EXPLAINING PSYCHOLOGY IN BIOLOGICAL TERMS

THE EVOLUTIONARY SCOPE OF DEPRESSION

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INTRODUCTION

"Everything is meaningless," says the Teacher, "completely meaningless!" What do people get for all their hard work under the sun? Generations come and generations go, but the earth never changes. The sun rises and the sun sets, then hurries around to rise again. The wind blows south, and then turns north. Around and around it goes, blowing in circles. Rivers run into the sea, but the sea is never full. Then the water returns again to the rivers and flows out again to the sea. Everything is wearisome beyond description. No matter how much we see, we are never satisfied. No matter how much we hear, we are not content.
History merely repeats itself. It has all been done before. Nothing under the sun is entirely new. Sometimes people say, "Here is something new!" But actually it is old; nothing is ever truly new. We do not remember what happened in the past, and in future generations, no one will remember what we are doing now (Holy bible, New living translation, Ecclesiastes 1:2-11).

Isn't this depressing? Everything is meaningless. What is the meaning of life on earth in itself? Of working hard and die? Of doing the dishes, paying the bills, cutting your hair, thinking you make progression but it all gets undone again. It is circular, like the way of the sun, the wind and the rivers. Life is not forward linear progression. People try to find routine and search for values, purpose and joy. People want to be powerful, rich, important, loved, and famous - though actually most of them only make the newspaper when they get born or die. In the middle of their life, they are completely ignored unless they do something catastrophic -. Life is not perfect. And every generation has its own way to cope with crookedness of life. Today, we know better than the generations before. We are finally here, evolution has its peak. People are more wealthy, affluent, educated and successful than ever. Though on the other side, divorce has tripled and depression is epidemic. Why?
In this essay I want to focus on depression; affecting over 300 million people today and the cause of a full 10% of lost productive years. According to the World Health Organization depression affects everyone, independent of gender, age, class, culture and; by 2020 depression will be the leading cause of disease burden worldwide, after ischemic heart disease (1, 2).

Table 1. Diagnostic Criteria for Major Depression
Depressed mood
Irritability
Low self esteem
Feelings of hopelessness, worthlessness, and guilt
Decreased ability to concentrate and think
Decreased or increased appetite
Weight loss or weight gain
Insomnia or hypersomnia
Decreased interest in pleasurable stimuli (e.g. sex, food, social interactions)
Recurrent thoughts of death and suicide

A diagnosis of major depression is made when a certain number of the above symptoms are reported for longer than a 2 week period of time, and when the symptoms disrupt normal social and occupational functioning (3).

Nowadays depression is seen as a syndrome rather than a symptom and its definition covers a variety of negative mood and negative affect. The official diagnosis rests on the

identification of a variety of symptoms which impair the functioning of an individual for certain duration of time, (Table 1 (3)). This symptom based diagnosis gives heterogeneity of clinical presentations and can be an obstacle for the interpretation of genetic studies, neuroimaging or post-mortem investigations which rely on the presence of psychological and behavioural symptoms alone and not on aetiology (4, 5).

Three major causes are defined for depression: genetic predisposition, biochemical imbalance and environmental causes; respectively blaming faulty genes, a decreased number of neurotransmitters in the brain or factors in the physical or social environment of the person. Though another explanatory theory is arising, combining psychiatry with evolutionary biology, arguing that depression can best be explained as "an adaptation mechanism which human beings have developed over time to deal with certain unpropitious situations" (1). For diseases are not shaped by evolution, though the body is and aspects of the body need an evolutionary explanation of why it is vulnerable to diseases.

In this essay I want to look at the evolutionary perspective on depression and the value of such an explanation. Therefore in first chapter I have to look into the being of depression in biological terms first. Then try to identify the possible evolutionary explanations, the so-called socio-biology. Chapter 3 provides some thoughts about the biggest difficulty in evolutionary explanation for depression, which is suicide. This is viewed within the scope of Western society. At last, the use of an evolutionary perspective will be discussed.

1. NEUROBIOLOGY OF DEPRESSION

There is still a rudimentary knowledge of the neural circuitry in mood conditions. It is likely that different brain regions mediate different symptoms of a negative mood in depression. Normal brains and the brains of depressed persons show structural changes within the neuroanatomical circuitry, revealed by post-mortem studies and neuro-imaging studies.
The function of the affected regions - prefrontal and cingulate cortex, hippocampus, striatum and thalamus – relate to the different phenotypic aspects of depression. For example, the neocortex and hippocampus mediate cognitive aspects as memory impairments and feelings of guilty, worthlessness and hopelessness. Sheline *et al.* put all hypothesized interacting factors in depression in a figure. Beside stress, many comorbid illnesses are associated with structural brain changes as seen in depression; like Parkinson, Alzheimer's disease and stroke. The dotted arrow represents the contribution of depression to volume changes in the brain. It is not clear if this is an independent contribution, or even if the converse is true; how brain changes might induce depressive symptoms. Also brain signature differs from patient to patient (6).

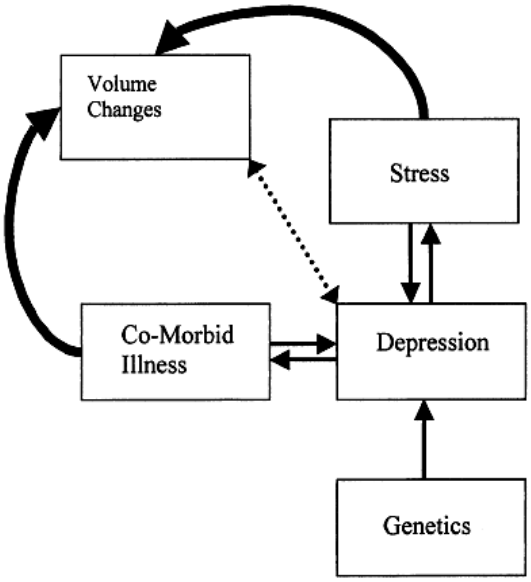

Fig 2. Hypothesized interacting factors in depression (7).

