Biological substrates underpinning diagnosis of major depression

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Abstract

Major depression is characterized by low mood, a reduced ability to experience pleasure and frequent cognitive, physiological and high anxiety symptoms. It is also the leading cause of years lost due to disability worldwide in women and men, reflecting a lifelong trajectory of recurring episodes, increasing severity and progressive treatment resistance. Yet, antidepressant drugs at best treat only one out of every two patients and have not fundamentally changed since their discovery by chance >50 yr ago. This status quo may reflect an exaggerated emphasis on a categorical disease classification that was not intended for biological research and on oversimplified gene-to-disease models for complex illnesses. Indeed, genetic, molecular and cellular findings in major depression suggest shared risk and continuous pathological changes with other brain-related disorders. So, an alternative is that pathological findings in major depression reflect changes in vulnerable brain-related biological modules, each with their own aetiological factors, pathogenic mechanisms and biological/environment moderators. In this model, pathological entities have low specificity for major depression and instead co-occur, combine and interact within individual subjects across disorders, contributing to the expression of biological endophenotypes and potentially clinical symptom dimensions. Here, we discuss current limitations in depression research, review concepts of gene-to-disease biological scales and summarize human post-mortem brain findings related to pyramidal neurons, γ-amino butyric acid neurons, astrocytes and oligodendrocytes, as prototypical brain circuit biological modules. Finally we discuss nested aetiological factors and implications for dimensional pathology. Evidence suggests that a focus on local cell circuits may provide an appropriate integration point and a critical link between underlying molecular mechanisms and neural network dysfunction in major depression.

Keywords

Corticolimbic; dimensional; major depression; microcircuitry; post-mortem

A categorical (*vs.* biological) definition of major depression

The classification of mental illnesses, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) in the USA and the International Statistical Classification of Diseases and Related Health Problems internationally, was borne out of the necessity to provide a common language for descriptive purposes and delivery of care (Fischer, 2012). This categorical system is broad and somewhat arbitrary, but has been successful in clinical practices and overall for the health care system. Yet, although a biological basis was not a factor in the initial classification, the system has fostered a general attitude that psychiatric disorders are biologically distinct. As defined by DSM-IV, major depressive disorder (MDD) is diagnosed by a variable set of five symptoms for a continuous 2-wk period (APA, 2000). Depressed mood or reduced interest in activities previously enjoyable (anhedonia) represent core symptoms, but other cognitive (attention, concentration, recurrent thoughts of suicide) and physiological (weight, locomotor and sleep pattern changes) symptoms need to co-occur. Depression is a biological syndrome that affects the brain and possibly peripheral organs also (Musselman et al., 1998; Ciechanowski et al., 2000; Steptoe and Whitehead, 2005; McIntyre et al., 2007), but whether its clinical definition corresponds to a coherent biological entity and whether 'categorical' is the appropriate model for characterizing the biological underpinnings of depression, remain open questions. The lifelong trajectory of depression does provide strong evidence for a biological basis (Fig. 1). For many patients, this includes recurring episodes with increasing symptom severity, longer duration, shorter or partial remission period and increasing resistance to antidepressant modalities, together leading to states of chronic and treatment-resistant depression (Kessler et al., 2005b; Moylan et al., 2012). This suggests a progressive strengthening of biological underpinnings over time, although the nature of these lifelong pathological changes is not known. Finally, although most research implicitly assumes a framework based on depression being a single entity, the primary evidence of biological disturbances observed in depressed subjects suggests a more equivocal picture. For general reviews on depression, see Pariante (2009) and López-Muñoz and Álamo González (2012).

Molecular *vs.* syndromal specificity of pathological mechanisms from a multi-scale biological perspective

Neuropsychiatric disorders are unique in the span of affected biological scales (Fig. 2*a*). Characterized in a top-down fashion, they are defined at the highest level by complex behavioural symptoms, differing from diseases of other organ systems, which are defined at lower biological scales by aberrations in gene function, signal transduction and cellular growth (e.g. cancer) or peptide/hormone production and release (e.g. insulin function in diabetes) and for which any behavioural syndromes associated with the diseases are secondary to their clinical pathophysiological core. In depression, clinical and neuroimaging studies operate at the top of biological scales, whereas molecular and cellular research uses bottom-up approaches (Fig. 2*a*). Accordingly, the former has the highest syndromal specificity and the latter displays highest specificity for genes, molecules, signalling cascades and cells. Therapeutic agents, such as serotonin reuptake inhibitors (SSRI), similarly have high specificity for molecules and low specificity for complex heterogeneous

clinical syndromes (Fig. 2*b*), displaying moderate efficacy for a range of psychiatric and systemic disorders (Wong and Licinio, 2001; Warden et al., 2007). To move forward in therapeutic discovery, it will be critical to develop fully integrated models, informed by detailed knowledge of the human pathology within respective biological scales, that bridge top-down clinical with bottom-up molecular findings and that are predictive across biological scales.

Keeping biological complexity in mind

Given the opposing scales of diagnosis and treatment, it is not surprising that major depression has proven difficult to treat and that novel treatments have been rare. Reductionist approaches convert a multi-scale perspective into a linear pathway and posit that the disease is caused by an as-yet unknown biological factor (e.g. gene; Fig. 3), which, once identified and targeted, may treat the illness and associated symptoms. However, this gives the false impression of a straightforward linear pathway from gene to syndrome, whereas the reality is that molecular and cellular components assemble into local integrated functional units, defined here as biological modules, which are then combined and re-used in intricate networks, with the complexity increasing with each biological scale (Fig. 3, right). Biological modules differ from endophenotypes (Gottesman and Gould, 2003), which emerge behaviourally at the neural network level and above and therefore still functionally integrate various and complex sets of underlying biological modules. The gene-to-disease linear approach is supported by forward genetic studies in rodents, where single gene manipulations can cause complex rodent behavioural changes. However, neuropsychiatric disorders are complex diseases implicating large number of genes, which do not strictly follow classic Mendelian structure (Kendler, 2012) and screening for genetic impact on behavioural outcomes in rodent systems does not equate to identifying primary pathological changes in complex human brain disorders. Moreover, current rodent preclinical models used for screening and testing gene-to-behaviour paradigms and novel compounds are often oversimplified, streamlined and validated by monoaminergic pharmacological compounds with moderate efficacy in human subjects.

How do we move forward in identifying and characterizing biological bases of depression? Here, we focus on selected findings on the primary pathology of the illness, as directly identified in brains of human subjects with major depression. We place an emphasis on cells and local circuitry, as integrated functional units with intrinsic biological vulnerabilities implicated across psychiatric disorders. After briefly reviewing genetic findings in major depression, we focus on four cell-based biological modules emerging from post-mortem studies: altered pyramidal neuron structure; altered γ-amino butyric acid (GABA) circuitry; astrocyte dysfunction; oligodendrocyte dysfunction. Finally, we discuss disease-specificities and aetiological factors implicated in affected biological modules. Given the relevance of corticolimbic structures to low mood and affect dysregulation in depression (Seminowicz et al., 2004; Phillips et al., 2008; Price and Drevets, 2012) we limit the scope of the review to these structures.

