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SPECIAL ARTICLE

Medical models and metaphors for depression

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Background. The aetiology of depression is not fully understood, which allows many different perspectives on aetiology to be adopted. Researchers and clinicians may be attracted to concepts of aetiology that parallel other diagnoses with which they are familiar. Such parallels may assume the role of informal models or metaphors for depressive disorders. They may even function as informal scientific theories of aetiology, energising research activities by guiding hypothesis generation and organising new knowledge. Parallels between different types of disease may ultimately prove valuable as frameworks supporting the emergence and maturation of new knowledge. However, such models may be counterproductive if their basis, which is likely to lay at least partially in analogy, is unacknowledged or overlooked. This could cause such models to appear more compelling than they really are. Listing examples of situations in which models of depression may arise from, or be strengthened by, parallels to other familiar conditions may increase the accessibility of such models either to criticism or support. However, such a list has not yet appeared in the literature. The present paper was written with the modest goal of stating several examples of models or metaphors for depression.

Method. This paper adopted narrative review methods. The intention was not to produce a comprehensive list of such ideas, but rather to identify prominent examples of ways of thinking about depression that may have been invigorated as a result parallels with other types of disease.

Results. Eight possible models are identified: depressive disorders as chemical imbalances (e.g., a presumed or theoretical imbalance of normally balanced neurotransmission in the brain), degenerative conditions (e.g., a brain disease characterised by atrophy of specified brain structures), toxicological syndromes (a result of exposure to a noxious psychological environment), injuries (e.g., externally induced brain damage related to stress), deficiency states (e.g., a serotonin deficiency), an obsolete category (e.g., similar to obsolete terms such as 'consumption' or 'dropsy'), medical mysteries (e.g., a condition poised for a paradigm-shifting breakthrough) or evolutionary vestiges (residual components of once adaptive mechanisms have become maladaptive in modern environments).

Conclusions. Conceptualisation of depressive disorders may be partially shaped by familiar disease concepts. Analogies of this sort may ultimately be productive (e.g., through generating hypotheses by analogy) or destructive (e.g., by structuring knowledge in incorrect, but intellectually seductive, ways).

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Background

A scientific theory can be defined as a well-substantiated explanation of some aspect of the natural world that is acquired through scientific methods and repeatedly tested and confirmed through observation and experimentation (Anonymous, 2014*a*). Theories are animating and energising forces in research because they organise ideas and generate testable hypotheses. In medical research representations (models) of disease pathophysiology serve a similar purpose. In clinical practice, an understanding of pathophysiology is a component of the expertise that clinicians bring to their encounters with patients, helping to guide their decisions and facilitating communication about what has gone wrong when an illness occurs.

Although there are strong aetiological models for many diseases, psychiatric research has not yet established comprehensive scientific theories to explain the aetiology of depressive disorders, nor has a solid pathophysiological description emerged. This reality may reflect the complexity and multi-factorial aetiology of depressive disorders. Where detailed theories have emerged they have tended to focus on specific therapeutic modalities, such as the cognitive (Beck *et al*. 1979) or behavioural (Abramson *et al*. 1978) formulations.

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The term 'biomedical model' has been used to draw attention to an exclusion or devaluation of psychological and social factors in some aspects of psychiatric research (Anonymous, 2014*b*). In distinction, social psychiatry can be defined as a 'branch of psychiatry that focuses on the interpersonal and cultural context of mental disorder and mental wellbeing' (Anonymous, 2014*c*). Such models stand in contrast to the biopsychosocial model, a framework that encourages simultaneous attention to biological, psychological and social factors (Engel, 1980). However, whereas all of these terms convey ideas about what may, or should be, considered important, they do not resemble more compelling types of theories or models that can organise and integrate factual observations and generate specific testable predictions. They do not provide, in themselves, a satisfying explanation of why mood disorders occur.