Deregulation of the hippocampus and the Hypothalamic-pituitary-adrenal axis

Early clinical studies show small increase in glucocortoid concentrations in depression. This finding raised interest in the role of the hypothalamus-pituitary-adrenal (HPA) axis in the pathophysiology of depression. An excess of glucocorticoids, induced by physiological or psychological stress, reduces activity of the subgranular zone (SGZ) in the hippocampus where adult neurogenesis occurs. This might contribute to hippocampal volume reductions observed in patients with depression (4, 7). Although the precise nature of this damage is not completely understood this might involve reduction of dendritic branching and loss of specialized dendritic spines, where glutamatic synaptic input is received. Yet, studies examining this hippocampal stress-atrophy hypothesis have found less apoptotic cells and stress markers than expected (8). Therefore decreased afferent synaptic innervation/activity seems to be more plausible than presynaptic pathology (8, 9).
The activity of the HPA axis is controlled by several brain pathways. The hippocampus exerts an inhibitory influence on the hypothalamic corticotropin-relasingfactor (CRF)-containing neurons in the paraventricular nucleus (PVN) of the hypothalamus. This effect is exerted indirectly via the polysynaptic circuitry, while the amygdala has a direct excitatory role. Neurons in of the hypothalamus secrete this CRF which subsequently stimulates the production of adrenocorticotropin (ACTH) from the anterior pituitary. The ACTH is responsible for stimulating synthesis of glucocorticoids from the adrenal cortex. Glucocorticoids exert their feedback on the HPA-axis by regulating the PV neurons.
Current hypotheses about the contribution of a hyperactive HPA-axis to depression focus on the role of cortisol and CRF and there is a strong case for limiting hypercortisolism as antidepressant treatment (3). CRF is critical in mediating emotional memory to aversive as

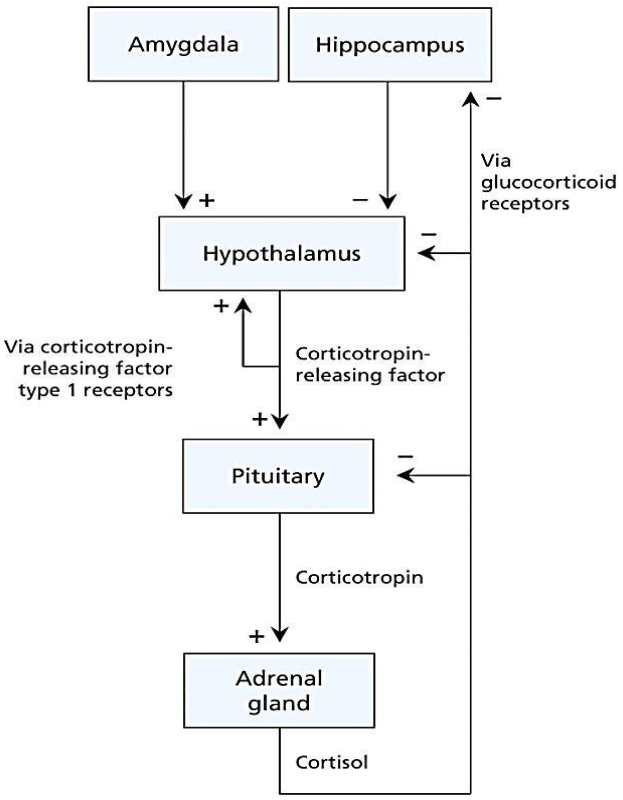

Figure 1. The hypothalamic–pituitary–adrenal axis. Structural changes in the brains of patients diagnosed for depressive disorder attribute to a disturbed function of the HPA-axis. Hypercortisolemia induced by chronic stress, leads to the downregulation of glucocortoid receptors in the hippocampus (19).

well as rewarding stimuli. High, and in particular chronically high, levels of cortisol can be toxic to hippocampal neurons. Because of its inhibitory function towards the HPA-axis, hippocampal loss of function increases circulating levels of glucocorticoids. Both the impaired negative feedback of the glucocorticoid-receptor and adrenal hyper-responsiveness from the adrenal gland to circulating ACTH might further contribute to hypercortisolaemia in depression, FIG 1 (10, 11).

Endogenous neurogenesis in the hippocampal dentate gyrus and its connection to depression-related phenotypes have been the subject of intensive research (12, 13). Preliminary data suggest that enhancing hippocampal neurogenesis, pharmacologically or by cellular transplantation could be interesting for antidepressant therapies (14-16). Reductions in hippocampal proliferation can be interpreted as a marker of its plasticity. Plasticity is affected at least in some types of depression (12), though a model of hippocampal degeneration as base of depression and a road to remission by neurogenesis might be over-simplified (17).

Impairment of neutrotrophic mechanisms

Another factor related to depressive disorders is the Brain Derived Neurotrophic Factor (BDNF). This factor regulates survival and maturation of neural cells during development, not only cell-growth but also changes in synapses between neurons and synaptic plasticity throughout life by activating DNA-binding factors and stimulating gene transcription. For instance genes involved in serotonin function like the serotonin transporter and tryptophan hydrolase (18, 19). Normally serum levels of BDNF are negatively correlated to sensitivity to stress and positively to brain levels of *N*-acetyl-aspartate (20). BDNF, next to fibroblast growth factor and vascular endothelial growth factor, is at least in part causative of cognitive impairment and hippocampal atrophy in depression. Modulating these factors appeared to mediate reduction of hippocampal neurogenesis rate, atrophic changes and declined plasticity of synapses of hippocampal neurons and may further contribute to a compromised function of the HPA-axis (12, 21).

Also levels of BDNF are moderately increased with enhanced glutamate signalling, one of the amino-acid neurotransmitters, in response to acute stress. In periods of chronic stress, *N*-methyl-D-aspartic acid type glutamate receptors on both neural and glial cells, increase intracellular calcium levels and lead to a decreased BDNF level, inducing atrophy and cell death. Glial cells normally inhibit the toxic build-up of glutamate. Glial cell death then leads to further disruption of the glutamate system (22, 23). The role of the neurotrophic growth factors and especially its extra-hippocampal and downstream signalling pathways needs more understanding for it can be a target in chemotherapy (12, 24, 25).

