically additional contributing variables such as hereditary, temperament and early-life experiences[1,3,55]. Continued development of imaging and multivariate statistical strategies that optimally integrate these factors will be a critical next step in fully characterizing the depression phenotype at the neural systems level. The additional goal is that this approach will also lead to brain-based algorithms that optimize care of individual depressed patients.

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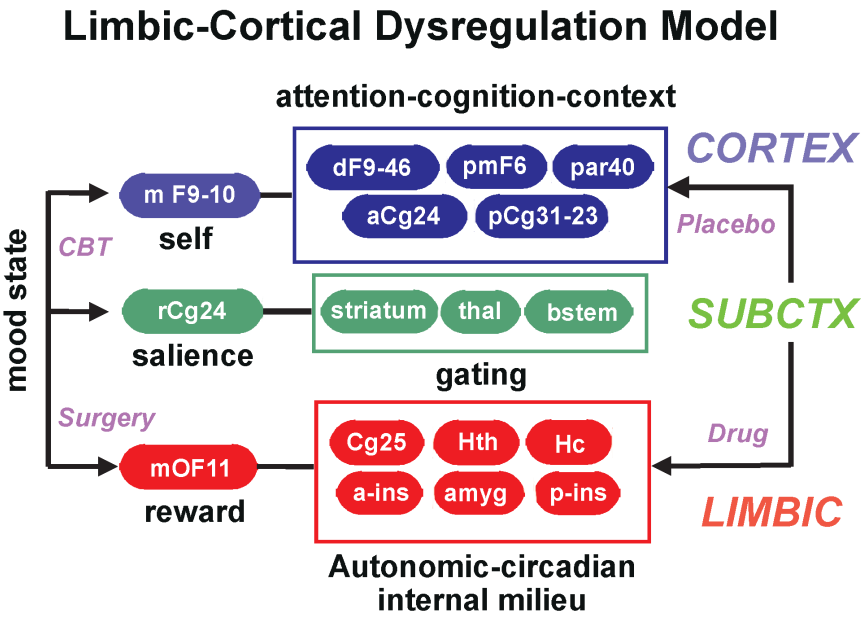

Plate XI Limbic-cortical dysregulation model. Regions with known anatomical interconnections[27–29], that also show synchronized changes using PET in 3 behavioural states – base-line depressed (unipolar and Parkinson's disease patients), post-treatment (medication, cognitive therapy, placebo, surgery), and transient induced sadness (controls, patients, neurotics) – form the basis of this schematic. Failure of this regional network is hypothesized to explain the combination of clinical symptoms seen in depressed patients (*i.e.* mood, motor, cognitive, vegetative). Regions are grouped into 3 main compartments, cortical (blue), limbic (red) and subcortical (green). The frontal-limbic (dorsal-ventral) segregation additionally identifies those brain regions where an inverse relationship is seen across the different PET paradigms. Sadness and depressive illness are both associated with decreases in dorsal neocortical regions and relative increases in ventral limbic and paralimbic areas. The model, in turn, proposes that illness remission occurs when there is appropriate modulation of dysfunctional limbic-cortical interactions (solid black arrows) – an effect facilitated by various forms of treatment. It is further postulated that initial modulation of unique subcortical targets by specific treatments facilitates adaptive changes in particular pathways necessary for network homeostasis and resulting clinical recovery. Dorsal medial frontal (mF9), rostral anterior cingulate (rCg24) and medial orbital frontal cortex (oF11) are separated from their respective 'compartments' in the model to highlight their critical primary interactions both within and between 'levels' in the integration self-referential, emotionally salient, exogenous stimuli relevant to reward, punishment and learning in the healthy and depressed state. Abbreviations: mF, medial prefrontal; dF, prefrontal; pm, premotor; par, parietal; aCg, dorsal anterior cingulate; pCg, posterior cingulate; rCg, rostral cingulate; thal, thalamus; bstem, brainstem; mOF, medial orbital frontal; Cg25, subgenual cingulate; Hth, hypothamus; Hc, hippocampus; a-ins, anterior insula; amyg, amygdala; p-ins, posterior insula. Numbers are Brodmann designations.