From outside of the field of medicine, the biomedical model is often perceived as a 'dominant paradigm' of psychiatric research (Bennett Johnson, 2012). However, the term is less frequently used by biomedical researchers. A Web of Science search for articles with the phrase 'biomedical model' in their title (search conducted on October 24, 2014) yielded only 60 papers. These had attracted (at that time), in aggregate, less than 600 citations. The most highly cited paper was concerned with swine genomics and the 2nd and 3rd most cited ones discussed breeding and laboratory techniques for opossums. In contrast, a similar search for titles containing the phrase 'evidence-based medicine' yielded nearly 3000 papers, attracting approximately 30 000 citations. Yet, the framework of evidence based medicine is not a theory or model. It is a general approach to clinical practice, one that favours the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients (Sackett *et al*. 1996).

Some of the ideas that organise the thinking of depression researchers and animate their research activities may arise from informal models that are based, at least partially, on analogies to well-known disease processes. This idea cannot be decisively proven or disproven. However, it deserves to be articulated since such analogies may play a role in shaping the psychiatric knowledge-base. When models of depression are communicated to the public, they may tend to take the form of familiar disease-related scenarios. When decisions are made about research funding and acceptance of papers for publication, ideas that excite reviewers are likely to be the ones supported. Some such excitement may arise, at least partially, through models that arise as analogies or metaphors of familiar diseases. The goal of this paper is not to evaluate such models. The goal is simply to articulate these models.

Depression as a chemical imbalance

Many diseases are viewed as imbalances in allostatic or homeostatic physiological processes. Normal physiology includes countless examples of tightly regulated feedback loops and self-limiting processes. A good example is the regulation of thyroid and other endocrine hormones. A perturbation of regulatory mechanisms (e.g., due to a thyroid tumour that has escaped suppression or a thyroid gland unable to produce sufficient hormone despite maximal stimulation) leads to physiological imbalances that produce disease states (Larsen, 1982). Another example is Parkinson's disease, where motor symptoms are attributed to a dopamine–acetylcholine imbalance resulting from reduced striatal dopaminergic tone and subsequent cholinergic overactivity (Calabresi *et al*. 2006). This general idea of an imbalance between physiological processes that are normally (in health) tightly regulated may contribute to the popularity of the common metaphor of a 'chemical imbalance'. This particular metaphor has been criticised as representing something more akin to a cultural narrative than a theoretical driver of scientific thinking in psychiatry (France *et al*. 2007). It may be used by clinicians who feel that it reduces stigma (perhaps by diminishing any implication of moral responsibility for depression), although available evidence suggests that such explanations may actually be associated with increased stigma (Speerforck *et al*. 2014).

Depression as a degenerative condition

Many familiar diseases are degenerative, involving decline or deterioration. A classic example is osteoarthritis which is often viewed as a 'wear and tear' condition that involves degenerative changes in joints such as the loss of articular cartilage, development of osteophytes, etc. (Bennell *et al*. 2012). As a concept, degeneration is an emotive term. It is quite alarming to think about a disease process that involves tissue destruction.

A few authors have directly posited an effect of 'wear and tear' on mental health, e.g. (Charles *et al*. 2013). However, the concern most often expressed is that of neurotoxicity due to hypothalamic–pituitary–adrenal axis activation and leading to progressive processes associated with brain atrophy, particularly in the hippocampus (Sheline *et al*. 1996). Such degenerative processes are also viewed as possible links between affective disorders and dementia (da Silva *et al*. 2013). These ideas evoke powerful analogies. If

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anti-tumour necrosis factor biologic agents, for example, can prevent the progressive destruction of joints in rheumatoid arthritis (Taylor & Feldmann, 2009) can neuroprotective factors prevent the brain atrophy associated with depression (Boldrini *et al*. 2013; Ladea *et al*. 2014)?