Impairment of the brain reward pathways; dopamine

Neurons in certain brain structures carry specific signals about past en future rewards. Subcortical regions in the brain, the nucleus accumbens (NAc) and the striatum are critical for reward and appetitive behaviour (3, 26). The NAc, target of the mesolimbic dopamine system provides dopaminergic input from the ventral tegmental area (VTA) of the midbrain. The VTA neurons innervate other structures, including the amygdala and limbic regions of the neocortex (3, 26). The mesolimbic system is associated with rewarding effects of food, sex, drugs or even abuse (27). It is likely that similar mechanisms in the VTA and NAc mediate the response to natural reinforcers under normal conditions as well as under pathological conditions like overeating, gambling etc.
Cell bodies of dopamine neurons are mostly located in the substantia nigra and the VTA. Their axons project differentially to the striatum (the caudate nucleus and putamen), the ventral striatum, the NAc and areas of the neocortex i.e. the prefrontal cortex. Under basic conditions, dopaminergic neurons in the VTA oscillate between tonic and phasic bursts of action potentials following actual and predicted rewards. This reward response is graded in magnitude by the responsiveness of individual neurons and the fraction of neurons responding (27, 28). In rodents the long-term administration of antidepressants reduced the firing rate of dopamine neurons in the VTA region, also physiological stressors are shown to increase NAc dopamine levels (12, 29-31). The NA, which integrates reward related dopaminergic signals as well as glutaminergic input form the prefrontal cortex, hippocampus and amygdala, showed to be changed by stress and antidepressants. This change occurred via the modulation of key proteins as cAMP response element (CREB), dynorphin, BDNF, MCH, or Clock (12, 26). CREB activity is observed to be modulated by various stressors and related to anxious behaviour or anhedonia (26, 32). At last neuroimaging studies in depressed patients show an association between reduced NAc's volume and anhedonia and hypoactivation during tasks of incentive reward (33, 34).

Heritability

A relationship between genes and susceptibility to depression has been expected on the basis of family and twin studies (35). Genetic polymorphisms influence a person's risk for depressive disorder by changed expression of a gene-product; for example of production of growth factors that act in the brain or genes influencing neurotransmitter action or genes that interact with environmental factors.
Techniques used in the research of genetics of depression are candidate gene studies, linkage studies and genome-wide association studies. Linkage studies are mostly based on pedigrees with a clear pattern of Mendelian inheritance, though this is not really the case for depression. Still, a few notable linkage studies have been published, well-reviewed by Levinson in 2006 and Shyn in 2010 (36, 37) including a range of major phenotypes and varieties.
As an alternative to linkage studies, in association studies the frequencies of specific alleles are investigated for being enriched in one group versus another. Genes then are chosen for their location within a linkage peak; often these are related to monoamine signalling, neurotrophins, neuroendocrinology and or immunology/inflammation. Several recent publications on candidate gene studies show that there a hundreds of them, including the polymorphism in the apolipoprotein E (APOE), variants in the guanine nucleotide-binding protein β3 (GNB3), the methylene tetrahydrofolate reductase (MTHFR) and the polymorphism in the promotor region of the serotonin transporter SLC6A4 (38). APOE is also the locus known for susceptibility for late-onset Alzheimer's disease. The problem with candidate gene studies is that they have yielded few solidly replicated findings, which even do not have a clear mechanistic connection to depression; like APOE, GNB3 and MTHFR(39). Further they only bestow upon very small amounts of risk in predisposition to depression.
Genome wide association studies in contrast are a better method to find multiple variants with modest effect which are relatively common in the normal population. Genotyping technologies have improved the last couple of years and hundreds of thousands to a million

of bi-allelic SNP's can be checked out throughout the genome. For major depressive disorder there are four GWAS described (36, 40).
Because epidemiological studies have shown that suicidal behaviour is partly heritable association studies between suicide and genes were also performed. Various markers are located within serotonergic genes (36, 41-44), though replication studies are needed. GWA studies did not uncover really strong and consistent risk modifiers yet. Part of the reason for this might be the heterogeneity of phenotypes in depressive disorder.

Genes and environment

Gene environment interaction might explain why some individuals become depressed and others do not. Genetics only explain part of the depressive phenotypes. Some think gene-environment interactions predict the risk of major depressive disorder better than one of the gene variations itself. The challenge is to set up a multifactorial design which enables us to integrate environmental factors, and those should be jointly assessed. One example of genetic-environmental interaction is the finding of Caspi *et al.* in 2003. They found an abbreviation of the 5HTTLPR gene that increased the possibility that stressful life events could cause major depression (45). Subsequently a SNP in the CHR1 gene, coding for corticotropin releasing hormone receptor was related to child hood abuse, and a SNP in BDNF coding region was connected to early life stress (46, 47). Interaction studies are still few in number; it is difficult to standardize and quantify disparate life stress and test multiple-hypotheses (48).
Another way of understanding how genes interact with non-genetic factors is provided by epigenetics. For slow progress of identifying genetic risk factors, dissimilarities of depression between monozygotic twins and the fact that females seems to be more prone, epigenetics might explain these variability (12). Epigenetics are all factors that modify the DNA directly, via methylation, histone acetylation or non-coding RNA's regulating gene expression or via interaction with transcription factors or polymerases altering the mRNA level (49, 50). An epigenetic profile for depressive disorder would give insight in how genes interact with non-genetic factors, e.g. environmental stress. Some epigenetic processes have been linked to depression. Increased methylation of the glucocortoid receptor gene would influence the corticosteroid stress response, early life stress causes hypomethylation of the arginine vasopressin gene and socially defeated mice show increased histone acetylation at various BDNF promotors (50-53). However, it is not easy to explain epigenetics into clinical phenomena. Some epigenetic changes are tissue specific or affect enzymes which occur in several isoforms. A new direction in the field focusses more on chromatin regulation instead of examining candidate genes (12, 54, 55).