Genetic findings in major depression

Unbiased large-scale studies seeking to identify conserved DNA variants across a population of affected individuals have provided only weak evidence for a core biological underpinning of major depression. In a recent mega-analysis of genome-wide association studies (GWAS) of 1.2 million single nucleotide polymorphisms in 9249 major depression cases and 9518 control subjects, no single nucleotide polymorphisms achieved genome-wide significance, nor did exploratory approaches provide robust leads for further studies (MDD GWAS Consortium, 2012). The negative findings were recently replicated by meta-analysis of GWAS using measures of depressive symptoms in large epidemiological cohorts ($n =$ 34549; Hek et al., 2013). The interpretation of these and similar previous findings (Wray et al., 2010) is often a lack of statistical power due to the large number of variants investigated or the engagement of too many genes with very small effects, suggesting that sample sizes in the tens of thousands of subjects will be needed to detect significant gene variant effects (Hek et al., 2013). Alternative explanations are that the 'soft' nature of the disease characterization, together with a high heterogeneity and a robust environmental component, may prevent the identification of consistent biological findings (Wray et al., 2010). Yet this reflects circular reasoning, as the clinical cohorts that are chosen for these studies are based on the broad symptomatic definition of the illness, rather than on evidence of biological homogeneity. An alternative interpretation is that the association with depression as a distinct illness is weakened, either by the presence of behavioural endophenotypes or subtypes of depression, or at a lower level by the recruitment of various biological modules which are often similarly affected across other major mental disorders, albeit in different combinations, together contributing to the apparent low (or diluted) heritability of depression (~40%; Kessler et al., 2005a). Indeed, there is some GWAS-based evidence for shared genetic vulnerability across major mental illnesses, consistent with a dimensional basis of risk (Schulze et al., 2012).

Studies of variants associated with single genes are mostly equivocal in terms of effect sizes and specificity. For instance, studies of the promoter polymorphism of the serotonin transporter (SERT) suggest a weak moderating effect on major depression and associated traits and more robust effects on neural endophenotypes that relate to general risk for psychopathology and vulnerability to affective disorders (Canli and Lesch, 2007). Conversely, rare coding or gain-or-function mutation in genes such as SERT (Ozaki et al., 2003), monoamine oxidase A (Brunner et al., 1993) and disrupted in schizophrenia (Millar et al., 2005) implicate single genes in severe major mental illnesses, but the observed phenotypes are complex, mixed and often severe, including combinations of depression, obsessive-compulsive disorder, substance abuse disorders, with aggression, schizoaffective and psychotic features, and in some cases suggesting strong developmental contributions. Together these studies significantly contributed to lowering boundaries between major depression and other categorical psychiatric disorders and provided leads for investigating pathophysiological mechanisms with implications beyond their original areas of investigation (Brandon and Sawa, 2011).

Altered cortical neuronal structure in major depression

In contrast to neurodegenerative disorders, depression does not include major cell loss. However, studies have reported reduced density of neuronal cell bodies with large cell body size in cortical layers 2–5 of the orbitofrontal cortex (OFC) and in layers 2, 3 and 6 of the dorsolateral prefrontal cortex (dlPFC), concurrent with increased density of small body size neurons in layer 3 (OFC) and layers 3 and 6 (dlPFC; Rajkowska et al., 1999; Rajkowska, 2000). Region-specific reports of decreased mean neuronal cell body size include layers 3 and 6 (dlPFC), layers 2 and 3 (OFC) and layer 6 [anterior cingulate cortex (ACC); Rajkowska et al., 1999; Cotter et al., 2001]. These findings are consistent with lower combined neuron density in both dorsal and ventral PFC in depressed suicides (Underwood et al., 2012) and reduced neuronal size in layer 6 of the dlPFC in major depression (Cotter et al., 2002a). In a study designed for more focused analysis of cell-specific changes, lower density of N200-positive pyramidal neurons was found in the dlPFC [Brodmann area (BA) 9, 32, 46] in major depression compared to bipolar disorder and schizophrenia, although *post hoc* comparisons between controls and depressed subjects were not significant (Law and Harrison, 2003). No difference in packing density of pyramidal neurons in layer 3 of the BA 9 between depressed and control subjects was found in a separate study using NF200 as a pyramidal marker (Miguel-Hidalgo et al., 2005). For cohorts of elderly MDD or older mood-disorder subjects, reduced pyramidal neuron density in layers 3 and 5 of the OFC (Rajkowska et al., 2005) and layer 5b of the ACC (Gittins and Harrison, 2011) but not in the dlPFC (Van Otterloo et al., 2009), was reported.

Although it appears unlikely that neuronal loss underlies these changes, whether decreased neuronal density reflects changes in neuropil and dendritic complexity is not known. Using Golgi staining of neuronal processes, reduced numbers of third-order basilar dendritic branches were observed in ACC layer 6 of depressed suicide victims, although the subgroup with major depression demonstrated only a trend towards reduction (Hercher et al., 2010). Furthermore, a decrease in total dendritic length and somal area was observed in deep and superficial layer 3, respectively, in dlPFC in a cohort enriched in MDD patients (Glantz and Lewis, 2000). Reduced density of synapses was also observed by electron microscopy in frontal cortex in a small cohort of MDD patients (Kang et al., 2012), together supporting the hypothesis of altered neuronal densities and potentially reduced dendritic complexity in depression. However, further studies are needed in larger post-mortem cohorts to confirm and firmly establish these findings.

Altered glutamate homeostasis in major depression

Large cortical neurons contain glutamate and are excitatory, but glutamatergic function cannot be measured under post-mortem conditions. *In vivo* glutamate levels can be measured using proton magnetic resonance spectroscopy (^{1}H-MRS). MRS studies frequently report glutamate-related metabolite levels using the combined term Glx (Valentine and Sanacora, 2009; Maddock and Buonocore, 2012). As reviewed in (Yuksel and Ongur, 2010), MRS studies have shown reduced Glx and/or glutamate concentrations across multiple cortical and subcortical brain regions, including ACC (Auer et al., 2000; Pfleiderer et al., 2003; Zhang et al., 2012); PFC (Michael et al., 2003a; Hasler et al., 2007), amygdala (Michael et

al., 2003b) and hippocampus (Block et al., 2009), although others have found no change in the hippocampus (Milne et al., 2009) and occipital cortex (Price et al., 2009) and even increased glutamate levels (Sanacora et al., 2004) in occipital cortex. In several of these studies, both Glx (Michael et al., 2003a; Pfleiderer et al., 2003) and glutamate (Zhang et al., 2012) were shown to increase with electroconvulsive therapy (ECT) treatment response. Although these findings present strong evidence that glutamate, glutamine and related metabolites are altered in brain tissue of depressed patients, given that only a small amount of measured metabolites are synaptic, any conclusions about altered glutamatergic neurotransmission on the basis of these studies would be premature (Sanacora et al., 2012).