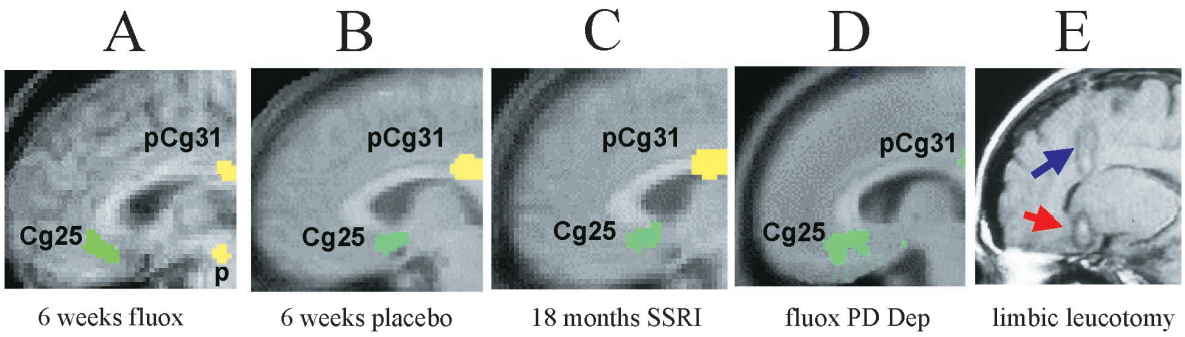

Plate XII Common changes in subgenual cingulate (Cg25) with different treatments. Decreases in subgenual cingulate, relative to patient base-line pretreatment scans are seen with clinical response to both 6 weeks of fluoxetine in unipolar depressed (A) and Parkinson's depressed patients (C). A similar pattern is seen with response to 6 weeks of placebo (B). Persistence of this pattern is seen in a separate group of patients in full remission on maintenance medication (D). Limbic leucotomy (E), a surgical procedure that combines subcaudate tractotomy (red arrow) and cingulotomy (blue arrow), disrupts both afferent and efferent subgenual cingulate pathways as well as inter-cingulate connections, demonstrating additional anatomical concordance. Abbreviations: fluox, fluoxetine; SSRI, selective serotonin re-uptake inhibitor. [Image (E) courtesy of G.R. Cosgrove, MD.]