The mono-amine hypothesis

The monoamine theory of depression proposed that a deficit of certain neurotransmitters is responsible for different features of depression. As many antidepressant drugs, which increased synaptic levels of mono-amine neurotransmitters serotonin, dopamine, norepinephrine and epinephrine, where shown to improve the mood and consent of patients with depressive disorder, it was concluded that the deficit of mono-amines might be low because of, or result in, depression or that there is a third factor responsible for both lowered synthesis rate and depressive symptoms (18, 56).
But not all the serotonergic and noradrenergic drugs are effective and sometimes there is only a gradual clinical response while rapid increase in monoamine availability (57, 58). It is observed that monoamine reuptake inhibitors and other medicines modulating monoaminergic function improve symptoms of only 50% of depressed patients. Also serotonin reductions do not induce depression in all people as some individuals without family history of depression tend not to show differences in mood after tryptophan depletion.
The monoamine hypothesis is weakened after a decade of PET studies to quantify receptor and transporter numbers, monoamine depletion and genetic association studies and the mechanism of action of treatment might not be the opposite of disease pathology per se. This

contradicts the originated public misconception that depression is a chemical imbalance per se (12, 59).

2. EVOLUTIONARY HYPOTHESES TO DEPRESSION

The year 2009 was the 150th anniversary of the publication of Charles Darwin's *On the Origin of Species*. Today his (r) evolutionary approach to selection and animal behaviour is extended to psychiatry. Evolutionary psychology seeks to find how depression may have been a beneficial adaptation in evolution to improve the fitness of individuals or their relatives. An ethological approach to study animals' behaviour in its individual, social and environmental world could be useful in psychiatry, for there are close analogies between human and non-human behaviour. For example, one of the most widespread avoidance behaviours is anxiety; the presence of fear allows modulating between exploration and protection. And neurological or neurochemical substrates of anxiety are similar in a wide range of species (60). Other defending strategies as withdrawal, immobility, aggression and deflection of attack are common across vertebrates. And here the same mammalian structures in the brain are involved as in the human; the limbic system, basal ganglia, hypothalamus, brain stem and cerebellar nuclei (60, 61). Jones *et al.* concluded from this an evolutionary approach to behaviour, where normal survivor behaviour and inappropriate adaptive behaviour lie within a spectrum, Fig 3 (60, 61). Seeking for Darwinian explanations for depression can be useful. If negative mood states are ubiquitous in all kinds of species, they are an appropriate target for evolutionary analysis. Furthermore their output is characterized by complex but coordinated behaviour and conscious experiences.
According to evolutionary biologists, physiology provides medicines based on an integrated understanding of structure and function, but by sticking to the proximate approach we forget the other half of biology, seeking for evolutionary explanations. It gives insight into why people experience depression. If their depressive state evolves as a response to certain adaptive problems in evolutionary history this might have an adaptive function (62).

Normal Including survival and maintenance behaviours		**Stage of biological development**		**Abnormal Including excessive/ inappropriate adaptive behaviours and pathological distortions of behaviour**
		Genetic coding		
		↓		
Normal physical and psychological development	←	Neural and muscular development	→	Intellectual and behavioural disabilities
		↓		
Survival behaviours given appropriate environmental releasers	←	Dispositions to particular behaviours, other learning*	→	Abnormal survival behaviour (e.g. anxiety, paraphylias, abnormal social behaviour such as attention seeking, aggression)
		↓		
Planned survival strategies (cognitive maps)	←	Consciousness of behaviour and environment, other learning	→	Abnormal strategies (e.g. obsessive, borderline personalities involving abnormal cognition)
		↓		
Augmented and directed behaviour	←	Will, affect other learning	→	Abnormal affective and volition behaviour (e.g. depression, schizophrenia)
		↓		
Abstract maps	←	Abstract, cognitive systems	→	Delusions

* Associative and non-associative learning occurs throughout evolutionary development and is influenced by memory.

Figure 3. Evolutionary approach to behaviour, showing the normal and abnormal consequences that follow increasingly complex biological development (71).

This function can be isolated and give a new type of explanation of depression which is rooted in the lives of the ancestors. Secondly, it challenges the traditional view that depressive states are associated with dysfunction (63). Probably it provided some reproductive benefit in some situations. Finally, the Darwinian framework gives a broader view to psychological phenomena en new hypotheses to test (64). Because if depression was only pathological and a harmful state, it would have been gradually selected out of the human gene pool in time. Further, not all depressive episodes are clearly linked to life events; they must be adaptations rather than defences, like fever is a defence against infection and pain against tissue damage (1, 72). Strengths of the evolutionary approach are that in the inexact science of mood disorders the evolutionary hypotheses gives at least an explanation for the range of symptoms, for the overlap between emotive states of mood, grief, guilt etc. Second, this explanation fits the modern view on the relationship between health and disease; diseases that persist as the result of evolutionary compromises.

Evolutionary explanations of clinical depression

1. *Theories of resource/energy conservation*

Theories about the conservation of resources are based on the observed low levels of energy and loss of pleasure and appetite. It allows an individual to conserve his resources for redirecting them to more productive endeavours later on. The depressive mood state could then be activated by the feeling of insufficient positive reward of helplessness, as seen with animal exhibiting helpless behaviour when subjected to uncontrollable events (65). Nesse argues in his resource allocation model that depressive mood causes to inhibit investments in so-called 'poor pay-off activities'. People prone to depression often tend to invest in unobtainable goals. When the goal is not reached the incentive and motivation are lost as well (66, 67).

Prolonged anhedonia is also called analytical rumination. When depression is triggered by complex problems extensive analysis of the problem is required, diverting time and cognitive resources away from daily activities. A depressed person can ruminate extensively about his life problems. Depression promotes analytical thinking by activating the left ventrolateral prefrontal cortex which increases attention control and maintains the active 'working memory'. Though there is no evidence they perform better in reasoning tasks (68, 69).

2. *The social competition theory*

As seen in marsupials, some depressive syndromes might occur after a loss of dominance. This led to the social competition hypothesis of depression (70, 71). A central claim in the theory is that position or ranks within a social group determine the individuals' access to reproductive resources. Status is acquired in competition with others (72). According to the social competition hypothesis major depression is an 'involuntary subordinate strategy'. If an individual in a social group is losing in a lengthy fight for dominance, depression causes him to back down. It functions to create a subjective sense of incapacity which limits aggression towards higher-ranked people. In this way the individual is protected from unnecessary harm and the social hierarchy is maintained. The ranking theory seems attractive since depression is associated with the strong feeling of powerlessness, loss of control, entrapment and defeat (70, 73-77). But there are some difficulties about the social competition theory. First, depressive episode are known to last for months, while the best way to avoid harm is to yield quickly. So, a depressed mood might be a pathological failure to yield or due to continued uncertainty about the best course of action (69, 74). Second, this theory has little to say about suicide. Why would submission to dominants, which protects a person from harm, be associated with thoughts of killing oneself? And a last remark is about the association of depression with adversity; for example the loss of a loved one has nothing to do with rank (69).