Together, evidence of reduced neuronal density and dendritic morphology, altered glutamatergic signalling, reduced neurotrophic support through low brain-derived neurotrophic factor (BDNF) function (Duman et al., 2000) and of the rapid antidepressant effects of ketamine (Berman et al., 2000; Zarate et al., 2006), a glutamatergic NMDA receptor antagonist, have contributed to the neurotrophin hypothesis of major depression. Note that this first potential major breakthrough for novel and efficacious antidepressant modalities in >50 yr, i.e. ketamine-related NMDA antagonism, does not rely on direct evidence for dysregulated NMDA function in major depression, but rather on clinical observations and recently on a growing number of rodent pre-clinical studies (Li et al., 2010; Autry et al., 2011). This long delay between identifying novel therapeutic modalities highlights the need to focus on characterization of the primary pathology of the illness, in order to accelerate target and mechanism identifications.

Low GABA and reduced markers of dendritic-targeting GABA neurons in major depression

Studies using cellular markers for small cortical neurons have reported a reduction in the density of GABA neurons immunoreactive for specific calcium binding proteins in the dlPFC in major depression (Rajkowska et al., 2007), but for negative findings, see also Beasley et al., (2002) and Cotter et al., (2002b). The density of calbindin (CB)-positive neurons was reduced by 50% in dlPFC, but no difference in parvalbumin (PV)-positive neurons were observed. Recently, our group has reported reduced somatostatin (SST), a modulatory neuropeptide, in the dlPFC (Sibille et al., 2011), subgenual (sg) ACC (Tripp et al., 2011, 2012) and amygdala (Guilloux et al., 2011) of subjects with major depression. These studies are consistent with the prior CB-related findings since SST is mostly expressed in CB-positive cells (Hayes et al., 1991; Conde et al., 1994; DeFelipe, 1997; reviewed in Viollet et al., 2008). SST GABA neurons target pyramidal neuron dendrites. Interestingly, neuropeptide Y (NPY) and cortistatin, two neuropeptides that also target dendrites, showed similar low expression in the sgACC and amygdala (Guilloux et al., 2011; Tripp et al., 2012). In contrast, other GABAergic cellular markers, including cholecystokinin (CCK) and calretinin (CR) were unaffected in ACC and amygdala in depression, although PV expression was lower in ACC but not in dlPFC (Sibille et al., 2011; Tripp et al., 2012). PV and CCK neurons target pyramidal cell bodies and axon initial segment, while CR neurons target other GABA neurons. Expression of genes coding for GABA-producing enzyme (GAD65 and GAD67) has been reported either unchanged or

reduced in combined grey matter samples in major depression (Sibille et al., 2011; Tripp et al., 2012). These results suggest selective changes affecting the CB/SST-positive and potentially other dendritic targeting GABA neuron subtypes, although studies using double markers or laser captured cells will need to confirm the extent of cell type-specific deficits.

The findings are consistent with reports of decreased GABA concentration in subjects with major depression as observed by ^{1}H-MRS in occipital and frontal cortices or by transcranial magnetic stimulation (Hasler et al., 2007; Levinson et al., 2010; Hasler and Northoff, 2011; Gabbay et al., 2012), which was reversed after therapy with SSRI or ECT (Sanacora et al., 2002, 2003), hence correlating with the depressed state. Reduced ACC GABA levels also correlated with measures of anhedonia across depressed and control adolescents (Gabbay et al., 2012). Studies combining functional imaging and resting-state MRS suggest that the concentration of GABA in the ACC mediates default-mode network negative responses during emotion processing (Northoff et al., 2007). Hence, converging evidence from several biological scales, supported by early studies showing low GABA in the plasma of depressed subjects (Gold et al., 1980) and genetic manipulation studies in rodents (Earnheart et al., 2007), have together formed the basis of a GABA hypothesis of emotion dysregulation in depression (Brambilla et al., 2003; Luscher et al., 2011).

Astrocyte-related findings in major depression

Observations of a marked 24% decrease in number of sgACC (BA 24) glial cells, concurrent with decreased cell density, in patients with familial major depression provided early evidence for glial changes in depression (Ongur et al., 1998). Several studies have reported reduced glial cell density in the dlPFC and ACC in major depression (Rajkowska et al., 1999; Cotter et al., 2001, 2002a) and low glial numbers in the amygdala (Bowley et al., 2002); whereas others identified no changes in overall glial cells in OFC and dlPFC in late-life depression (Khundakar et al., 2009, 2011). Interestingly, a meta-analysis of 174 subjects revealed increased levels of serum S100B, a glial marker protein expressed in astrocytes, but also in oligodendrocytes (Hachem et al., 2005), in major depression and bipolar disorder; higher levels were also observed in older subjects compared to younger subjects with mood disorders (Schroeter et al., 2011).

Astrocytes are glial cells that primarily regulate the neuronal chemical environment and extracellular clearance of glutamate and partly GABA (Brodal, 2010). Investigations of astrocyte-specific glial pathologies suggest cellular hypertrophy in ACC white matter (Torres-Platas et al., 2011). However, decreases in glial fibrillary acidic protein (GFAP), another astrocytic marker, and in glutamate clearance transporters (EAAT1, EAAT2) expressed in astrocytes have also been observed in PFC of subjects with major depression (Miguel-Hidalgo et al., 2000, 2010; Si et al., 2004; Choudary et al., 2005). GFAP expression increases with age (Nichols et al., 1993) and diagnostic-based differences in GFAP levels were not observed in older depressed subjects (Si et al., 2004). Expression of astrocyte connexins 43 and 30 were down-regulated in suicide victims with a range of psychiatric diagnoses, including bipolar disorder, schizophrenia and major depression (Ernst et al., 2011). Connexins 43 and 30 mediate gap junction-based direct communication between astrocytes and also participate in astrocyte–oligodendrocyte junctions (Orthmann-Murphy et

al., 2008). Together, these findings suggest dysregulated astrocytic function in depression, leading to a model in which alterations in glutamate/GABA neurotransmission and loss of GABA-mediated inhibition, may be partially explained by astrocytic deficits, specifically related to neurotransmitter recycling and homeostasis (Valentine and Sanacora, 2009; Oh et al., 2012).