Depression as an outcome of toxicity

A particular perspective on the idea of degeneration in depressive disorders is the idea that abnormal development or degeneration may be precipitated by a toxic exposure. The poisoning metaphor is a compelling narrative, perhaps rendered even more so by analogy to the many types of poisoning that are encountered in medicine. Needleman, for example, described the 'fourth stage' understanding of lead toxicity in children as the recognition (starting in the 1970s) that lead-exposed children with no history of acute toxicity had deficits in IQ scores, attention, and language (Needleman, 2004). Similarly, a 2012 technical report from the American Academy of Pediatrics (Shonkoff *et al*. 2012) referred to 'extensive evidence of the disruptive impacts of toxic stress, offering intriguing insights into causal mechanisms that link early adversity to later impairments in learning, behaviour, and both physical and mental well-being'. In alignment with the idea that stress can be a toxic exposure, depression was listed as an outcome of exposure to toxic stress, along with cognitive and language problems, similar long-accepted problems with lead exposure.

Depression as an injury

Although the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) has a general philosophy of avoiding incorporation of judgments about aetiology into its diagnostic criteria, the incorporation of aetiology into some definitions is inevitable. Indeed, one of the new DSM-5 chapters is that for trauma- and stressor-related disorders (American Psychiatric Association, 2013). This type of cause–effect relationship resembles that of an injury – damage done by an external cause. The intuitive appeal of reducing long-term impacts by effective acute care for injuries, extended by analogy to post-transmatic stress discorder (PTSD), may have contributed to the rapid uptake and prolonged persistence of critical incident debriefing, despite inadequate evidence for its effectiveness (and evidence of possible harmfulness) (Rose & Bisson, 1998). The idea of an injury due to stress has been extended to the domain of depression, manifesting for example as a lasting effect of psychosocial trauma on the brain, with reduced left hippocampal volumes following traumatisation in women (Vythilingam *et al*. 2002) or possible stress-sensitising (e.g., epigenetic or neurodevelopmental) effects of trauma (Taylor *et al*. 2004; McLaughlin *et al*. 2010*a*, *b*; Taylor, 2010).

Depression as a deficiency state

There are many familiar illnesses that result from a deficiency, either of a nutrient or of the internal production of a hormone. The idea that illnesses such as depression are due to a deficit in the production of a neurotransmitter has been, perhaps due to analogy, a very compelling idea. Within medical circles, this idea was popular in the 1960s and 1970s, with the monoamine theory of depression (Schildkraut, 1995). This model conceived of depression as a deficiency of one or more neurotransmitters. The metaphor was perhaps especially compelling as a result of the fact that many antidepressants increase synaptic levels of neurotransmitters involved in the regulation of mood. Another factor may have been the observation that mona-amine depleting drugs such as reserpine were purported to cause depression (Baumeister *et al*. 2003). This deficiency model is now rarely put forward in the medical literature; however, an internet search using the search term 'serotonin deficiency' produces thousands of hits, suggesting that the idea has persisted. There continues to be occasional reference to this idea in the scientific literature as well (Angoa-Perez *et al*. 2014).

Depression as a progressive disease

The idea of a progressive disease is another compelling idea. It is one that suggests a need for urgent intervention. Cancer is perhaps the classical example. Malignancies begin at a microscopic level and are often difficult to detect early. They may be more difficult to treat after they have progressed to more advanced stages. The idea of a progressive disease lends credence to efforts at earlier detection, including the idea that detection should ideally occur in presymptomatic stages of a disease. A model of depression as a progressive disease may explain persisting interest in screening for depression, even though evidence for the effectiveness of this strategy has generally been lacking (Linden & Vodermaier, 2012; Thombs *et al*. 2012).

It has become generally accepted that the majority of common mental disorders have their onset during childhood or early adulthood, e.g., 75% by age 24 (Kessler *et al*. 2005), which suggests that later

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presentations may represent advanced stages of a longstanding process. For example, Lin *et al*. (2013) posited that an initially non-specific clinical picture for severe depression is followed by a worsening of symptoms and subsequently by acquisition of new symptoms that occur together with progressive neurobiological changes until a clearly recognisable disorder appears. The analogy to cancer is made even more explicit in a quotation from this paper: 'the cancer analogy is useful here: minor surgery and local radiotherapy may be appropriate for early stages of breast cancer, whereas in later stages this would not be sufficient and more radical treatment such as mastectomy and chemotherapy might be indicated' (Lin *et al*. 2013).