3. *The social risk hypothesis*

Quite similar to the rank hypothesis is the social risk hypothesis. Fighting and competition might not be the most effective strategy for humans as is for other primates and competition

in a social group is not only settled with aggression. This traditional behaviour is replaced by an individuals' ability to elicit help from others through attraction, so it's about social approval instead of dominance contests (64). Gilbert *et al.* wrote about this in their notion of Social Attention Holding Power (SAHP) which refers to the ability to elicit attention and social rewards like acceptance, respect and admiration (78). Depression therefore might be a response to loss of approval, support and respect. It reduces tension between group members and secondly might serve as signal of an individual's need for aid or desire to restore social bonds (64). These social bonds are critical for maintaining fitness prospect. And perceived threat of exclusion from the community might lead to this adaptive response (64).
The hypothesis was inspired by animals' behaviour of risk-sensitive foraging and translated to social risk-taking in humans. As energy reserve threshold influences a choice of foraging, low mood reduces social risk-taking (66, 69, 79). But again there are some difficulties with this hypothesis. It is observed that animals in poor conditions take more risks, which creates the possibility to exceed their low energy threshold. This risk seeking behaviour might reflect manic states in people, in response to social adversity (80, 81). And depressed people work and parent less which means a reduction in critical social relationships (69, 82). Also the hypothesis does not explain how suicidality emerges from risk-aversion and rather is a function or dysfunction of the system (69).

4. *The attachment theory of depression*

Attachment theory describes the dynamics of long-term relationships between people and the proposed consequences of affective bonding on the fitness of an individual; for "mate retention, reciprocal dyadic alliance formation and coalition building are among the principal social selection pressures that have shaped human evolution" (64, 72). The development of a child's attachment patterns is highly influenced by its parent's relationship. Their responses influence its perception, emotions and expectations in later relationships (83). The attachment style, which depends on personality traits and relation characteristics, seems to be associated with stress response including bereavement reactions. Only 10-20% of people coping with loss are fraught with difficulties; feelings of anger, bitterness and resistance to accept a new painful reality with loss of interest in on-going life, according to Hofer's model of attachment, loss and complicated grief (84). Depression then is maladaptive sadness and might sometimes be a distortion in cognitions about the self or childhood problems (85, 86). For psychiatrist John Bowlby grief is a by-product of attachment mechanisms. Sadness is rooted in the child-mother relationship, seen in numerous species. It is an evolved reaction to loss, like the separation from a mother/ primary caretaker; it served to re-establish the physical proximity and care (85, 87, 88). Hypotheses concerning the adaptive function of depression suggest that it "inhibits exploratory or risk-laden activities in the absence of secure attachment bonds, and instigates appeasement-related behaviours designed to maintain relationships". The depressive response can serve as a distress call, provoke a search for the lost relationship or motivates the sufferer to avoid further deterioration of pre-existing bonds' (64). Childhood adversities indeed have been associated with adult psychopathology, though parental losses as in divorce of death of one of the parents only have modest association with adult mood disorder. Also, grief after the loss of a loved one cannot serve to re-establish proximity (69, 89).

5. *The social navigation hypothesis*

The Social Navigation Hypothesis (SNH) actually combines the theory about energy conservation with the social risk hypothesis. It suggests that depression is associated with social problems and conflicts and functions to perform two complimentary problem-solving functions. The first function is social rumination and refers to the induction of cognitive changes that change an individual's capacities enabling accurate analyses and solutions of social problems (90). When social problems are too complex it is likely to shut down hedonic interest or cognitive resources on physical activities in order to focus with all energy on the social matter at hand (64, 90). The second function is called the social motivation function; the costs associated with the anhedonia and psychomotor perturbation of depression can persuade reluctant social partners to provide help or make concessions towards the

depressive (90). The two mechanisms for social motivation are honest signalling and passive, unintentional fitness extortion. Publicly displayed symptoms of depression like the reduced ability to conduct basic life activities, in the first place function as a signal, a serious cry-for-help, thereby motivating people with a positive fitness to provide such. Though, it is likely that depression is not just an evolved signal of social need because depression elicit negative reactions in social partners, which is opposite of the reaction to normal emotions of sadness, grief and crying. Depression also functions to compel support. In small communities group members depended on one another for mutual well-being. Loss of interest in all activities put the well-being of all group members at risk (91). Therefore, depression also functions as a strategy for extorting increased investment form the entire social network (64, 90).

6. *The bargaining model of depression*

The bargaining theory is quite similar to the social navigation theory. It adds only one thing; the fitness of the social partners in general is correlated. Depression is not only costly to the depressive. Social partners feel a burden imposed on them and are compelled to respond to the unmet needs of the depressive in order to prevent their own fitness from being reduced (92). Though bargaining, as in withholding benefits to compel changes by others can only work and is only necessary in particular social circumstances that would have occurred repeatedly in the environment of evolutionary adaptedness (EEA). Those are often dangerous circumstances in which cognitive impairment would have been disastrous (92, 93). Depression may just be such a strategy. If this is true you might wonder whether depression is mental illness at all when major life improvements, like getting a new job, sufferers of depression can experience a complete recovery. Then unpleasant experiences like physical pain and nausea are adaptation designed to protect from further harm.
Recently Rosenström combined the bargaining model with the evolution of cooperation. He argues that the depressed withhold benefits from other by not participating to joint enterprises and explains how selection and social-strategies even favour depressive behaviour (94).

7. *Physical pain hypothesis*

Sadness and low mood are painful. One reason for why depression is thought to be pathological. Like physical pain, psychic pain might function to withdraw from the source of injury and encourage cautious behaviour in future. Depression informs the sufferer that current circumstances are being a threat to his biological fitness. Clinical depression only is a dysfunctional extreme of this mechanism (95, 96). The behavioural shutdown model supports this psychic pain hypothesis. If a person faces more risk than reward from activities it might be an evolutionary strategy to avoid them. Emotional pain, negative emotions like disappointment, grief, fear and anger have an adaptive purpose for the identification and avoidance of specific problems.