Reduced oligodendrocyte numbers in major depression

Using morphological cell-type determination, reports have suggested that the decreased glial cell numbers in amygdala and PFC may be attributed to reduced oligodendrocytes (Hamidi et al., 2004; Uranova et al., 2004). Oligodendrocytes are glial cells that form myelin sheaths around axons, thereby facilitating axonal conduction (Brodal, 2010). A gene array study in the amygdala of male subjects with major depression from our laboratory showed reduced expression of numerous genes related to oligodendrocyte structure and function (Sibille et al., 2009), consistent with reduced expression of similar transcripts in the PFC in other studies in major depression (Klempan et al., 2009; Kim and Webster, 2010). Decreased oligodendrocytes were also reported by flow cytometry, using fluorescently labelled suspended nuclei from the frontopolar cortex in major depression (Hayashi et al., 2011). However, down-regulation of oligodendrocyte transcripts was not reported for the ACC (Sibille et al., 2009) or amygdala in female subjects (Guilloux et al., 2011). Due to their role in supporting axonal conduction and of specific dysregulation of genes coding for proteins located at the nodes of Ranvier, dysregulated oligodendrocyte function has been suggested to mediate impaired communication and altered integrity of neuronal information transfer in major depression (Edgar and Sibille, 2012).

Disease-independent and module-specific cellular pathologies

The post-mortem evidence summarized above suggests cellular alterations that include altered neuronal densities and glial pathologies in major depression, which may affect specific aspects of glutamate and GABA homeostasis, although many of these findings are not specific to major depression and have been observed in other brain disorders. For instance, morphometric studies show reductions in dlPFC neuronal size, dendrite and spines in schizophrenia and in Alzheimer's and Huntington's diseases (Rajkowska et al., 1998, 1999; Glantz and Lewis, 2000; Cotter et al., 2002b), as well as layer specific reductions in neuronal density (layers 5 and 6) in dlPFC in bipolar disorder (Cotter et al., 2002a). Changes in the same SST GABA neuron marker are observed in schizophrenia (Morris et al., 2008), bipolar disorder (Konradi et al., 2004, 2010) and in Huntington's (Timmers et al., 1996), Alzheimer's (reviewed in Davies et al., 1980; Epelbaum et al., 2009) and Parkinson's diseases (reviewed in Epelbaum et al., 1989), although in the context of additional pathologies, such as robust down-regulation of PV in perisomatic targeting GABA neurons in schizophrenia (Hashimoto et al., 2003; Volk et al., 2012), suggesting different functional outcomes despite similar changes in some of the individual components (see later sections). Similarly, oligodendrocyte abnormalities were reported in schizophrenia (Hof et al., 2003; Uranova et al., 2004; Kolomeets and Uranova, 2008) and to some extent in bipolar disorder (reviewed in Edgar and Sibille, 2012; Fields, 2008). These changes appear widespread in schizophrenia (Haroutunian et al., 2007) but neuropathological evidence in bipolar disorder

is primarily from PFC (Uranova et al., 2004). Notably, the same oligodendrocyte-related genes as in major depression have been implicated in older subjects with schizophrenia, prompting a related hypothesis of reduced oligodendrocyte axonal support as the basis of the disconnectivity syndrome in schizophrenia (Roussos et al., 2012). Finally, reduced astrocyte densities were reported in multiple brain regions in schizophrenia (Katsel et al., 2011; Williams et al., 2012). Together, this brief survey of the non-selectivity of gross cellular findings across brain disorders illustrates the main points that pathological entities observed in depression often display a continuum of changes with other brain-related syndromes and occur in combinatorial patterns across cohorts and syndromes.

Integrating cell-based findings suggests altered information processing at the local circuit level in major depression

The cell-based findings in major depression described herein suggest the presence of deregulated biological modules that are integral components of canonical local cell circuits, at least in cortical and related structures (i.e. amygdala basolateral complex) (Fig. 4). Altered integrity of information transfer and processing, where 'information' is defined as excitatory output of pyramidal or principal cells, could occur as follows (Fig. 4*a*): (1) altered integrity of incoming and outgoing information, through decreased oligodendrocyte support of axonal function; (2) altered synaptic transfer of information, through altered glutamate availability; (3) altered sharpening of glutamatergic signalling-coded information through deficient fine-tuning of excitatory post-synaptic signals by SST-positive GABAergic neuron dendritic targeted inhibition; (4) maintenance of a dysregulated glutamate/GABA homeostasis through altered astrocyte recycling of neurotransmitters. Anatomical studies suggest that these deregulated modules may occur in various cortical layers, overall affecting information flow within and across cortical areas (Fig. 4*a*). As this speculative set of events is based on corticolimbic findings, its impact on higher biological scales may include altered sensing (by the amygdala) and processing (by the sgACC and dlPFC) of emotionally-salient information. Hence, reduced GABA-mediated inhibition on incoming information onto pyramidal dendrites may represent a putative local circuit-level phenotype underlying the increased sgACC and amygdala activation frequently reported in major depression (Mayberg et al., 1999; Siegle et al., 2007; Suslow et al., 2010), potentially tipping the balance towards bias for negative salience detection, rumination and overall low affect in depressed subjects. Local circuit changes may also impact the function of brain regions in overlapping neural networks implicated in cognitive symptoms (dlPFC) and emotion dysregulation (medial PFC, ACC and amygdala) in depression (Kupfer et al., 2012). Moreover, restoring dendritic inhibitory function may reduce pyramidal cell activation and excitatory tone and contribute to reduced ACC activation with positive response to therapeutic intervention (e.g. deep brain stimulation, antidepressants; Mayberg et al., 2000, 2005; Agid et al., 2007).

This emerging framework suggests a core biological disruption in depression onto which one can integrate additional biological findings (i.e. phenotypic moderators), but it also needs multiple qualifiers. (1) Cellular findings were not systematically reported in the same subjects and cohorts, supporting a combinatorial basis for pathogenesis, which may also