The idea of depression as a progressive disease may also augment a current perception of the need for biomarkers for depressive disorders. Biomarkers may precede clinical symptoms and thereby facilitate earlier intervention (Owens *et al*. 2014).

Depression as an obsolete diagnostic term

There are examples in medicine of situations in which a primitive understanding of pathophysiological processes has led to inappropriate classification. Examples may be found in terms such as 'dropsy' or 'consumption' which became obsolete when more specific disease entities accounting for broadly defined clinical syndromes were described. Such conditions reflect diverse pathophysiological processes and their non-specific nature was an impediment to the selection of appropriate treatment and progress in research. If, by analogy, this applies to depressive disorders as currently defined, then deconstruction or elimination of existing categories may lead to more useful classifications. These historical scenarios resonate with discussions surrounding the emergence of alternative approaches to classification, such as RDoCs (Weinberger & Goldberg, 2014).

Depressive disorders as mysterious conditions waiting for a breakthrough

The most well-known version of this metaphor is peptic ulcer disease and the discovery of helicobacter pylori. Prior to this discovery, the aetiology of this condition was poorly understood and a variety of poorly replicated associations with aetiological factors had been reported. Everything changed with the discovery of this, previously unknown, determinant (Marshall & Warren, 1984). Similarly, the discovery of the role of human pappiloma virus in cervical cancer was a 'game changing' breakthrough (Walboomers *et al*. 1999). This virus is now regarded as a necessary case of most cervical cancers, guiding the field in a whole new direction for prevention (primary prevention through vaccination as opposed to reliance on secondary prevention through Pap tests). The idea that there may be a hidden secret to the aetiology of poorly understood conditions such as depressive disorders is perhaps made more compelling by these examples. Perhaps the best evidence of the power of this idea is the great interest in the microbiome as a determinant of depression and other common disorders (Foster & Neufeld, 2013). There is naturally a great excitement attached to the idea that a 'game changing' discovery might completely reorganise thinking about a mysterious condition such as depression.

Depression as an evolutionary vestige

Evolutionary models of depression are usually based on the idea that symptoms such as sadness or loss of interest have an adaptive role and that depressive disorders arise as dysregulated or malignant version of this, evolutionarily adaptive, response (Hagen, 2011). The adaptive mechanisms may include displays of emotion that reinforce social or parental connections, act as involuntary subordination strategies arising during social competition, or that may play a role analogous to physical pain in motivating avoidance of harmful situations (Hagen, 2011). Such strategies may have had an adaptive role during evolutionary history but may more often be maladaptive in the modern context. As with the other examples listed in this commentary, this concept aligns with other examples of disease pathophysiology. For example, the caecal appendix has often been regarded an evolutionary vestige that is nevertheless capable of producing disease. Recent insights into the function of the appendix as a well-adapted maintainer of mutualistic intestinal flora during intestinal infections (a 'safe house') have not challenged the idea that this function is largely obsolete in post-industrialised settings (Laurin *et al*. 2011). Related concepts may be found in the asthma and allergy literature, where the hygiene hypothesis posits that a mismatch between evolutionarily determined aspects of immune responsiveness and modern living environments may be partially responsible for epidemics of such illnesses (Eder *et al*. 2006; Brooks *et al*. 2013). Indeed, the hygiene hypothesis and its associated implications for inflammatory regulation have been invoked with reference to the aetiology of depressive disorders (Raison & Miller, 2013). Another example is obesity since adiposity may be understood as reflecting a 'thrifty genotype' that was adaptive in the evolutionary past or as a complex risk

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management system poorly adapted to contemporary social and economic environments (Wells, 2012).