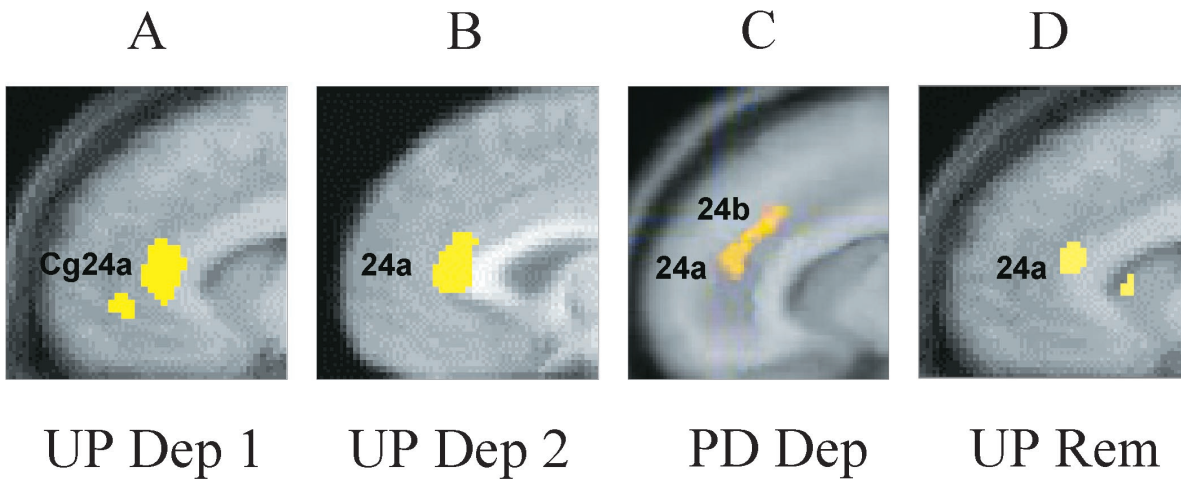

Plate XIII Predictive value of baseline rostral cingulate metabolism. Glucose metabolic activity in rostral anterior cingulate (Cg24a) measured prior to treatment predicts 6-week response to pharmacotherapy in three patient groups (A–C): Non-responders are hypometabolic and responders hypermetabolic relative to healthy controls. Location of significant rostral cingulate increases in responders compared to non-responders is demonstrated in yellow. This pattern continues long-term, as demonstrated by persistent increases in a separate group of fully remitted patients on maintenance medication (D). Abbreviations: UP Dep1, unipolar depression group 1 (n = 18; 10 responders, 8 non-responders); UP Dep2, unipolar group 2 (n = 45; 25 responders, 20 non-responders); PD Dep, Parkinson's disease patients with major depression (n = 15; 9 responders, 5 non-responders); UP Rem, unipolar depression in full remission (n = 10 *versus* 10 healthy controls).

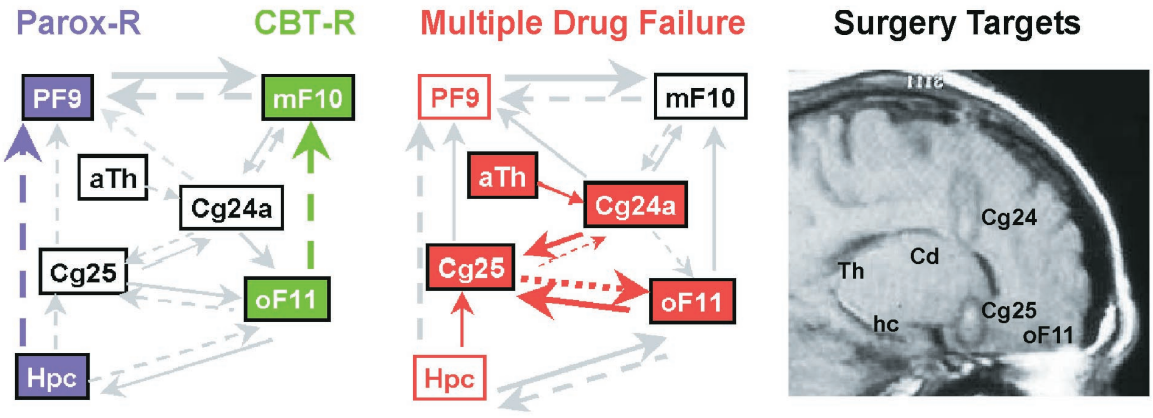

Plate XIV Regional relationships predicting treatment outcome identified using structural equation modelling. A prescribed analytic model linking prefrontal (F9), medial frontal (mF10), orbital frontal (OF11), subgenual cingulate (Cg25), rostral cingulate (Cg24a), anterior thalamus (aTh), and hippocampus (hc) was used to test first for overall differences between 3 separate cohorts of depressed subjects subdivided as a function of treatment type and response outcome. Pathways within each treatment group demonstrating differences with response are illustrated. Solid arrows represent positive path coefficients (positive effect of a region on its target); dotted arrows represent negative path coefficients. Values of path coefficients are not shown but are represented by thickness of arrows. Grey, common across comparison groups; green, CBT response pathways; blue, drug response pathways; red, unique abnormalities in drug non-responsive patients. MRI demonstrates limbic leucotomy lesions with regions of interest from the model superimposed. Note the overlap between site of subcaudate tractotomy and overactive pathways seen in the drug failure group.