form a cellular basis for variable phenotypic severity. (2) This integrated set of findings displays potential phenotypic specificity in depression (altered local circuit-mediated incoming information processing), but interactions with various 'pathophysiological modifiers' in other categorical diseases will affect the phenotypic presentation. Such 'modifiers' may include reduced PV-mediated GABAergic inhibitory control on pyramidal cell body and axon initial segment in schizophrenia (Hashimoto et al., 2003), or reduced cortical input from affected subcortical cell population in neurodegenerative diseases (i.e. cholinergic neurons in Alzheimer's; McGeer et al., 1984; Lehericy et al., 1993; Mesulam, 2012). (3) Local circuit modules and associated pathological entities have their own aetiological factors (see next section), but also interact with neuromodulatory input, including monoaminergic (Arango et al., 2002) and neuropeptidergic systems (Griebel and Holsboer, 2012), neuroendocrine and other hormonal factors, inflammatory factors and the immune system, for which ample evidence suggest roles in depression (reviewed in Nestler et al., 2002; Belmaker and Agam, 2008; Moylan et al., 2012). Notably, since cellular changes are mediated by changes in gene expression and function, cell-specific gene and molecular studies in human post-mortem subjects may help identify adaptive changes and relative contributions of these neuromodulatory systems onto cortical local circuits. (4) Whereas post-mortem studies are essential in characterizing the primary brain pathology, the sequence of pathological events cannot be determined and information on time-dependent trajectories are sparse. However, one can argue that post-mortem studies are more than simple snapshots in time, since they inform on stable biological adaptations that sustained the pre-morbid state or that mediated the cumulative and neuroprogressive pathology of the illness. This is an important consideration to have in mind for studies of cellular pathology, as models propose a trajectory affecting glial and neuronal cells at different time-points throughout the progression of the illness, suggesting varying cellular pathology based on both age of the subject and stage of the illness. As proposed by Rajkowska and Miguel-Hidalgo (2007), early glial reductions as a result of a combination of stress-related biological insults and genetic vulnerability may lead to neuronal damage due to dysfunctional or insufficient support and clearance of extracellular glutamate. In this model, compensatory increases in glia in response to damage to neurons may occur with increasing age and illness progression. Subjects with late-life depression may enter at the stage of neuronal damage and loss through other pathways, such as vascular lesions or neuronal atrophy associated with age. (5) Local circuit-mediated changes in the function of specific brain regions and neural networks will feedback on its cellular components, through activity- and hormone-dependent transcriptional changes. Indeed, post-mortem studies preclude detection of short-term effects (h), yet gene expression is under the control of multiple rhythms across several time-frames, from circadian clock to hormonal fluctuations, including metabolic (insulin, thyroid), sex and stress hormones, often through nuclear hormone receptor-orchestrated changes in transcriptional programmes. Moreover, genes are also influenced by acute 'out-of-sync' effects of hormones during stress or inflammation, which will contribute to altered synchronous cell function. For instance, there is indirect evidence for multiple hormonal systems deregulation in depression, using corticolimbic gene synchrony as an assay for common upstream regulation (Gaiteri et al., 2010).

Module-specific and nested aetiological factors: the example of SST

As referred to in this review, biological modules and endophenotypes are not interchangeable. Endophenotypes, as originally described by Gottesman and Gould (2003) encompassed biological (neurophysiological, biochemical, endocrinological), neuroanatomical and behavioural (cognitive, neuropsychological; i.e. working memory, sensory motor gating) categories, which in fact reflect functions over a large panel of biological scales (Fig. 2). Conversely, GABAergic and glutamatergic synapses, with their associated glial cells (Fig. 4) participate in biological modules that are repeated across cortical layers and throughout the brain. Moreover, biological modules have their own aetiological pathways, meaning that pathologies in these modules often do not show specificity to categorically-defined brain disorders. Rather, various risk factors may together orchestrate pathological changes across sets of vulnerable modules. Here we use pathological findings and known modulators of SST expression and function to illustrate module-specific factors and frequent lack of adherence to a categorically-defined disorder.

In MDD, reports of low SST expression are more robust in female subjects (Tripp et al., 2011, 2012). SST expression also appears lower in aged-matched normal healthy women compared to male subjects (Tripp et al., 2012), consistent with a moderating, rather than interacting effect of sex on SST and potentially contributing to the heightened female vulnerability to develop episodes of depression. Similarly, normal subjects lose on average 50% SST expression between ages 20 and 70 yr (Glorioso et al., 2011), consistent with age-related changes in brain neurotrophic environment (Erraji-Benchekroun et al., 2005). SST expression also depends on BDNF (Glorioso et al., 2006), a neuropeptide responsible for maintaining neuroplasticity, which itself shows age-dependent decreased expression in control subjects (Webster et al., 2002; Erraji-Benchekroun et al., 2005) and reduced expression in depression (Dwivedi, 2009; Guilloux et al., 2011) and other brain-related disorders (Lu and Martinowich, 2008; Rakofsky et al., 2012). The extent of depression-related decreases in SST and other neuropeptides expressed in dendritic-targeting GABAergic neurons (cortistatin and NPY) varies based on brain region and aspects of BDNF signalling (i.e. activity-dependent *vs.* constitutive function; B *vs.* BDNF decreases; Guilloux et al., 2011; Sibille et al., 2011; Tripp et al., 2011, 2012). More proximal cell-specific risk factors include vulnerability to oxidative stress, since neuronal nitric oxide synthase, a source of cytotoxic nitric oxide, is mostly expressed in SST and NPY neurons (Jaglin et al., 2012). These cell-specific factors may also be sex-dependent, in view of human–mouse conserved sex-bias in expression of mitochondria-related genes (Lin et al., 2011). Together, these observations suggest that SST expression and potentially dendritic inhibition, is subject to sets of nested regulatory pathways (i.e. occurring on consecutive biological scales), which include cell-specific (oxidative stress), neuron and circuit factors (BDNF), regional (ACC *vs.* amygdala), individual (sex) and general (age) factors. Finally, individual genetic liabilities, environmental factors and longitudinal trajectories (developmental and age-dependent changes) will impinge on most factors discussed.

Conclusions and implications of a modular perspective on the biological substrates underpinning diagnosis of major depression

Molecular and cellular evidence suggest that several components of local canonical cortical (or related) cell circuits are deregulated in major depression, affecting the structure and function of glutamatergic neurons and dendritic-targeting GABAergic neurons, as well as oligodendrocytes and astrocytes. The data suggest that cumulative pathological changes in each of these cell types may affect the integrity of information transfer across these local cell circuits, in turn affecting the processing capacity across cortical layers, brain regions and neural networks (summarized in Fig. 4). The fact that these changes have been identified in brain regions participating in sensing and assessment of emotional salience suggests a direct contribution to core symptoms of depression, such as low affect and anhedonia. The assumption is that deregulated cell circuits may affect the functional balance of individual brain regions, 'pushing' the corticolimbic neural network towards maladaptive states that favour negative bias, rumination and lack of pleasure/reward. This latter link is however speculative and illustrates the inherent limitations of bridging bottom-up cellular and molecular post-mortem studies with top-down clinical and brain imaging studies in subjects with major depression.

Evidence also suggests a modular and combinatorial model, where pathological findings do not represent biomarkers for respective categorical syndromes, but rather correspond to cellular and molecular pathological entities affecting distinct and vulnerable brain-related biological modules. The interactions between these biological modules identify multiple potential pathological routes and suggest that a network-based approach to biological modules and pathological entities may be more appropriate to characterize the biological substrates of major depression, compared to linear causal pathways (Fig. 2). However, a potential caveat of the network approach is the frequent focus on seeking affected network 'hubs', a masked alternative of reductionist approaches geared toward finding 'silver bullet' targets. Early evidence suggests that hubs are stable and not affected in psychiatric disorders, at least from the gene network perspective (Gaiteri and Sibille, 2011). Additional forms of deregulated transfer of genetic information in gene networks have not been investigated yet.