8. *Prevention of infection*

In most cases, rates of dysfunction increase with age. Organ dysfunction or major mental retardation appear to have low rates in adolescents and young adults and highest rates in elderly people, which is consistent with an evolutionary theory of aging; the selection against dysfunctional traits decreases with age, because of lower survival probability to later age. In contrast with this pattern depression is an outlier. The occurrence and persistence of depression is higher in younger age categories.
Rates of infectious disease are high in young people, of course, but clinical depression is not thought to be caused by an infection. But it is hypothesized that depression helps prevent infection in both the affected individual and his offspring (97, 98). Inactivity and lethargy, symptoms of depression, also encourage rest and energy conservation. This allows allocating energy to the immune system for fighting infections. Further the decreased interest in social activities prevents exchange of infections as the loss of appetite might reduce exposure to food-borne parasites (97). From an evolutionary perspective, suicide is a puzzle, but environmental factors which increase vulnerability for infection are associated with

prevalence of suicide. Infections and immune factors increase the risk for mental disorders by well-established mechanisms (99).

Three theories described above are very similar; they posit a mechanism for the social behaviour and social risk-taking. The risk aversion theory fits Nesse's theory that environmental propitiousness regulates investment. In fact all investment is risky. And both are similar to the social competition theory since is a risky undertaking for group living animals to challenge higher ranked group member (73).
At last if Nesse hypothesis is right, depression will become common in people who cannot disengage from unreachable goals. A remark about the testability of his hypotheses is the fact that you cannot exclude a lot of variables and also it is not ethical to test this in an individual while not taking every possibility of improving his situation. Also, a lot of evolutionary hypotheses are withdrawn from animal studies which are difficult to extent to humans. The implications of his theory then for the prevention of depressive disorders are less clear. Finally, some of the arguments are rather speculative. The fact that depression affects a large proportion of the population does not mean it is a 'normal' condition. Concepts of health and disease are of fundamental importance in this discussion. And because evolutionary hypotheses cannot explain the prevalence of suicide this will be attended in the next chapter.

3. HEALTH AND DISEASE IN SOCIETY

What is the boundary between healthy low mood and pathological depression? This emphasizes the need of identifying a mechanism that mediate and regulates normal mood conditions as well as methods to asses motivational structures of people's lives; getting crucial resources, trade-offs and reaching goals, to test the hypothesis that depressive symptoms arise when people get trapped in the pursuit of unreachable goals (68, 69). Concepts of health and disease change over age and in every culture. Since 1970 the diagnosis of depression was on symptom-based criteria. In their book '*the loss of sadness*' Allen Horwitz and Jerome Wakefield criticize the current diagnosis of depressive disorder and give a description how it has evolved over the last 2,500 years. They write that this method of diagnosing resulted in large overestimates or 'false positives' of number of people diagnosed having a depressive disorder, explaining the high rate. From antiquity to modern times, clinicians never considered depressive symptoms in themselves an indication of psychopathology. Instead this diagnosis was only when symptoms occurred without cause or in severity or duration disproportionate (69, 100). However, the question is not about definition or semantics but whether we consider sadness as an inherent part of our human beings or a problem we should eradicate from our lives through medicalization (100).
In distinguishing disordered responses from normal sadness at least three essential components can be characterized; normal sadness is context-specific, its intensity is roughly proportional to the provoking loss and it often ends when the loss situation ends (100). In examining the function of sadness the authors give three main adaptive functions; lay in attraction of social support, progression from aggression after status losses and promotion of disengagement from non-productive activities (100).

Suicide and western culture

The idea that people only seek pleasure and avoid pain, the hedonic principle which formed an important part of the philosophies of later British Enlightenment thinkers, was a foundation of Freudian psychoanalysis, and still is a basic assumption across much of psychology and neurobiology (69, 101). All humans have a powerful instinct of self-preservation and self-fulfilment, cling to live and seek for satisfaction. All what moves us perhaps can be defined as self-love. And maybe even suicide is pursued out of this principle of self-love. In the midst of a feeling of utter meaningless and hopelessness and numbness, of depression a person can say: "It can't get any worse than this. So even if I don't know what I will gain through death, I do know what I will escape." And so suicide is an attempt to escape the intolerable.
In examining the cultural roots of suicidal behaviour, Pridmore and McArthur explored suicides from antiquity till the recent periods. They compared the precipitating circumstances and attendant emotions and concluded those are part of western culture and can be traced back for more than 2000 years (102). But then, what cultural changes should be needed to minimize suicide?
Also Horwitz *et al.* state that modern society make humans face challenges that inherited loss responses were not 'designed for'; shifting and changeable interactions that are often being lost, status hierarchies that constantly test one's worth, mobility away from close kin and less common rituals of solidarity. Ideologies that emphasize personal responsibility rather than fate and status comparisons through mass media, which motivate to pursue unachievable goals. They confront people's response mechanisms with environments natural selection did not anticipate for (100). What people traditionally strived for; working hard, family and virtues is in western culture of today translated into individual freedom, self-development, personal welfare and self-fulfilment.
In the opinion of Belgium psychologist Paul Verhaeghe, we, and our identity, is not defined by our brain though is it rather a construction defined by social relationships and values. Important here are the concepts of freedom and responsibility. These definitions can only be understood in their context and within history. Till the sixties there was strong conformity

and central authority. Since then we escaped out of too compelling values towards autonomy and self-determination. Social mobility ensured sons and daughters of farmers to go to university. The idea of the manufacturable life was born. The sociologist Bauman (103) notices there is a paradox in this; we never felt so free but also never felt so powerless. Why is that?

Verhaeghe states that identity is largely a social construct built on an evolutionary-biological fundament. Humans are social creatures. When a person is alone, he might be ill or expelled. We are not made to live alone. A second characteristic of our social identity is that individuals aren't always equal, in whatever group there will be social stratification and hierarchy. Then thirdly, there is the choice between two different behaviours, cooperation and sharing or egoism. Both are extremes. A society with a high level of inequality will be as negative as a society with mandatory equality (104, 105).