Discussion

Because scientific theories are clearly articulated and lead to testable assumptions, they play an important role in the advancement of research, and ultimately in clinical and public health practices. Well established disease models may also assist clinicians with the selection and personalisation of treatment. Pathophysiological models can also effectively guide research. However, good theories and models depend on an advanced state of knowledge that has thus far eluded the sciences underlying much of psychiatric practice.

When they are not clearly articulated, theoretical ideas and models may nevertheless retain their influence. As the examples listed above may serve to illustrate, there are several ideas, empowered by parallels to other clinical conditions in medicine that may act as informal theories guiding psychiatric research and practice in particular directions. Their ability to impact on the emerging understanding of depression may unfold at many levels such as: the popular depiction of these disorders in media, the prioritisation of research funding and the selection of papers for publication through peer review processes. It is important to recognise that some of this influence may arise by analogy with other diseases. These ideas may take on greater intellectual weight because of their 'pedigrees' in the history of medicine rather than through their actual scientific promise or the weight of scientific evidence behind them.

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Conflict of Interest

None.

Ethical Standards

As a narrative literature review, this project did not require ethical approval.

References

Abramson LY, Seligman MEP, Teasdale JD (1978). Learned helplessness in humans: critique and reformulation. *Journal of Abnormal Psychology* **87**, 49–74.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, 5th edn. Washington, DC: American Psychiatric Publishing.

Angoa-Perez M, Kane MJ, Briggs DI, Herrera-Mundo N, Sykes CE, Francescutti DM, Kuhn DM (2014). Mice genetically depleted of brain serotonin do not display a depression-like behavioral phenotype. *ACS Chemical Neuroscience* **5**, 908–919.

Anonymous (2014a). Scientific theory 2014 [updated: 16 October 2014; cited: 24 October 2014]. Available from: http://en.wikipedia.org/wiki/Scientific_theory

Anonymous (2014b). Definition: 'biomedical model' 2014 [cited: 24 October 2014]. Available from: http://www.medilexicon.com/medicaldictionary.php?t=55643

Anonymous (2014c). Social psychiatry 2014 [updated: 30 January 2014; cited: 24 October 2014]. Available from: http://en.wikipedia.org/wiki/Social_psychiatry

Baumeister AA, Hawkins MF, Uzelac SM (2003). The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. *Journal of the History of the Neurosciences* **12**, 207–220.

Beck AT, Rush AJ, Shaw BF, Emery G (1979). *Cognitive Therapy of Depression*. Guilford: New York.

Bennell KL, Hunter DJ, Hinman RS (2012). Management of osteoarthritis of the knee. *British Medical Journal* **345**, e4934.

Bennett Johnson S (2012). President's Column. Medicine's paradigm shift: an opportunity for psychology. *Monitor on Psychology* **43**, 5.

Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H, Arango V, John Mann J (2013). Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. *Neuropsychopharmacology* **38**, 1068–1077.

Brooks C, Pearce N, Douwes J (2013). The hygiene hypothesis in allergy and asthma: an update. *Current Opinion in Allergy and Immunology* **13**, 70–77.

Calabresi P, Picconi B, Parnetti L, Di Filippo M (2006). A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *Lancet Neurology* **5**, 974–983.

Charles ST, Piazza JR, Mogle J, Sliwinski MJ, Almeida DM (2013). The wear and tear of daily stressors on mental health. *Psychological Science* **24**, 733–741.

da Silva J, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB (2013). Affective disorders and risk of developing dementia: systematic review. *British Journal of Psychiatry* **202**, 177–186.

Eder W, Ege MJ, von Multius E (2006). The asthma epidemic. *New England Journal of Medicine* **355**, 2226–2235.

Engel GL (1980). The clinical application of the biopsychosocial model. *American Journal of Psychiatry* **137**, 535–544.

Foster JA, Neufeld KAM (2013). Gut-brain axis: how the microbiome influences anxiety and depression. *Trends in Neuroscience* **36**, 305–312.

France CM, Lysaker PH, Robinson RP (2007). The 'chemical imbalance' explanation for depression: origins, lay endorsement, and clinical implications. *Professional Psychology: Research and Practice* **38**, 411–420.