Here we have focused on depression-related cell-based findings and implications for local circuits in cortical and related structures, but additional biological subcellular modules, modulatory systems and neural network areas are involved. From a research perspective, the apparent non-selectivity of a biological module perspective should not detract from putative causal roles in major depression, as characterizing individual modules in terms of aetiology, molecular pathology and phenotypic output will contribute to our understanding of the biological complexity of brain dysfunction and their combinatorial recruitment may offer insight into mechanisms underlying the clinical presentation of depression. For instance, numerous preclinical studies demonstrate that affecting components of the described local networks can affect behavioural emotionality in rodents (Banasr and Duman, 2008; Banasr et al., 2010; Edgar et al., 2011). Similarly, one can speculate that genetic studies of behavioural endophenotypes based on knowledge of vulnerable underlying biological

modules and associated pathological changes within a broader depression syndrome may yield more robust findings, informing mechanisms beyond mood disorders. A modular perspective is consistent with the emerging dimensional understanding of symptom co-occurrence across syndromes and provides a bottom-up approach to identify relevant biological modules and associated pathological entities, which is complementary to the research domain criteria top-down effort to cluster clinical symptoms into a coherent and biologically-informed endophenotype structure (Insel et al., 2010). Given the stasis and problems associated with antidepressant drug discovery, and due to its reliance on simplified assumptions and models, it is critical to develop integrated models that are predictive across biological scales. A focus on local cell circuitry integrates molecular mechanisms with neural network function, bridging the gap between molecular drug targets and clinical syndromes that has thus far impeded novel drug discovery for neuropsychiatric diseases.

Acknowledgments

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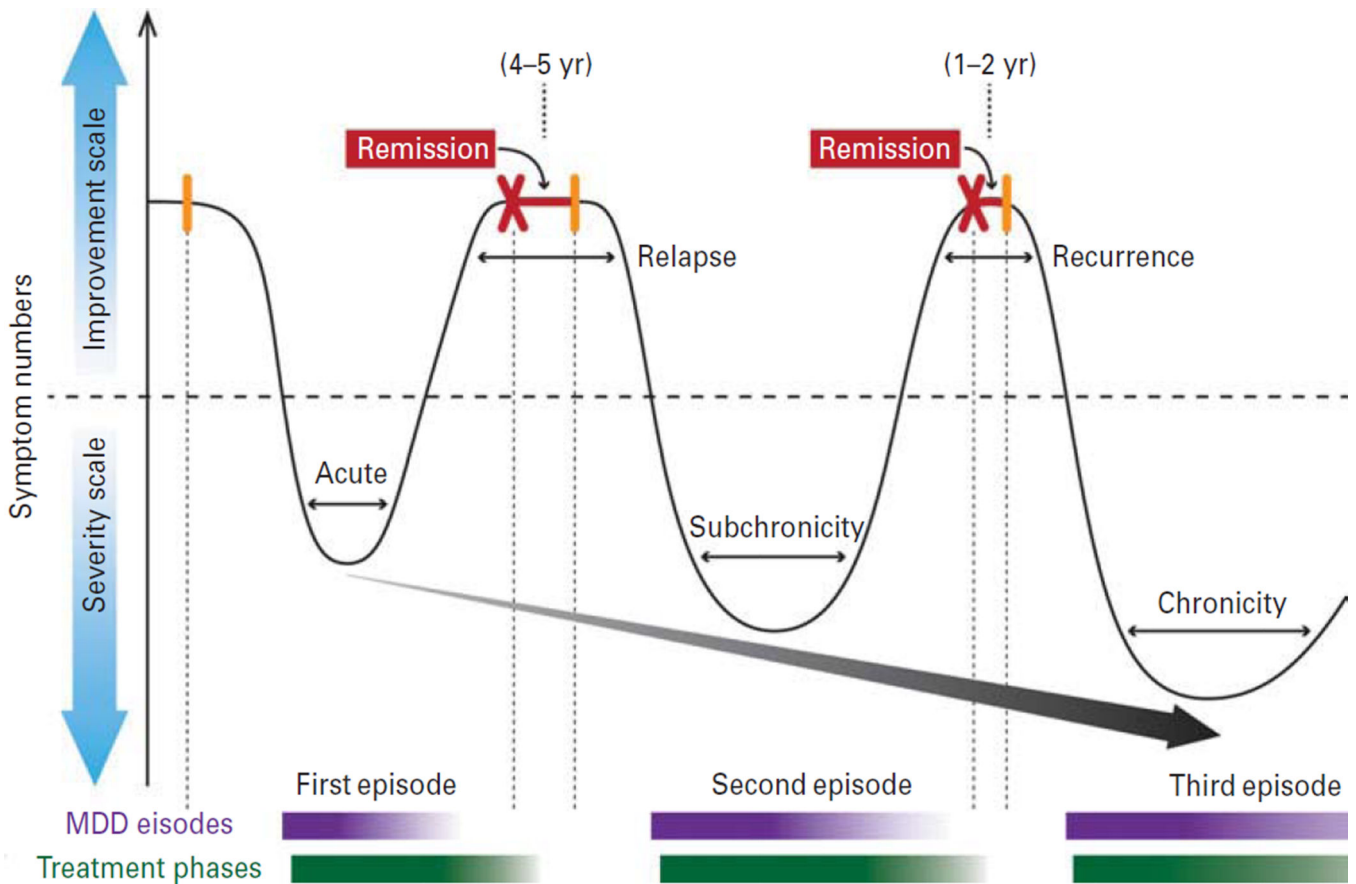
Fig. 1.