Verhaeghe emphasizes that identity is very determined by relationships and ethics is a construction of the social group you live in, though there is no overall determination. We are probably the only species that make choices well thought through on the basis of self-reflection. And on behalf of a mandatory social narrative, a new identity evolved about thirty years ago, the neoliberalism and its total marketing (106, 107). The new norm is efficiency and productivity. This human resource management caused good fellowship to disappear. People should work hard, be flexible, rational and so egoistic-efficient. Poverty becomes a symptom of laziness, who does not produce benefits from those who does (108, 109). Decreus describes a dichotomy of winners, who owe their success to their effort and talent, and losers whose loss is their own fault. A perfect life, perfect body, perfect relationships it is all manufacturable material success. Everything depends on your own choices and your own personal effort.

Scientists revealed three negative effects of the current neoliberal organised society. First on social level: the increasing gap between high and low incomes, cause social inequality, stress, aggression, criminality *etc.* (55). The second is on individual level, in a *Rank and Yank* community, other individuals are potential threat. The exponential increase in contacts on social media is an expression of distrust, besides, individualism causes loneliness, the most painful symptom or our times. Finally, on ecological and environmental level: For example disastrous CO_2 emissions (110).

The neoliberal model wants people to function economically efficient. When a person becomes ill, mentally or physically, clients – we no longer call them patients – therapy is focussed on walking in line again, and being productive again, as soon as possible (104, 111, 112). Another example is that our current psychiatric diagnosis criteria are not value free, though reflect current normative social expectations. Further, there are concerns about medicalization of natural and normal responses to experiences, which do not reflect illness so much as normal individual variation. Classifying such problems as illnesses misses also the relational contexts of problems and social causation. For our well-being and mental health also stems from our frameworks of understanding the world, which itself is the product of experiences and learning throughout life (15, 16, 95, 113, 114).

4. THE EVOLUTIONARY PERSPECTIVE

> *"With me the horrid doubt always arises whether the convictions of man's mind, which has been developed from the mind of the lower animals, are of any value or at all trustworthy. Would anyone trust in the convictions of a monkey's mind, if there are any convictions in such a mind?"* Charles Darwin

Evolutionary psychology is very popular at present and growing in popularity; trying to explain various features of organisms in Darwinian terms; to show how the trait in question contributes to fitness of the organism. Though when a researcher tries to seek the ultimate purpose of a trait, in this case depression, in evolution, evolution which is a biological/physical mechanism and a purposeless process, is elevated to a higher category of explanation, as I will try to argue here.
This subject is rather philosophical. But one of the first tasks of philosophy in fact is to study the limits of modern scientific knowledge, trying to recognize what can and what cannot be understood by the existing methods. There is something to say about psychophysical reductionism and Neo-Darwinism in this subject. Science has been very successful in the method of reduction followed by reconstruction; discovering basic elements of which everything is composed and subsequently combined to yield the observed complexity. In fact materialism is the view that only the physical world can be real.
In the contemporary world a scientific theory, biological macro-evolution, stands in close relationship to naturalistic philosophy. If you take naturalism as true and all we have is matter/energy and the forces of physics, then the only option is that matter/energy together with the forces of nature have produced life. It is a logical implication of naturalism that it needs evolution as philosophical necessity (117).

Mind and body

What came to be known as Darwin's doubt was his unsolved problem, the place of consciousness in evolutionary world. Darwin had a lifelong interest in the relationship between mind, brain and behaviour. For him the availability of language is vital for the development of mental characteristics as self-consciousness and general idea's. Though he did not think the lower animals are unaware of themselves. Therefore he pointed to emotions like shame and guilt. "Does not the emotion of shame imply consciousness of the self?" he wonders in his *Expression of emotions in Man and Animals.* And he was amazed by children in their infanthood; "it is one of their chief charms that they think nothing about what others think of them". As he thought of this, it was not only the question how, but also when, consciousness started to commence (115).
Though the question about consciousness leads to a greater dilemma; "If a material element, or a combination of a thousand material elements in a molecule, are like unconsciousness, it is impossible for us to believe that the mere addition of one, two or a thousand other material elements to form a more complex molecule could in any way tend to produce a self-consciousness existence. There is no escape from the dilemma, either all matter is conscious or consciousness is, or pertains to something, something distinct from matter", a quote from Alfred Russell Wallace (115). Therefore, physical science cannot provide a theory of everything, which is shown by the mind-body problem, the irreducibility of conscious experience to the physical. As if evolutionary biology is only a physical theory it cannot account for the appearance of consciousness and if mind is a product from evolution then biology cannot be purely physical science (116).

Edge to evolution

> "*The only watchmaker in nature is the blind force of physics… natural selection, the blind unconscious, automatic process which Darwin discovered, and which we now know is the explanation for the existence and apparently purposeful form of life has no purpose in mind…* Richard Dawkins

In Neo-Darwinism some claims are made that takes us beyond Darwin himself; that the (blind) forces of physics are the only one in nature, natural selection is as an automatic and purposeless process and the explanation for the existence and form of all life.
So what is the nature and scope of evolution? At least there are different ideas for which the term is used:

1. *Change, development, variation*. The word is used to describe change, normal processes of the sea, wind, flora and fauna which change over time.
2. *Micro-evolution: variation within prescribed limits of complexity, quantitative variation of already existing organs or structures*. Such processes were observed by Darwin in connection to the Galapagos fish species. Such effects of natural selection; mutation, genetic drift etc. are constantly recorded. One classic example is the way bacteria develop resistance to antibiotics.
3. *Macro-evolution*. Large-scale innovation, coming to existence of new structures, new genetic material. Single-celled structures evolve to multicellular. In fact the extrapolation form the process that drives micro-evolution. Compared to micro-evolution, "Large evolutionary innovations are not well understood. None has ever been observed, and we have no idea whether any may be in progress. There is no good fossil record of any" (Wesson 1993). By contrast micro-evolutionary variations have been observed.
4. *Artificial selection, for example in plant and animal breeding*. Humans can do in a relatively short time what nature could do in a long time. Breeders produced many different kinds of roses, sheep or whatever from basic stocks.
5. *Molecular evolution*. Some scientists argue that, strictly speaking, evolution presupposes the existence of self-replicating genetic material. Since natural selection needs mutating replicators, in fact prebiological natural selection is a contradiction in terms. Like the chicken and the egg story; what would exist first, DNA or protein? However, 'molecular evolution' is commonly used to describe the emergence of a living cell from non-living material (117).