Hagen EH (2011). Evolutionary theories of depression: a critical review. *Canadian Journal of Psychiatry* **56**, 716–726.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Ladea M, Bran M, Medrea M (2014). Brain derived neurotrophic factor levels and hippocampal volume in depressed patients treated with escitalopram. *Farmacia* **62**, 183–193.

Larsen PR (1982). Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormones. *New England Journal of Medicine* **306**, 23–32.

Laurin M, Everett ML, Parker W (2011). The cecal appendix: one more immune component with a function disturbed by post-industrial culture. *The Anatomical Record* **294**, 567–579.

Lin A, Reniers RL, Wood SJ (2013). Clinical staging in severe mental disorder: evidence from neurocognition and neuroimaging. *British Journal of Psychiatry (Supplement)* **54**, s11–s17.

Linden W, Vodermaier A (2012). Re-rethinking the article by Thombs and colleagues. *Canadian Medical Association Journal* **184**, 438.

Marshall BJ, Warren JR (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* **1**, 1311–1315.

McLaughlin KA, Conron KJ, Koenen KC, Gilman SE (2010*a*). Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychological Medicine* **40**, 1647–1658.

McLaughlin KA, Kubzansky LD, Dunn EC, Waldinger R, Vaillant G, Koenen KC (2010*b*). Childhood social environment, emotional reactivity to stress, and mood and anxiety disorders across the life course. *Depression and Anxiety* **27**, 1087–1094.

Needleman H (2004). Lead poisoning. *Annual Review of Medicine* **55**, 209–222.

Owens M, Herbert J, Jones PB, Sahakian BJ, Wilkinson PO, Dunn VJ, Croudace TJ, Goodyer IM (2014). Elevated morning cortisol is a stratified population-level biomarker for major depression in boys only with high depressive symptoms. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 3638–3643.

Raison CL, Miller AH (2013). Malaise, melancholia and madness: the evolutionary legacy of an inflammatory bias. *Brain, Behavior and Immunity* **31**, 1–8.

Rose S, Bisson J (1998). Brief early psychological interventions following trauma: a systematic review of the literature. *Journal of Traumatic Stress* **11**, 697–710.

Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996). Evidence based medicine: what it is and what it isn't. *British Medical Journal* **312**, 71–72.

Schildkraut JJ (1995). The catecholamine hypothesis of affective disorders: a review of supporting evidence. 1965. *Journal of Neuropsychiatry and Clinical Neuroscience* **7**, 524–533; discussion 3–4.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 3908–3913.

Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of C, Family H, Committee on Early Childhood A, Dependent C, Section on D, Behavioral P (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* **129**, e232–e246.

Speerforck S, Schomerus G, Pruess S, Angermeyer MC (2014). Different biogenetic causal explanations and attitudes towards persons with major depression, schizophrenia and alcohol dependence: is the concept of a chemical imbalance beneficial? *Journal of Affective Disorders* **168**, 224–228.

Taylor PC, Feldmann M (2009). Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. *Nature Reviews Rheumatology* **5**, 578–582.

Taylor SE (2010). Mechanisms linking early life stress to adult health outcomes. *Proceedings of the National Academy of Science* **107**, 8507–8512.

Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE (2004). Early environment, emotions, responses to stress, and health. *Journal of Personality* **72**, 1365–1393.

Thombs BD, Coyne JC, Cuijpers P, de JP, Gilbody S, Ioannidis JP, Johnson BT, Patten SB, Turner EH, Ziegelstein RC (2012). Rethinking recommendations for screening for depression in primary care. *Canadian Medical Association Journal* **184**, 413–418.

Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB, Bremner JD (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry* **159**, 2072–2080.

Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *The Journal of Pathology* **189**, 12–19.

Weinberger DR, Goldberg TE (2014). RDoCs redux. *World Psychiatry* **13**, 36–38.

Wells JCK (2012). The evolution of human adiposity and obesity: where did it all go wrong? *Disease Models and Mechanisms* **5**, 595–607.