Schematic representation of a common trajectory towards chronic recurrent depression. Major depression frequently follows a lifelong and recurrent trajectory, with many features of a neuroprogressive disease, such as recurring episodes of increasing severity, reduced therapeutic response and shorter remission period. Depressive episodes are represented by the valleys in the curve (high on severity scale), whereas each peak represents periods of remission (high on improvement scale). MDD, Major depressive disorder.
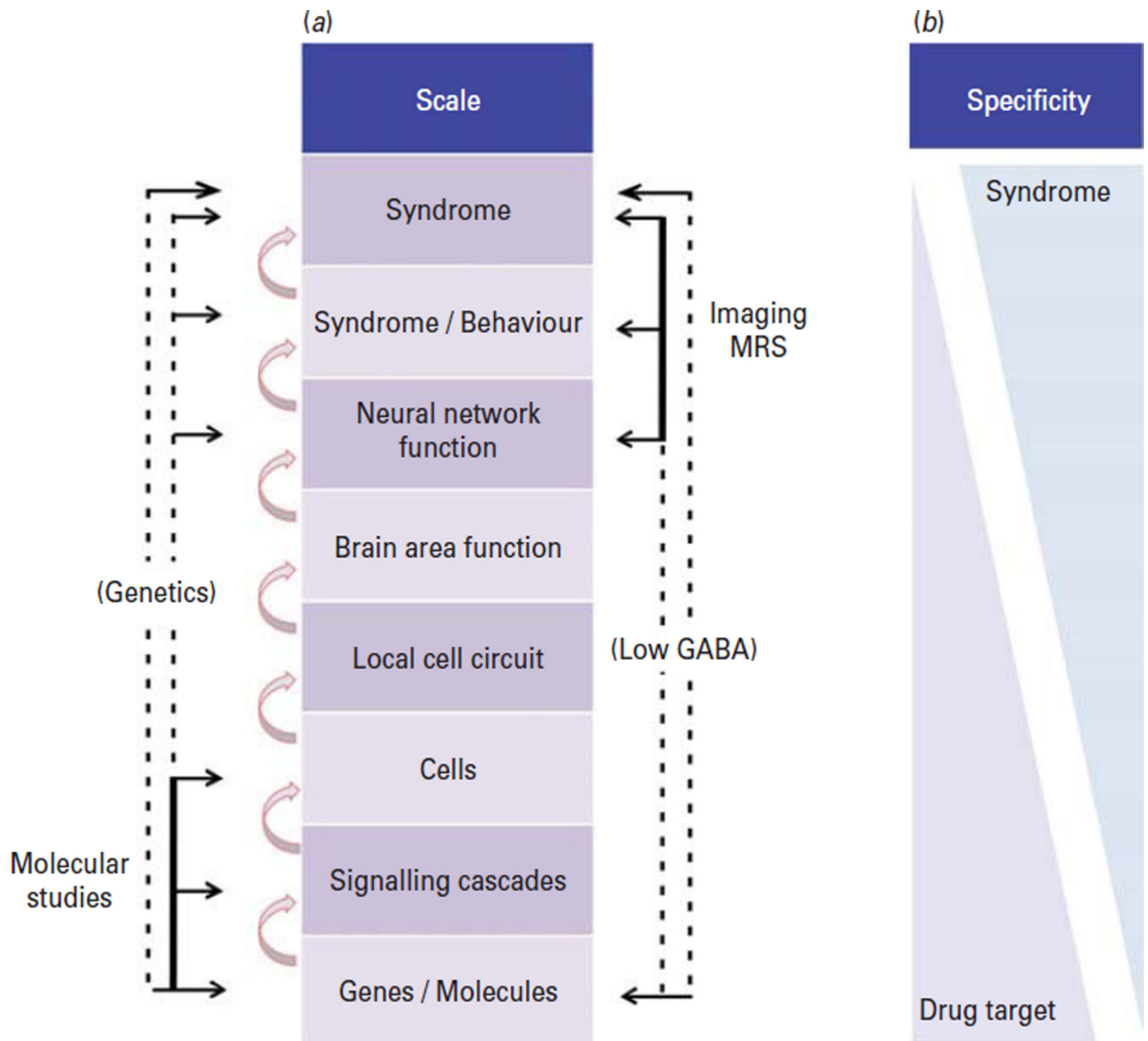
Fig. 2.
A multi-scale biological perspective on mechanisms of depression and its relationship to
specificity of drug treatment and diagnoses. (*a*) The functionality of complex biological
systems emerges from the integration of events occurring across hierarchical biological
scales, starting from the bottom with genes, molecules, cells, microcircuits, and neural
networks. Each scale depends on the function of level below, and determines the function of
the level above. Feedback and modulation occur across levels and from the environment
(not shown). Brain functions, behaviours, and endophenotypes emerge at the neural network
levels, which then define individual symptoms and syndromes. Molecular and brain imaging
studies investigate opposite ends of the spectrum (*b*) and can only speculate on mechanisms
underlying causal links between those opposite ends (dashed lines). More direct links are

provided by molecular genetics and imaging magnetic resonance spectroscopy (MRS) studies, but these studies do not inform on changes at intermediate scales. This results in inverse correlations between specificities of findings for disease and molecular/ pharmacological studies (*b*). Therapeutic drugs have high specificities for their molecular targets, but lowest specificities in terms of treating complex behavioural syndromes; conversely, imaging and associated studies have high syndromal specificity (due to the Diagnostic and Statistical Manual of Mental Disorders-based clinical diagnosis), but low molecular target specificity (due to low consideration of biological phenotypes in diagnosis). GABA, γ-amino butyric acid.
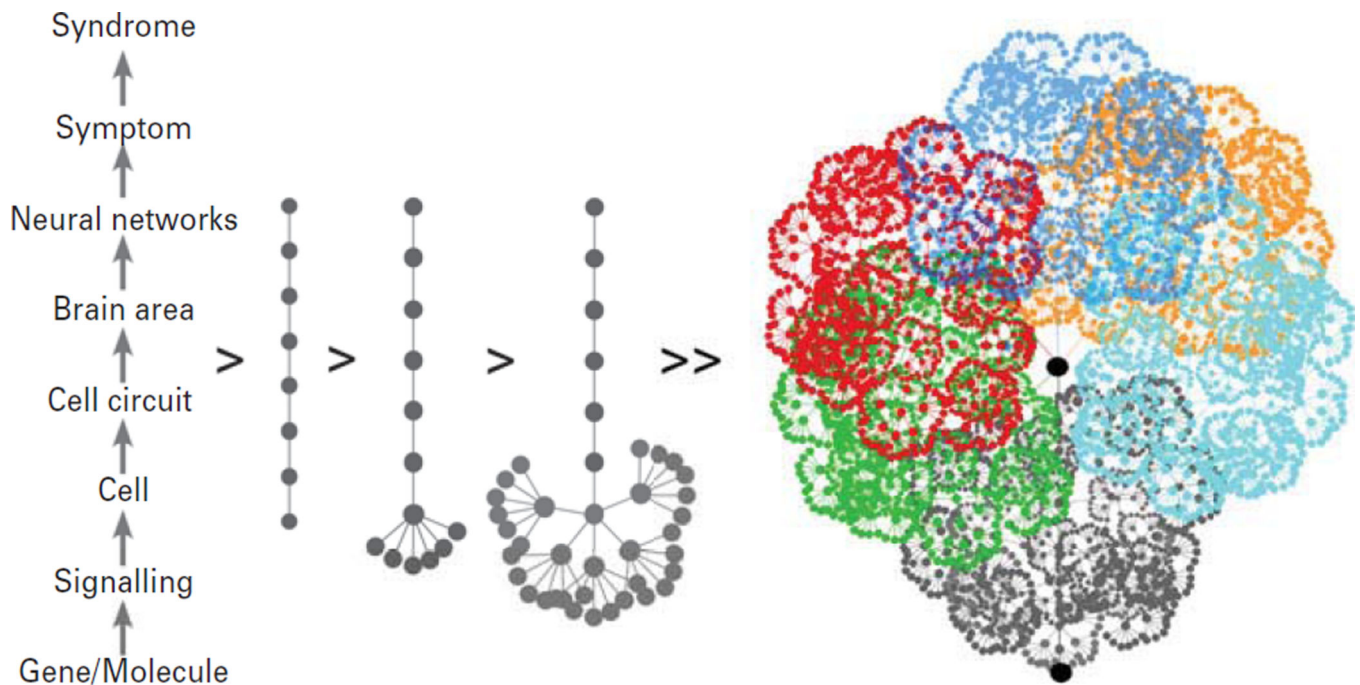
Fig. 3.