To the biologists evolution is a (technical) hypothesis. It covers more of the facts than any other hypothesis on the market and is accepted until a new proposal covers more facts, with fewer assumptions. Most of the time natural selection is describing the process by which the strain in a population that produces the weaker progeny eventually gets weeded out. Or, presented as a deductive argument by Colin Patterson: All organisms must reproduce > all organisms exhibit hereditary variations > hereditary variation differ in their effect on reproduction > therefore variations with favourable effects will fail, and organisms will change. If you take the first three points for granted then the fourth point follows logically. It shows that evolution must occur but does not say natural selection is the only cause of evolution. But when generalized to be the explanation of all evolutionary change or every feature of every organism, it becomes so all-embracing that it is in fact not falsifiable anymore (Poppers criteria). Like the Freudian statement that adult behaviour is due to childhood trauma is not falsifiable (117).
Two other questions might be asked about credibility of the evolution theory; first, given our knowledge about the chemical and genetic basis of biology, what is the likelihood of self-producing organisms coming into existence solely on behalf of the laws of physics and chemistry. Natural selection by definition assumes, that there is something to select from. It requires life in itself. Also to describe creative power to physic forces is disputable. Nature which produces plants and animals is blind in itself (117). And a second question can be whether genetic mutations could actually occur on the first life forms appearing on earth that permitted the natural selection to produce this variation in life as we know now? (116). There are limits on the efficacy of random mutation(118).
Again if we talk about body and mind, how can an immortal self or soul evolve in this way? What kind of genetic mutation would result in the coming to existence of an immaterial soul? What section of DNA codes for a self (118)? 'If contemporary molecular biology leaves open a possibility of doubt about fully mechanistic account on the origin and evolution of life, dependent on only laws of chemistry and physics, this can combine with the failure of psychophysical reductionism to suggest that principles of a different kind are also at work in

the history of nature, principles of growth of order that are in logical form teleological rather than mechanistic. 'A teleological account will hold that in addition to the laws governing the behaviour of the elements in every circumstance, there are also principles in self-organisation or the development of complexity over time that are not explained by those elemental laws' (116). Therefore trying to explain depression in evolutionary terms feels like making evolution teleological rather than mechanistic, by seeing it as adaptive response rather than a syndrome.

Conclusions and future directions

Significant heritability for depression would be strong evidence against the adaptation-hypothesis. It would be a disease which high prevalence can be explained by the mutations in sufficiently large number of loci. However, once genetic control is taken into account, for exposure to environments that predispose to depression, direct heritability seems to be quite modest (73, 119). GWA studies did not uncover really strong and consistent risk modifiers yet. Part of the reason for this might be the heterogeneity of phenotypes in depressive disorder. This heterogeneity might just be similar to normal heritable variation when triggering the threshold of a complex and mutagen adaptation. On the other way around, there is little evidence that people who never suffer from depression are genetically incapable of it (93). As negative life events will not cause depression in all individuals.
Maybe negative states and mood affects which deserve help and intervention are not best considered illnesses. Regarding them as such brings the danger of misunderstanding their nature and cause. Depressive state is characterized by a lot of symptoms. It is important as for physic pain to early recognize psychic pain as an internal signal of need. Remission of depression is associated with important life improvements. There is no evidence that the depressive symptoms themselves will bring about life improvements as the evolutionary hypotheses require (69). Chemo- and psychotherapy provide relief of symptoms and may offer the depressive the positive state to have the courage to face and cope with causative problems. Proximate research should focus more on understanding mood, sadness, response mechanisms and early diagnoses.

Animals & Personalized medicine
The capacity for mood appears to be phylogenetic. Mechanisms underlying mood are widespread and the adaptive function of mood involves the integration of emotional experiences over time (120). Defining mood in animals will help in understanding human mood, the way in which is affected by environmental conditions, life events and developmental history. Animal models are long used to study genetic, molecular, cellular and environmental parameters in neuropsychiatric disorders including depression. For example, they have shown dysfunction of serotonin neurotransmission and a positive role for dopamine antagonists etc. There are promising (113, 121, 122) but not yet conclusive biomarkers or imaging tests available for diagnosing psychiatric disorders. Therefore animal models are still interesting (123). Although symptoms such as guilt and suicidality are impossible to reproduce in animal models understanding the neural circuitry involved in mental disorders helps therapeutics to target a small section instead of overloading the entire brain, give new options for treatment (17, 124).
The human genome project was expected to revolutionize medicine and offer treatment based on the genetic make-up of an individual. This promise, by identification of biomarkers of disease is not fulfilled yet and progress is slow. Also for depression a few possible biomarkers, including serum levels of neurotrophic factors, inflammatory cytokines and HPA axis hormones, have been identified but none has proven sufficiently powerful for clinical use. On the other side the role of the genome in drug metabolism helps personalizing description of antidepressants; genotyping test help identifying responders and non-responders, providing alerts to possible adverse drug events and optimizing doses (125, 126).

In the end

Every theory, biochemical, environmental or genetic, proposes its own solutions; pharmacological, psychotherapeutic or correction of faulty genes in future. There is scepticism about whether evolutionary psychiatry will result in accurate diagnoses and effective prevention or treatment of mental illnesses (1).

Still when depression is suggested to be an evolutionary adaptive response, it does not say it is a beneficial response, by the standards of modern society. But it does suggest that currently approaches treat symptoms rather than causes, instead of addressing the underlying social problems.

Reducing a complex thing like depression to chemical imbalance will not do justice to a human being; with Francis Crick I wonder whether 'you, your sorrows, your memories and ambitions, your sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules' (127). Classical science has this functional preference for reducing complex problems to a few controlling factors of causality, which is successful for simple systems. But most of the phenomena in biology as well as human society are irreducible complex systems. Mentally illnesses which deal with the mind, with psychology, sociology and physiology, are less clear to define in such a short essay like this.

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