Complex biological pathways from gene to syndrome. In a linear gene-to-disease pathway (left), single genes code for syndromes in direct step-by-step upward trajectory, across all biological scales. However, in reality the biological complexity greatly increases with each higher scale. From the bottom-up, genes have multiple functions and coalesce in signalling pathways and structural entities in various combinations across cell types (left-to-right arrows). Cells assemble in local circuits, which are re-used, modified and repeated across brain regions. In turn, assemblies of these biological modules form the functional bases of brain areas and neural networks. The result is a massively interlinked and multi-scale network, whose output contributes to the expression of symptom dimensions, including mood, cognition and physiological changes in major depression (illustrated as various shades of colour). This redundancy in the use of genes and biological modules, combined with their putative distal impact on neural networks and putative symptom dimensions represents a core challenge in research on complex heterogeneous neuropsychiatric disorders, in which dominant roles of genes are rare and ambiguous, compared to neurodegenerative or peripheral organ diseases.
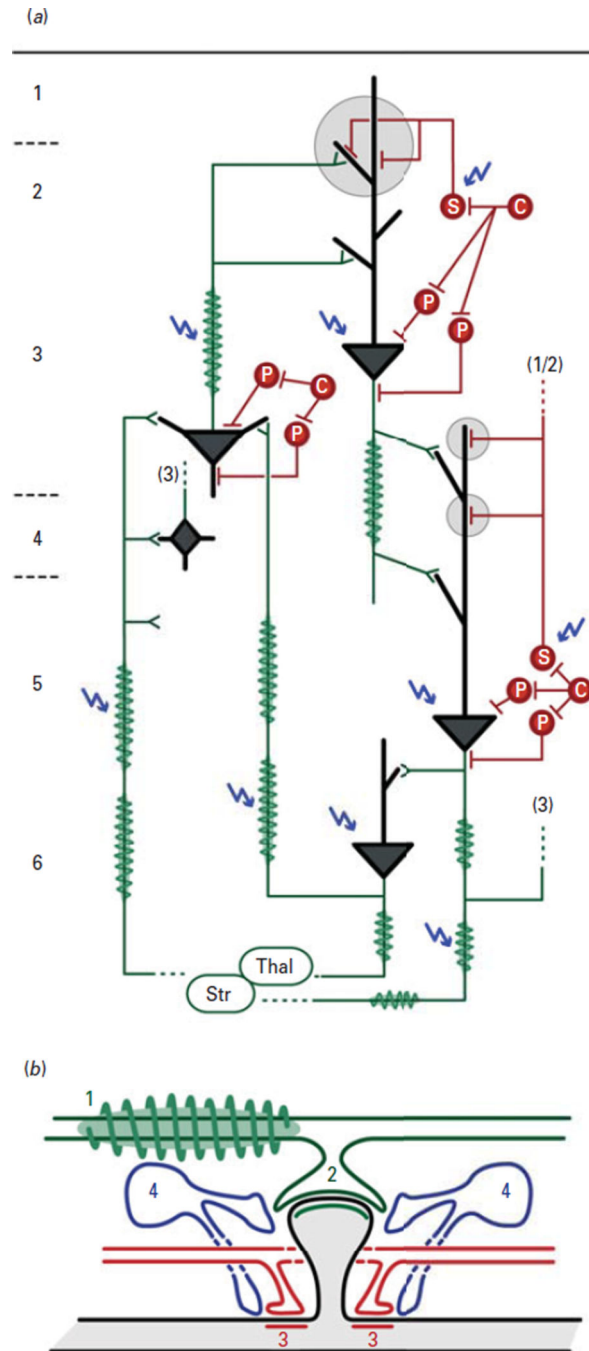
Fig. 4.

Local circuit summary of depression-related pathological findings in human post-mortem brain cortex. (*a*) Human post-mortem studies suggest reduced oligodendrocyte (green spindles) number and/or integrity, reduced size, density or altered dendritic branching of pyramidal cells (grey triangles) in layers 3, 5 and 6, and reduced number and/or functionally-altered calbindin/somatostatin (SST)-positive γ-amino butyric acid (GABA) neurons (S-labelled red circle and grey circles). Calretinin- and parvalbumin-positive (C- and P-labelled red circles) GABA neurons are mostly unaffected. A close-up schematic of

the large grey circle in (*a*) is shown in (*b*), representing synapses between an excitatory axonal terminal (green, with myelin sheath) and a GABAergic inhibitory terminal (red) onto a pyramidal dendritic spine (black). The close-up also depicts intercalated astrocytes (blue), which show evidence of deregulated function in depression. Sites of putative pathology are marked by blue arrows. The integrity of information transfer and processing, where 'information' is defined as excitatory output of pyramidal or principal cells, could be compromised at several levels: (1) decreased oligodendrocyte support of axonal function leading to suboptimal conduction of action potentials along the axon; (2) disruption of synaptic transfer of information, due to changes in the structure of pyramidal neurons and availability of glutamate; (3) suboptimal modulation or 'fine-tuning' of excitatory post-synaptic signals onto dendritic spines due to reduced SST-positive GABAergic dendritic targeted inhibition; (4) impaired astrocyte function resulting in decreased extracellular neurotransmitter clearance, affecting the homeostatic GABA/glutamate balance. Together, the various alterations may manifest as deregulated information transfer in corticocortical [thalamus (Thal)→layer 3/4→layer 5/6→layer 3], thalamocortical (Thal→layer 3/4→layer 5/6→Thal) and corticostriatal circuit loops within corticolimbic brain areas, leading to altered processing of emotion-salient information, and affect and mood symptoms. Structural variants of this schematic loop include lack of layer 4 in the anterior cingulate cortex and lack of cortical structure in the basolateral complex of the amygdala. Str, Striatum.